

# Comparison of Urticaria Activity Score Over 7 Days (UAS7) Values Obtained from Once-Daily and Twice-Daily Versions: Results from the ASSURE-CSU Study

Kelly Hollis<sup>1</sup> · Christina Proctor<sup>1</sup> · Doreen McBride<sup>2</sup> · Maria-Magdalena Balp<sup>3</sup> · Lori McLeod<sup>1</sup> · Shannon Hunter<sup>1</sup> · Haijun Tian<sup>4</sup> · Sam Khalil<sup>3</sup> · Marcus Maurer<sup>5</sup>

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## Abstract

**Background** The Urticaria Activity Score summed over 7 days (UAS7) assesses the itch severity and hive count in chronic spontaneous urticaria (CSU) using once- or twice-daily diary-based documentation.

**Objective** The aim of this study was to evaluate the comparability of twice-daily versus once-daily versions of the UAS and the resulting UAS7 values.

**Methods** Data came from the ASSURE-CSU study. The twice-daily and once-daily UAS7 was calculated from morning and evening ratings, as well as from exact 24-h evening ratings of hive count and itch severity, respectively. Three UAS7 scores were computed: UAS7 twice

daily (UAS7<sub>TD</sub>), UAS7 once daily for maximum itch (UAS7<sub>OD1MAX</sub>), and UAS7 once daily for average itch (UAS7<sub>OD2AVG</sub>). UAS7 values were assigned to five score bands (0, 1–6, 7–15, 16–27, 28–42), reflecting urticaria-free to severe disease activity. The score values and score band ratios of the UAS7<sub>TD</sub> and UAS7<sub>OD</sub> versions were compared and assessed for correlation by weighted Cohen's kappa statistics.

**Results** Data from 614 patients were analyzed. All three versions of the UAS7 yielded very similar results, with a mean (standard deviation) UAS7<sub>TD</sub>, UAS7<sub>OD1MAX</sub>, and UAS7<sub>OD2AVG</sub> of 17.3 (10.49), 17.7 (8.90), and 16.2 (8.68), respectively. Correlation coefficients between UAS7<sub>TD</sub> and UAS7<sub>OD1MAX</sub>, UAS7<sub>TD</sub> and UAS7<sub>OD2AVG</sub>, and UAS7<sub>OD1MAX</sub> and UAS7<sub>OD2AVG</sub> were 0.94, 0.95, and 0.99, respectively, showing very high positive pairwise correlation. The weighted kappa coefficient,  $\kappa$  (95% confidence interval) was 0.78 (0.75–0.82) for UAS7<sub>TD</sub> versus UAS7<sub>OD1MAX</sub>, and 0.82 (0.78–0.85) for UAS7<sub>TD</sub> versus UAS7<sub>OD2AVG</sub>, demonstrating substantial agreement.

**Conclusions** The once- and twice-daily UAS7 scores were highly consistent, supporting the use of either version when evaluating CSU activity.

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✉ Kelly Hollis  
khollis@rti.org

<sup>1</sup> RTI Health Solutions, Research Triangle Park, NC, USA

<sup>2</sup> RTI Health Solutions, Manchester, UK

<sup>3</sup> Novartis Pharma AG, Basel, Switzerland

<sup>4</sup> Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

<sup>5</sup> Charité-Universitätsmedizin Berlin, Berlin, Germany

## Key Points

The Urticaria Activity Score (UAS) is a commonly used diary-based patient-reported outcome measure that assesses itch severity and hive count in chronic spontaneous urticaria (CSU), using once- or twice-daily diary-based documentation.

The current study aimed to evaluate the comparability of twice-daily versus once-daily versions of the UAS and the resulting UAS7 values using data from a multinational, non-interventional study.

The study found that weekly UAS-based measurements of disease activity in CSU by twice-daily or once-daily assessments were highly consistent and yielded very similar results.

The findings provide evidence to support the use of either of the UAS versions when evaluating CSU activity as long as the same version is used over time for the same patients within a specific study or clinical practice.

