Title

Analysis of Disease Activity Categories in Chronic Spontaneous/Idiopathic Urticaria

Running Head

Measuring Disease Activity in Chronic Spontaneous Urticaria

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What is already known about this topic?

- Increased urticaria disease activity, as measured by the continuous twice-daily UAS7$_{TD}$ score, impacts health-related quality of life and interferes with sleep and daily activity.

What does this study add?

- Categorising continuous UAS7$_{TD}$ activity scores into disease states defined by UAS7$_{TD}$ score ranges can discriminate between different levels of disease activity, simplify clinical assessment, and facilitate evaluation of treatment efficacy.

ABSTRACT

Background: Measurement of disease activity guides treatment of chronic spontaneous urticaria (CSU). A weekly Urticaria Activity Score—here, the average of twice-daily patient assessment of itch and hives scores summed over 1 week ($UAS7_{TD}$)—measures severity from 0 to 42. Insufficient evidence exists whether disease activity states, defined by categorical $UAS7_{TD}$ scores, correlate with other patient-reported outcomes and treatment response.

Objective: To evaluate and compare categorical $UAS7_{TD}$ scores with selected measures of disease-related quality of life and impact.

Methods: Data from three randomised clinical trials of omalizumab in CSU were pooled. Continuous $UAS7_{TD}$ scores were categorised into five disease activity states: urticaria-free, well-controlled, mild, moderate, and severe urticaria. Total scores from the Dermatology Life Quality Index (DLQI); the Chronic Urticaria Quality of Life questionnaire ($CU-Q_2oL$); and questions on sleep and daily activity interference, presence of angioedema, and diphenhydramine use were compared within categorised $UAS7_{TD}$ disease-state scores, using one-way analyses of variance for analysis at different time points and mixed-effects regressions for analysis of all data pooled.

Results: Pooled analyses showed that categorical $UAS7_{TD}$ disease states accurately predicted differences among treated CSU patients with different levels of disease activity. A consistent pattern existed between categories, with higher-activity disease states associated with significantly higher impact and an increase in angioedema frequency. Results at different treatment time points were consistent.

Conclusion: Categorical UAS7$_{TD}$ disease states can discriminate between measures when considering the impact of urticaria activity. Using five categorical disease states could simplify clinical assessment and monitoring of treatment efficacy.

KEY WORDS

Chronic urticaria, disease states, clinical assessment, health-related quality of life

INTRODUCTION

Chronic spontaneous (also known as idiopathic) urticaria (CSU) is defined as the occurrence of itchy wheals/hives, angioedema, or both for more than 6 weeks with or without known causes.[1] CSU is known to have a substantial impact on the patient's quality of life (QoL), including effects on daily living activities and work productivity, and by causing sleep disturbance, loss of energy, and emotional problems.[2,3]

Various types of patient-reported outcome (PRO) measures are used to assess CSU disease activity and its impact on daily activities and health-related quality of life (HRQoL).[4] CSU activity is assessed based on the occurrence of signs (wheals/hives) and symptoms (pruritus/itch). Since the appearance of hives and the intensity of itch can change on a daily basis, assessment of both is best performed by patients with the daily Urticaria Activity Score (UAS), summed to a weekly score (UAS7).[5,6] In addition, the impact of CSU on HRQoL can be measured with dermatological-specific measures such as Dermatology Life Quality Index (DLQI)[7] and the urticaria-specific Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL).[8]

The UAS is recommended for routine clinical practice,[1] however, it may be challenging to compare patients in terms of their disease activity using the UAS's continuous scoring. It could be informative to know whether grouping the continuous score of the UAS7 into a smaller number of categories that would reflect different levels of CSU activity, or disease states, could discriminate among CSU patients with different levels of disease activity. Specifically, there is insufficient evidence as to whether disease states defined by categorical UAS7 scores correlate with CSU disease activity and response to treatment. If categorical

UAS7 disease states could be shown to be informative as to the impact of disease on patients' life, QoL, and response to treatment, they could be an efficient tool for clinical practice. The purpose of this initial validation of these CSU activity categories was to describe categorical UAS7 scores in terms of DLQI and CU-Q$_2$oL scores, as well as selected measures of disease activity and impact, and to assess whether a clear significant discrimination exists between the categories.

METHODS

Data

Data for the analysis came from three randomised, double-blind, placebo-controlled phase 3 global clinical trials (ASTERIA I,[9] N = 319; ASTERIA II,[10] N = 323; and GLACIAL,[11] N = 336) evaluating the effect of omalizumab on symptoms of patients with inadequately controlled CSU. Figure 1 presents the treatment and follow-up periods of the trials, as well as the dosing regimens and timing of the PRO data collection for the three trials. Patients in ASTERIA I[9] and II[10] trials received licensed dose of second-generation H_1 antihistamines as background therapy, whereas patients recruited into the GLACIAL study[11] received second-generation H_1 antihistamines (up to four times the licensed dose), H_2 blockers, and/or leukotriene receptor antagonists. Treatment was administered once every 4 weeks for 24 weeks in ASTERIA I[9] and GLACIAL[11] and for 12 weeks in ASTERIA II.[10] All three trials had a follow-up period with no active treatment of 16 weeks. The studies conformed to the Declaration of Helsinki.[12] All studies were ethically approved and all patients gave informed consent.

