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Received Date : 30-Jun-2016

Revised Date : 03-Mar-2017

Accepted Date : 08-Mar-2017

Article type : Original Article

Analysis of Disease Activity Categories in Chronic Spontaneous/Idiopathic Urticaria

Running Head

Measuring Disease Activity in Chronic Spontaneous Urticaria

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.15454

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Funding Source

This study was funded by Novartis Pharma AG.

Conflict of Interest

Drs Stull and McBride are employed by RTI Health Solutions, which provides consulting and other research services to pharmaceutical, device, governmental, and non-government organisations. In their salaried positions, they work with a variety of companies and organisations. They receive no payment or honoraria directly from these organisations for services rendered. Dr Giménez-Arnau has received institutional grants and/or honoraria for consulting and lectures from Novartis, Uriach Pharma, Genentech, Menarini, GSK, MSD, and Almirall. Dr Grattan has received honoraria for consulting and lectures from Novartis, Sunpharma, and CSL Behring. Dr Marsland has received travel assistance to conferences and honoraria for consulting and lectures from Galderma, GSK, Novartis, and UCB Pharma. Dr Maurer has received institutional grants and/or honoraria for consulting and lectures from FAES, Genentech, Moxie, Novartis, and Uriach Pharma. Drs. Tian and Balp are employees of Novartis.

All co-authors been involved in all aspects of the manuscript, with one exception: Dr Stull has responsibility for data analysis. However, results were shared with co-authors at each step, and their input was sought regarding discussion and implications of the results. All authors have approved the final version of this manuscript prior to submission.

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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-Q2oL); 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-Q₂oL).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-Q₂oL 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 I⁹ and II¹⁰ trials received licensed dose of second-generation H₁ antihistamines as background therapy, whereas patients recruited into the GLACIAL study¹¹ received second-generation H₁ antihistamines (up to four times the licensed dose), H₂ blockers, and/or leukotriene receptor antagonists. Treatment was administered once every 4 weeks for 24 weeks in ASTERIA I⁹ and GLACIAL¹¹ 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-Q₂oL.⁸

UPDD

The validated UPDD¹³ 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 I⁹ and GLACIAL¹¹ 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 DLQI⁷ 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 I⁹ and GLACIAL¹¹ 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-Q2oL 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-Q2oL data were collected at baseline and weeks 4, 12, 24, and 40 for ASTERIA I⁹ and GLACIAL¹¹ 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-Q2oL, 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.

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 I⁹ and GLACIAL¹¹ and week 28 for ASTERIA II¹⁰). UAS7_{TD} disease states were compared on the following measures: DLQI total score; CU-Q₂oL 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} = 1-6); 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-Q₂oL 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 GLACIAL¹¹ 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-QoL 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-Q2oL 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 itch²² 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 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 criticised²³; 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-Q₂oL, 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 guidelines¹ 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

The authors wish to thank Katherine Houghton, MSc. and Adrian Vickers, PhD of RTI Health Solutions for their invaluable statistical advice and support in these analyses.

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FIGURE LEGENDS

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

CU-Q_{2oL} = 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_{2oL}. 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_{2oL} = 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.

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)
DLQI score			
Mean (SD)	13.4 (6.6)	12.7 (6.2)	13.6 (6.7)
CU-Q_{2oL} score			

Characteristic	ASTERIA I		
	N = 318 ^a	ASTERIA IIN = 322 ^a	GLACIALN = 335 ^a
Mean (SD)	44.6 (18.7) ^d	42.7 (17.0) ^d	43.9 (17.1) ^d

CSU = chronic spontaneous urticaria; CU-Q₂oL = 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.

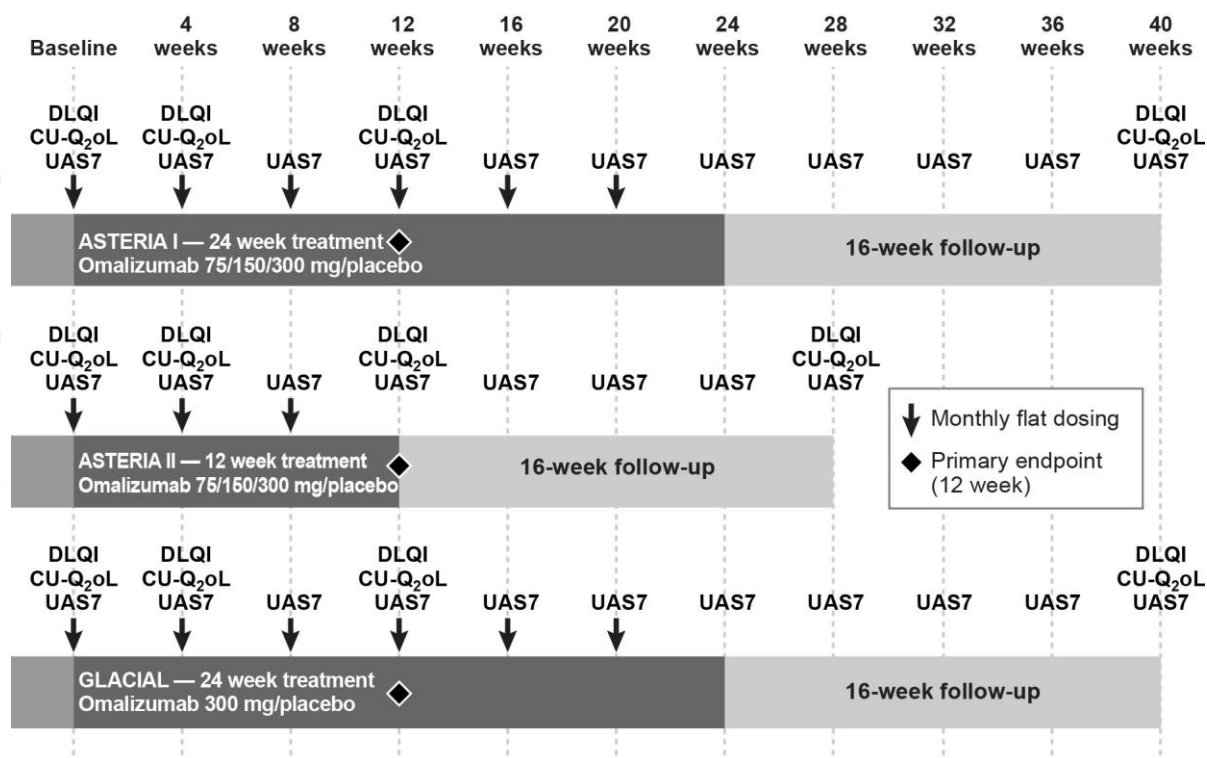
^a Includes patients from all treatment arms.

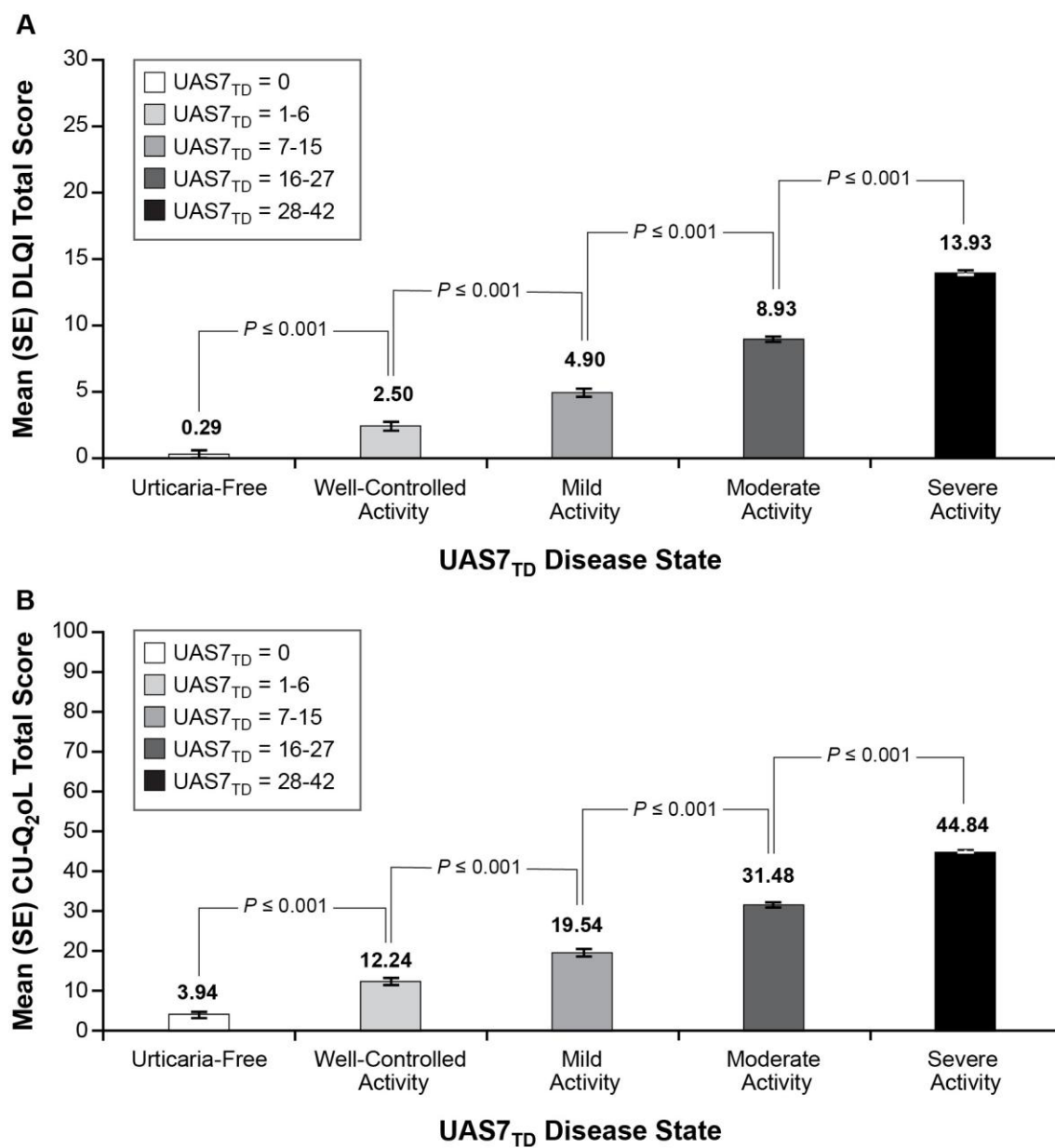
^b Based on data collected via the UPDD.

