






## ORIGINAL ARTICLE

# Development and validation of IHS4-55, an IHS4 dichotomous outcome to assess treatment effect for hidradenitis suppurativa

Thrasivoulos Tzellos<sup>1,2</sup> | Kelsey R. van Straalen<sup>1,3</sup> | Athanassios Kyrgidis<sup>1,4</sup>  | Afsaneh Alavi<sup>1,5</sup>  | Noah Goldfarb<sup>6,7</sup> | Wayne Gulliver<sup>1,8</sup> | Gregor B. E. Jemec<sup>1,9</sup> | Michelle A. Lowes<sup>10</sup> | Angelo Valerio Marzano<sup>1,11,12</sup>  | Errol P. Prens<sup>1,13</sup> | Christopher J. Sayed<sup>14</sup>  | Hessel H. van der Zee<sup>1,13</sup> | Christos C. Zouboulis<sup>1,15</sup> 

<sup>1</sup>European Hidradenitis Suppurativa Foundation e.V., Dessau, Germany

<sup>2</sup>Department of Dermatology, Nordland Hospital Trust, Bodø, Norway

<sup>3</sup>Department of Dermatology, University of Michigan, Ann Arbor, Michigan, USA

<sup>4</sup>Department of Maxillofacial Surgery, Papanikolaou General Hospital of Thessaloniki, Aristotle University of Thessaloniki, Thessaloniki, Greece

<sup>5</sup>Department of Dermatology, Mayo Clinic, Rochester, Minnesota, USA

<sup>6</sup>Departments of Medicine and Dermatology, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA

<sup>7</sup>Departments of Medicine and Dermatology, University of Minnesota, Minneapolis, Minnesota, USA

<sup>8</sup>Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland, Canada

<sup>9</sup>Department of Dermatology, Zealand University Hospital, Roskilde and Health Sciences Faculty, University of Copenhagen, Copenhagen, Denmark

<sup>10</sup>The Rockefeller University, New York, New York, USA

<sup>11</sup>Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

<sup>12</sup>Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

<sup>13</sup>Department of Dermatology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

<sup>14</sup>Department of Dermatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

<sup>15</sup>Departments of Dermatology, Venereology, Allergy and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane and Faculty of Health Sciences Brandenburg, Dessau, Germany

## Correspondence

Christos C. Zouboulis, Departments of Dermatology, Venereology, Allergy and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane and Faculty of Health Sciences Brandenburg, Auenweg 38, 06847 Dessau, Germany.

Email: [christos.zouboulis@mhb-fontane.de](mailto:christos.zouboulis@mhb-fontane.de)

## Abstract

**Background:** Validated, inclusive and easy-to-use outcomes for hidradenitis suppurativa are essential both in the clinical trial setting and clinical practice. The continuous IHS4 is a validated tool that dynamically assesses nodules/abscesses/draining tunnels and classifies disease severity as mild/moderate/severe. However, dichotomous outcomes are often required for clinical trials reporting.

**Objective:** To develop and validate a dichotomous outcome based on IHS4 that can be used in clinical trial settings and day-to-day clinical practice.

**Methods:** De-identified data from the PIONEER-I and -II studies were accessed through Vivli. Potential IHS4 thresholds were analysed using baseline to Week 12 data from adalimumab- and placebo-treated hidradenitis suppurativa patients in the PIONEER-I trial. The final threshold was chosen based on its ability to discriminate between patients treated with adalimumab or placebo and its association with

Thrasivoulos Tzellos and Kelsey R. van Straalen share first authorship

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Journal of the European Academy of Dermatology and Venereology* published by John Wiley & Sons Ltd on behalf of European Academy of Dermatology and Venereology.

reduction in inflammatory lesions. The final threshold was validated using data from baseline to Week 12 from adalimumab- and placebo-treated hidradenitis suppurativa patients in both the PIONEER-II and the combined PIONEER-I and -II studies.

**Results:** The best performing cut-off for the IHS4 was a 55% reduction of the IHS4 score (IHS4-55). Patients who achieved the IHS4-55 had an odd's ratio of 2.00 [95%-CI 1.26–3.18,  $p = 0.003$ ], 2.79 (95%-CI 1.76–4.43,  $p < 0.001$ ) and 2.16 (95%-CI 1.43–3.29,  $p < 0.001$ ) for being treated with adalimumab rather than placebo in PIONEER-I, PIONEER-II and the combined dataset, respectively. Additionally, the achievement of the IHS4-55 was associated with a significant reduction in inflammatory nodules, abscesses and draining tunnels in all analysed datasets.