Measures

Three primary PRO measures, capturing signs and symptoms, dermatologic QoL, and disease-specific QoL, were used to obtain information on patients' experiences with CSU in the clinical trials: the twice-daily version of the Urticaria Activity Score over 7 days $(UAS7_{TD})$[6] as part of the Urticaria Patient Daily Diary (UPDD),[13] the DLQI,[7,14] and the CU-Q_2oL.[8]

UPDD

The validated UPDD[13] contains the UAS assessed every 12 hours and daily activity interference, sleep interference, and presence of angioedema, all of which are assessed every 24 hours, as well as the use of rescue medication.

UAS7$_{TD}$ Score

In the UAS7$_{TD}$ version, patients record the morning and evening itch severity score (ISS) and hives scores. ISS is assessed each time as 0 = no itch, 1 = mild, 2 = moderate, and 3 = severe, and the number of hives are assessed as 0 = none, 1 = 1-6 hives; 2 = 7-12 hives, and 3 = ≥ 12 hives. A daily UAS score is obtained from the sum of the average daily ISS and average daily hives score. The weekly UAS7$_{TD}$ score is obtained by summing the daily UAS scores over 7 days. Scores were reported at baseline and every 4 weeks until week 40 for ASTERIA I[9] and GLACIAL[11] and until week 28 for ASTERIA II.[10]

The UAS7$_{TD}$ score ranges from 0 to 42, with higher scores reflecting higher activity.[6] Scores were categorised into five disease states: urticaria-free (UAS7$_{TD}$ = 0), well-controlled urticaria (UAS7$_{TD}$ = 1-6), mild activity urticaria (UAS7$_{TD}$ = 7-15), moderate activity urticaria (UAS7$_{TD}$ = 16-27), and severe activity urticaria (UAS7$_{TD}$ = 28-42).[15] Two of these disease states (urticaria-free and well-controlled urticaria) were predefined endpoints for the clinical trials. Patients had to have a UAS7$_{TD}$ score of 16 or higher to be included in the trials, so 16 was considered the lower threshold for the moderate disease state. In addition, a score of 28 and above was considered severely-active disease.[16] The remaining UAS7$_{TD}$ scores (7-15) were used to define a mild urticaria disease state. All categorical ranges of scores were developed with expert input.[15,17]

Additional Questions in the UPDD

Several additional questions collected in the UPDD were included to make comparisons among the $UAS7_{TD}$ disease states. In the diary, patients were asked to rate how much their hives and itch interfered with sleep and with daily activities during the previous 24 hours (0 = no interference; 1 = mild, little interference; 2 = moderate, some interference; and 3 = substantial, severe interference). Patients were asked whether they had used antihistaminic rescue medications (number of diphenhydramine [DPH] 25-mg pills) during the previous 24 hours to control symptoms of their skin condition, such as hives or itch (0-3 pills). Finally, patients were asked about the presence of angioedema (yes or no) in the previous 24 hours. For the sleep, daily activities, and medication items, the mean of the sum of the daily scores for the 7 days prior to the study visit of interest was calculated (range: 0-21, with higher score indicating higher impact). For the presence of angioedema, patients were categorised as "yes" if they responded yes to the angioedema question on any of the 7 days prior to the visit of interest. The weekly mean scores on all items were used as comparison variables to test whether different $UAS7_{TD}$ disease states were characterised by different mean scores on these parameters' comparison variables.

DLQI

The DLQI[7] has a total score that ranges from 0 to 30, with higher scores reflecting worse HRQoL. The recall period for the DLQI is 1 week. DLQI data were collected at baseline and weeks 4, 12, 24, and 40 for ASTERIA I[9] and GLACIAL[11] and at baseline and weeks 4, 12, and 28 for ASTERIA II.[10] The DLQI has been validated for use in patients with CSU.[7,14,18] Validated score ranges exist for the DLQI to explain the impact on dermatologic-related

QoL: no effect: 0-1; small effect: 2-5; moderate effect: 6-10; very large effect: 11-20; extremely large effect: 21-30.[19]

CU-Q2oL

The CU-Q$_2$oL is a disease-specific, 23-item PRO measure designed to assess HRQoL in patients with CSU.[8,20] The recall period is 2 weeks. Patients are asked how bothered they have been by each symptom in the previous 2 weeks. Each item is assessed on a 5-point scale ranging from 1 (never) to 5 (very much). The total score is transformed to range from 0 to 100, with higher scores indicating worse HRQoL. CU-Q$_2$oL data were collected at baseline and weeks 4, 12, 24, and 40 for ASTERIA I[9] and GLACIAL[11] and at baseline and weeks 4, 12, and 28 for ASTERIA II.[10]