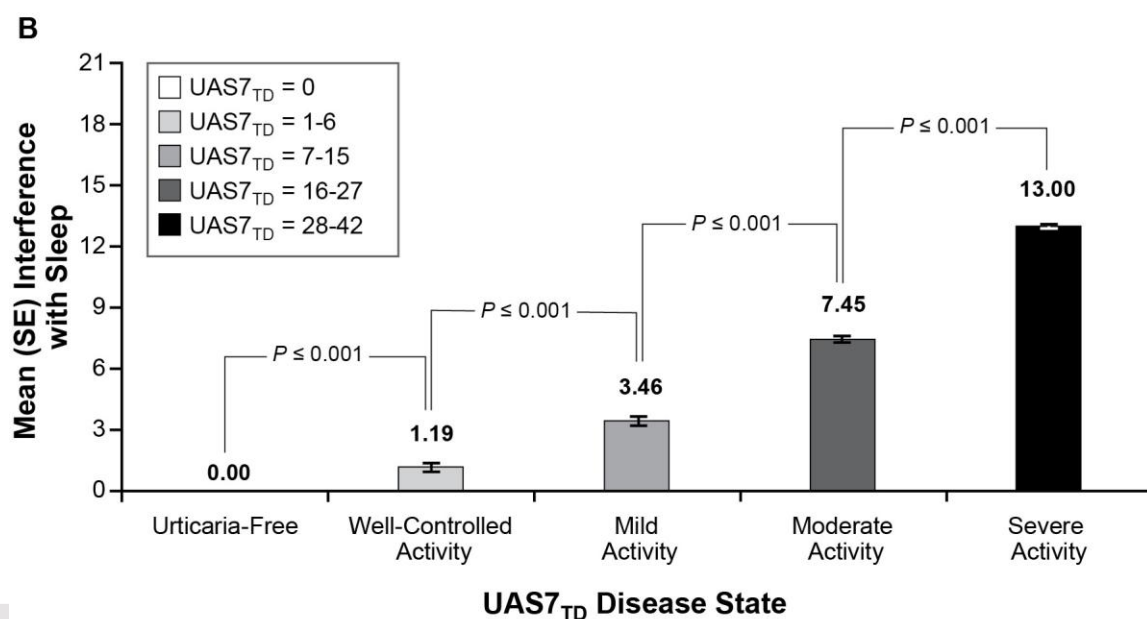
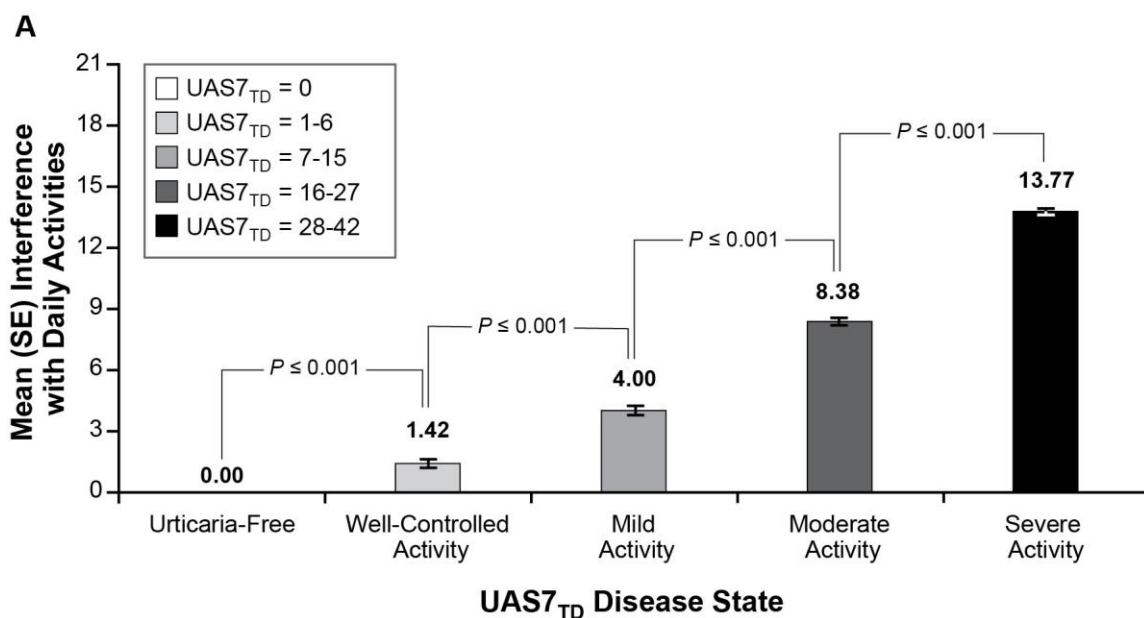
^c The clinical report form allowed for up to 3 pills per day or up to 21 pills in the prior 7 days. However, a small number of patients reported values outside this range. Across the three trials, 97.7% reported between 0 and 21 pills in the prior 7 days, while 2.3% reported between 22 and 63 pills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

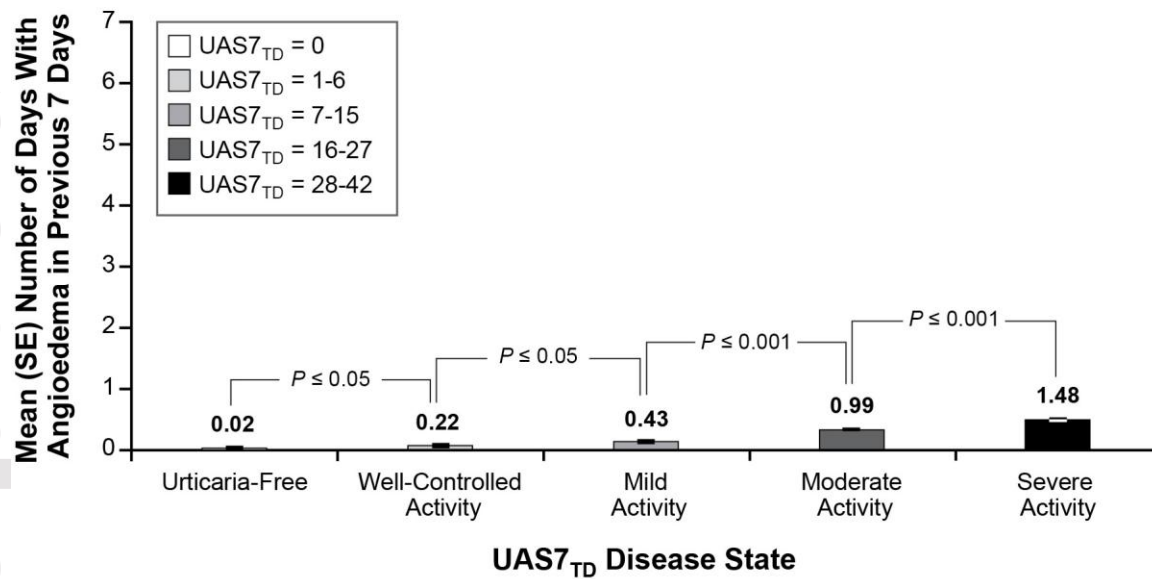
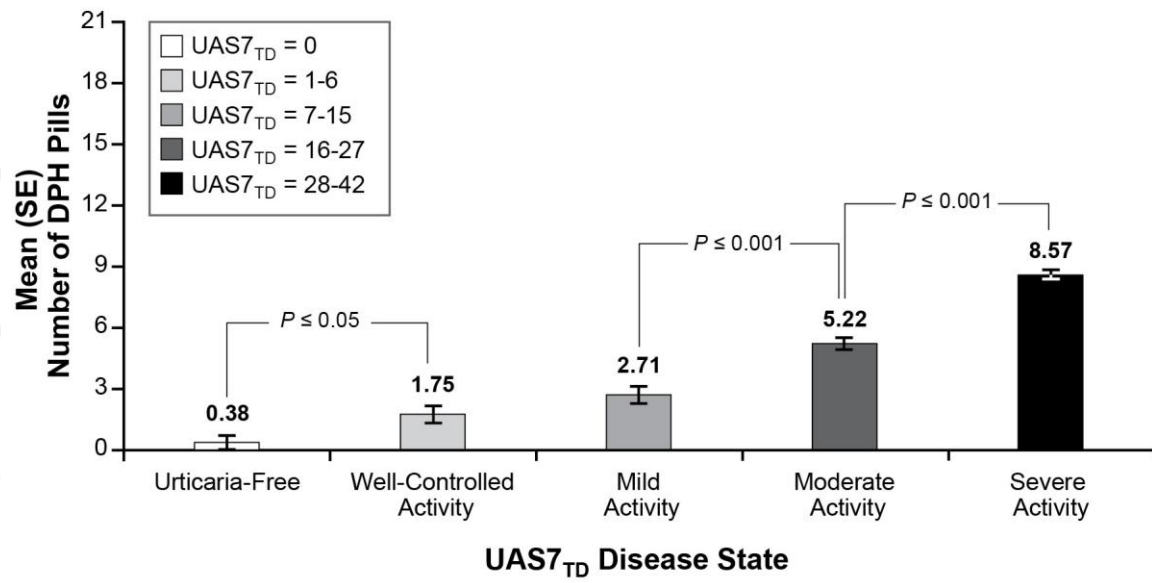
^d ASTERIA I: n = 246; ASTERIA II: n = 280; GLACIAL: n = 323.

* $P < 0.05$ versus ASTERIA II.









ANALYSIS OF DISEASE ACTIVITY CATEGORIES IN CHRONIC SPONTANEOUS/IDIOPATHIC URTICARIA

SUPPORTING INFORMATION

Individual Trial Analyses

Distributions of Scores on Comparator Variables by UAS7_{TD} Health State

For ASTERIA I, ASTERIA II and GLACIAL, Tables SI-1 (Baseline), SI-2 (Week 12), SI-3 (Week 24) and SI-4 (End of Study) present the results of descriptive analyses for the values of the comparator variables for each UAS7_{TD} health state at the key time points in each of the three clinical trials. As noted earlier, no significance tests were performed, but the pattern of results was examined across the health states. For example, the general trend of DLQI scores (subscale and total scores) showed an increase with each increasing severity of UAS7_{TD} health state. In fact, for most of the comparator variables, there is a relatively large increase in scores between mild and moderate urticaria and again between moderate and severe urticaria. This pattern is seen in all three trials.

Table SI-1 Comparator Value by UAS7_{TD} Disease States at Baseline, by Trial

ASTERIA I Baseline

	Moderate Urticaria (UAS7=16-27) Mean (SD) [n]	Severe Urticaria (UAS7=28-42) Mean (SD) [n]
DLQI Symptoms/Feelings	3.40 (1.32) [89.00]	4.23 (1.25) [226.00]
DLQI Daily Activities	2.38 (1.70) [89.00]	3.10 (1.81) [226.00]
DLQI Leisure	1.94 (1.51) [89.00]	2.79 (1.90) [226.00]
DLQI Work/ School	1.22 (1.09) [89.00]	1.51 (1.22) [226.00]
DLQI Personal Relationships	1.16 (1.39) [89.00]	1.94 (1.72) [226.00]
DLQI Treatment	0.52 (0.66) [89.00]	0.89 (0.87) [226.00]
DLQI Total Score	10.63 (5.52) [89.00]	14.45 (6.72) [226.00]
CUQ20L Total Score	37.37 (16.62) [75.00]	47.75 (18.76) [171.00]
Sleep Interference	9.12 (4.18) [90.00]	13.52 (4.65) [228.00]
Activity Interference	10.62 (3.54) [90.00]	13.96 (4.47) [228.00]
Diphenhydramine Pills	4.80 (6.17) [90.00]	8.80 (8.70) [228.00]
Angioedema (Proportion Yes)	0.38 (0.49) [90.00]	0.51 (0.50) [228.00]

ASTERIA II Baseline

	Moderate Urticaria (UAS7=16-27) Mean (SD) [n]	Severe Urticaria (UAS7=28-42) Mean (SD) [n]
DLQI Symptoms/Feelings	3.43 (1.24) [109.00]	4.26 (1.32) [212.00]
DLQI Daily Activities	2.16 (1.59) [109.00]	3.02 (1.76) [212.00]
DLQI Leisure	1.80 (1.49) [109.00]	2.54 (1.84) [212.00]
DLQI Work/ School	1.15 (0.97) [109.00]	1.48 (1.05) [212.00]
DLQI Personal Relationships	1.32 (1.51) [109.00]	1.81 (1.82) [212.00]
DLQI Treatment	0.54 (0.81) [109.00]	0.84 (0.88) [212.00]
DLQI Total Score	10.39 (5.50) [109.00]	13.94 (6.21) [212.00]
CUQ20L Total Score	36.91 (15.10) [98.00]	45.82 (17.25) [182.00]
Sleep Interference	8.74 (3.76) [109.00]	13.22 (4.82) [213.00]
Activity Interference	9.67 (3.02) [109.00]	14.22 (4.38) [213.00]
Diphenhydramine Pills	5.12 (5.61) [109.00]	8.41 (8.52) [213.00]
Angioedema (Proportion Yes)	0.35 (0.48) [109.00]	0.44 (0.50) [213.00]

