

LETTER TO THE EDITOR

Treatment of chronic spontaneous urticaria with benralizumab: Report of primary endpoint per-protocol analysis and exploratory endpoints

Standard treatments for chronic spontaneous urticaria (CSU) including the second-generation H1-antihistamines (SGAH) are often ineffective even with four times the FDA-recommended dose.^{1,2} Eosinophilic infiltrates and an abundance of interleukin-5 (IL5) in CSU lesions (hives) support a role for IL5 in the pathomechanism(s)

of CSU.³ Thus, the use of biologic therapies, for example, benralizumab targeting IL5-receptor- α , in treating SGAH-resistant CSU was hypothesized.

A repeated-measures, 24-week study was designed and conducted at an urticaria clinic to determine clinical efficacy of

Clinical Efficacy of Benralizumab in Chronic Spontaneous Urticaria

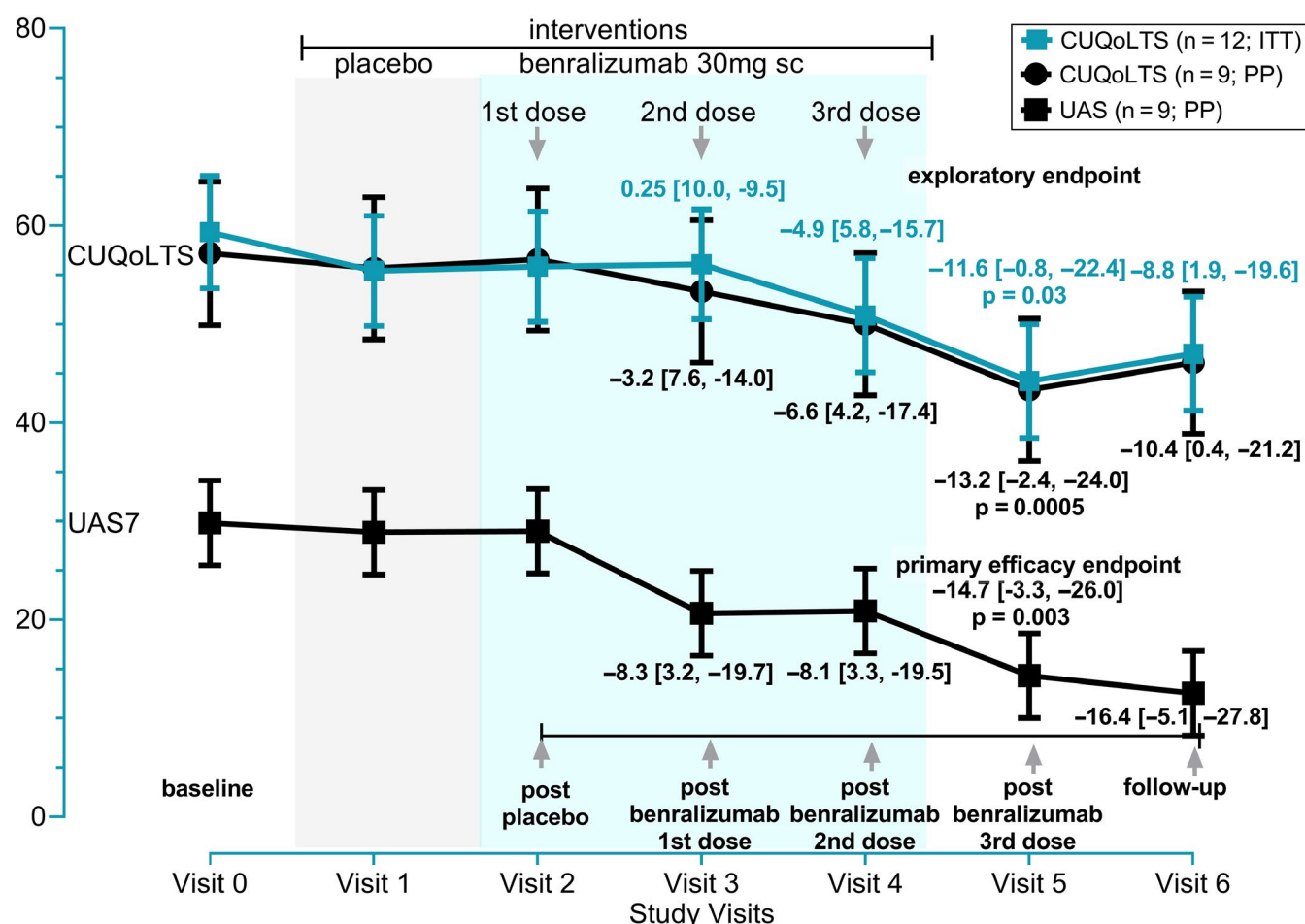


FIGURE 1 Mean UAS7 and CUQoLTS at each visit during the study. Mean difference (95% CI) from the post-placebo visit (visit 2) to the respective visits is shown

TABLE 1 Differences between benralizumab responders (either complete, ie, UAS7 = 0 at visit 5, or partial, ie, UAS7 ≤ 6 at visit 5, $n = 7$) versus non-responders ($n = 2$) using per-protocol analysis (ie, subjects completing the study, $n = 9$)

Parameter	Responder	Non-responder	p-Value
Average Symptom Duration	5.1	9.0	.06
Average Age of Subjects	51.6	53.0	.69
Average UAS7(Visit 2) ±SE	26 ± 3	37 ± 5	.12
Average UAS7(Visit 5) ±SE	7 ± 3	38 ± 4	.0003
Average ΔUAS7(Visit 5–Visit 2)	–84%	+7.5%	.0009