**Conclusions:** IHS4-55, a novel dichotomous IHS4 version, based on a 55% reduction of the total score was developed. The IHS4-55 performs similarly to the HiSCR in discriminating between adalimumab- and placebo-treated hidradenitis suppurativa patients and shows significant associations with reductions in lesion counts. Moreover, the IHS4-55 addresses some of the HiSCR drawbacks by dynamically including draining tunnels in a validated manner. By allowing the analysis of hidradenitis suppurativa patients with an abscess and nodule count below 3 but many draining tunnels, this outcome measure will improve inclusivity in clinical trials.

## INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, debilitating skin disease originating from the hair follicles, which affects around 0.4% of the Western population.<sup>1</sup> Lesions arise mainly in the axillae, groin and gluteal areas and include inflammatory nodules, painful abscesses and draining tunnels. The treatment options for this debilitating disease are limited and often lack high quality evidence.<sup>2–4</sup> Despite the prevalence and high burden of this disease, there is currently only one EMA- and FDA-approved biologic for HS; adalimumab. However, only around 40%–60% of patients achieve clinical response on adalimumab highlighting the pressing need for additional effective treatments.<sup>5,6</sup>

In order to identify effective treatments in clinical trials for HS, a good primary outcome measure is vital. The current gold standard primary outcome in HS clinical trials is the Hidradenitis Suppurativa Clinical Response (HiSCR).<sup>7</sup> This dichotomous, FDA-supported outcome was designed retrospectively in a phase 2 adalimumab trial study population.<sup>7</sup> The HiSCR identifies treatment responders as those who achieve at least a 50% reduction in abscess and nodule count (AN-count) without an increase in the number of abscesses or draining tunnels relative to baseline.<sup>7</sup> Despite its wide use, the drawbacks of this score have become increasingly apparent in recent clinical trials.

Firstly, patients with an AN-count under 3 were excluded from the clinical trial in which the HiSCR was developed. This means that HiSCR may be less stable in patients with an AN-count <3, and it is therefore generally not used in patients with an AN-count <3 but multiple draining tunnels. Consequently, these patients are currently excluded from

participating in all clinical trials that use HiSCR as the primary endpoint. Secondly, the HiSCR does not dynamically take into account draining tunnels.

Taken together, these drawbacks of the HiSCR demonstrate the need for a new dichotomous outcome that captures the full range of clinical response to therapy.<sup>8</sup> Therefore, we used the International Hidradenitis Suppurativa Severity Score System (IHS4), a continuous score that incorporates inflammatory nodules, abscesses and draining tunnels to develop a novel dichotomous outcome.<sup>9</sup>

## METHODS

### Development of dichotomous IHS4

#### Data

Access to data from the PIONEER-I and II studies was obtained through the Vivli online platform (Microsoft). Data from patients receiving either adalimumab 40 mg weekly or placebo treatment were included from baseline (W0) and Week 12 (W12). Development of the dichotomous IHS4 score was done using the PIONEER-I dataset, validation was conducted in the PIONEER-II and in the combined dataset (PIONEER-I and PIONEER-II).

### Development of dichotomous IHS4

Eight different IHS4 thresholds were analysed as potential dichotomous variables: IHS4-30, IHS4-50, IHS4-55, IHS4-60,

**TABLE 1** Baseline data of included patients from PIONEER-I and PIONEER-II studies

	PIONEER-I		PIONEER-II	
	Adalimumab, <i>n</i> = 144	Placebo, <i>n</i> = 145	Adalimumab, <i>n</i> = 149	Placebo, <i>n</i> = 140
<b>Sex</b>				
Female, <i>n</i> (%)	85 (59.0)	100 (69.0)	97 (65.1)	98 (70.0)
Age, mean ± SD	36.3 ± 10.9	38.1 ± 11.2	34.9 ± 10.0	36.2 ± 12.7
<b>Hurley staging</b>				
Hurley stage II, <i>n</i> (%)	80 (55.6)	79 (54.5)	76 (51.0)	79 (56.4)
Hurley stage III, <i>n</i> (%)	64 (44.4)	66 (45.5)	73 (49.0)	61 (43.6)
<b>Lesion counts</b>				
Inflammatory nodules, mean (SD)	11.5 (11.0)	11.6 (14.1)	8.7 (8.2)	9.3 (10.0)
Abscesses, mean (SD)	2.9 (3.4)	2.8 (3.5)	2.1 (2.8)	2.4 (3.5)
Draining tunnels, mean (SD)	4.6 (5.1)	3.8 (4.3)	3.1 (4.4)	3.7 (5.0)
IHS4 score, mean (SD)	35.3 (27)	32.8 (28.1)	26.1 (24.7)	28.9 (33.4)

Abbreviations: SD, standard deviation.