## 1 Introduction

Chronic spontaneous urticaria (CSU), formerly also known as chronic idiopathic urticaria (CIU), is characterized by the occurrence of wheals/hives, angioedema, or both for 6 weeks or longer in the absence of a specific trigger [1]. Chronic urticaria (CU) affects 0.5–1% of the general population worldwide [2], with CSU accounting for more than two-thirds of CU cases [3]. CSU affects several domains of health-related quality of life (HRQOL), such as activities of daily living, sleep, emotional and psychological well-being, and work productivity [4, 5]. Several types of patient-reported outcome (PRO) instruments, such as the EQ-5D (generic) [6], Dermatology Life Quality Index [DLQI] (dermatological) [7], and disease-specific Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) [8], have been used to assess quality of life and disease burden in CSU patients. The inclusion of PRO instruments in clinical practice is increasingly recommended because it allows assessment of the patients' view of their disease and the effect of treatment. Additionally, it can help inform treatment decisions and improve physician–patient communication [9, 10]. This is even more relevant in CSU because symptoms are unpredictable and vary over time.

The Urticaria Activity Score (UAS) is a commonly used diary-based PRO measure that assesses the key sign (hives) and symptom (itch) of CSU. The international EAACI/

GA<sup>2</sup>LEN/EDF/WAO guidelines for urticaria recommend use of the UAS in clinical practice to determine disease activity and response to treatment [1]. Currently, two versions of the daily UAS exist—one that assesses the number of hives and the intensity of itch twice daily (every 12 h), and one that assesses hive number and itch intensity once daily (every 24 h). Both versions can generate a weekly score (UAS7), calculated as the sum of the daily number of hives score and the itch severity score over 7 days. UAS7 values range from 0 to 42, with higher values reflecting higher disease activity [11, 12]. The twice-daily UAS [12, 13] has been accepted by the US FDA as a PRO measure supporting a label claim for drugs in CSU, and validated as per FDA guidelines for PRO instruments [14]. Although it is more burdensome for patients, the twice-daily assessment can capture more time-of-day nuances of disease activity. On the other hand, the once-daily diary [11] has been recommended by the EAACI/GA<sup>2</sup>LEN/EDF/WAO international urticaria guidelines [1], and has less patient burden of administration; however, it may be more prone to recall bias compared with the twice-daily UAS. No publications resulting from qualitative or quantitative work are currently available to confirm the validity of the once-daily version and the detailed instructions for its completion by patients. Additionally, different score ranges are used for the number of hives between the once-daily and twice-daily UAS questionnaires. It is thus important to understand whether the two UAS versions capture the same levels of disease activity. The objective of the present study was to evaluate the comparability of UAS7 scores obtained from the once-daily versus twice-daily versions of the UAS.

## 2 Methods

### 2.1 Data Source

Data came from the ASSURE-CSU study [15, 16], the first international study to quantify the humanistic and economic burden of illness of patients with CSU who are symptomatic despite treatment. This non-interventional, multinational study was conducted across seven countries (Canada, France, Germany, Italy, The Netherlands, Spain and the UK). Details of the study design have been previously published [15, 16] and are summarized below.

### 2.2 Study Sample and Design

The study enrolled adult patients (aged  $\geq 18$  years) with a clinician-confirmed, guideline-defined diagnosis of CSU who had been symptomatic for more than 12 months at

least 3 days per week and were currently symptomatic despite treatment. The study included a 1-year retrospective medical record abstraction, a cross-sectional PRO survey, and a 7-day prospective urticaria patient daily diary (UPDD). The twice-daily version of the UAS diary was part of the UPDD and included morning and evening ratings of hives and itch severity (Table 1). Patients were asked the following question to report their itch intensity and hive count: “Thinking about the past 12 hours, please record the severity of itch and the number of hives you have, associated with your skin condition”. In addition, the exact 24-h hive counts was reported by patients in the UAS diary each evening (Table 1). These data were then used to compute the following three UAS7 scores: UAS7 twice daily (UAS7<sub>TD</sub>), UAS7 once daily for maximum itch (UAS7<sub>OD1MAX</sub>), and UAS7 once daily for average itch (UAS7<sub>OD2AVG</sub>) (Table 2). It is not known whether patients consider the maximum or average itch when reporting itch severity; therefore, both maximum and average daily itch

severity scores were computed in the current study prior to calculating a daily score.