GLACIAL Baseline

	Moderate Urticaria (UAS7=16-27) Mean (SD) [n]	Severe Urticaria (UAS7=28-42) Mean (SD) [n]
DLQI Symptoms/Feelings	3.58 (1.38) [105.00]	4.25 (1.31) [228.00]
DLQI Daily Activities	2.60 (1.81) [105.00]	3.20 (1.71) [228.00]
DLQI Leisure	2.17 (1.77) [105.00]	2.67 (1.90) [228.00]
DLQI Work/ School	1.35 (1.07) [105.00]	1.49 (1.12) [228.00]
DLQI Personal Relationships	1.21 (1.45) [105.00]	1.82 (1.89) [228.00]
DLQI Treatment	0.83 (0.86) [105.00]	0.97 (1.01) [228.00]
DLQI Total Score	11.74 (6.25) [105.00]	14.40 (6.77) [228.00]
CUQ20L Total Score	39.48 (16.07) [103.00]	45.94 (17.27) [220.00]
Sleep Interference	8.92 (3.70) [105.00]	13.03 (4.86) [230.00]
Activity Interference	10.05 (3.66) [105.00]	13.77 (4.45) [230.00]
Diphenhydramine Pills	6.88 (10.16) [105.00]	8.14 (8.60) [230.00]
Prior H1 antihistamines (Proportion Yes)	0.99 (0.10) [105.00]	0.98 (0.15) [230.00]
Prior H2 antihistamines (Proportion Yes)	0.84 (0.37) [105.00]	0.82 (0.39) [230.00]
Prior LTRAs (Proportion Yes)	0.43 (0.50) [105.00]	0.40 (0.49) [230.00]
Concomitant H1 antihistamines (Proportion Yes)	0.99 (0.10) [105.00]	1.00 (0.00) [230.00]
Concomitant H2 antihistamines (Proportion Yes)	0.88 (0.33) [105.00]	0.87 (0.34) [230.00]
Concomitant LTRAs (Proportion Yes)	0.47 (0.50) [105.00]	0.46 (0.50) [230.00]
Angioedema (Proportion Yes)	0.53 (0.50) [105.00]	0.53 (0.50) [230.00]

Descriptive statistics only, no significance testing conducted

CU-Q20L = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index;

LTRA = leukotriene receptor antagonist; SD = standard deviation; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-2 Comparator Value by UAS7_{TD} Disease States at Week 12, by Trial

ASTERIA I Week 12

	Urticaria-Free (UAS7=0) Mean (SD) [n]	Well-Controlled Urticaria (UAS7=1-6) Mean (SD) [n]	Mild Urticaria (UAS7=7-15) Mean (SD) [n]	Moderate Urticaria (UAS7=16-27) Mean (SD) [n]	Severe Urticaria (UAS7=28-42) Mean (SD) [n]
DLQI Symptoms/Feelings	0.27 (0.65) [56.00]	1.09 (0.80) [47.00]	1.78 (1.08) [59.00]	2.70 (1.33) [54.00]	3.87 (1.63) [46.00]
DLQI Daily Activities	0.14 (0.70) [56.00]	0.38 (0.87) [47.00]	0.88 (1.26) [59.00]	1.94 (1.56) [54.00]	2.96 (1.97) [46.00]
DLQI Leisure	0.14 (0.82) [56.00]	0.23 (0.52) [47.00]	0.59 (1.15) [59.00]	1.30 (1.27) [54.00]	2.52 (1.97) [46.00]
DLQI Work/ School	0.04 (0.27) [56.00]	0.21 (0.66) [47.00]	0.41 (0.83) [59.00]	0.80 (0.98) [54.00]	1.41 (1.29) [46.00]
DLQI Personal Relationships	0.04 (0.27) [56.00]	0.11 (0.37) [47.00]	0.42 (0.81) [59.00]	0.91 (1.23) [54.00]	1.89 (1.92) [46.00]
DLQI Treatment	0.04 (0.19) [56.00]	0.06 (0.25) [47.00]	0.29 (0.64) [59.00]	0.57 (0.77) [54.00]	0.83 (1.00) [46.00]
DLQI Total Score	0.66 (2.71) [56.00]	2.09 (2.56) [47.00]	4.37 (4.52) [59.00]	8.22 (5.20) [54.00]	13.48 (7.91) [46.00]
CUQ20L Total Score	4.71 (10.43) [42.00]	11.16 (10.34) [34.00]	19.54 (15.39) [43.00]	28.34 (15.94) [45.00]	41.12 (16.59) [37.00]
Sleep Interference	0.00 (0.00) [56.00]	0.81 (1.48) [48.00]	3.63 (3.07) [58.00]	7.72 (4.32) [54.00]	12.59 (5.60) [46.00]
Activity Interference	0.00 (0.00) [57.00]	1.01 (1.51) [46.00]	4.62 (3.27) [58.00]	8.00 (4.02) [55.00]	13.14 (5.35) [47.00]
Diphenhydramine Pills	0.21 (1.59) [57.00]	1.09 (3.10) [46.00]	3.35 (5.37) [58.00]	5.17 (6.62) [55.00]	11.24 (9.38) [47.00]
Angioedema-Proportion Yes	0.00 (0.00) [57.00]	0.13 (0.34) [46.00]	0.21 (0.41) [58.00]	0.20 (0.40) [55.00]	0.45 (0.50) [47.00]
Proportion Angioedema-Free Days, Wk4-12	99.24 (2.79) [57.00]	96.91 (8.78) [46.00]	90.74 (18.58) [59.00]	91.35 (17.78) [55.00]	76.32 (30.23) [48.00]

ASTERIA II Week 12

	Urticaria-Free (UAS7=0) Mean (SD) [n]	Well-Controlled Urticaria (UAS7=1-6) Mean (SD) [n]	Mild Urticaria (UAS7=7-15) Mean (SD) [n]	Moderate Urticaria (UAS7=16-27) Mean (SD) [n]	Severe Urticaria (UAS7=28-42) Mean (SD) [n]
DLQI Symptoms/Feelings	0.18 (0.49) [68.00]	1.21 (1.11) [56.00]	1.91 (1.29) [53.00]	2.53 (1.34) [57.00]	3.63 (1.41) [43.00]
DLQI Daily Activities	0.07 (0.43) [68.00]	0.52 (0.91) [56.00]	0.96 (1.33) [53.00]	1.32 (1.27) [57.00]	2.53 (1.65) [43.00]
DLQI Leisure	0.15 (0.70) [68.00]	0.39 (0.95) [56.00]	0.68 (1.07) [53.00]	1.30 (1.43) [57.00]	1.74 (1.63) [43.00]
DLQI Work/ School	0.00 (0.00) [68.00]	0.27 (0.59) [56.00]	0.30 (0.75) [53.00]	0.75 (0.97) [57.00]	1.19 (1.18) [43.00]
DLQI Personal Relationships	0.00 (0.00) [68.00]	0.18 (0.66) [56.00]	0.62 (1.35) [53.00]	1.00 (1.46) [57.00]	1.30 (1.52) [43.00]
DLQI Treatment	0.01 (0.12) [68.00]	0.14 (0.44) [56.00]	0.17 (0.38) [53.00]	0.40 (0.65) [57.00]	0.63 (0.82) [43.00]
DLQI Total Score	0.41 (1.36) [68.00]	2.71 (3.59) [56.00]	4.64 (4.94) [53.00]	7.30 (5.57) [57.00]	11.02 (6.19) [43.00]
CUQ20L Total Score	3.79 (7.23) [62.00]	12.09 (11.02) [52.00]	19.49 (13.01) [45.00]	29.75 (17.64) [45.00]	35.33 (17.43) [42.00]
Sleep Interference	0.00 (0.00) [70.00]	0.95 (1.70) [56.00]	3.32 (3.04) [53.00]	6.42 (5.00) [58.00]	12.25 (5.30) [47.00]
Activity Interference	0.00 (0.00) [67.00]	1.26 (2.01) [55.00]	3.80 (3.00) [51.00]	7.54 (4.77) [58.00]	12.69 (5.20) [49.00]
Diphenhydramine Pills	0.45 (2.70) [67.00]	1.29 (2.48) [55.00]	2.40 (4.82) [51.00]	4.57 (8.09) [58.00]	8.90 (7.86) [49.00]
Angioedema-Proportion Yes	0.00 (0.00) [67.00]	0.13 (0.34) [55.00]	0.16 (0.37) [51.00]	0.28 (0.45) [58.00]	0.37 (0.49) [49.00]
Proportion Angioedema-Free Days, Wk4-12	98.85 (5.91) [68.00]	95.38 (13.49) [53.00]	90.51 (21.54) [52.00]	90.35 (16.19) [58.00]	89.43 (16.66) [47.00]

GLACIAL Week 12

	Urticaria-Free (UAS7=0) Mean (SD) [n]	Well-Controlled Urticaria (UAS7=1-6) Mean (SD) [n]	Mild Urticaria (UAS7=7-15) Mean (SD) [n]	Moderate Urticaria (UAS7=16-27) Mean (SD) [n]	Severe Urticaria (UAS7=28-42) Mean (SD) [n]
DLQI Symptoms/Feelings	0.22 (0.56) [89.00]	0.86 (0.78) [58.00]	1.91 (1.48) [43.00]	2.90 (1.43) [49.00]	3.25 (1.45) [40.00]
DLQI Daily Activities	0.02 (0.15) [89.00]	0.26 (0.81) [58.00]	1.44 (1.91) [43.00]	1.98 (1.52) [49.00]	2.13 (1.54) [40.00]
DLQI Leisure	0.01 (0.11) [89.00]	0.31 (0.82) [58.00]	1.02 (1.60) [43.00]	1.65 (1.69) [49.00]	1.75 (1.66) [40.00]
DLQI Work/ School	0.00 (0.00) [89.00]	0.22 (0.62) [58.00]	0.58 (0.93) [43.00]	0.82 (1.05) [49.00]	1.10 (1.10) [40.00]
DLQI Personal Relationships	0.00 (0.00) [89.00]	0.17 (0.75) [58.00]	0.70 (1.39) [43.00]	0.88 (1.05) [49.00]	1.25 (1.51) [40.00]
DLQI Treatment	0.00 (0.00) [89.00]	0.10 (0.31) [58.00]	0.28 (0.70) [43.00]	0.57 (0.79) [49.00]	0.78 (0.80) [40.00]
DLQI Total Score	0.26 (0.61) [89.00]	1.93 (2.74) [58.00]	5.93 (6.65) [43.00]	8.80 (5.28) [49.00]	10.25 (5.83) [40.00]
CUQ20L Total Score	2.89 (4.27) [86.00]	9.97 (9.29) [58.00]	20.78 (16.71) [42.00]	31.57 (14.98) [44.00]	33.98 (14.76) [39.00]
Sleep Interference	0.05 (0.43) [88.00]	0.80 (1.18) [58.00]	3.77 (3.40) [43.00]	6.31 (4.20) [49.00]	11.17 (4.87) [43.00]
Activity Interference	0.00 (0.00) [88.00]	1.10 (1.60) [57.00]	4.46 (4.22) [43.00]	7.21 (3.87) [50.00]	11.83 (4.41) [42.00]
Diphenhydramine Pills	0.64 (3.85) [88.00]	2.94 (8.23) [57.00]	3.02 (5.27) [43.00]	5.52 (7.23) [50.00]	6.47 (7.18) [42.00]
Angioedema-Proportion Yes	0.02 (0.15) [88.00]	0.12 (0.33) [57.00]	0.09 (0.29) [43.00]	0.50 (0.51) [50.00]	0.36 (0.48) [42.00]
Proportion Angioedema-Free Days, Wk4-12	99.38 (2.90) [88.00]	91.36 (21.26) [58.00]	91.45 (17.65) [43.00]	84.33 (22.83) [50.00]	78.42 (28.98) [43.00]

Descriptive statistics only, no significance testing conducted

CU-Q₂₀L = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index;

LTRA = leukotriene receptor antagonist; SD = standard deviation; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-3 Comparator Value by UAS7_{TD} Disease States at Week 24, by Trial