IHS4-65, IHS4-70, IHS4-75, IHS4-80, reflecting a 30%–80% reduction in IHS4 score between W0 and W12. Following tests for normality, correlation matrices (Pearson's *r* or Spearman's rho coefficient where appropriate) were constructed between dichotomous IHS4 thresholds and (1) dichotomous active treatment or placebo as intention to treat and per protocol variable, (2) reduction in number of inflammatory nodules, (3) reduction in abscesses and (4) reduction in draining tunnels. HiSCR was included in the correlation matrices as a reference. The choice of the final threshold for the dichotomous IHS4 score was based on these analyses: its ability to discriminate between adalimumab- and placebo-treated patients and its associations with lesion count reductions after 12 weeks of treatment.

### Association of final dichotomous IHS4 outcome and HiSCR with clinical outcomes

Associations of final dichotomous IHS4 outcome and HiSCR with the reduction in lesion counts and C-reactive protein (CRP) were further assessed using either paired *t* test or Wilcoxon signed-rank on the differences between W0 and W12 for achievers and non-achievers separately. Associations between treatment arm and dichotomous IHS4 achievement (or HiSCR achievement) were further assessed using Pearson's Chi Square test and binary logistic regression to quantify the odds ratios for these associations. In addition, subgroup analyses were performed for Hurley stage II and Hurley stage III patients separately.

### External validation datasets PIONEER-II and combined dataset

Similar analyses as those mentioned in the above paragraph were performed to assess the validity of the dichotomous IHS4 outcome in the PIONEER-II and the combined PIONEER-I and PIONEER-II dataset.

### Statistical analysis

Statistical analysis of the PIONEER-I, PIONEER-II and combined datasets were performed within the online Vivli environment (Microsoft) using STATA (Stata Statistical Software: Release 16., StataCorp LP).

## RESULTS

### Study population PIONEER-I, PIONEER-II and combined dataset

Overall, the PIONEER-I development dataset contained 289 patients, of which 49.8% (144/289) were treated with adalimumab and 50.2% (145/289) with placebo (Table 1). Fifty-five percent (159/289) of the patients in the PIONEER-I dataset had Hurley stage II disease; the remainder had Hurley stage III (130/289). In addition, 289 patients were included from the PIONEER-II validation dataset [51.6% (149/289) were treated with adalimumab and 48.4% (140/289) with placebo]. Of these patients, 53.6% (155/289) had Hurley stage II and 46.4% (134/289) Hurley stage III disease. The combined validation dataset (PIONEER-I and PIONEER-II) comprised 578 patients of which 50.7% (293/578) received adalimumab and 49.3% (285/578) placebo. The mean IHS4 score among adalimumab-treated patients was 35.3 and 26.1 in the PIONEER-I and II datasets, respectively. Among placebo-treated patients the median IHS4 score was 32.8 and 28.9, respectively.

### Development of IHS4-55 in PIONEER-I dataset

Based on the correlation matrices for the treatment group and reduction in lesion counts, the best performing IHS4 threshold in the PIONEER-I dataset was found to be a 55% reduction in overall IHS4 score (Table S1). This

dichotomous IHS4-55 had an odds ratio (OR) of identifying adalimumab treated patients of 2.00 [95% confidence interval (CI) 1.26–3.18] in the PIONEER-I dataset (Table 2). Moreover, the achievement of IHS4-55 was associated with a significant reduction in inflammatory nodules, abscesses and draining tunnels in the PIONEER-I dataset (Table 3), while non-achievers did not show a significant reduction in any of the lesion counts. In the PIONEER-I dataset, 65/144 (45%) of patients treated with adalimumab achieved the IHS4-55 and 62/144 (43%) achieved HiSCR, compared with 41/145 (28%, IHS4-55) and 40/145 (28%, HiSCR) of patients treated with placebo. Moreover, the achievement of the IHS4-55 was associated with a significant reduction in CRP (Table 3).