### 2.3 Calculation of Urticaria Activity Score over 7 Days (UAS7)

Table 2 presents the calculation of scores for the three scoring methods, i.e. UAS7<sub>TD</sub>, UAS7<sub>OD1MAX</sub> and UAS7<sub>OD2AVG</sub>. The UAS7<sub>TD</sub> method averaged each day’s morning and evening hive scores and itch scores respectively and then added the average daily hive and itch score values over 7 days. The UAS7<sub>OD1MAX</sub> method evaluated maximum itch and was calculated as the sum total of each day’s hive score (derived from an exact 24-h hive count) and each day’s maximum itch severity score (between morning and evening), over 7 days. The UAS7<sub>OD2AVG</sub> method evaluated average itch score and was calculated as the sum of each day’s hive score values (derived from an exact 24-h hive count) and each day’s average itch severity scores over 7 days.

**Table 1** UAS twice-daily vs. once-daily questionnaire scoring

UAS twice-daily version: scoring for itch and hives at each assessment point			
Itch severity score	Itch severity at each assessment (am/pm)	Hives severity score	Number of hives at each assessment
0	None	0	None
1	Mild, minimal awareness, easily tolerated	1	1–6
2	Moderate, definite awareness, bothersome but tolerable	2	7–12
3	Severe, difficult to tolerate	3	>12
UAS once-daily version: daily scoring for itch and hives			
Itch severity score	Itch severity (once every 24 h)	Hives severity score	Number of hives per 24 h
0	None	0	None
1	Mild (present but not annoying or troublesome)	1	< 20
2	Moderate (troublesome but does not interfere with normal daily activity or sleep)	2	20–50
3	Intense (interferes with normal daily activity or sleep)	3	> 50

UAS Urticaria Activity Score

**Table 2** Calculation of UAS7 values computed in the ASSURE-CSU study

Score	Daily itch scoring	Daily hives scoring	Scoring methodology
UAS7 <sub>TD</sub>	Daily average of 12-h morning and evening itch severity ratings	Daily average of 12-h morning and evening hive scores	The UAS7 <sub>TD</sub> score was obtained as the sum of the daily average itch and hive scores over 7 days
UAS7 <sub>OD1MAX</sub>	Daily maximum of 12-h morning and evening itch severity ratings	Derived from daily 24-h exact counts of total hives	The UAS7 <sub>OD</sub> scores were calculated by adding the daily hive and (maximum or average) itch scores over 7 days
UAS7 <sub>OD2AVG</sub>	Daily average of 12-h morning and evening itch severity ratings		

OD1MAX once daily, maximum itch, OD2AVG once daily, average itch, OD once daily, TD twice daily, UAS7 Urticaria Activity Score over 7 days

**Table 3** UAS7 disease activity score bands

UAS7 band	Rationale
0	Itch and hive free—indicative of no symptoms of CSU and considered a full treatment response
1–6	Well-controlled urticaria—indicates a good response to treatment
7–15	Mild urticaria—indicates also a lower response level
16–27	Moderate activity urticaria—entry criteria for clinical trials in CSU
28–42	Severe activity urticaria

CSU chronic spontaneous urticaria, UAS7 Urticaria Activity Score over 7 days

UAS7 values were assigned to five score ranges (bands), reflecting urticaria-free to severe disease activity, measured by the weekly UAS7 as follows: UAS7 = 28–42, severe activity CSU; UAS7 = 16–27, moderate activity CSU; UAS7 = 7–15, mild activity CSU; UAS7 = 1–6, well-controlled CSU; UAS7 = 0, urticaria-free (Table 3) [17].