ASTERIA I Week 24

	Urticaria-Free (UAS7=0) Mean (SD) [n]	Well-Controlled Urticaria (UAS7=1-6) Mean (SD) [n]	Mild Urticaria (UAS7=7-15) Mean (SD) [n]	Moderate Urticaria (UAS7=16-27) Mean (SD) [n]	Severe Urticaria (UAS7=28-42) Mean (SD) [n]
DLQI Symptoms/Feelings	0.28 (0.75) [81.00]	1.27 (0.95) [44.00]	1.75 (1.19) [48.00]	2.41 (1.36) [37.00]	3.41 (1.74) [27.00]
DLQI Daily Activities	0.10 (0.34) [81.00]	0.64 (1.22) [44.00]	1.00 (1.50) [48.00]	1.86 (1.67) [37.00]	2.74 (2.03) [27.00]
DLQI Leisure	0.11 (0.45) [81.00]	0.43 (0.90) [44.00]	0.75 (1.26) [48.00]	1.41 (1.82) [37.00]	2.11 (1.93) [27.00]
DLQI Work/School	0.06 (0.37) [81.00]	0.36 (0.81) [44.00]	0.40 (0.71) [48.00]	0.86 (1.08) [37.00]	1.33 (1.24) [27.00]
DLQI Personal Relationships	0.02 (0.16) [81.00]	0.09 (0.36) [44.00]	0.58 (1.11) [48.00]	1.03 (1.62) [37.00]	1.59 (1.78) [27.00]
DLQI Treatment	0.01 (0.11) [81.00]	0.05 (0.21) [44.00]	0.31 (0.69) [48.00]	0.70 (0.94) [37.00]	0.56 (0.75) [27.00]
DLQI Total Score	0.59 (1.53) [81.00]	2.84 (3.49) [44.00]	4.79 (5.38) [48.00]	8.27 (7.21) [37.00]	11.74 (7.13) [27.00]
CUQ20L Total Score	4.64 (7.86) [59.00]	13.95 (10.17) [36.00]	19.48 (16.89) [40.00]	29.83 (18.13) [27.00]	39.37 (21.65) [22.00]
Sleep Interference	0.05 (0.35) [81.00]	1.16 (1.81) [45.00]	3.88 (2.98) [48.00]	6.80 (5.08) [37.00]	13.31 (5.14) [29.00]
Activity Interference	0.00 (0.00) [80.00]	0.99 (1.46) [45.00]	4.33 (3.20) [48.00]	7.11 (4.03) [37.00]	13.74 (4.78) [28.00]
Diphenhydramine Pills	0.29 (1.65) [80.00]	1.37 (4.19) [45.00]	3.09 (5.00) [48.00]	4.02 (6.73) [37.00]	13.09 (11.58) [28.00]
Angioedema-Proportion Yes	0.01 (0.11) [80.00]	0.09 (0.29) [45.00]	0.15 (0.36) [48.00]	0.16 (0.37) [37.00]	0.54 (0.51) [28.00]

GLACIAL Week 24

	Urticaria-Free (UAS7=0) Mean (SD) [n]	Well-Controlled Urticaria (UAS7=1-6) Mean (SD) [n]	Mild Urticaria (UAS7=7-15) Mean (SD) [n]	Moderate Urticaria (UAS7=16-27) Mean (SD) [n]	Severe Urticaria (UAS7=28-42) Mean (SD) [n]
DLQI Symptoms/Feelings	0.15 (0.38) [109.00]	1.06 (0.94) [47.00]	2.03 (1.38) [38.00]	2.31 (1.20) [32.00]	3.67 (1.36) [33.00]
DLQI Daily Activities	0.05 (0.21) [109.00]	0.62 (1.01) [47.00]	1.34 (1.51) [38.00]	1.34 (1.45) [32.00]	2.70 (1.88) [33.00]
DLQI Leisure	0.01 (0.10) [109.00]	0.45 (1.06) [47.00]	0.89 (1.41) [38.00]	0.91 (1.25) [32.00]	2.12 (1.69) [33.00]
DLQI Work/ School	0.02 (0.13) [109.00]	0.23 (0.48) [47.00]	0.82 (1.09) [38.00]	0.59 (0.87) [32.00]	1.39 (1.14) [33.00]
DLQI Personal Relationships	0.02 (0.19) [109.00]	0.15 (0.55) [47.00]	0.76 (1.22) [38.00]	0.38 (0.79) [32.00]	1.79 (1.87) [33.00]
DLQI Treatment	0.02 (0.13) [109.00]	0.15 (0.42) [47.00]	0.47 (0.76) [38.00]	0.31 (0.47) [32.00]	0.85 (0.91) [33.00]
DLQI Total Score	0.26 (0.69) [109.00]	2.66 (3.69) [47.00]	6.32 (5.90) [38.00]	5.84 (4.39) [32.00]	12.52 (6.74) [33.00]
CUQ20L Total Score	3.49 (5.69) [107.00]	13.12 (13.55) [46.00]	21.57 (13.45) [38.00]	23.63 (10.37) [30.00]	39.10 (17.99) [31.00]
Sleep Interference	0.00 (0.00) [109.00]	0.74 (1.29) [47.00]	4.48 (3.41) [40.00]	5.63 (4.15) [31.00]	12.60 (4.46) [33.00]
Activity Interference	0.01 (0.10) [110.00]	1.31 (3.35) [46.00]	4.12 (3.68) [40.00]	5.83 (4.04) [33.00]	12.93 (4.66) [34.00]
Diphenhydramine Pills	0.59 (3.17) [110.00]	0.67 (1.38) [46.00]	4.04 (9.05) [40.00]	5.82 (9.39) [33.00]	5.45 (7.47) [34.00]
Angioedema-Proportion Yes	0.00 (0.00) [110.00]	0.09 (0.28) [46.00]	0.25 (0.44) [40.00]	0.33 (0.48) [33.00]	0.47 (0.51) [34.00]

Descriptive statistics only, no significance testing conducted

CU-Q₂₀L = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index;

LTRA = leukotriene receptor antagonist; SD = standard deviation; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-4 Comparator Value by UAS7_{TD} Disease States at Study End, by Trial

ASTERIA I Week 40

	Urticaria-Free (UAS7=0)	Well-Controlled Urticaria (UAS7=1-6)	Mild Urticaria (UAS7=7-15)	Moderate Urticaria (UAS7=16-27)	Severe Urticaria (UAS7=28-42)
	Mean (SD) [n]	Mean (SD) [n]	Mean (SD) [n]	Mean (SD) [n]	Mean (SD) [n]
DLQI Symptoms/Feelings	0.39 (0.75) [33.00]	1.15 (0.78) [26.00]	1.74 (0.86) [27.00]	2.96 (1.37) [50.00]	3.83 (1.64) [41.00]
DLQI Daily Activities	0.09 (0.38) [33.00]	0.35 (0.63) [26.00]	0.96 (1.51) [27.00]	1.90 (1.59) [50.00]	2.71 (1.90) [41.00]
DLQI Leisure	0.09 (0.52) [33.00]	0.38 (0.75) [26.00]	0.63 (1.33) [27.00]	1.68 (1.81) [50.00]	2.63 (2.11) [41.00]
DLQI Work/School	0.09 (0.52) [33.00]	0.12 (0.33) [26.00]	0.37 (0.79) [27.00]	1.04 (1.14) [50.00]	1.39 (1.30) [41.00]
DLQI Personal Relationships	0.06 (0.24) [33.00]	0.12 (0.43) [26.00]	0.26 (0.71) [27.00]	1.28 (1.73) [50.00]	1.73 (1.98) [41.00]
DLQI Treatment	0.00 (0.00) [33.00]	0.04 (0.20) [26.00]	0.26 (0.45) [27.00]	0.62 (0.90) [50.00]	0.88 (0.84) [41.00]
DLQI Total Score	0.73 (1.88) [33.00]	2.15 (2.07) [26.00]	4.22 (4.40) [27.00]	9.48 (6.85) [50.00]	13.17 (7.98) [41.00]
CUQ20L Total Score	6.07 (11.30) [24.00]	9.51 (5.54) [20.00]	16.49 (11.18) [24.00]	32.05 (19.76) [35.00]	43.31 (20.84) [33.00]
Sleep Interference	0.00 (0.00) [34.00]	1.07 (1.89) [26.00]	2.86 (3.11) [28.00]	7.41 (4.57) [48.00]	14.13 (5.97) [42.00]
Activity Interference	0.00 (0.00) [33.00]	1.60 (1.92) [24.00]	3.15 (3.20) [26.00]	8.29 (4.42) [50.00]	15.01 (5.84) [40.00]
Diphenhydramine Pills	0.85 (3.02) [33.00]	1.28 (2.35) [24.00]	1.20 (2.36) [26.00]	6.01 (7.58) [50.00]	8.66 (11.95) [40.00]
Angioedema-Proportion Yes	0.03 (0.17) [33.00]	0.17 (0.38) [24.00]	0.15 (0.37) [26.00]	0.14 (0.35) [50.00]	0.28 (0.45) [40.00]

ASTERIA II Week 28

	Urticaria-Free (UAS7=0) Mean (SD) [n]	Well-Controlled Urticaria (UAS7=1-6) Mean (SD) [n]	Mild Urticaria (UAS7=7-15) Mean (SD) [n]	Moderate Urticaria (UAS7=16-27) Mean (SD) [n]	Severe Urticaria (UAS7=28-42) Mean (SD) [n]
DLQI Symptoms/Feelings	0.11 (0.39) [38.00]	1.52 (1.30) [29.00]	2.06 (1.36) [49.00]	2.72 (1.47) [46.00]	3.86 (1.59) [51.00]
DLQI Daily Activities	0.08 (0.36) [38.00]	0.93 (1.46) [29.00]	1.22 (1.37) [49.00]	1.61 (1.65) [46.00]	2.55 (1.99) [51.00]
DLQI Leisure	0.00 (0.00) [38.00]	0.38 (0.68) [29.00]	0.92 (1.08) [49.00]	1.07 (1.42) [46.00]	2.00 (1.97) [51.00]
DLQI Work/School	0.00 (0.00) [38.00]	0.31 (0.66) [29.00]	0.76 (0.88) [49.00]	0.76 (0.95) [46.00]	1.25 (1.07) [51.00]
DLQI Personal Relationships	0.00 (0.00) [38.00]	0.34 (0.72) [29.00]	0.63 (1.15) [49.00]	0.70 (1.49) [46.00]	1.45 (1.55) [51.00]
DLQI Treatment	0.00 (0.00) [38.00]	0.17 (0.47) [29.00]	0.41 (0.70) [49.00]	0.37 (0.61) [46.00]	0.67 (0.79) [51.00]
DLQI Total Score	0.18 (0.69) [38.00]	3.66 (3.96) [29.00]	6.00 (4.65) [49.00]	7.22 (6.19) [46.00]	11.78 (7.34) [51.00]
CUQ20L Total Score	2.70 (4.73) [37.00]	12.50 (10.06) [22.00]	23.48 (15.12) [43.00]	28.05 (15.88) [40.00]	40.10 (20.40) [46.00]
Sleep Interference	0.03 (0.16) [37.00]	0.75 (1.50) [27.00]	4.08 (3.02) [48.00]	6.17 (4.88) [44.00]	12.65 (5.82) [50.00]
Activity Interference	0.00 (0.00) [35.00]	1.15 (1.86) [27.00]	5.01 (3.61) [49.00]	7.28 (4.83) [43.00]	13.70 (4.95) [48.00]
Diphenhydramine Pills	0.20 (1.18) [35.00]	0.81 (2.86) [27.00]	4.08 (4.87) [49.00]	2.98 (4.79) [43.00]	8.96 (8.65) [48.00]
Angioedema-Proportion Yes	0.03 (0.17) [35.00]	0.00 (0.00) [27.00]	0.16 (0.37) [49.00]	0.19 (0.39) [43.00]	0.29 (0.46) [48.00]