### Validation of IHS4-55 in PIONEER-II and combined datasets

Similar results for the IHS4-55 with regard to discrimination between adalimumab- and placebo-treated patients as well as associations with decreased lesions counts were found in both validation datasets. In the PIONEER-II and combined dataset, the IHS4-55 demonstrated an OR of identifying adalimumab-treated patients of 2.79 (95% CI 1.76–4.43) and 2.16 (95% CI 1.43–3.29), respectively (Table 2). The achievement of IHS4-55 was associated with a significant reduction in inflammatory nodules, abscesses and draining tunnels in both validation datasets (Table 3). Non-achievers of the IHS4-55 showed no significant reduction in lesion counts, except for inflammatory nodules in both datasets. IHS4-55 achievers demonstrated a significant reduction of CRP.

Overall, in the PIONEER-II dataset, 91/149 (61%) of adalimumab patients achieved the IHS4-55 and 89/149 (60%) achieved the HiSCR. Among placebo patients, 43/140 (30%) achieved the IHS4-55 and 41/140 (29%) the HiSCR.

Subgroup analysis of patients with Hurley stage II or Hurley stage III in the combined dataset showed that IHS4-55 achievers had a significant reduction in inflammatory lesion counts and CRP, where non-achievers did not, except for inflammatory nodules in Hurley stage II patients (Tables S2 and S3).

## DISCUSSION

In this study, we developed a new dichotomous outcome, the IHS4-55, to measure treatment efficacy in HS. In all datasets, patients achieving the IHS4-55 were 2–3 times more likely to have received adalimumab treatment than placebo. In addition, the achievement of the IHS4-55 was associated with significant reduction in inflammatory nodules, abscesses and draining tunnels, in both the development and validation datasets.

The IHS4-55 and HiSCR were shown to perform relatively similarly in the PIONEER datasets regarding identifying adalimumab-treated patients and their associations with a reduction in inflammatory lesion counts. Nonetheless, the two scores have an important difference that could become increasingly important in ongoing and future clinical trials. The primary difference between these scores is that the HiSCR only takes into account inflammatory nodules and abscesses where the IHS4-55 additionally includes draining tunnels in a validated and dynamic manner.<sup>7,9</sup> Failing to account for draining tunnels can have a dramatic impact on the outcome of clinical trials and development of promising new therapies as was demonstrated by a recent phase II trial assessing the efficacy of different dosages of IFX-1 (vilobelimab) in patients with moderate–severe HS compared with placebo.<sup>10,11</sup> In this trial, the difference in reduction of AN-count after 16 weeks of treatment was not significant between the placebo and the highest dosed vilobelimab groups. As a result, the HiSCR rate was not statistically different between the vilobelimab- and placebo-treated groups, and the trial did not meet its primary endpoint.<sup>10</sup> Additional analyses, however, demonstrated that the reduction in draining tunnels after 16 weeks of treatment was, indeed, significant between the placebo and highest dosed vilobelimab group. Consequently, the continuous IHS4 score was shown to be significantly different between placebo and the highest dosed treatment group.<sup>11</sup> This underlines the need for a dichotomous endpoint that dynamically includes draining tunnels, as is the case with the new IHS4-55.

Importantly non-achievers for both IHS4-55 and HiSCR also showed a statistically significant reduction in inflammatory nodule count between baseline and W12 in the PIONEER-II and combined datasets. Inflammatory nodules in HS are known to have a high natural variability in relation to tunnels, which are more likely to be chronically inflamed and draining.<sup>12</sup> Weighted scaling in the IHS4,

**TABLE 2** IHS4-55 and HiSCR correlation with treatment

	Adalimumab treatment								
	PIONEER-I			PIONEER-II			Combined dataset		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
IHS4-55 achievement	2.00	1.26–3.18	0.003	2.79	1.76–4.43	<0.001	2.16	1.43–3.29	<0.001
HiSCR achievement	1.96	1.28–3.27	0.003	2.95	1.85–4.69	<0.001	2.35	1.54–3.59	<0.001

Abbreviations: 95% CI, 95% confidence interval; HiSCR, Hidradenitis Suppurativa Clinical Response; IHS4, International Hidradenitis Suppurativa Severity Score System; OR, odds ratio.