Parameter	Comparison Group-Visit	Absolute Value ±SE	Mean difference ±SE	Adj. p
UAS7 ^a	(Responder-Visit 1) vs. (Non-responder-Visit 1)	26 ± 3 vs. 37 ± 5	–11 ± 7	.7
	(Responder-Visit 5) vs. (Non-responder-Visit 5)	7 ± 3 vs. 38 ± 4	–31 ± 7	.003
Blood Neutrophil %	(Responder-Visit 1) vs. (Non-responder-Visit 1)	57 ± 3 vs. 49 ± 6	8 ± 7	.7
	(Responder-Visit 5) vs. (Non-responder-Visit 5)	59 ± 3 vs. 62 ± 5	–3.0 ± 5	.9
Blood Eosinophil %	(Responder-Visit 1) vs. (Non-responder-Visit 1)	2 ± 0 vs. 8 ± 1	–6 ± 1	.001
	(Responder-Visit 5) vs. (Non-responder-Visit 5)	0 ± 0 vs. 0 ± 1	0 ± 1	1.00
	(Non-responder-Visit 1) vs. (Non-responder-Visit 5)	8 ± 1 vs. 0 ± 1	8 ± 1	.006
	(Responder-Visit 1) vs. (Responder-Visit 5)	2 ± 0 vs. 0 ± 0	2 ± 0	.02
Blood Lymphocyte %	(Responder-Visit 1) vs. (Non-responder-Visit 1)	31 ± 3 vs. 34 ± 6	–3 ± 7	.98
	(Responder-Visit 5) vs. (Non-responder-Visit 5)	33 ± 3 vs. 29 ± 5	3 ± 6	.95
	(Non-responder-Visit 1) vs. (Non-responder-Visit 5)	34 ± 6 vs. 29 ± 5	5 ± 6	.88
	(Responder-Visit 1) vs. (Responder-Visit 5)	31 ± 3 vs. 33 ± 3	–2 ± 3	.94
Blood Basophil %	(Responder-Visit 1) vs. (Non-responder-Visit 1)	0.3 ± 0.1 vs. 1.5 ± 0.2	–1.2 ± 0.2	.02
	(Responder-Visit 5) vs. (Non-responder-Visit 5)	0.4 ± 0.1 vs. 0.2 ± 0.1	0.2 ± 0.2	.88
	(Non-responder-Visit 1) vs. (Non-responder-Visit 5)	1.5 ± 0.2 vs. 0.2 ± 0.1	1.3 ± 0.2	.05
	(Responder-Visit 1) vs. (Responder-Visit 5)	0.3 ± 0.1 vs. 0.4 ± 0.1	–0.1 ± 0.1	.93

^aDetermined by regression analysis adjusted for symptom duration, subject age, and eos% at baseline.