## 2.4 Statistical Analysis

Descriptive statistics were used to compute the overall mean UAS7 values, which were stratified into the abovementioned score ranges (UAS7: 0, 1–6, 7–15, 16–27 and 28–42) describing the disease activity. Pearson correlation coefficients were computed pairwise between the three UAS7 methods (UAS7<sub>TD</sub>, UAS7<sub>OD1MAX</sub>, and UAS7<sub>OD2AVG</sub>) and other PROs (DLQI, CU-Q2oL, EQ-5D). Scatterplots were used to understand the clustering of score values in patients who exhibited mismatches between score bands, from UAS7<sub>TD</sub> versus UAS7<sub>OD1MAX</sub>, and UAS7<sub>TD</sub> versus UAS7<sub>OD2AVG</sub>. Weighted Cohen's kappa coefficients ( $\kappa$ ) were computed to measure the agreement of disease activity score band assignments based on UAS7<sub>TD</sub> versus UAS7<sub>OD1MAX</sub>, and UAS7<sub>TD</sub> versus UAS7<sub>OD2AVG</sub>. A  $\kappa$  value of 0.61–0.80 denotes substantial agreement between the scores, whereas a  $\kappa$  value in the range of 0.81–1.00 indicates almost perfect agreement [18].

## 3 Results

### 3.1 Study Sample Characteristics

A total of 673 patients from 64 centers across seven countries were included in the study. The majority of enrolled patients were female (72.7%) and White/Caucasian (90.4%). The mean (standard deviation [SD]) age of patients at enrollment was 48.8 years (15.47).

Medical records were abstracted for all 673 patients, of whom 614 (91.2%) returned the 7-day UAS questionnaire. Of these 614 patients, 605 (98.5%) had non-missing values for UAS7<sub>TD</sub>, and 504 (82.1%) had non-missing values for UAS7<sub>OD1MAX</sub> and UAS7<sub>OD2AVG</sub>. The concordance

analyses were restricted to 501 (81.6%) patients with non-missing UAS7 values for all three scoring methods (i.e. UAS7<sub>TD</sub>, UAS7<sub>OD1MAX</sub>, and UAS7<sub>OD2AVG</sub>).

### 3.2 All Versions of the UAS Yielded Similar UAS7 Score Values

All three versions of the UAS7, i.e. UAS7<sub>TD</sub>, UAS7<sub>OD1MAX</sub>, and UAS7<sub>OD2AVG</sub>, yielded very similar results, with a mean (SD) score value of 17.3 (10.49), 17.7 (8.90), and 16.2 (8.68), respectively (Fig. 1a, b). As expected, the overall mean (SD) weekly itch score values based on the daily maximum of twice-daily ratings [9.9 (5.28)] was higher than that based on the daily average of twice-daily ratings [8.4 (4.97)]. The mean (SD) weekly hive score values based on the daily average of twice-daily ratings was slightly higher [9.0 (6.58)] than that based on exact 24-h hive counts [7.7 (5.04)].