GLACIAL Week 40

	Urticaria-Free (UAS7=0) Mean (SD) [n]	Well-Controlled Urticaria (UAS7=1-6) Mean (SD) [n]	Mild Urticaria (UAS7=7-15) Mean (SD) [n]	Moderate Urticaria (UAS7=16-27) Mean (SD) [n]	Severe Urticaria (UAS7=28-42) Mean (SD) [n]
DLQI Symptoms/Feelings	0.24 (0.48) [42.00]	1.18 (0.90) [28.00]	2.06 (1.24) [31.00]	3.05 (1.77) [55.00]	3.76 (1.67) [38.00]
DLQI Daily Activities	0.02 (0.15) [42.00]	0.46 (0.84) [28.00]	1.16 (1.13) [31.00]	2.09 (1.84) [55.00]	3.05 (2.14) [38.00]
DLQI Leisure	0.00 (0.00) [42.00]	0.57 (1.10) [28.00]	0.81 (1.25) [31.00]	1.58 (1.74) [55.00]	2.32 (2.04) [38.00]
DLQI Work/ School	0.00 (0.00) [42.00]	0.43 (0.96) [28.00]	0.55 (0.85) [31.00]	1.07 (1.03) [55.00]	1.61 (1.26) [38.00]
DLQI Personal Relationships	0.00 (0.00) [42.00]	0.14 (0.45) [28.00]	0.61 (1.05) [31.00]	0.69 (1.18) [55.00]	1.63 (1.95) [38.00]
DLQI Treatment	0.00 (0.00) [42.00]	0.21 (0.50) [28.00]	0.52 (0.72) [31.00]	0.49 (0.77) [55.00]	0.92 (1.08) [38.00]
DLQI Total Score	0.26 (0.50) [42.00]	3.00 (3.66) [28.00]	5.71 (4.68) [31.00]	8.98 (6.32) [55.00]	13.29 (8.25) [38.00]
CUQ20L Total Score	3.00 (4.01) [42.00]	13.09 (10.80) [26.00]	25.19 (10.80) [29.00]	28.79 (18.72) [53.00]	40.16 (20.02) [37.00]
Sleep Interference	0.07 (0.47) [41.00]	1.01 (1.59) [28.00]	3.76 (3.03) [31.00]	6.25 (4.18) [54.00]	12.29 (5.23) [36.00]
Activity Interference	0.00 (0.00) [41.00]	0.92 (1.18) [26.00]	4.29 (2.95) [30.00]	8.42 (5.35) [53.00]	12.81 (5.21) [35.00]
Diphenhydramine Pills	0.17 (1.09) [41.00]	1.94 (6.23) [26.00]	1.64 (3.87) [30.00]	6.57 (12.46) [53.00]	6.98 (8.72) [35.00]
Angioedema-Proportion Yes	0.00 (0.00) [41.00]	0.08 (0.27) [26.00]	0.10 (0.31) [30.00]	0.32 (0.47) [53.00]	0.46 (0.51) [35.00]

Descriptive statistics only, no significance testing conducted

CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index;

LTRA = leukotriene receptor antagonist; SD = standard deviation; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Cross-tabulations Between Changes in UAS7_{TD} Disease States and Changes in DLQI Effect Sizes

Tables SI-5 (baseline-week 12), SI-6 (baseline-week 24), SI-7 (week 12-week 24), SI-8 (Baseline-end of study) and SI-9 (week 12/24-end of study) present the cross-tabulations between changes in UAS7 disease states and changes in DLQI effect sizes. For ASTERIA I and GLACIAL, comparisons were made in changes between baseline and week 12, baseline and week 24, week 12 and week 24, baseline and week 40, and week 24 and week 40. For ASTERIA II, the same types of comparisons were made between baseline and week 12, baseline and week 28, and week 12 and week 28. All comparisons between changes in UAS7_{TD} disease states and DLQI bands for all three trials were highly statistically significant by both Pearson chi2 and Fischer's Exact Test, indicating that when patients improve by one UAS7_{TD} disease state they are very likely to show a comparable improvement in DLQI band. In fact, the majority of cases can be seen on the diagonal in all tables, which shows that there is consistency in changes between UAS7_{TD} disease states and DLQI bands.

Table SI-5 Cross-Tabulation of Changes in UAS7_{TD} Disease States and Changes in DLQI Effect on Dermatological Quality of Life: Baseline to Week 12

ASTERIA I

Change in UAS7 Health States, Baseline to Week 12	Change in DLQI Bands, Baseline to Week 12						Total
	Improve by 4	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	
Improve by 4	8	16	10	5	1	.	40
Improve by 3	2	17	14	9	.	.	42
Improve by 2	2	13	19	20	5	.	59
Improve by 1	.	3	11	16	23	3	56
No Change	.	1	8	11	33	4	57
Worsen by 1	.	.	.	.	3	2	5
Total	12	50	62	61	65	9	259

Pearson chi2(25) = 159.3275 Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

ASTERIA II

Change in UAS7 Health States, Baseline to Week 12	Change in DLQI Bands, Baseline to Week 12							Total
	Improve by 4	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	Worsen by 2	
Improve by 4	3	24	9	5	.	.	.	41
Improve by 3	3	15	22	11	4	.	.	55
Improve by 2	2	11	26	17	8	.	.	64
Improve by 1	.	5	14	28	6	2	.	55
No Change	.	.	6	24	18	7	2	57
Worsen by 1	.	.	1	1	2	.	1	5
Total	8	55	78	86	38	9	3	277

Pearson chi2(30) = 150.7765 Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

GLACIAL

Change in UAS7 Health States, Baseline to Week 12	Change in DLQI Bands, Baseline to Week 12							Total
	Improve by 4	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	Worsen by 2	
Improve by 4	7	27	13	6	.	.	.	53
Improve by 3	5	32	27	9	.	.	.	73
Improve by 2	2	7	10	14	9	1	.	43
Improve by 1	1	3	7	17	23	2	.	53
No Change	.	.	4	20	25	.	2	51
Worsen by 1	.	.	.	.	2	3	.	5
Total	15	69	61	66	59	6	2	278

Pearson $\chi^2(30) = 240.0828$ Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

DLQI = Dermatology Life Quality Index; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-6 Cross-Tabulation of Changes in UAS7_{TD} Disease States and Changes in DLQI Effect on Dermatological Quality of Life: Baseline to Week 24

ASTERIA I

Change in UAS7 Health States, Baseline to Week 24	Change in DLQI Bands, Baseline to Week 24						Total
	Improve by 4	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	
Improve by 4	5	29	15	8	1	.	58
Improve by 3	1	21	13	10	1	.	46
Improve by 2	2	8	11	14	11	2	48
Improve by 1	.	5	12	20	9	2	48
No Change	.	1	2	7	20	4	34
Total	8	64	53	59	42	8	234

Pearson chi2(20) = 110.6880 Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

GLACIAL

Change in UAS7 Health States, Baseline to Week 24	Change in DLQI Bands, Baseline to Week 24								Total
	Improve by 4	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	Worsen by 2	Worsen by 3	
Improve by 4	9	33	18	8	.	.	.	.	68
Improve by 3	5	24	29	7	3	.	.	.	68
Improve by 2	.	7	14	14	4	1	.	1	41
Improve by 1	1	4	7	15	11	3	.	.	41
No Change	.	.	2	9	16	5	.	.	32
Worsen by 1	.	.	.	3	2	2	1	.	8
Total	15	68	70	56	36	11	1	1	258

Pearson chi2(35) = 185.7116 Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

DLQI = Dermatology Life Quality Index; UAS7TD = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-7 Cross-Tabulation of Changes in UAS7_{TD} Disease States and Changes in DLQI Effect on Dermatological Quality of Life: Week 12 to Week 24

ASTERIA I

Change in UAS7 Health States, Week 12 to Week 24	Change in DLQI Bands, Week 12 to Week 24								Total
	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	Worsen by 2	Worsen by 3	Worsen by 4	
Improve by 4	.	1	.	.	.	.	.	.	1
Improve by 3	.	1	3	.	.	.	.	.	4
Improve by 2	2	.	5	12	.	.	.	.	19
Improve by 1	.	7	22	40	3	.	.	.	72
No Change	1	4	12	69	18	2	1	.	107
Worsen by 1	.	.	5	12	4	1	.	.	22
Worsen by 2	.	.	.	.	.	4	1	.	5
Worsen by 3	.	.	.	1	.	.	.	1	2
Total	3	13	47	134	25	7	2	1	232

Pearson chi2(49) = 311.0876 Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

GLACIAL

Change in UAS7 Health States, Week 12 to Week 24	Change in DLQI Bands, Week 12 to Week 24								Total
	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	Worsen by 2	Worsen by 3	Worsen by 4	
Improve by 4	.	.	2	.	.	.	.	.	2
Improve by 3	.	2	2	.	.	.	.	.	4
Improve by 2	1	2	4	5	1	.	.	.	13
Improve by 1	1	5	17	35	2	.	.	.	60
No Change	2	2	8	107	19	2	1	.	141
Worsen by 1	.	.	3	16	7	1	.	.	27
Worsen by 2	.	.	.	2	5	1	.	.	8
Worsen by 4	.	.	.	.	.	.	.	1	1
Total	4	11	36	165	34	4	1	1	256

Pearson $\chi^2(49) = 366.2133$ Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

DLQI = Dermatology Life Quality Index; UAS7TD = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-8 Cross-Tabulation of Changes in UAS7_{TD} Disease States and Changes in DLQI Effect on Dermatological Quality of Life: Baseline to End-of-Study

ASTERIA I

Change in UAS7 Health States, Baseline to Week 40	Change in DLQI Bands, Baseline to Week 40							Total
	Improve by 4	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	Worsen by 2	
Improve by 4	3	10	7	1	2	.	.	23
Improve by 3	.	9	7	7	.	.	.	23
Improve by 2	1	6	9	10	6	.	.	32
Improve by 1	.	1	8	14	17	3	1	44
No Change	.	1	2	16	23	5	2	49
Worsen by 1	.	.	.	2	2	1	1	6
Total	4	27	33	50	50	9	4	177

Pearson chi2(30) = 98.7516 Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

ASTERIA II

Change in UAS7 Health States, Baseline to Week 28	Change in DLQI Bands, Baseline to Week 28						Total
	Improve by 4	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	
Improve by 4	.	16	6	3	.	.	25
Improve by 3	2	9	8	7	1	.	27
Improve by 2	.	5	15	10	7	1	38
Improve by 1	.	1	12	23	16	3	55
No Change	.	2	9	23	19	10	63
Worsen by 1	.	.	.	1	2	2	5
Total	2	33	50	67	45	16	213

Pearson chi2(25) = 117.8129 Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

GLACIAL

Change in UAS7 Health States, Baseline to Week 40	Change in DLQI Bands, Baseline to Week 40						Total
	Improve by 4	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	
Improve by 4	4	7	11	1	.	.	23
Improve by 3	2	14	11	8	1	.	36
Improve by 2	.	1	8	8	4	1	22
Improve by 1	.	4	9	17	20	7	57
No Change	1	.	4	16	19	8	51
Worsen by 1	.	.	.	1	2	.	4
Total	7	26	43	51	46	16	193

Pearson $\chi^2(30) = 118.1441$ Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

DLQI = Dermatology Life Quality Index; UAS7TD = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-9 Cross-Tabulation of Changes in UAS7_{TD} Disease States and Changes in DLQI Effect on Dermatological Quality of Life: Week 24 to End-of Study

ASTERIA I

Change in UAS7 Health States, Week 24 to Week 40	Change in DLQI Bands, Week 24 to Week 40								Total
	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	Worsen by 2	Worsen by 3	Worsen by 4	
Improve by 3	1	1	.	.	.	.	.	.	2
Improve by 2	3	.	4	5	1	.	.	.	13
Improve by 1	1	1	5	14	1	.	.	.	22
No Change	.	2	7	34	12	3	.	.	58
Worsen by 1	.	.	2	16	6	3	1	.	28
Worsen by 2	.	.	1	3	10	2	3	1	20
Worsen by 3	.	.	.	1	6	4	2	1	14
Worsen by 4	.	.	.	1	2	7	7	.	17
Total	5	4	19	74	38	19	13	2	174

Pearson chi2(49) = 178.2699 Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

ASTERIA II

Change in UAS7 Health States, Week 12 to Week 28	Change in DLQI Bands, Week 12 to Week 28								Total
	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	Worsen by 2	Worsen by 3	Worsen by 4	
Improve by 4	.	2	.	.	.	.	.	.	2
Improve by 3	2	1	7	1	.	.	.	.	11
Improve by 2	.	3	3	1	.	.	.	.	7
Improve by 1	.	.	7	13	2	1	.	.	23
No Change	.	3	16	44	17	4	1	.	85
Worsen by 1	.	1	3	10	17	6	.	.	37
Worsen by 2	.	.	.	5	10	5	3	.	23
Worsen by 3	.	.	.	.	4	6	4	.	14
Worsen by 4	.	.	.	.	1	1	3	1	6
Total	2	10	36	74	51	23	11	1	208

Pearson chi2(56) = 270.3347 Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

GLACIAL

Change in UAS7 Health States, Week 24 to Week 40	Change in DLQI Bands, Week 24 to Week 40								Total
	Improve by 3	Improve by 2	Improve by 1	No Change	Worsen by 1	Worsen by 2	Worsen by 3	Worsen by 4	
Improve by 4	1	.	.	.	.	.	.	.	1
Improve by 3	.	1	1	.	.	.	.	.	2
Improve by 2	.	2	2	2	1	.	.	.	7
Improve by 1	.	1	5	16	1	.	.	.	23
No Change	1	2	11	45	8	2	.	.	69
Worsen by 1	1	.	2	19	7	4	3	.	36
Worsen by 2	.	.	.	1	5	7	4	.	17
Worsen by 3	.	.	.	2	7	6	6	2	23
Worsen by 4	.	.	.	.	1	3	4	3	11
Total	3	6	21	85	30	22	17	5	189

Pearson $\chi^2(56) = 236.6288$ Pr = 0.000

Fisher's Exact Test = Pr < 0.00001

DLQI = Dermatology Life Quality Index; UAS7TD = Urticaria Activity Score for the past 7 days, assessed twice daily.