Data Analyses

Exploratory Analyses of Individual Trials at Different Time Points

Initial analyses of data, by individual trial at different time points, were performed by simple descriptive statistics (means, standard deviations, proportions) for each of the measures detailed in the previous section. These analyses were conducted using available data at each time point, since they were exploratory in nature and the results were specific point estimates (e.g., means, proportions). The results of these analyses indicated a pattern: as UAS7$_{TD}$ disease-state activity increased, the scores on the comparator variables, such as the DLQI and CU-Q$_2$oL, became worse (Tables SI-1-SI-4). In addition, cross-tabulations of the UAS7$_{TD}$ disease states with the DLQI response categories, as well as with changes in DLQI effect sizes, were conducted and significance testing conducted with Pearson χ^2 (Tables SI-5 to SI-13). The means of continuous UAS7$_{TD}$ scores for each DLQI effect size then were examined

using one-way analyses of variance with Bonferroni correction for multiple pairwise comparisons to see if adjacent DLQI effect sizes had significantly different mean $UAS7_{TD}$ scores (Tables SI-14 to SI-17). The number of patients in each subgroup was insufficient to provide robust summary statistics; however, because the patient population (Table 1) and study design (Fig. 1) were similar; data were pooled to increase sample size.

Pooled Data Analyses

Comparison of $UAS7_{TD}$ Disease States on Comparator Variables at Different Time Points

Trial data were pooled (all trials, all treatment arms) and assessed at baseline, 12 weeks, and end of study (week 40 for ASTERIA I[9] and GLACIAL[11] and week 28 for ASTERIA II[10]). $UAS7_{TD}$ disease states were compared on the following measures: DLQI total score; $CU-Q_2oL$ total score; sleep interference, activity interference, number of DPH pills, and the proportion of patients with angioedema in the previous 7 days. At 12 weeks, comparison of the proportion of angioedema-free days from weeks 4 through 12 also was assessed.

Mean scores of selected comparator variables for adjacent $UAS7_{TD}$ disease states were compared using one-way analyses of variance. Bonferroni correction for multiple comparisons helped guard against significant differences in mean scores for each comparator variable between $UAS7_{TD}$ disease states arising due to chance. To add to our conservative approach, comparisons for statistically significant differences were limited to adjacent disease states only, such that patients who were in the urticaria-free disease state ($UAS7_{TD} = 0$) were compared with those in the well-controlled urticaria disease state ($UAS7_{TD} = 1\text{-}6$);

those in the well-controlled urticaria disease state ($UAS7_{TD}$ = 1-6) were compared with those in the mild urticaria disease state ($UAS7_{TD}$ = 7-15), and so forth.

Prediction of Outcomes by $UAS7_{TD}$ Disease States

A second set of analyses was conducted in which all trials, all treatment arms, and all time points were pooled. The data were analysed using mixed-effects regressions models (linear mixed models across multiple time points with fixed effects for baseline covariates) to predict selected outcomes by $UAS7_{TD}$ disease states. $UAS7_{TD}$ disease states were used to predict, separately, the DLQI total score, the CU-Q$_2$oL total score, sleep interference, activity interference, the number of DPH pills, and the number of days with angioedema. Trial and treatment arm were included in the models as fixed effects. Covariates included gender, age, and duration of disease. The health state of "urticaria-free" (i.e., $UAS7_{TD}$=0) was used as the reference category for each initial mixed-effects regression model predicting the selected outcome. Each analysis then used these regression estimates to calculate the marginal mean scores and standard errors for the selected outcome, for each $UAS7_{TD}$ disease state, adjusted for the covariates in the model.

For exploratory descriptive analyses, observed data were used. Predictive analyses were conducted on two datasets: first using the pooled trials datasets in which missing data were accounted for by applying multiple imputation method and secondly on the observed data, under the assumption that the missing data mechanism was missing at random. *P*-values of 0.05 or below were considered significant. All analyses were conducted using Stata (version 13.0 or higher; StataCorp, College Station, Texas).

RESULTS

Baseline Characteristics

A total of 975 patients were available for analysis; 318 in ASTERIA I, 322 in ASTERIA II, and 335 in GLACIAL. The demographic and baseline characteristics of the study population are shown in Table 1. The majority (72%-76%) were female, with a median age ranging from 41 to 44 years and a mean disease duration of approximately 7 years. The populations across the three trials were similar, with no significant differences found, except a greater proportion of patients presenting with baseline angioedema in GLACIAL[11] versus ASTERIA II.[10]

Categorical UAS7$_{TD}$ Disease States Distinguish Patients With Different QoL Impairments

Pooled trial analyses confirmed that categorical UAS7$_{TD}$ disease states can accurately predict differences in QoL impairment. When all trials, all treatment arms, and all time points were pooled, the differences between each adjacent disease state were highly significant ($P \leq 0.001$) in the DLQI and CU-Q$_2$oL total scores (Fig. 2A and B; Table SI-18 in Supporting Information), with a 50% to 100% increase in HRQoL scores between improving UAS7$_{TD}$ disease states. We found similar results by pooled trial analyses at different time points, particularly after 12 weeks of treatment and at the study-end assessment, i.e., 16 weeks following end of treatment (Table SI-19 in Supporting Information). A consistent pattern was revealed: the greater the disease activity, the higher the impact on HRQoL, and this impact is independent of type and duration of treatment.