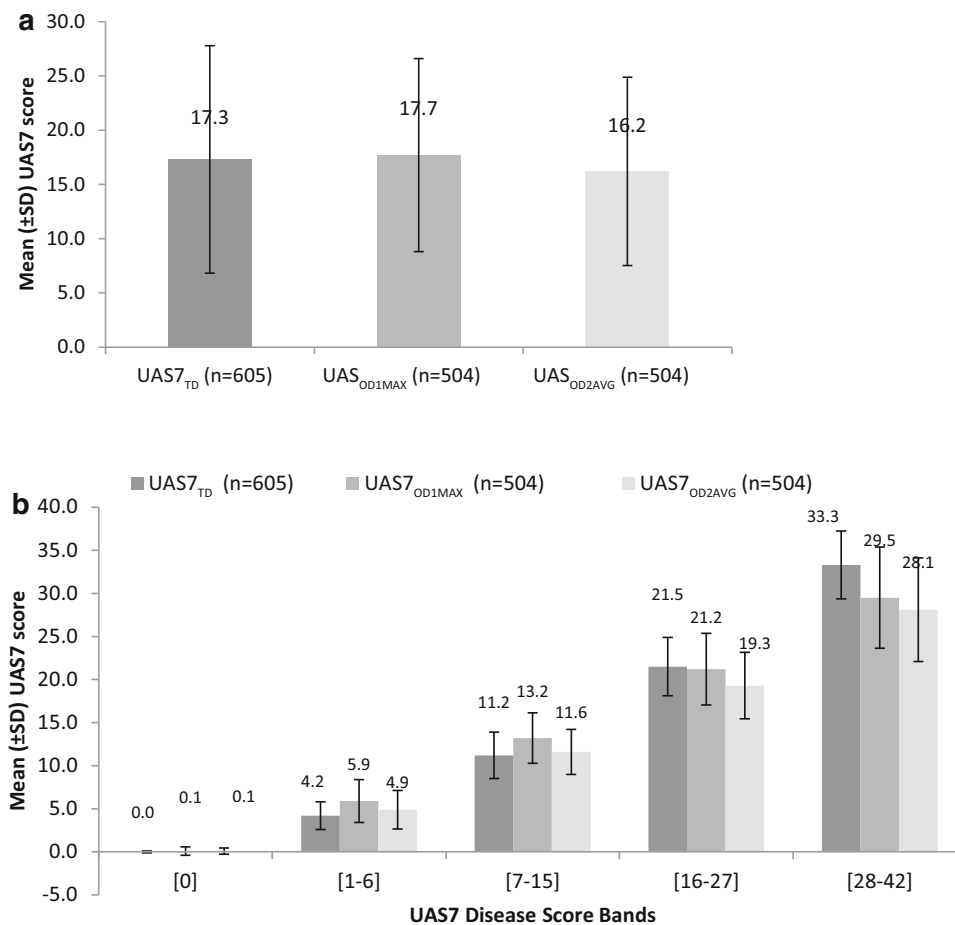
### 3.3 Pairwise Correlation among UAS7<sub>TD</sub>, UAS7<sub>OD1MAX</sub>, and UAS7<sub>OD2AVG</sub>

Of the 501 patients with complete data for the three scores, the correlation coefficients between UAS7<sub>TD</sub> and UAS7<sub>OD1MAX</sub>, UAS7<sub>TD</sub> and UAS7<sub>OD2AVG</sub>, and UAS7<sub>OD1MAX</sub> and UAS7<sub>OD2AVG</sub> were 0.94, 0.95, and 0.99, respectively, indicating very high positive pairwise correlation (Table 4). The pattern of correlation between each UAS7 version and other PRO measures was also consistent. For example, the correlation coefficient of UAS7<sub>TD</sub>, UAS7<sub>OD1MAX</sub> and UAS7<sub>OD2AVG</sub> to CU-Q2oL total score was 0.44, 0.45, and 0.44, respectively, and 0.45, 0.47 and 0.46, respectively, to DLQI total score (Table 4).

### 3.4 Concordance and Agreement Across UAS7 Scoring Methods

#### 3.4.1 UAS7<sub>TD</sub> Versus UAS7<sub>OD1MAX</sub>

Of the patients with complete data for all three scores ( $N = 501$ ), 388 (77.4%) were assigned to the same disease activity score band for UAS7<sub>TD</sub> versus UAS7<sub>OD1MAX</sub>



**Fig. 1** Comparison of mean UAS7 values analyzed by the three scoring methods of UAS7 **a** for the entire cohort and **b** stratified by UAS7 disease activity score band. *OD1MAX* once daily for maximum itch, *OD2AVG* once daily for average itch, *SD* standard deviation, *TD* twice daily, *UAS7* Urticaria Activity Score over 7 days