UAS7_{TD} Disease States by DLQI Effect Size

Tables SI-10 (baseline), SI-11 (week 12), SI-12 (week 24) and SI-13 (end of study) present the relationships between UAS7_{TD} disease state and DLQI effect size. For each of these cross-tabulations, the relationships are statistically significant. For example, in ASTERIA I, for those who had moderate urticaria at baseline, they were more likely to have a DLQI effect size of moderate (28.1%) or very large (47.2%) (Pearson $\chi^2 = 22.7197$; $P < 0.001$). Likewise, those who had severe urticaria were more likely to have a DLQI effect size of moderate (19.9%), very large (49.1%), or extremely large (20.4%). This same pattern was seen across the other two trials and time points: Those with a more severe disease state had a larger DLQI effect size.

Table SI-10 UAS7_{TD} Disease States by DLQI Effect Size: Baseline

ASTERIA I												Extremely
		No Effect:		Small Effect:		Moderate Effect:		Very Large Effect:		Large Effect:		
		DLQI=0-1		DLQI=2-5		DLQI=6-10		DLQI=11-20		DLQI=21-30		
Baseline UAS7 _{TD}		n	%	n	%	n	%	n	%	n	%	
Health States												
16-27: Moderate urticaria		3	3.4	17	19.1	25	28.1	42	47.2	2	2.2	
28-42: Severe urticaria		2	0.9	22	9.7	45	19.9	111	49.1	46	20.4	
Total		5		39		70		153		48		

Pearson $\chi^2(4) = 22.7197$ Pr = 0.000

ASTERIA II												Extremely
		No Effect:		Small Effect:		Moderate Effect:		Very Large Effect:		Large Effect:		
		DLQI=0-1		DLQI=2-5		DLQI=6-10		DLQI=11-20		DLQI=21-30		

Baseline UAS7TD										
Health States	n	%	n	%	n	%	n	%	n	%
16-27: Moderate urticaria	1	0.9	17	15.6	46	42.2	41	37.6	4	3.7
28-42: Severe urticaria	0	0	16	7.6	55	25.9	110	51.9	31	14.6
Total	1		33		101		151		35	

Pearson chi2(4) = 23.5673 Pr = 0.000

GLACIAL										
										Extremely
										Large
										Effect:
										DLQI=21-30
Baseline UAS7_{TD} Health										
States	n	%	n	%	n	%	n	%	n	%
16-28: Moderate urticaria	3	2.9	16	15.2	32	30.5	44	41.9	10	9.5
28-42: Severe urticaria	0	0	22	9.7	52	22.8	113	49.6	41	18
Total	3		38		84		157		51	

Pearson chi2(4) = 14.4110 Pr = 0.006

DLQI = Dermatology Life Quality Index; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-11 UAS7_{TD} Disease States by DLQI Effect Size: Week 12

ASTERIA I			Small		Moderate		Very Large		Extremely	
	No Effect:		Effect:		Effect:		Effect:		Large Effect:	
	DLQI=0-1		DLQI=2-5		DLQI=6-10		DLQI=11-20		DLQI=21-30	
Week 12 UAS7 _{TD}	n	%	n	%	n	%	n	%	n	%
Health States										
Urticaria-Free	52	92.9	3	5.4	0	0	1	1.8	0	0
1-6: Well-controlled urticaria	29	61.7	13	27.7	4	8.5	1	2.1	0	0
7-15: Mild urticaria	19	32.2	28	47.5	5	8.5	7	11.9	0	0
16-27: Moderate urticaria	0	0	22	40.7	17	31.5	14	25.9	1	1.9
28-42: Severe urticaria	1	2.2	10	21.7	5	10.9	20	43.5	10	21.7
Total	101		76		31		43		11	

Pearson chi2(16) = 211.6536 Pr = 0.000

ASTERIA II			Small		Moderate		Very Large		Extremely	
	No Effect:		Effect:		Effect:		Effect:		Large Effect:	
	DLQI=0-1		DLQI=2-5		DLQI=6-10		DLQI=11-20		DLQI=21-30	
Week 12 UAS7 _{TD}	n	%	n	%	n	%	n	%	n	%
Health States										
Urticaria-Free	63	92.7	4	5.9	1	1.5	0	0	0	0
1-6: Well-controlled urticaria	28	50	20	35.7	6	10.7	2	3.6	0	0
7-15: Mild urticaria	17	32.1	22	41.5	9	17	4	7.6	1	1.9
16-27: Moderate urticaria	7	12.3	21	36.8	15	26.3	13	22.8	1	1.8

28-42: Severe urticaria	2	4.7	7	16.3	12	27.9	19	44.2	3	7
Total	117		74		43		38		5	

Pearson chi2(16) = 164.7517 Pr = 0.000

GLACIAL	Extremely									
			Small		Moderate		Very Large		Large	
	No Effect:		Effect:		Effect:		Effect:		Effect:	
	DLQI=0-1		DLQI=2-5		DLQI=6-10		DLQI=11-20		DLQI=21-30	
Week 12 UAS7 _{TD}										
Health States	n	%	n	%	n	%	n	%	n	%
Urticaria-Free	86	96.6	3	3.4	0	0	0	0	0	0
1-6: Well-controlled										
urticaria	38	65.5	14	24.1	3	5.2	3	5.2	0	0
7-15: Mild urticaria	11	25.6	17	39.5	7	16.3	6	14	2	4.7
16-28: Moderate										
urticaria	2	4.1	15	30.6	12	24.5	20	40.8	0	0
28-42: Severe										
urticaria	0	0	11	27.5	11	27.5	17	42.5	1	2.5
Total	137		60		33		46		3	

Pearson chi2(16) = 201.3839 Pr = 0.000

DLQI = Dermatology Life Quality Index; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-12 UAS7_{TD} Disease States by DLQI Effect Size: Week 24

ASTERIA I											
		No Effect:		Small Effect:		Moderate Effect:		Very Large Effect:		Extremely Large Effect:	
		DLQI=0-1		DLQI=2-5		DLQI=6-10		DLQI=11-20		DLQI=21-30	
Week 24 UAS7 _{TD}		n	%	n	%	n	%	n	%	n	%
Health States											
Urticaria-Free		71	87.7	8	9.9	2	2.5	0	0	0	0
1-6: Well-controlled											
urticaria		22	50	15	34.1	5	11.4	2	4.5	0	0
7-15: Mild urticaria		15	31.3	18	37.5	9	18.8	5	10.4	1	2.1
16-27: Moderate											
urticaria		4	10.8	17	45.9	3	8.1	11	29.7	2	5.4
28-42: Severe											
urticaria		2	7.4	6	22.2	1	3.7	14	51.9	4	14.8
Total		114		64		20		32		7	

Pearson chi2(16) = 144.5037 Pr = 0.000

GLACIAL											
		No Effect:		Small Effect:		Moderate Effect:		Very Large Effect:		Extremely Large Effect:	
		DLQI=0-1		DLQI=2-5		DLQI=6-10		DLQI=11-20		DLQI=21-30	
Week 24 UAS7 _{TD}		n	%	n	%	n	%	n	%	n	%
Health States											
Urticaria-Free		103	94.5	6	5.5	0	0	0	0	0	0
1-6: Well-controlled											
urticaria		27	57.5	15	31.9	3	6.4	2	4.3	0	0
7-15: Mild urticaria		6	15.8	14	36.8	13	34.2	2	5.3	3	7.9

16-28: Moderate										
urticaria	3	9.4	15	46.9	11	34.4	3	9.4	0	0
28-42: Severe urticaria	1	3	4	12.1	9	27.3	14	42.4	5	15.2
Total	140		54		36		21		8	

Pearson $\chi^2(16) = 226.9185$ Pr = 0.000

DLQI = Dermatology Life Quality Index; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-13 UAS7_{TD} Disease States by DLQI Effect Size: End of Study

ASTERIA I		Small		Moderate		Very Large		Extremely	
No Effect:		Effect:		Effect:		Effect:		Large Effect:	
DLQI=0-1		DLQI=2-5		DLQI=6-10		DLQI=11-20		DLQI=21-30	
Week 40 UAS7 _{TD}		n	%	n	%	n	%	n	%
Health States									
Urticaria-Free		29	87.9	2	6.1	2	6.1	0	0
1-6: Well-controlled									
urticaria		12	46.2	12	46.2	2	7.7	0	0
7-15: Mild urticaria		8	29.6	14	51.9	3	11.1	2	7.4
16-27: Moderate									
urticaria		3	6	14	28	12	24	17	34
28-42: Severe urticaria		2	4.9	6	14.6	9	22	18	43.9
Total		54		48		28		37	10

Pearson chi2(16) = 120.6065 Pr = 0.000

ASTERIA II		Small		Moderate		Very Large		Extremely	
No Effect:		Effect:		Effect:		Effect:		Large Effect:	
DLQI=0-1		DLQI=2-5		DLQI=6-10		DLQI=11-20		DLQI=21-30	
Week 28 UAS7 _{TD}		n	%	n	%	n	%	n	%
Health States									
Urticaria-Free		37	97.4	1	2.6	0	0	0	0
1-6: Well-controlled									
urticaria		12	41.4	9	31	7	24.1	1	3.5
7-15: Mild urticaria		9	18.4	16	32.7	17	34.7	7	14.3

16-27: Moderate										
urticaria	7	15.2	16	34.8	13	28.3	8	17.4	2	4.4
28-42: Severe urticaria										
	2	3.9	13	25.5	9	17.7	19	37.3	8	15.7
Total	67		55		46		35		10	

Pearson chi2(16) = 137.6675 Pr = 0.000

GLACIAL					Moderate	Very Large		Extremely		
	No Effect:		Small Effect:		Effect:		Effect:		Large Effect:	
	DLQI=0-1		DLQI=2-5		DLQI=6-10		DLQI=11-20		DLQI=21-30	
Week 40 UAS7 _{TD}										
Health States	n	%	n	%	n	%	n	%	n	%
Urticaria-Free	41	97.6	1	2.4	0	0	0	0	0	0
1-6: Well-controlled										
urticaria	15	53.6	9	32.1	2	7.1	2	7.1	0	0
7-15: Mild urticaria	4	12.9	15	48.4	7	22.6	5	16.1	0	0
16-28: Moderate										
urticaria	2	3.6	17	30.9	17	30.9	16	29.1	3	5.5
28-42: Severe										
urticaria	3	7.9	2	5.3	12	31.6	14	36.8	7	18.4
Total	65		44		38		37		10	

Pearson chi2(16) = 159.9846 Pr = 0.000

DLQI = Dermatology Life Quality Index; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Mean UAS7_{TD} Scores for Each DLQI Effect on Dermatological Quality of Life

Tables SI-14 (baseline), SI-15 (week 12), SI-16 (week 24) and SI-17 (end of study) present the mean UAS7_{TD} score for each DLQI effect size. For these tables, the adjacent DLQI effect sizes were compared to see if the mean UAS7_{TD} score was significantly different. For ASTERIA I at baseline, there is no significant difference in mean UAS7_{TD} scores between those with a DLQI effect size of No Effect (DLQI = 0-1) and those with a Small Effect (DLQI = 2-5; mean UAS7 = 26.9 vs. 27.7). However, when comparing those who have a Very Large Effect (DLQI = 11-20) with those who have an Extremely Large Effect (DLQI = 21-30), the difference is significant (31.4 vs. 36.2; $P < 0.001$). At later assessment points, differences in mean UAS7_{TD} scores between No Effect and Small Effect or between Small Effect and Moderate Effect or between Moderate Effect and Very Large Effect are more likely to be significant, for all three trials. This is most likely due to a shift in the number of patients to the No Effect and Small Effect categories, thus increasing these subsample sizes and allowing for a more sensitive test of significance.