Categorical UAS7$_{TD}$ Disease States Are Associated With Disease Impact on Daily Activities and Sleep

The impact of disease activity on daily activities and interference with sleep was significantly different for each category band of UAS7$_{TD}$ disease states and doubled consistently between each subsequent increase in disease activity (Fig. 3A and B; Table SI-18 in Supporting Information). These differences were also consistently significant at different time points in treatment (Table SI-19 in Supporting Information), indicating that control of CSU activity allows patients to carry out their normal daily activities without sleep deprivation.

Categorical UAS7$_{TD}$ Disease States Reflect Use of On-Demand Antihistamine Medication

The use of DPH rescue medication increased significantly as the categorical UAS7$_{TD}$ disease activity increased (Fig. 4; Table SI-18 in Supporting Information). Patients in the severe urticaria score band (UAS7$_{TD}$ = 28-42) required four times the number of DPH pills as those patients with well-controlled or no urticaria (UAS7$_{TD}$ ≤ 6). These results again were seen at different time points (Table SI-19 in Supporting Information); however, significance was not consistent, particularly between the lower-activity disease states.

Higher UAS7$_{TD}$ Disease States Are Linked to Higher Prevalence Rates of Reported Angioedema

The pooled trial analyses showed that the higher categorical disease activity states are generally associated with significantly higher rates of reported days with angioedema when looking at data pooled across trials, time points, and all patients. These rates rise noticeably

with a UAS7$_{TD}$ score greater than 15 (Fig. 5; Table SI-18 in Supporting Information). At different time points (e.g., weeks 12 and 40), the pattern of increased rates of angioedema in higher categorical disease activity states also was seen, but most differences were non-significant (Table SI-19 in Supporting Information).

Results using observed data are similar, both with all data pooled (Table SI-20 in Supporting Information) and at different time points (Table SI-21 in Supporting Information).

DISCUSSION

This study assessed whether patients with different categorical $UAS7_{TD}$ scores, reflecting different levels of CSU activity, have significantly different levels of HRQoL impairment, interference with daily activities and sleep, use of on-demand medications, and prevalence of angioedema. Our findings indicated that this is the case: patients with different categorical $UAS7_{TD}$ have significantly different disease impacts on their daily lives. Thus, these five $UAS7_{TD}$ disease states can significantly differentiate CSU patients in terms of the effects that CSU has on their lives. . Patients with lower $UAS7_{TD}$ categories have better-controlled CSU, less angioedema, significantly better QoL, and experience less interference with daily activities and sleep. These analyses also showed that, irrespective of the treatment a patient receives, a patient with a specific disease activity, as measured by the five categorical $UAS7_{TD}$ disease states, will have a particular HRQoL and that this HRQoL will be significantly different from that of a patient with another disease activity state.

The results of the pooled analyses, where mixed-effects regressions were performed for all patients, all treatment arms, and all time points, showed a consistent pattern: comparison variable scores were statistically significantly better ($P \leq 0.05$) for each improved $UAS7_{TD}$ disease state, with the majority of the tests significant at $P \leq 0.001$.

Previous analyses have shown a near-perfect correlation between changes in signs and symptoms of CSU, as measured by the $UAS7_{TD}$, and changes in the DLQI and CU-Q_2oL over the same time period.[21] These analyses provide further evidence of strength of these relationships, even when assessed in categorical activity states.

This first empirical look at disease states in CSU measured by itch and hives also provided new evidence that angioedema should be considered when analysing CSU patients' experiences and that angioedema increases with increased disease activity, particularly moderate to severe CSU activity. Because there was concern that comparisons among multiple $UAS7_{TD}$ disease states on multiple comparator variables would result in multiplicity and yield significant differences among disease states simply by chance, a limited number of selected variables were used for statistical comparisons, and only comparisons on the effects of urticaria between adjacent disease states were conducted. Mean scores on comparator variables were consistently worse for increasingly worse health states. Significance tests demonstrated the extent to which $UAS7_{TD}$ disease states were statistically different on these selected variables and added confidence to the hypothesis that the $UAS7_{TD}$ disease states can discriminate among patients in terms of their urticaria activity.

Perhaps the main limitation of this study is in regards to the analyses at specific time points. With the exception of robust results at week 12, not all differences at other time points were statistically significant, most likely due to small sample sizes. However, when all data were pooled, consistent and significant differences were seen. Further analyses, including sensitivity analyses using bands based on different $UAS7_{TD}$ scores and alternative anchor tools, such as visual analogue scores, to evaluate itch[22] would lend additional support to these $UAS7_{TD}$ disease states.

As noted earlier, the exploratory analyses made no adjustment for missing data. This was done intentionally, as using only available data allowed comparison of actual observed patient experiences by $UAS7_{TD}$ health states. For the predictive models using mixed-effects

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regressions, analyses were performed two ways: multiple imputation for missing data and using only available, observed data. Results were very similar and conclusions were the same in either case. The main difference in results was that there were more significant differences using the multiply imputed data. This is not surprising given the larger sample size that resulted from imputing data. Thus, as expected, using only available data is a more conservative approach which supports the UAS7$_{TD}$ health states' ability to discriminate between patient experiences with urticaria.