**Table 4** Correlation coefficients between PRO scores across UAS7 scoring methods and other PRO measures

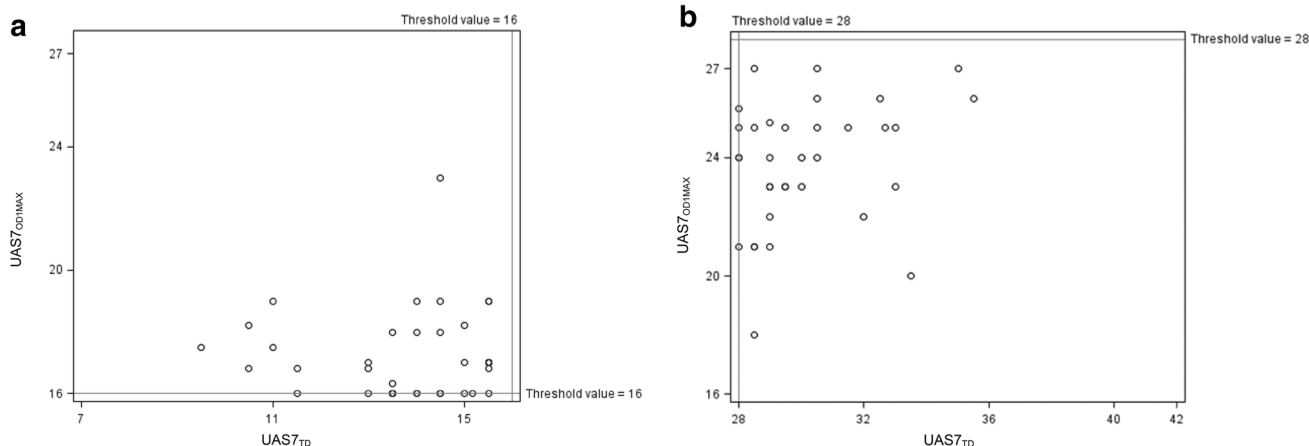
Score	UAS7 <sub>TD</sub> (n)	UAS7 <sub>OD1MAX</sub> (n)	UAS7 <sub>OD2AVG</sub> (n)
UAS7 <sub>TD</sub>	1.00 (605)		
UAS7 <sub>OD1MAX</sub>	<b>0.94</b> (501)	1.00 (504)	
UAS7 <sub>OD2AVG</sub>	<b>0.95</b> (501)	<b>0.99</b> (504)	1.00 (504)
CU-Q2oL Total Score	0.44 (586)	0.45 (490)	0.44 (490)
DLQI Total Score	0.45 (595)	0.47 (496)	0.46 (496)
EQ-5D Utility Index Score	-0.27 (585)	-0.29 (490)	-0.27 (490)
EQ-5D VAS	-0.30 (587)	-0.32 (492)	-0.31 (492)

Bolded text denotes the pairwise correlation coefficients between the three UAS7 scoring methods

*CU-Q2oL* Chronic Urticaria Quality of Life Questionnaire, *DLQI* Dermatology Life Quality Index Questionnaire, *OD1MAX* once daily for maximum itch, *OD2AVG* once daily for average itch, *PRO* patient-reported outcome, *TD* twice daily, *UAS7* Urticaria Activity Score over 7 days, *VAS* visual analogue scale

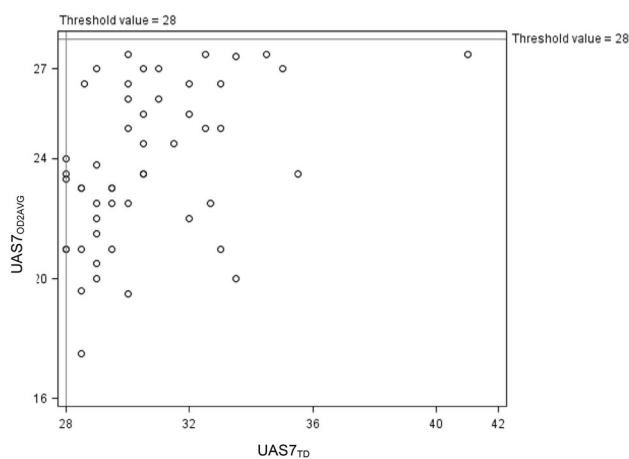
(electronic supplementary Table S1). Additionally, of the 113 (22.6%) patients with different disease activity score band assignments based on UAS7<sub>TD</sub> versus UAS7<sub>OD1MAX</sub>, the majority (111/113 [98.2%]) were classified in adjacent score bands very close to the respective thresholds. Among

these patients, the most commonly observed mismatches between UAS7<sub>TD</sub> and UAS7<sub>OD1MAX</sub> disease activity bands were seen in 36 (7.2%) patients classified in the 7–15 band based on UAS7<sub>TD</sub>, but with the UAS7<sub>OD1MAX</sub> in the higher activity band (16–27), and in 34 (6.8%) patients classified