benralizumab in CSU. Twelve SGAH-unresponsive CSU patients (3 males, 9 females; 2 blacks, 10 whites; between ages 32–65 years) having a median daily Urticaria Activity Score (UAS7)⁴ of 4 and pruritus severity ≥2 were enrolled. After a baseline run-in period, subjects were treated with a subcutaneous placebo dose followed by benralizumab 30 mg subcutaneously every month (×3 doses) followed by two off-medication monthly visits. Subject-reported responses to UAS7 and CU-QoL questionnaires were recorded at the monthly visits. The primary and exploratory endpoints were the change in UAS7 and Chronic Urticaria Quality-of-Life Total

Score (CUQoLTS) respectively, from 4 weeks after placebo dose (visit 2) to 4 weeks after last dose of benralizumab (visit 5). Nine subjects completed the study; three withdrew after the first benralizumab dose. An intent-to-treat (ITT) analysis ($n = 12$) of the primary endpoint has been reported previously.⁵ Per-protocol (PP) analysis ($n = 9$) of the primary endpoint, and PP vs. ITT of the exploratory endpoint are reported here. Because of the chronicity of disease that was unresponsive to conventional treatments during enrollment of subjects based on the inclusion criteria, it was presumed that lesions were not self-limiting, and any improvement

in outcomes during the study was because of intervention. Non-responders to benralizumab were identified if at the primary efficacy endpoint or at follow-up visit there was <40% improvement in UAS7 from baseline.

The average duration of urticarial symptoms was 7.0 years. Baseline UAS7 and CUQoLTS ranged between 22–42 and 36–95, respectively. Both UAS7 components (pruritus severity and wheal size in parallel) and CUQoLTS outcomes significantly improved at visit 5 vs. visit 2 in 7 of 9 (78%) subjects completing the study. The average difference (95% CL) between visit 2 and visit 5 for UAS7 was –15.5 (–4.1, –26.8, $p = .003$) and for CUQoLTS, using ITT analysis, was –13.2 (–2.4, –24.0, $p = .0005$) or, using PP analysis, was –11.6 (–0.8, –22.4, $p = .03$) (Figure 1). Five responders reported no hives/pruritus (UAS7 = 0) at visit 5 or 6.

Between responders and non-responders, the average age (51.6 vs. 53, $p = .9$) and symptom duration (5 vs. 9 years, $p = .5$) did not differ significantly. However, the adjusted mean UAS7 percentage difference, adjusted for symptom duration, age, and blood eosinophils (eos%), from visit 2 till visit 5 was –84% for responders and +7.5% for non-responders, $p = .0009$ (Table 1). The average baseline UAS7 was not statistically significant (27 vs. 37.5, $p = .5$) between responders vs. non-responders; however, the baseline mean difference for eos% was -6 ± 1 ($p = .001$), which were not observed at visit 5 (eos%: 0 ± 1 , $p = .9$) (Table 1). Thus, clinical improvement among responders was independent of baseline disease severity. Non-responsiveness to benralizumab, measured by changes in UAS7, is likely due to other mechanistic factors unrelated to eos% which are eliminated by blocking IL-5R with benralizumab (Figure S1). The observed reduction in eos% and basophil% is a well-known effect of the drug with unknown relationship with the drug's clinical effect. Additionally, benralizumab-induced basopenia may have been related to the poor response among the non-responders. The non-responders had a significant reduction in basophil% at visit 5 vs. baseline (-1.3% , $p = .05$) (Table 1).

UAS7 and CUQoLTS values were significantly correlated ($r^2 = 0.9$, $p < .0001$) (Table S3). CU-QoL components that improved significantly were the pruritus/wheal scores, urticarial interference with physical activities, sleep, and spare time (Table S4).

This study supports the use of benralizumab for treatment of SGAAH-unresponsive CSU. Benralizumab-related improvements in UAS7 and CUQoLTS reported here are similar to the efficacy of omalizumab in CSU reported in a previous study (Table S5).⁶ Of note, benralizumab-induced basopenia may lead to non-response and poor prognosis as previously reported for omalizumab which requires further investigation.⁷ The sustained significant improvement in urticarial lesions based on subject-reported outcomes by benralizumab warrants further investigation of underlying biologic pathways to better elucidate the role of IL-5 in CSU.