**TABLE 3** Reduction in lesion counts between baseline and Week 12

	IHS4-55			HiSCR		
	Achiever	Non-achiever	<i>p</i> -value <sup>a</sup>	Achiever	Non-achiever	<i>p</i> -value <sup>a</sup>
<b>PIONEER-I</b>						
Inflammatory nodules, mean ± SD	9.35 <sup>b</sup> ± 11.56	0.99 ± 6.58	<0.001	8.71 <sup>b</sup> ± 8.04	1.53 ± 8.77	<0.001
Abscesses, mean ± SD	2.35 <sup>b</sup> ± 3.31	0.44 ± 2.11	<0.001	2.44 <sup>b</sup> ± 3.22	0.44 ± 2.18	<0.001
Draining tunnels, mean ± SD	2.78 <sup>b</sup> ± 3.24	-0.46 ± 5.11	<0.001	2.20 <sup>b</sup> ± 3.05	0.10 ± 4.88	<0.001
CRP, mean ± SD	4.52 <sup>b</sup> ± 16.75	0.49 ± 17.65	<0.001	4.61 <sup>b</sup> ± 12.52	-0.47 ± 16.46	<0.001
<b>PIONEER-II</b>						
Inflammatory nodules, mean ± SD	5.76 <sup>b</sup> ± 6.60	1.06 <sup>b</sup> ± 5.93	<0.001	6.23 <sup>b</sup> ± 5.08	0.89 <sup>b</sup> ± 6.05	<0.001
Abscesses, mean ± SD	1.56 <sup>b</sup> ± 2.41	0.09 ± 2.65	<0.001	1.50 <sup>b</sup> ± 2.69 <sup>b</sup>	0.25 ± 2.79	<0.001
Draining tunnels, mean ± SD	1.62 <sup>b</sup> ± 3.61	-1.11 ± 4.93	<0.001	1.60 <sup>b</sup> ± 2.67 <sup>b</sup>	-1.03 ± 4.44	<0.001
CRP, mean ± SD	4.92 <sup>b</sup> ± 11.04	1.68 ± 16.42	<0.001	4.62 <sup>b</sup> ± 14.83	0.46 ± 19.47	<0.001
<b>Combined dataset</b>						
Inflammatory nodules, mean ± SD	6.89 <sup>b</sup> ± 7.62	0.61 <sup>b</sup> ± 6.27	<0.001	6.69 <sup>b</sup> ± 6.25	0.74 <sup>b</sup> ± 7.30	<0.001
Abscesses, mean ± SD	1.86 <sup>b</sup> ± 2.71	0.16 ± 2.77	<0.001	1.91 <sup>b</sup> ± 2.62	0.18 ± 2.81	<0.001
Draining tunnels, mean ± SD	2.12 <sup>b</sup> ± 3.49	-0.79 ± 4.29	<0.001	1.88 <sup>b</sup> ± 2.85	-0.53 ± 4.70	<0.001
CRP, mean ± SD	4.25 <sup>b</sup> ± 14.55	0.49 ± 16.48	<0.001	4.60 <sup>b</sup> ± 14.83	0.37 ± 16.61	<0.001

Abbreviations: HiSCR, Hidradenitis Suppurativa Clinical Response; IHS4, International Hidradenitis Suppurativa Severity Score System; SD, standard deviation.

<sup>a</sup>*p*-Value between groups (achievers vs. non-achievers) using corrected *t*-test with ANCOVA.

<sup>b</sup>*p*-Value within groups baseline to week 12 *p* < 0.05.

where inflammatory nodules are assigned 1 point, abscesses 2 points and draining tunnels 4 points puts emphasis on chronically draining lesions that patients report to have the highest impact on quality of life compared with more transient inflammatory nodules and abscesses.<sup>9</sup> Outcomes incorporating a change in IHS4 reflect improvement in chronically draining and inflamed lesions rather than transient lesions alone. In contrast, the HiSCR counts abscesses and nodules equally without specific value for chronically draining tunnels, potentially making it more vulnerable to natural lesion variation than the weighted score of the IHS4.<sup>7</sup>