**Fig. 2** Scatterplot of  $UAS7_{TD}$  versus  $UAS7_{OD1MAX}$  values **a** among patients with  $UAS7_{TD} = [7-15]$  and  $UAS7_{OD1MAX} = [16-27]$  ( $N=36$ ) **b** among patients with  $UAS7_{TD} = [28-42]$  and  $UAS7_{OD1MAX} = [16-$

$27]$  ( $N=34$ ). *OD1MAX* once daily for maximum itch, *TD* twice daily, *UAS7* Urticaria Activity Score over 7 days



**Fig. 3** Scatterplot of  $UAS7_{TD}$  versus  $UAS7_{OD2AVG}$  values among patients with  $UAS7_{TD} = 28-42$ , and  $UAS7_{OD2AVG} = 16-27$  ( $N = 51$ ). *OD2AVG* once daily for average itch, *TD* twice daily, *UAS* Urticaria Activity Score

in the 28–42 band with  $UAS7_{TD}$ , but with  $UAS7_{OD1MAX}$  in the lower disease activity band (16–27). Results from scatterplots indicated that the  $UAS7_{TD}$  and  $UAS7_{OD1MAX}$  values for these patients tended to cluster near the threshold values for each score band range, with stronger clustering observed in the 7–15 score band (Fig. 2a) than in the 28–42 score band (Fig. 2b).

### 3.4.2 $UAS7_{TD}$ Versus $UAS7_{OD2AVG}$

Among the 501 patients with complete data, 406 (81.0%) patients were grouped in the same band for  $UAS7_{TD}$  versus  $UAS7_{OD2AVG}$  (electronic supplementary Table S2). Similar to the previous analysis of 95 (19.0%) patients with

different score band assignments based on  $UAS7_{TD}$  versus  $UAS7_{OD2AVG}$ , the majority (93/95 [97.9%]) were classified in adjacent score bands (electronic supplementary Table S2). Of all 501 patients, the most commonly observed mismatch between  $UAS7_{TD}$  and  $UAS7_{OD2AVG}$  disease activity bands was observed in 51 (10.2%) patients classified based on  $UAS7_{TD}$  in the 28–42 band, but on  $UAS7_{OD2AVG}$  in the 16–27 band. Similar to the scatterplots for  $UAS7_{TD}$  versus  $UAS7_{OD1MAX}$ , Fig. 3 shows that the  $UAS7_{TD}$  and  $UAS7_{OD2AVG}$  values for these patients are clustered toward the threshold values of the two score bands.

The coefficient of agreement [ $\kappa$  (95% confidence interval)] was 0.78 (0.75–0.82) for  $UAS7_{TD}$  versus  $UAS7_{OD1MAX}$ , and 0.82 (0.78–0.85) for  $UAS7_{TD}$  versus  $UAS7_{OD2AVG}$ , demonstrating substantial to almost perfect agreement between the scores [18].

## 4 Discussion

This study shows that weekly UAS-based measurements of disease activity in CSU by twice-daily or once-daily assessments by the same patients over the same time period yielded very similar results. We used well-known established methods to analyze the concordance of the scores and their correlation with other PRO measures and found a high positive correlation among the three UAS7 versions analyzed ( $UAS7_{TD}$ ,  $UAS7_{OD1MAX}$  and  $UAS7_{OD2AVG}$ ), indicating that they provide similar results for the same patient. This analysis was conducted for the first time and the results represent a unique contribution to a better understanding of the instruments used to assess disease activity in CSU, along with their performance. These



findings provide evidence to support the use of either of the UAS versions (once-daily/twice-daily assessment) when evaluating CSU activity, as long as the same version is used over time for the same patients within a specific study or clinical practice.