KEYWORDS

basophil, biologics, chronic spontaneous urticaria, eosinophils, IL-5

FUNDING INFORMATION

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CONFLICT OF INTEREST

Dr. Bernstein reports grants and personal fees from AstraZeneca, during the conduct of the study, grants and personal fees from Shire/Takeda, grants and personal fees from CSL Behring, grants and personal fees from Pharming, grants and personal fees from Biocryst, grants and personal fees from Kalvista, grants and personal fees from Ionis, grants and personal fees from Novartis, grants and personal fees from Genentech, grants and personal fees from Sanofi-Regeneron, grants and personal fees from Allakos, outside the submitted work, and reports being a member of the Joint Task Force for the AAAAI and ACAAI, a member of the CU UCARE guideline committee and a UCARE center of excellence, and a member of the MAB of the HAEA organization. All other authors have nothing to disclose.

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REFERENCES

- Amin P, Levin L, Holmes SJ, Picard J, Bernstein JA. Investigation of patient-specific characteristics associated with treatment outcomes for chronic urticaria. *J Allergy Clin Immunol In Pract.* 2015;3(3):400-407.
- Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy.* 2018;73(7):1393-1414.
- Caproni M, Giomi B, Volpi W, et al. Chronic idiopathic urticaria: infiltrating cells and related cytokines in autologous serum-induced wheals. *Clin Immunol.* 2005;114(3):284-292.
- Hawro T, Ohanian T, Schoepke N, et al. The Urticaria Activity Score—Validity, Reliability, and Responsiveness. *J Allergy Clin Immunol In Pract.* 2018;6(4):1185-1190.
- Bernstein JA, Singh U, Rao MB, Berendts K, Zhang X, Mutasim D. Benralizumab for Chronic Spontaneous Urticaria. *N Engl J Med.* 2020;383(14):1389-1391.
- Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol.* 2008;122(3):569-573.

7. Kolkhir P, Church MK, Altrichter S, et al. Eosinopenia, in Chronic Spontaneous Urticaria, Is Associated with High Disease Activity, Autoimmunity, and Poor Response to Treatment. *J Allergy Clin Immunol Pract*. 2020;8(1):318-325.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplemental Appendix

Supplementary Text, Tables and Figures

OBJECTIVES OF THE STUDY

Primary Objective	Outcome Measure
<i>To determine the clinical efficacy of Benralizumab when compared to placebo in patients with chronic spontaneous urticaria (CSU) refractory to treatment with H1-antihistamines.</i>	<i>Urticarial Activity Score averaged over 7 days (UAS7)</i>
Exploratory Objective:	Outcome Measure:
<i>To demonstrate an improvement in health-related quality of life in the study subjects in subjects treated with Benralizumab when compared to placebo.</i>	<i>Health Status as determined by Chronic Urticaria Quality of Life Questionnaire (CU-QoL)</i>

METHODS

Study Design and Outcomes

The study was a single-blinded, one-group, repeated-measures, without cross-over design conducted at a single center. After signing an informed consent, each subject meeting inclusion and exclusion criteria (**S-Table-1**) were initially treated with a single subcutaneous matching drug placebo dose at study visit 1 followed by treatment with benralizumab 30 mg subcutaneously over three successive 4-week interval visits (visits 2, 3, and 4). During each visit, subjects were asked to provide a record of their weekly disease activity score (UAS7) for each of the previous 4 weeks and were assessed for their overall disease specific quality of life using the CU-QoL questionnaire^{1,2} as an exploratory end-point. Study coordinators ensured that the participants did not receive any other anti-urticarial medication during the study period (**S-Table-1**). Medication history for the use of H1-antihistamines and other urticarial treatments including biologics were obtained from subjects at their baseline visit. Patients were permitted to continue their H1-antihistamine dose during the study and use rescue diphenhydramine up to 50mg four times a day as needed.