The new IHS4-55 will also allow for the inclusion of a broader range of patients in clinical trials, as it was already shown by an additional external validation of the IHS4-55 in a European antibiotics dataset (Van Straalen KR, Tzellos T, Alavi A et al. External validation of the IHS4-55 in a European antibiotics dataset. Under review). For the development of the HiSCR, patients with a AN-count under 3 were excluded. This ensured that a reduction of one abscess or nodule would not result in achieving the endpoint.<sup>5</sup> However, this has led to the exclusion of patients with a large number of draining tunnels but an AN-count under 3 from clinical trials. Although the novel IHS4-55 was developed in the same dataset, the combination of all inflammatory lesion counts in this score makes it suitable to include patients with few inflammatory nodules or abscesses and many draining tunnels. This might be of increasing value as certain treatments have been shown to be more effective in reducing the drainage from tunnels rather than the absolute AN-count.<sup>11</sup>

It should be noted that by using the PIONEER datasets to calculate the novel IHS4-55, the threshold is calculated in relation to the clinical response achieved by adalimumab treatment. However, with newer treatments in development, it is likely that future clinical trials will yield increasingly higher clinical response rates, similar to developments in other diseases, such as psoriasis. While the current data suggest a 55% threshold, when the goal of treatment shifts, this dichotomous IHS4 can easily be updated similar to the increasing threshold of the Psoriasis Area and Severity Index (PASI) to accommodate newer, more effective treatments.

In conclusion, the novel IHS4-55 performs similarly to the current gold standard of HiSCR in discriminating between adalimumab and placebo treatment and its associations with reductions in inflammatory lesion counts. Simultaneously, the IHS4-55 addresses the main drawbacks of the HiSCR; it dynamically includes draining tunnels in a validated manner and it allows for the inclusion of patients with an AN-count under 3 but multiple draining tunnels. Moreover, the fact that the continuous IHS4 is based on standard lesion counts and the use of the continuous IHS4 as a secondary endpoint in many ongoing clinical trials has already paved the way for implementation of the new dichotomous IHS4-55 as a secondary and future primary outcome in HS clinical trials.

## ACKNOWLEDGEMENTS

The Department of Dermatology, Zealand University Hospital, Roskilde, Denmark; the Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands; and

the Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Dessau, Germany are health care providers of the European Reference Network for Rare and Complex Skin Diseases (ERN Skin-ALLOCATE Skin group). This publication is based on research using data from the data contributor Abbvie that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for the contents of this publication. Open Access funding enabled and organized by Projekt DEAL.

## FUNDING INFORMATION

None.

## CONFLICT OF INTEREST

The authors declare that none of the mentioned conflicts of interest had any influence to the content of this manuscript. TZ reports consultancy/advisory boards/speaker fees from AbbVie and UCB. He is Treasurer of the EHSF e.V. KRvS is holder of a Rubicon Fellowship from The Netherlands Organization for Health Research. AA declares consultancy fees from Abbvie, Boehringer-Ingelheim, InflaRx, Novartis and UCB. NG declares consultancy/advisory board fees from Boehringer-Ingelheim and Novartis. He is a site principal investigator for clinical trials with Abbvie, Pfizer and Chemocentryx; he has edited a UpToDate article. GBEJ reports consultancy fees from Novartis and UCB; has received grants from Abbvie, Chemocentryx, LEO, InflaRx, Novartis and UCB; support for attending meetings from Sanofi. He is Vice President of the EHSF e.V. and in the Board of C3 and CHORD; is co-coordinator of the ALLOCATE Skin group of the ERN Skin and vice chair of the ARHS Task Force group of the EADV. He is Editor-in-Chief of Dermatology. MAL has served on the advisory boards for Abbvie, InflaRx, Janssen, UCB and Viela Bio and consulted for Almirall, BSN medical, Incyte, Janssen, Kymera, Phoenixis and XBiotech. She is a Board member of the HSF Inc (USA). EPP reports advisory boards/speaker fees from AbbVie, Amgen, Celgene, Eli Lilly, Janssen-Cilag, Galderma, InflaRx, Novartis, UCB, Regeneron and Pfizer. His employer has received investigator-initiated grants from AbbVie, Celgene, Janssen-Cilag and UCB. CJS has received advisory boards/speaker fees from Abbvie, InflaRx, Novartis and UCB and grants from Abbvie, Chemocentryx, Incyte, InflaRx, Novartis and UCB. He is a Board member of the HSF Inc (USA). HHvdZ declares consultancy/speaker fees from AbbVie, InflaRx, Insmad and Novartis. CCZ reports consultancy/advisory boards disease-relevant honoraria from AbbVie, Bayer, Boehringer-Ingelheim, Incyte, InflaRx, Janssen-Cilag, Novartis, Regeneron and UCB. He has received speaker fees from AbbVie, Biogen and UCB; is President of the EHSF e.V., coordinator of the ALLOCATE Skin group of the ERN Skin and chair of the ARHS Task Force group of the EADV. He is Editor of the EADV News; is co-copyright holder of IHS4 on behalf of the EHSF e.V.