One potential consideration of relevance to this research relates to the instruments used in measuring CSU. Some aspects of the psychometric properties of the DLQI (e.g., dimensionality and differential item function) have been criticised[23]; however, the DLQI has been validated for use in CSU[14,24,25] and a minimally important difference has been determined.[18,26] The CU-Q$_2$oL, a relatively recent addition to the study of HRQoL in CSU, is recommended as the disease-specific assessment tool by the international guidelines.[1] These disease states were obtained using the UAS7$_{TD}$. However, international guidelines[1] also have a preference for use of a once-daily (UAS7$_{OD}$) version of UAS. The UAS7$_{OD}$[5] differs from the UAS7$_{TD}$[6] in that the itch and hive assessment is conducted once every 24 hours and in the number of hives included in the daily hive score. The daily itch and hives score ranges are the same (0-3) in both versions, as are the scoring and weekly ranges (0-42) (Table SI-20 in Supporting Information), but differ in the number of 24-hour hives that compose the same daily hives score. Further studies examining the equivalency of the UAS7$_{TD}$ scores with scores obtained with UAS7$_{OD}$ are ongoing.

Overall, our results suggested that categorising continuous UAS7$_{TD}$ scores ranges into categorical UAS7$_{TD}$ disease states can discriminate between different levels of urticaria activity. Different levels of disease activity correlated with PROs. A pattern of greater consistently significant impact on HRQoL, daily activities, sleep, and use of on-demand antihistamine treatment was seen with each higher UAS7$_{TD}$ category. Reducing the continuous UAS7$_{TD}$ score from 42 points to five categorical disease states, much like the DLQI scoring bands,[19] could simplify clinical assessment and facilitate evaluation of treatment efficacy. Further research and analyses of these correlations is warranted.

ACKNOWLEDGEMENTS

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FIGURE LEGENDS

Figure 1. Phase 3 Randomised, Double-Blind, Placebo-Controlled Trials of Omalizumab

CU-Q$_2$oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; UAS7 = Urticaria Activity Score, assessed twice daily, calculated over 7 days.

Figure 2. Effect of CSU on Health-Related Quality of Life, by Categorical UAS7$_{TD}$ Disease States

A: DLQI; B: CU-Q$_2$oL. Both pooled data with multiple imputation of missing data; estimated marginal mean scores from mixed-effects regression analysis. Significance shown is based on comparison with the next-worst disease state.

CSU = chronic spontaneous urticaria; CU-Q$_2$oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; SE = standard error; UAS7$_{TD}$ = Urticaria Activity Score for the past 7 days, assessed twice daily.

Figure 3. CSU Interference With Daily Activities and Sleep, by Categorical UAS7$_{TD}$ Disease States

A: Interference with daily activities from UPDD; B: Interference with sleep from UPDD. Both pooled data with multiple imputation of missing data; mixed-effects regression analysis. Significance shown to the next-worst disease state.

CSU = chronic spontaneous urticaria; SE = standard error; UAS7$_{TD}$ = Urticaria Activity Score for the past 7 days, assessed twice daily; UPDD: Urticaria Patient Daily Diary.

Figure 4. Effect of CSU on On-Demand Antihistamine Therapy in Previous 7 Days, by Categorical UAS7$_{TD}$ Disease States

Pooled data with multiple imputation of missing data mixed-effects regression analysis. Significance shown to the next-worst disease state.

CSU = chronic spontaneous urticaria; DPH = diphenhydramine; SE = standard error; UAS7$_{TD}$ = Urticaria Activity Score for the past 7 days, assessed twice daily.
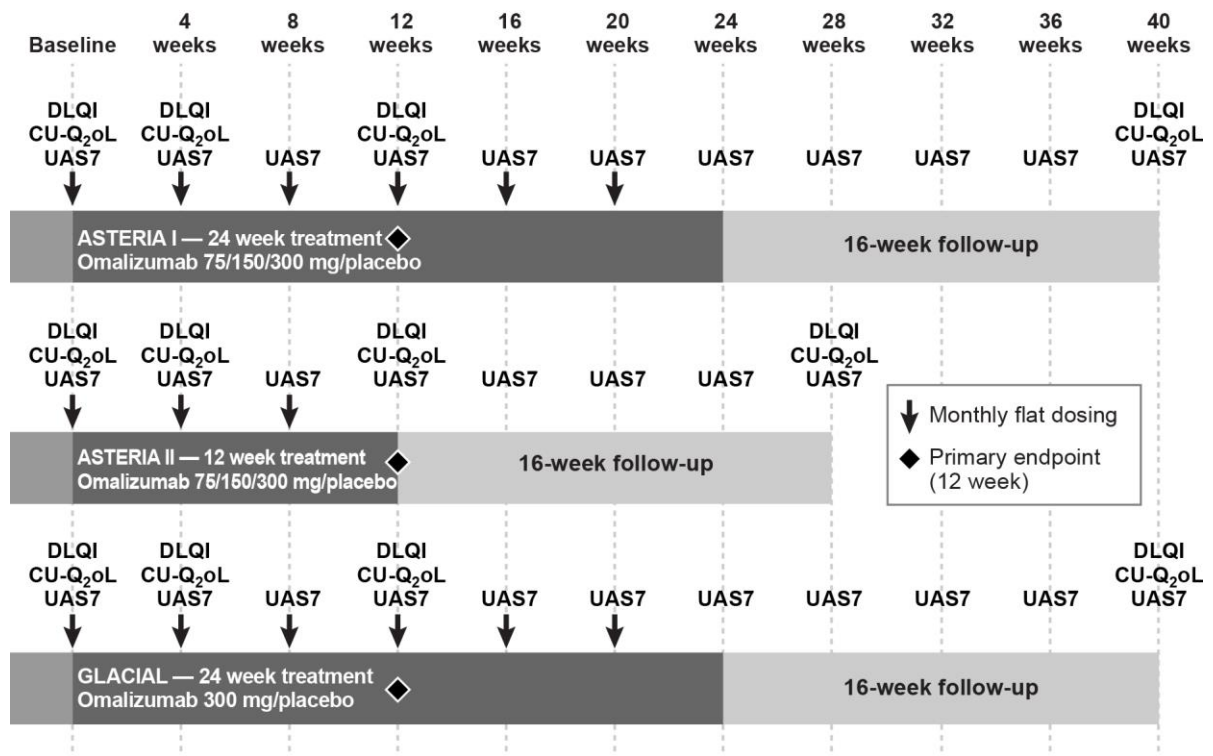