The CU-QoL questionnaire is a 23-item validated instrument each scored on a 5-point Likert scale by the subject to evaluate subjective response factors affecting quality of life related to CSU.³ High impact items on the questionnaire are pruritus, wheals, and impact on life activities. The CU-QoL total score is measured as the sum-total of points for all 23 items (**S-Table-2**). The primary endpoint was the percentage of CSU patients, unresponsive to 4-times FDA-approved doses of second generation H1-antihistamines, responding significantly and clinically meaningful to benralizumab versus a matching placebo control as measured by the Urticaria Activity Score 7 (UAS7).

STATISTICAL ANALYSIS

Clinical Efficacy Analysis: While analyzing the study results for comparison of UAS7 and CU-QoL total score between visits, it was assumed that hives were not self-limiting and thus any improvement in outcome measures during the study were due to the effect of interventions. A repeated measure mixed model regression analysis using the ‘glimmix’ procedure (SAS 9.4) was used to fit a generalized linear mixed model for comparison of UAS7 and CU-QoL total score between visits and between responder phenotypes (**Figure 1**). The variances of these outcome measures between individuals at each visit and within individuals across all visits were considered for determination of post-treatment statistically significant improvements in CSU symptoms. The statistical method assumes that the outcomes can have a non-normal distribution.⁴ It can incorporate random effects in the model which allows for subject-specific (conditional) and population-averaged (marginal) inference. It was assumed that the CSU subjects in this study can have varying degrees of disease severity as

assessed by the range of UAS7 at their baseline visit and therefore, the response to benralizumab may also depend on their baseline hive severity. A random intercept model was used to address this assumption. The statistical significance of difference in scores between post-placebo and each of the post-benralizumab visits, as well as between baseline and post-benralizumab visits were used to quantify the internal validity of the study design.

Determination Of Clinically Significant Difference in UAS7 Using Minimal Detectable Change of UAS7

A score greater than the minimal detectable change (MDC), considered to replicate a real clinical change, as measured by the Bland and Altman method was calculated for UAS7 as $1.96 \times \text{standard deviation (SD)}$ for the difference in the UAS7 at the pre- and post-benralizumab visits.

Comparison Between Responders And Non-Responders To Benralizumab.

In such analyses, the baseline UAS7 was used as a random effect in order to adjust the analysis for baseline heterogeneity in disease severity and thus obtain a more precise estimate of the effect of intervention ⁵.

ADDITIONAL RESULTS

Determination of Minimal Detectable Change of UAS7

The MDC for UAS7 was calculated as 1.96×7.51 (standard deviation (SD) for the difference in the UAS7 at the first and last visits for responders) = 14.7. The MDC for UAS7 determined in this study agrees with that from a previous urticaria study ⁶ which determined its significant correlation with the Physician Global Assessment of disease activity.

ADDITIONAL CONCLUSION

The improvement on disease severity was sustained for 8 weeks after the last dose of benralizumab as indicated by the significant differences in UAS7 at the final follow-up visit (Visit 6) compared to UAS7 at the post-placebo visit (Visit 2) (i.e., UAS7 difference: -15.2, $p=0.006$). Both components of UAS7 (pruritus severity and wheal size) improved in parallel. A decrease in UAS7 >14 , between baseline and post-Benralizumab visits, indicated that treatment with benralizumab was not only statistically significant but also clinically meaningful.

REFERENCES FOR SUPPORTING INFORMATION

1. Maurer M, Raap U, Staubach P, et al. Antihistamine-resistant chronic spontaneous urticaria: 1-year data from the AWARE study. *Clin Exp Allergy*. 2019;49(5):655-662.
2. Choi WS, Lim ES, Ban GY, et al. Disease-specific impairment of the quality of life in adult patients with chronic spontaneous urticaria. *Korean J Intern Med*. 2018;33(1):185-192.
3. Baiardini I, Pasquali M, Braidò F, et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). *Allergy*. 2005;60(8):1073-1078.
4. Tuerlinckx F, Rijmen F, Verbeke G, De Boeck P. Statistical inference in generalized linear mixed models: a review. *Br J Math Stat Psychol*. 2006;59(Pt 2):225-255.
5. Gebregziabher M, Egede L, Gilbert GE, Hunt K, Nietert PJ, Mauldin P. Fitting parametric random effects models in very large data sets with application to VHA national data. *BMC Med Res Methodol*. 2012;12:163.
6. Hawro T, Ohanyan T, Schoepke N, et al. The Urticaria Activity Score-Validity, Reliability, and Responsiveness. *The journal of allergy and clinical immunology In practice*. 2018;6(4):1185-1190 e1181.