Table SI-14 Mean UAS7_{TD} Scores for Each DLQI Effect on Dermatological Quality of Life: Baseline, by Trial

		DLQI Effect Size				
		No Effect (DLQI=0-1)	Small Effect (DLQI=2-5)	Moderate Effect (DLQI=6-10)	Very Large Effect (DLQI=11-20)	Extremely Large Effect (DLQI=21-30)
ASTERIA I						
Baseline	<u>Mean</u>	26.9	27.7	29.2	31.4*	36.2
UAS7 _{TD}	<u>SD</u>	3.5	6.9	6.0	6.4	4.8
	<u>n</u>	5	39	70	153	48
ASTERIA II						
Baseline	<u>Mean</u>	19.5	26.7	28.5*	32.1	34.9
UAS7 _{TD}	<u>SD</u>	0.0	5.4	6.4	6.5	6.9
	<u>n</u>	1	33	101	151	35
GLACIAL						

Baseline	<u>Mean</u>	25.7	27.9	29.1**	31.5**	34.4
UAS7 _{TD}	<u>SD</u>	1.9	6.7	5.8	6.1	7.3
	<u>n</u>	3	38	84	157	51

* $P = \leq 0.001$ to next-larger adjacent effect size

** $P \leq 0.05$ to next-larger adjacent effect size.

DLQI = Dermatology Life Quality Index; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-15 Mean UAS7_{TD} Scores for Each DLQI Effect on Dermatological Quality of Life: Week 12, by Trial

		DLQI Effect Size				
		No Effect (DLQI=0-1)	Small Effect (DLQI=2-5)	Moderate Effect (DLQI=6-10)	Very Large Effect (DLQI=11-20)	Extremely Large Effect (DLQI=21-30)
ASTERIA I						
Week 12 UAS7 _{TD}	<u>Mean</u>	3.4*	14.8*	20.8	24.8**	34.8
	<u>SD</u>	5.3	9.3	8.9	10.2	7.1
	<u>n</u>	101	76	31	43	11
ASTERIA II						
Week 12 UAS7 _{TD}	Mean	4.0*	13.0*	20.1**	27.5	28.5
	SD	6.9	9.7	11.4	11.0	12.6
	n	117	74	43	38	5
GLACIAL						
Week 12 UAS7 _{TD}	<u>Mean</u>	1.9*	15.2*	21.9	24.0	17.3
	<u>SD</u>	3.9	10.4	10.4	9.9	9.9
	<u>n</u>	137	60	33	46	3

* $P = \leq 0.001$ to next-larger adjacent effect size

** $P \leq 0.05$ to next-larger adjacent effect size.

DLQI = Dermatology Life Quality Index; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-16 Mean UAS7_{TD} Scores for Each DLQI Effect on Dermatological Quality of Life: Week 24, by Trial

		DLQI Effect Size				
		No Effect (DLQI=0-1)	Small Effect (DLQI=2-5)	Moderate Effect (DLQI=6-10)	Very Large Effect (DLQI=11-20)	Extremely Large Effect (DLQI=21-30)
ASTERIA I						
Week 24 UAS7 _{TD}	<u>Mean</u>	3.2*	12.2	11.7*	23.8	32.2
	<u>SD</u>	6.3	9.2	9.1	10.6	11.0
	<u>n</u>	114	64	20	32	7
GLACIAL						
Week 24 UAS7 _{TD}	<u>Mean</u>	1.7*	12.6*	20.2**	27.1	28.3
	<u>SD</u>	4.7	10.0	9.5	10.1	11.6
	<u>n</u>	140	54	36	21	8

* $P = \leq 0.001$ to next-larger adjacent effect size

** $P \leq 0.05$ to next-larger adjacent effect size.

DLQI = Dermatology Life Quality Index; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Table SI-17 Mean UAS7_{TD} Scores for Each DLQI Effect on Dermatological Quality of Life: End of Study, by Trial

		DLQI Effect Size				
		No Effect (DLQI=0-1)	Small Effect (DLQI=2-5)	Moderate Effect (DLQI=6-10)	Very Large Effect (DLQI=11-20)	Extremely Large Effect (DLQI=21-30)
ASTERIA I						
Week 40 UAS7 _{TD}	<u>Mean</u>	4.6*	14.3**	21.7	28.3	30.6
	<u>SD</u>	7.9	9.8	11.6	9.1	10.5
	<u>n</u>	54	48	28	37	10
ASTERIA II						
Week 28 UAS7 _{TD}	<u>Mean</u>	4.8*	17.5	17.3*	26.2	34.0
	<u>SD</u>	7.9	11.1	10.3	10.7	8.0
	<u>n</u>	67	55	46	35	10
GLACIAL						
Week 40 UAS7 _{TD}	<u>Mean</u>	3.2*	14.0*	21.4	23.1**	33.7
	<u>SD</u>	7.3	8.7	9.0	9.7	8.2
	<u>n</u>	65	44	38	37	10

* $P = \leq 0.001$ to next-larger adjacent effect size

** $P \leq 0.05$ to next-larger adjacent effect size.

DLQI = Dermatology Life Quality Index; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily.

Pooled Analyses

Table SI-18. Mixed-Effects Regressions Predicting Scores on Comparison Variables, by UAS7_{TD} Disease States, All Data Pooled, Multiple Imputation

<u>Measure</u>	<u>UAS7_{TD} Disease State</u>				
	<u>(% of N)</u>				
	<u>Well-</u>				
	<u>Urticaria-</u>	<u>Controlled</u>	<u>Mild</u>	<u>Moderate</u>	<u>Severe</u>
	<u>Free</u>	<u>Urticaria</u>	<u>Urticaria</u>	<u>Urticaria</u>	<u>Urticaria</u>
	<u>(UAS7_{TD} =</u>	<u>(UAS7_{TD} =</u>	<u>(UAS7_{TD} =</u>	<u>(UAS7_{TD} =</u>	<u>(UAS7_{TD} =</u>
	<u>0)</u>	<u>1-6)</u>	<u>7-15)</u>	<u>16-27)</u>	<u>28-42)</u>
	<u>(15.7%)</u>	<u>(11.1%)</u>	<u>(12.3%)</u>	<u>(25.6%)</u>	<u>(35.3%)</u>
<u>DLQI total score: mean</u>	<u>0.29</u>	<u>2.50</u>	<u>4.90</u>	<u>8.93</u>	<u>13.93 (0.21)</u>
<u>(SE)</u>	<u>(0.30)*</u>	<u>(0.34)*</u>	<u>(0.30)*</u>	<u>(0.20)*</u>	
<u>CU-Q2oL total score:</u>	<u>3.94</u>	<u>12.24</u>	<u>19.54</u>	<u>31.48</u>	<u>44.84 (0.54)</u>
<u>mean (SE)</u>	<u>(0.77)*</u>	<u>(0.89)*</u>	<u>(0.95)*</u>	<u>(0.64)*</u>	
<u>Sleep interference^a:</u>	<u>-0.25</u>	<u>1.19</u>	<u>3.46</u>	<u>7.45</u>	<u>13.00 (0.15)</u>
<u>mean (SE)</u>	<u>(0.20)*</u>	<u>(0.21)*</u>	<u>(0.21)*</u>	<u>(0.15)*</u>	
<u>Daily activity</u>	<u>-0.26</u>	<u>1.42</u>	<u>4.00</u>	<u>8.38</u>	<u>13.77 (0.14)</u>
<u>interference^a:</u>	<u>(0.20)*</u>	<u>(0.21)*</u>	<u>(0.23)*</u>	<u>(0.18)*</u>	
<u>mean (SE)</u>					
<u>Number of DPH pills in</u>	<u>0.38</u>	<u>1.75</u>	<u>2.71</u>	<u>5.22</u>	<u>8.57</u>
<u>previous 7 days^{a,b}:</u>	<u>(0.34)**</u>	<u>(0.41)</u>	<u>(0.42)*</u>	<u>(0.29)*</u>	<u>(0.26)</u>
<u>mean (SE)</u>					
<u>Number of days with</u>	<u>0.02</u>	<u>0.22</u>	<u>0.43 (0.06)*</u>	<u>0.99 (0.05)*</u>	<u>1.48 (0.05)</u>
<u>angioedema in</u>	<u>(0.06)**</u>	<u>(0.07)**</u>			
<u>previous 7 days^a</u>					
<u>mean (SE)</u>					

CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index;
DPH = diphenhydramine; SE = standard error; UAS7_{TD} = Urticaria Activity Score for the past 7 days,
assessed twice daily; UPDD = Urticaria Patient Daily Diary.

^a Based on data collected via the UPDD.

^b The case 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.

* $P \leq 0.001$ to next-worst adjacent disease state.

** $P \leq 0.05$ to next-worst adjacent disease state.

Table SI-19. One-Way ANOVAs Comparing Adjacent UAS7_{TD} Disease States on Comparison Variables at Baseline, Week 12, and End-of-Study Follow-up, Multiple Imputation

	<u>Urticaria-Free</u> <u>(UAS7_{TD} = 0)</u> <u>Mean (SE)</u>	<u>Well-Controlled</u> <u>Urticaria</u> <u>(UAS7_{TD} = 1-6)</u> <u>Mean (SE)</u>	<u>Mild</u> <u>Urticaria</u> <u>(UAS7_{TD} = 7-15)</u> <u>Mean (SE)</u>	<u>Moderate</u> <u>Urticaria</u> <u>(UAS7_{TD} = 16-27)</u> <u>Mean (SE)</u>	<u>Severe</u> <u>Urticaria</u> <u>(UAS7_{TD} = 28-42)</u> <u>Mean (SE)</u>
<u>DLQI total score</u>					
<u>Baseline</u>	=	=	=	<u>10.9 (0.4)*</u>	<u>13.2 (0.2)</u>
<u>Week 12</u>	<u>0.5 (0.3)*</u>	<u>2.2 (0.4)*</u>	<u>4.9 (0.4)*</u>	<u>7.9 (0.4)*</u>	<u>12.0 (0.4)</u>
<u>EoS week 28^a</u>	<u>0.2 (0.5)*</u>	<u>3.3 (0.8)**</u>	<u>5.3 (0.5)*</u>	<u>8.5 (0.5)*</u>	<u>13.7 (0.4)</u>
<u>EoS week 40^b</u>	<u>0.6 (0.5)*</u>	<u>3.0 (0.7)**</u>	<u>5.0 (0.7)*</u>	<u>8.8 (0.5)*</u>	<u>14.2 (0.4)</u>
<u>CU-Q2oL total score</u>					
<u>Baseline</u>	=	=	=	<u>37.9 (1.0)*</u>	<u>43.6 (0.6)</u>
<u>Week 12</u>	<u>4.0 (0.9)*</u>	<u>11.2 (1.1)*</u>	<u>19.7 (1.1)*</u>	<u>29.1 (1.3)*</u>	<u>39.8 (1.0)</u>
<u>EoS week 28^a</u>	<u>3.2 (1.6)*</u>	<u>14.3 (2.4)**</u>	<u>21.3 (1.6)*</u>	<u>30.7 (1.4)*</u>	<u>44.1 (1.2)</u>
<u>EoS week 40^b</u>	<u>4.3 (1.4)*</u>	<u>13.4 (1.8)**</u>	<u>20.2 (1.9)*</u>	<u>30.3 (1.2)*</u>	<u>45.5 (1.2)</u>
<u>Sleep interference^c</u>					
<u>Baseline</u>	=	=	=	<u>8.9 (0.3)*</u>	<u>11.9 (0.2)</u>
<u>Week 12</u>	<u>0.0 (0.2)**</u>	<u>0.9 (0.3)*</u>	<u>3.6 (0.3)*</u>	<u>6.9 (0.3)*</u>	<u>12.1 (0.3)</u>
<u>EoS week 28^a</u>	<u>-0.6 (0.4)*</u>	<u>1.5 (0.5)*</u>	<u>4.0 (0.4)*</u>	<u>7.2 (0.3)*</u>	<u>12.9 (0.3)</u>
<u>EoS week 40^b</u>	<u>-0.3 (0.4)**</u>	<u>1.5 (0.5)*</u>	<u>3.6 (0.5)*</u>	<u>7.2 (0.4)*</u>	<u>13.2 (0.3)</u>
<u>Daily activity interference^c</u>					
<u>Baseline</u>	=	=	=	<u>10.1 (0.2)*</u>	<u>12.8 (0.1)</u>