His employer has received disease-relevant grants from AbbVie, Boehringer-Ingelheim, InflaRx, Novartis and UCB for his participation as clinical investigator. AK, WG and AVM declare no conflict of interest.


## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.


## ORCID

Athanassios Kyrgidis  <https://orcid.org/0000-0003-3896-0309>

Afsaneh Alavi  <https://orcid.org/0000-0003-1171-4917>

Angelo Valerio Marzano  <https://orcid.org/0000-0002-8160-4169>

Christopher J. Sayed  <https://orcid.org/0000-0003-3201-4637>

Christos C. Zouboulis  <https://orcid.org/0000-0003-1646-2608>

## REFERENCES

1. Jfri A, Nassim D, O'Brien E, Gulliver W, Nikolakis G, Zouboulis CC. Prevalence of hidradenitis suppurativa: a systematic review and meta-regression study. *JAMA Dermatol.* 2021;157:924–31.
2. van Straalen KR, Prens EP, Gudjonsson JE. Insights into hidradenitis suppurativa. *J Allergy Clin Immunol.* 2022;149:1150–61.
3. Ingram JR, Woo PN, Chua SL, Ormerod AD, Desai N, Kai AC, et al. Interventions for hidradenitis suppurativa. *Cochrane Database Syst Rev.* 2015;2015:CD010081.
4. Ingram JR. Interventions for hidradenitis suppurativa: updated summary of an original cochrane review. *JAMA Dermatol.* 2017;153:458–9.
5. Kimball AB, Okun MM, Williams DA, Gottlieb AB, Papp KA, Zouboulis CC, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med.* 2016;375:422–34.
6. Zouboulis CC, Okun MM, Prens EP, Gniadecki R, Foley PA, Lynde C, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. *J Am Acad Dermatol.* 2019;80:60–9.
7. Kimball AB, Jemec GB, Yang M, Kageleiry A, Signorovitch JE, Okun MM, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. *Br J Dermatol.* 2014;171:1434–42.
8. van Straalen KR, Ingram JR, Augustin M, Zouboulis CC. New treatments and new assessment instruments for hidradenitis suppurativa. *Exp Dermatol.* 2022;31(Suppl 1):33–9.
9. Zouboulis CC, Tzello T, Kyrgidis A, Jemec GBE, Bechara FG, Giamarellos-Bourboulis EJ, et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. *Br J Dermatol.* 2017;177:1401–9.
10. InflaRx. InflaRx Announces Top-Line SHINE Phase IIb Results for IFX-1 in Hidradenitis Suppurativa. Available at: <https://www.inflarx.de/Home/Investors/Press-Releases/06-2019-InflaRx-Announces-Top-Line-SHINE-Phase-IIb-Results-for-IFX-1-in-Hidradenitis-Suppurativa.html> (Accessed June 05, 2022).
11. InflaRx. InflaRx Reports Additional Analysis of the SHINE Phase IIb Results for IFX-1 in Hidradenitis Suppurativa. Available at: <https://www.inflarx.de/Home/Investors/Press-Releases/07-2019-InflaRx-Reports-Additional-Analysis-of-the-SHINE-Phase-IIb-Results-for-IFX-1-in-Hidradenitis-Suppurativa.html> (Accessed June 05, 2022).

12. Frew JW, Jiang CS, Singh N, Navrazhina K, Vaughan R, Krueger JG. Quantifying the natural variation in lesion counts over time in untreated hidradenitis suppurativa: implications for outcome measures and trial design. *JAAD Int*. 2020;1:208–21.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Tzellos T, van Straalen KR, Kyrgidis A, Alavi A, Goldfarb N, Gulliver W, et al. Development and validation of IHS4-55, an IHS4 dichotomous outcome to assess treatment effect for hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. 2023;37:395–401. <https://doi.org/10.1111/jdv.18632>