SUPPLEMENTARY TABLES

S-TABLE-1. Inclusion and Exclusion Criteria for Subject Participation in the Study

Inclusion Criteria	Exclusion Criteria
• Age ≥ 18 - ≤ 75 yrs. • Urticarial lesions for > 6 weeks of unknown cause • Hives present most days of the week despite 4$\times$ the FDA approved H1-antihistamines • Daily pruritus severity ≥ 2 (out of 3) at baseline or after placebo-treatment. • Daily Urticaria Activity Score (UAS), the combined score of number of hives and pruritus severity ≥ 4, i.e., (# of hives + size of largest hive) ≥ 4 • Compliance $> 70\%$ with completion of daily diaries for recording disease activity (UAS7) and overall quality of life related to CSU (CU-QoL questionnaire).	• Inducible (physical) urticarias • Urticarial vasculitis • Secondary urticaria (underlying allergy to food/drugs or autoimmune disease, infection, malignancy, thyroid disease) • Medications other than H1-antihistamines at time of enrollment • History of oral or topical corticosteroids, methotrexate, cyclosporine, other biologics (i.e., omalizumab) and anti-inflammatory agents (hydroxychloroquine, sulfasalazine, dapsone or colchicine) within 4 weeks of enrollment

S-TABLE-2. Chronic Urticaria Quality of Life (CU-QoL) Questionnaire: Item List

Questionnaire Items
Pruritus Severity
Wheals Severity
Eye Swelling Severity
Lip Swelling Severity
Urticaria interferes with work
Urticaria interferes with physical activities
Urticaria interferes with sleep
Urticaria interferes with spare time
Urticaria interferes with social relationships
Urticaria interferes with eating behavior
Have difficulties in falling asleep?
Wake up during the night because of urticaria?
Feel tired during the day because of bad night sleep?
Have difficulties in keeping concentration?
Feel in a bad mood?
Any limitations in choosing your food?
Does urticaria limit sport activities?
Troubled by drugs' side effects?
Embarrassed due to urticaria symptoms?
Embarrassed in going to public places?
Have any problems in using cosmetics?
Have any limits in choosing clothes material?
Do you feel nervous
Response options: Not at all (0); A little (1); Somewhat (2); A lot (3); Very much (4)

S-TABLE-3. Chronic Urticaria Quality of Life (CU-QoL) Questionnaire: Item List

Correlation Matrix Between Clinical Outcomes				
	[ρ , (p-value)]			
	UAS7		CU-QOL TS	
eos%	0.48	(0.06)	0.46	(0.07)
CU-QOL TS	0.90			
	(<0.0001)			

ρ = correlation

Note: Results shown here are from for subjects who completed the study (n=9).

S-TABLE-4. CU-QoL components that were significantly improved post-benralizumab vs. baseline in antihistamine refractory CSU subjects