	<u>Urticaria-Free</u> (UAS7 _{TD} = 0) Mean (SE)	<u>Well-Controlled Urticaria</u> (UAS7 _{TD} = 1-6) Mean (SE)	<u>Mild Urticaria</u> (UAS7 _{TD} = 7-15) Mean (SE)	<u>Moderate Urticaria</u> (UAS7 _{TD} = 16-27) Mean (SE)	<u>Severe Urticaria</u> (UAS7 _{TD} = 28-42) Mean (SE)
<u>Week 12</u>	<u>-0.1 (0.2)*</u>	<u>1.2 (0.3)*</u>	<u>4.4 (0.3)*</u>	<u>7.7 (0.3)*</u>	<u>12.9 (0.3)</u>
<u>EoS week 28^a</u>	<u>-0.6 (0.4)*</u>	<u>1.9 (0.5)*</u>	<u>4.7 (0.3)*</u>	<u>7.9 (0.3)*</u>	<u>13.8 (0.3)</u>
<u>EoS week 40^b</u>	<u>-0.3 (0.3)**</u>	<u>1.9 (0.5)*</u>	<u>4.1 (0.4)*</u>	<u>8.2 (0.3)*</u>	<u>14.0 (0.3)</u>
<u>Number of DPH pills in previous 7 days^{c,d}</u>					
<u>Baseline</u>	<u>=</u>	<u>=</u>	<u>=</u>	<u>5.6 (0.5)*</u>	<u>7.6 (0.3)</u>
<u>Week 12</u>	<u>0.5 (0.4)</u>	<u>1.8 (0.5)</u>	<u>2.8 (0.6)**</u>	<u>5.2 (0.5)*</u>	<u>9.0 (0.6)</u>
<u>EoS week 28^a</u>	<u>0.1 (0.7)</u>	<u>1.6 (0.8)</u>	<u>3.4 (0.6)</u>	<u>4.7 (0.6)*</u>	<u>8.8 (0.5)</u>
<u>EoS week 40^b</u>	<u>0.4 (0.7)</u>	<u>1.5 (1.0)</u>	<u>2.4 (0.7)**</u>	<u>5.4 (0.6)*</u>	<u>8.4 (0.5)</u>
<u>Number of angioedema days in previous 7 days^c</u>					
<u>Baseline</u>	<u>=</u>	<u>=</u>	<u>=</u>	<u>1.4 (0.0)*</u>	<u>1.5 (0.0)</u>
<u>Week 12</u>	<u>0.0 (0.1)</u>	<u>0.3 (0.1)</u>	<u>0.5 (0.1)**</u>	<u>0.9 (0.1)*</u>	<u>1.4 (0.1)</u>
<u>EoS week 28^a</u>	<u>0.0 (0.1)</u>	<u>0.2 (0.1)</u>	<u>0.5 (0.1)</u>	<u>0.8 (0.1)*</u>	<u>1.4 (0.1)</u>
<u>EoS week 40^b</u>	<u>0.0 (0.1)</u>	<u>0.2 (0.1)</u>	<u>0.5 (0.1)**</u>	<u>0.8 (0.1)*</u>	<u>1.4 (0.1)</u>
<u>Proportion of angioedema-free days, weeks 4-12</u>					
<u>Week 12</u>	<u>98.6**</u>	<u>94.0</u>	<u>90.8</u>	<u>88.2**</u>	<u>81.8</u>

ANOVA = analysis of variance; CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire;

DLQI = Dermatology Life Quality Index; DPH = diphenhydramine; EoS = end-of-study follow-up;

SD = standard deviation; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily;

UPDD = Urticaria Patient Daily Diary.

^a ASTERIA II only.

^b ASTERIA I and GLACIAL.

^c Based on data collected via the UPDD.

^d The case 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.

^{*} $P \leq 0.001$ to next-worst adjacent disease state.

^{**} $P \leq 0.05$ to next-worst adjacent disease state.

Table SI-20. Mixed-Effects Regressions Predicting Scores on Comparison Variables, by UAS7_{TD} Disease States, All Data Pooled, Observed Data

Measure	Urticaria- Free (UAS7 _{TD} = 0) (n = 332)	Well- Controlled Urticaria (UAS7 _{TD} = 1-6) (n = 245)	Mild Urticaria (UAS7 _{TD} = 7-15) (n = 265)	Moderate Urticaria (UAS7 _{TD} = 16-27) (n = 619)	Severe Urticaria (UAS7 _{TD} = 28-42) (n = 942)
DLQI total score: mean (SE)	0.36 (0.32)*	2.47 (0.37)*	5.27 (0.37)*	9.83 (0.25)*	14.05 (0.21)
CU-Q2oL total score: mean (SE)	3.65 (0.89)*	11.69 (1.05)*	20.52 (1.08)*	34.12 (0.72)*	45.55 (0.62)
Sleep interference ^a : mean (SE)	-0.04 (0.22)*	0.99 (0.25)*	3.63 (0.26)*	7.91 (0.17)*	13.10 (0.15)
Daily activity interference ^a : mean (SE)	-0.05 (0.21)*	1.00 (0.25)*	4.34 (0.25)*	8.93 (0.17)*	13.91 (0.14)
Number of DPH pills in previous 7 days ^{a,b} : mean (SE)	0.68 (0.37)**	1.92 (0.43)**	3.55 (0.43)*	5.62 (0.30)*	8.12 (0.27)
Angioedema in previous 7 days ^a (% yes)	1.2	11.1	15.2*	34.6*	45.8

CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index;
DPH = diphenhydramine; SE = standard error; UAS7_{TD} = Urticaria Activity Score for the past 7 days,
assessed twice daily; UPDD = Urticaria Patient Daily Diary.

^a Based on data collected via the UPDD.

^b The case 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.

* $P \leq 0.001$ to next-worst adjacent disease state.

** $P \leq 0.05$ to next-worst adjacent disease state.

Table SI-21. One-Way ANOVAs Comparing Adjacent UAS7_{TD} Disease States on Comparison Variables at Baseline, Week 12, and End-of-Study Follow-up, Observed Data

	Urticaria-Free (UAS7 _{TD} = 0) Mean (SD)	Well-Controlled Urticaria (UAS7 _{TD} = 1-6) Mean (SD)	Mild Urticaria (UAS7 _{TD} = 7-15) Mean (SD)	Moderate Urticaria (UAS7 _{TD} = 16-27) Mean (SD)	Severe Urticaria (UAS7 _{TD} = 28-42) Mean (SD)
DLQI total score					
Baseline	—	—	—	10.9 (5.8)*	14.3 (6.6)
Week 12	0.4 (1.6)*	2.2 (3.0)*	4.9 (5.3)*	8.1 (5.4)*	11.7 (6.8)
EoS week 28 ^a	0.2 (0.7)	3.7 (4.0)	6.0 (4.7)	7.2 (6.2)*	11.8 (7.3)
EoS week 40 ^b	0.5 (1.3)	2.6 (3.0)	5.0 (4.6)*	9.2 (6.6)*	13.2 (8.1)
CU-Q2oL total score					
Baseline	—	—	—	38.0 (15.9)*	46.4 (17.7)
Week 12	3.6 (7.0)*	11.0 (10.2)*	19.9 (15.0)*	29.9 (16.2)*	36.7 (16.5)
EoS week 28 ^a	2.7 (4.7)	12.5 (10.1)	23.5 (15.1)	28.0 (15.9)*	40.1 (20.4)
EoS week 40 ^b	4.1 (7.6)	11.5 (9.0)*	21.2 (11.7)*	30.1 (19.1)*	41.6 (20.3)
Sleep interference^c					
Baseline	—	—	—	8.9 (3.9)*	13.3 (4.8)
Week 12	0.02 (0.3)	0.9 (1.5)*	3.6 (3.1)*	6.8 (4.6)*	12.0 (5.3)
EoS week 28 ^a	0.03 (0.2)	0.8 (1.5)*	4.1 (3.0)	6.2 (4.9)*	12.6 (5.8)
EoS week 40 ^b	0.04 (0.3)	1.0 (1.7)*	3.3 (3.1)*	6.8 (4.4)*	13.3 (5.7)
Daily activity interference^c					
Baseline	—	—	—	10.1 (3.4)*	14.0 (4.4)

	Urticaria-Free (UAS7 _{TD} = 0) Mean (SD)	Well-Controlled Urticaria (UAS7 _{TD} = 1-6) Mean (SD)	Mild Urticaria (UAS7 _{TD} = 7-15) Mean (SD)	Moderate Urticaria (UAS7 _{TD} = 16-27) Mean (SD)	Severe Urticaria (UAS7 _{TD} = 28-42) Mean (SD)
Week 12	0 (0)*	1.1 (1.7)*	4.3 (3.5)*	7.6 (4.2)*	12.6 (5.0)
EoS week 28 ^a	0 (0)	1.1 (1.9)*	5.0 (3.6)*	7.3 (4.8)*	13.7 (4.9)
EoS week 40 ^b	0 (0)	1.2 (1.6)*	3.8 (3.1)*	8.4 (4.9)*	14.0 (5.6)
Number of DPH pills in previous 7 days^{c,d}					
Baseline	—	—	—	5.6 (7.7)*	8.5 (8.6)
Week 12	0.5 (3.0)	1.8 (5.5)	2.9 (5.1)*	5.1 (7.3)*	9.0 (8.4)
EoS week 28 ^a	0.2 (1.2)	0.8 (2.9)	4.1 (4.9)	3.0 (4.8)*	9.0 (8.7)
EoS week 40 ^b	0.5 (2.2)	1.6 (4.7)	1.4 (3.2)*	6.3 (10.3)	7.9 (10.5)
Angioedema in previous 7 days^c (% yes)					
Baseline	—	—	—	42.1*	49.5
Week 12	0.9*	12.7	15.8*	31.9	39.1
EoS week 28 ^a	2.9	0	16.3	18.6	29.2
EoS week 40 ^b	1.4	12.0	12.5	23.3	36.0
Proportion of angioedema-free days, weeks 4-12					
Week 12	99.2	94.3	90.9	88.8*	81.4

ANOVA = analysis of variance; CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire;

DLQI = Dermatology Life Quality Index; DPH = diphenhydramine; EoS = end-of-study follow-up;

SD = standard deviation; UAS7_{TD} = Urticaria Activity Score for the past 7 days, assessed twice daily;

UPDD = Urticaria Patient Daily Diary.

^a ASTERIA II only.

^b ASTERIA I and GLACIAL.

^c Based on data collected via the UPDD.

^d The case 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.

* $P \leq 0.05$ to next-worse adjacent disease state.

Table SI-22. Comparison Between the Once-Daily and the Twice-Daily Assessment of Itch and Hives of the UAS7

Score	UAS Once Daily		UAS Twice Daily	
Daily itch severity and score	24-hour itch severity	Daily itch score	12-hour itch severity	Daily itch score
	None	0	None	0
	Mild	1	Mild	1
	Moderate	2	Moderate	2
	Intense	3	Severe	3
Daily hive count and score	24-hour hive count	Daily hives score	12-hour hive count	Daily hives score
	0	0	0	0
	1-20	1	1-6	1
	20-50	2	7-12	2
	> 50	3	> 12	3
Daily itch scoring method	Itch severity score over previous 24 hours; range 0-3		Average of 12-hour morning and evening itch severity scores; range 0-3	
Daily hives scoring method	Score representing hive count over previous 24 hours; range 0-3		Average of morning and evening hives score; range 0-3	
Daily UAS	Sum of daily itch score + daily hive score; range 0-6		Sum of daily itch score + daily hive score; range 0-6	
UAS7	Sum of daily UAS over 7 days; range 0-42		Sum of daily UAS over 7 days; range 0-42	

UAS = Urticaria Activity Score; UAS7 = Urticaria Activity Score, assessed twice daily, calculated over 7 days.