While the descriptive statistics and cross-table analyses show that the majority of patients were assigned to the same disease activity bands of the different scores, some minor discrepancies between score band classifications were observed, which may be due to the differences between the instructions and scoring of the once-daily and twice-daily questionnaires. In the absence of clear guidance for the once-daily version, patients might not be consistent in how they assess and report itch severity over 24 h, and whether they consider average itch or maximum itch when rating their itch severity once daily. Similarly, as the number of hives can fluctuate over 24 h, patients might not be consistent in how they count their hives when they need to report a single total hive count. This is an example that reiterates the need for specific and detailed guidance when developing a PRO instrument; however, as long as the same instrument is used over time in a specific study, the same methodology will apply and scoring should be consistent over time. The high values of weighted kappa coefficients suggest that despite a minority of patient assignments to non-matching score bands between versions, the score bands from the two once-daily scoring methods ( $UAS7_{OD1MAX}$  and  $UAS7_{OD2AVG}$ ) have a high level of overall agreement with the score bands of the  $UAS7_{TD}$ .

In addition,  $UAS7_{OD2AVG}$  showed higher overall agreement with  $UAS7_{TD}$  across analyses than  $UAS7_{OD1MAX}$ . This could also be driven by the fact that itch severity is assessed as the average over 24 h in both the  $UAS7_{OD2AVG}$  and  $UAS7_{TD}$ , whereas in the  $UAS7_{OD1MAX}$  it is assessed as the maximum over 24 h. The results of twice-daily itch scores show a difference between morning and evening reports, which confirms the fluctuation over 24 h. Currently, no validation paper or guidance exists for recommending which is a more accurate way of capturing itch severity among CSU patients for the once-daily UAS version. More validation work is required for the once-daily assessment and a manual can be helpful for consistently evaluating itch severity in future studies.

## 5 Limitations

The current study used descriptive analyses to demonstrate the extent of correlation and level of agreement across the three UAS7 versions and other PRO measures. Multivariable analyses showing how each unit change in each UAS7

version might lead to a corresponding increase/decrease in other scores can be helpful in quantifying the relationship across scores. All analyses were conducted for patients who had non-missing UAS7 values. A higher percentage of patients completed the twice-daily UAS7 version (98.5%) than the once-daily version (82.1%), with the difference being driven by a comparatively low response to the once-daily 24-h exact count of hives question compared with the twice-daily hive ratings question. This could lead to unobserved confounding and might impact the study estimates. In order to facilitate the comparison of twice-daily versus once-daily UAS administrations, the average and maximum score values for the 12-h itch severity scores were used as the 24-h values. An additional limitation for this study is that we do not know how patients quantify itch over the 24-h period when responding to the once-daily version, or even how they quantify it over the 12-h period when answering the twice-daily version. It is known that urticaria symptoms vary from day to day, or even hour to hour [19]. The results of the UAS diary in this study also show that many patients reported different itch scores in the morning and evening, which indicates some variation over a 24-h period. Neither the once-daily nor twice-daily versions of the UAS clearly instruct the patient to consider the overall maximum or average itch severity over the assessment period. Qualitative research could be considered to investigate this for future applications and could provide additional support for this study's quantitative results.

## 6 Conclusions

The study found that UAS7 values based on twice-daily versus once-daily evaluation of itch severity and number of hives are highly consistent and correlated. These findings provide evidence to support the use of either version of the weekly UAS when evaluating CSU activity, as long as the chosen version is used consistently over time.

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### Compliance with Ethical Standards

**Conflict of interest** KH, DMcB, LMcL, SH are employed by RTI Health Solutions and as salaried employees did not receive direct compensation from the sponsor. CP was employed by RTI Health Solutions as a salaried employee at the time of the study. In their salaried positions, they work(ed) with a variety of companies and organizations and do not receive direct payments from any company or organization. RTI Health Solutions is a research unit of RTI International, a US not-for profit research Institute, and received consultancy fees from Novartis Pharma AG for this work. RTI Health Solutions and Novartis were involved in the analysis and

interpretation of data and the decision to submit these data for publication. MMB and SK are employees of Novartis Pharma AG, who funded the study and the manuscript. HT is an employee of Novartis Pharmaceuticals Corporation, and owns stock from Novartis Pharmaceuticals Corporation. MM is, or recently was, a speaker and/or advisor, and/or received research funding from Novartis.

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