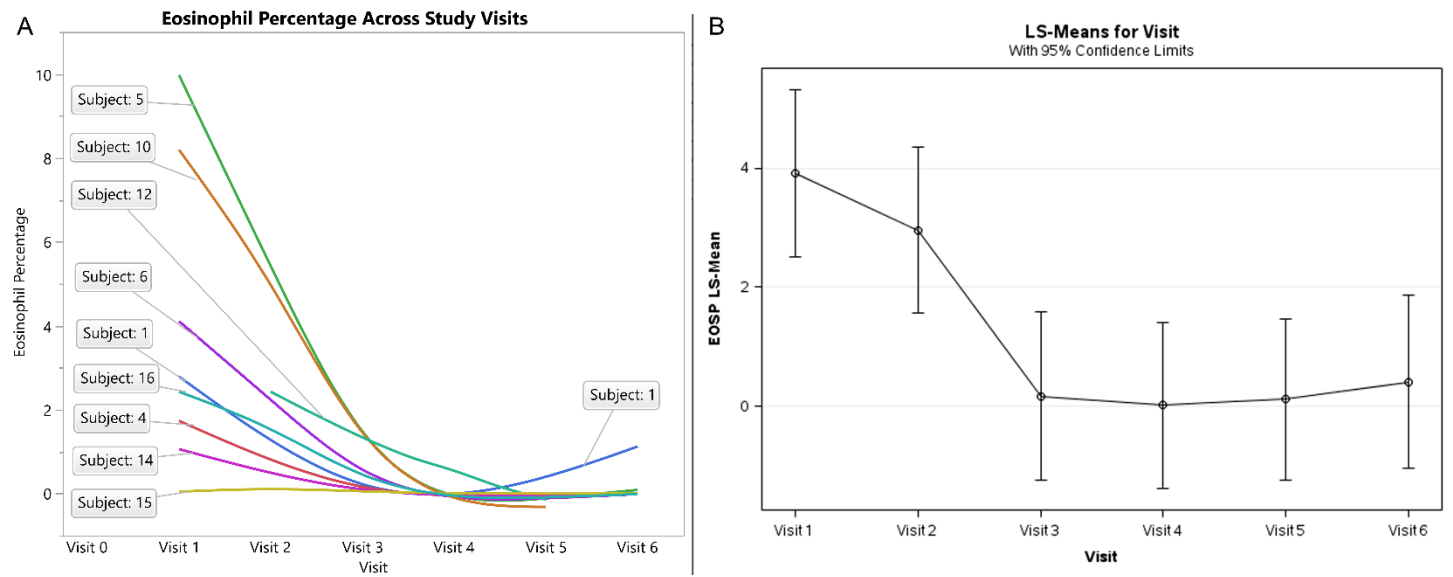
CU-QoL Component	Visit 0-Visit 5 Mean Difference (CL)	Adj. P-Value
Pruritus	2.0 (0.99, 3.0)	<0.0001
Wheal	2.1 (1.2, 3.1)	<0.0001
Interference with work	0.7 (-0.1, 1.4)	0.1
Interference with physical activities	0.9 (0.1, 1.8)	0.03
Interference with sleep	1.5 (0.4, 2.7)	0.0001
Interference with spare time	1.2 (0.2, 2.1)	0.0003
Interference with eating behavior	1.1 (-0.04, 2.1)	0.06

S-TABLE-5. Comparison of Current Pilot Study with the Omalizumab Pilot Study

Comparison	Studies	
	Bernstein Study	Kaplan Study*
# of subjects	12	12
Assessment tool	UAS7 (Scale 0-42)	UAS (Scale 0-9)
Treatment vs. placebo	Benralizumab	Omalizumab
Duration of Treatment	3 doses, 4 weeks apart	4 doses, 4 weeks apart
Mean change in score after treatment from baseline at the end of the study	-54%	-64.5%
Statistically Significant Effect after 1 st dose	Yes; p=0.008 for unadjusted comparisons; p=0.09 for multiple comparisons after adjustment)	Yes (unknown if difference was adjusted for multiple comparisons)
# of patients with $\geq 50\%$ reduction in mean score from baseline	7 of 9 subjects completing the study**; 100% resolution (i.e., UAS7 = 0) in 5 subjects. Three patients (25%) withdrew or were withdrawn after the first dose of benralizumab (visit 3): one withdrew for personal reasons, one withdrew who didn't respond after the first dose, and one was withdrawn due to loss of follow-up. Among them, 2 had an improvement in the UAS7 and one had no UAS7 improvement, however this later patient also previously had no response to omalizumab). The remaining 9 of 12 patients (75%) completed the study.	8 of 12 subjects
# of non-responders	2 (one with 0% and another with -15% change from baseline)	1
Quality of life improvement using CU-QoL (Bernstein) or Dermatology Life Quality Index (Kaplan)	Significant improvement from baseline in interference with sleep, interference with daily activities, and overall therapeutic response was observed and paralleled the reduction in mean UAS.	

*Kaplan, A.P., et al., *Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol*, 2008. 122(3): p. 569-73.

SUPPLEMENTARY FIGURES



S-Figure-1. Mean values of peripheral blood eosinophil percentage between study visits. (Visit 1- baseline pre-placebo; visit 2 – post-placebo/pre-benralizumab; Visits 3 and 4 - post-Benralizumab treatments; Visit 5 – four weeks post-benralizumab; Visit 6 - eight weeks post-benralizumab)