Figure 5. Angioedema in the Previous 7 Days, by Categorical UAS7$_{TD}$ Disease States

Pooled data with multiple imputation of missing data; mixed-effects regression analysis. Significance shown to the next-worst disease state.

SE = standard error; UAS7$_{TD}$ = Urticaria Activity Score for the past 7 days, assessed twice daily.
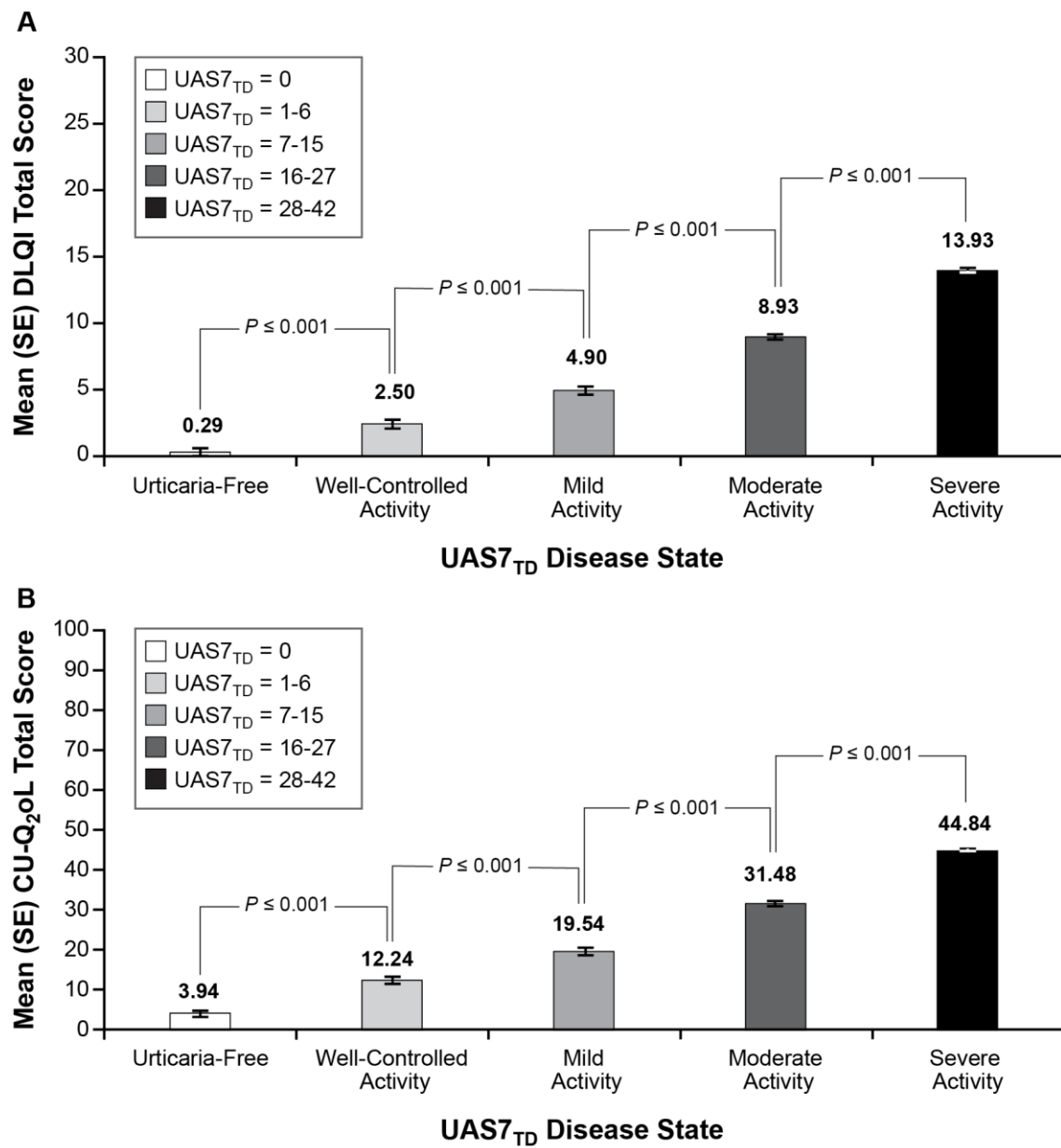
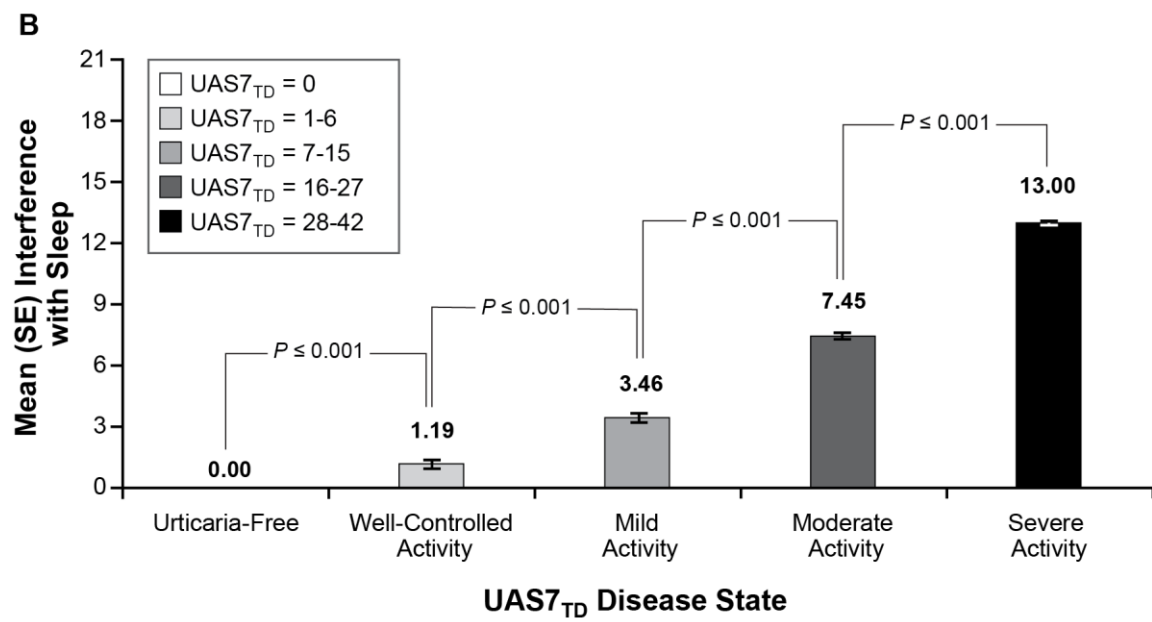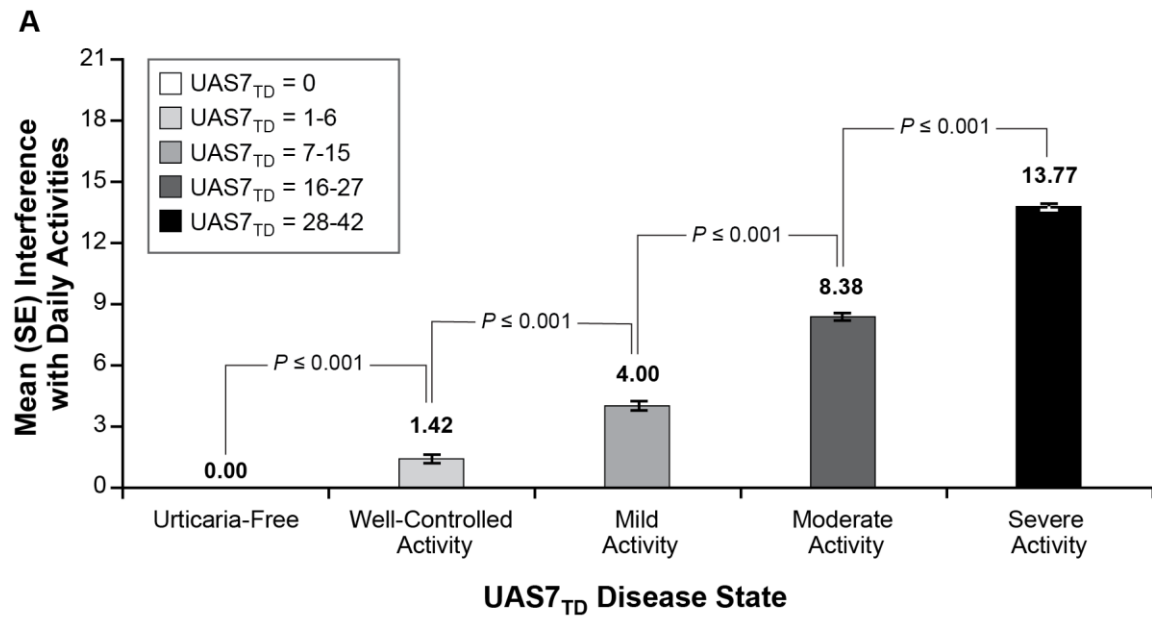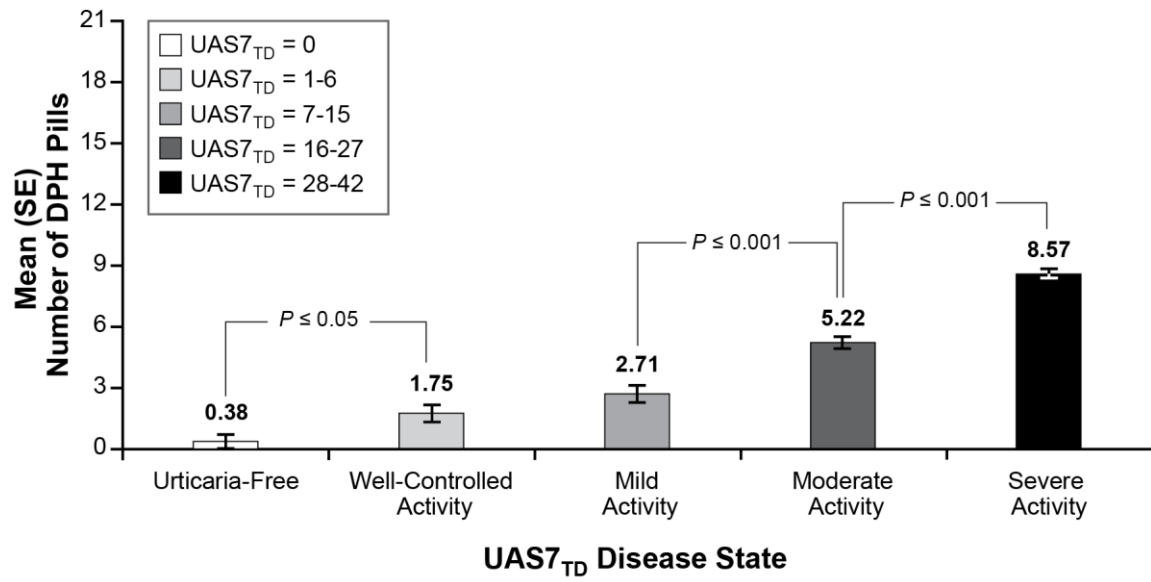# FIGURES

Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Mean (SE) Number of Days With Angioedema in Previous 7 Days

Legend:
- □ $UAS7_{TD} = 0$
- ▨ $UAS7_{TD} = 1-6$
- ▨ $UAS7_{TD} = 7-15$
- ▨ $UAS7_{TD} = 16-27$
- ■ $UAS7_{TD} = 28-42$

$P \leq 0.05$ (Urticaria-Free to Well-Controlled Activity)
$P \leq 0.05$ (Well-Controlled to Mild Activity)
$P \leq 0.001$ (Mild to Moderate Activity)
$P \leq 0.001$ (Moderate to Severe Activity)

Urticaria-Free	Well-Controlled Activity	Mild Activity	Moderate Activity	Severe Activity
0.02	0.22	0.43	0.99	1.48

$UAS7_{TD}$ Disease State

TABLES

Table 1. Baseline Characteristics

Characteristic	ASTERIA I N = 318[a]	ASTERIA IIN = 322[a]	GLACIALN = 335[a]
Age (years)			
Mean (SD)	41.2 (14.5)	42.5 (13.7)	43.1 (14.1)
Median	41.0	42.0	44.0
Sex (% female)	72.6	75.8	71.9
Duration of disease (years)			
Mean (SD)	6.9 (9.1)	6.5 (8.6)	7.4 (9.5)
Median	3.7	3.3	3.6
Previous number of CSU medications taken			
Mean (SD)	4.7 (2.8)	4.3 (2.7)	6.0 (2.6)
Median	4.0	4.0	6.0
Presence of angioedema[b]			
% yes	47.5	40.7	53.1*
Weekly number of DPH (25-mg) tablets taken[b,c]			
Mean (SD)	7.7 (8.3)	7.3 (7.8)	7.7 (9.1)
Median	6.0	5.0	5.0
UAS7$_{TD}$ score[b]			
Mean (SD)	31.1 (6.6)	30.7 (6.8)	30.9 (6.6)

Characteristic	ASTERIA I N = 318[a]	ASTERIA II N = 322[a]	GLACIAL N = 335[a]
DLQI score			
Mean (SD)	13.4 (6.6)	12.7 (6.2)	13.6 (6.7)
CU-Q$_2$oL score			
Mean (SD)	44.6 (18.7)[d]	42.7 (17.0)[d]	43.9 (17.1)[d]

CSU = chronic spontaneous urticaria; CU-Q$_2$oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; DPH = diphenhydramine; SD = standard deviation; UAS7$_{TD}$ = Urticaria Activity Score for the past 7 days, assessed twice daily; UPDD = Urticaria Patient Daily Diary.

[a] Includes patients from all treatment arms.

[b] Based on data collected via the UPDD.

[c] The clinical report form allowed for up to 3 pills per day or up to 21 pills in the prior 7 days. However, a small number of patients reported values outside this range. Across the three trials, 97.7% reported between 0 and 21 pills in the prior 7 days, while 2.3% reported between 22 and 63 pills taken in the prior 7 days.

[d] ASTERIA I: n = 246; ASTERIA II: n = 280; GLACIAL: n = 323.

* $P < 0.05$ versus ASTERIA II.