

## Letter to the Editor

**A randomized trial of quilizumab in adults with refractory chronic spontaneous urticaria***To the Editor:*

Chronic spontaneous urticaria (CSU) presents as recurrent itchy wheals, angioedema, or both for at least 6 weeks without a specific trigger.<sup>1</sup> Roughly half of the patients with CSU achieve symptomatic control with H<sub>1</sub>-antihistamine therapy at approved doses, increased doses, or with additional therapies such as leukotriene receptor antagonists.<sup>1</sup> CSU can be unpredictable and debilitating for patients because of a lack of clinical response.<sup>2</sup> Recently, omalizumab, a neutralizing anti-IgE mAb, has gained approval for treatment of patients with CSU on the basis of evidence of substantial efficacy.<sup>3</sup> However, the treatment benefit with omalizumab is usually lost when treatment is stopped.

CSU may have infectious or autoimmune origins. Approximately 30% to 40% of patients with CSU have an autoimmune component, indicated by a positive autologous serum skin test or basophil histamine release.<sup>4</sup> Omalizumab's efficacy implicates IgE, although its role is currently unclear. Specific IgE may target an endogenous antigen, a hypothesis supported by evidence that approximately 50% of patients with CSU have elevated levels of antithyroperoxidase IgE.<sup>5</sup>

Quilizumab, a humanized, afucosylated, monoclonal IgG<sub>1</sub> antibody, binds membrane IgE at the M1-prime segment, which is absent in soluble IgE.<sup>6</sup> In animal studies, quilizumab bound membrane IgE on IgE-switched B cells and plasmablasts and depleted them through apoptosis and antibody-dependent cell-mediated cytotoxicity.<sup>6</sup> In clinical trials, quilizumab reduced serum total and specific IgE levels in healthy volunteers and in patients with allergic rhinitis or mild asthma.<sup>7,8</sup> These reductions were sustained for at least 6 months after the last dose, suggesting that quilizumab affected long-term IgE memory. Quilizumab also prevented allergen-induced increases in serum total and specific IgE levels in a lung allergen-challenge study in patients with asthma.<sup>8</sup> Given the hypothesized role of IgE in CSU and the potential for a sustained effect compared with omalizumab, we evaluated the efficacy and safety of quilizumab in patients with CSU.

The QUAIL study (NCT01987947, [ClinicalTrials.gov](http://ClinicalTrials.gov)) was a randomized, double-blinded, placebo-controlled trial of quilizumab for treatment of refractory CSU, conducted at 3 centers in Canada and Germany. Thirty-two patients with CSU, who remained symptomatic despite treatment with H<sub>1</sub> antihistamines (at up to 4 times the approved doses), with or without leukotriene receptor antagonists, were randomly allocated 1:1 to 450 mg quilizumab or placebo: 15 patients to quilizumab and 17 patients to placebo (see Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Screening occurred from days -7 to -14, followed by 20 weeks of treatment and 8 weeks of follow-up. Patients received subcutaneous injections at week 0 (day 1) and week 4 (day 29). Primary and secondary outcomes were measured through a daily diary in which patients recorded itch-severity scores (ISS), urticaria activity scores, and hive scores. We also assessed quilizumab's effect on serum IgE levels and evaluated its safety, pharmacokinetic profile, and

**TABLE I.** Efficacy outcomes (intention-to-treat population)

| Primary outcome                                       | Placebo<br>(n = 17) | Quilizumab<br>450 mg<br>(n = 15) |
|-------------------------------------------------------|---------------------|----------------------------------|
| <b>Weekly ISS* (at week 20)</b>                       |                     |                                  |
| Mean ± SD                                             | -3.8 ± 6.2          | -6.7 ± 7.3                       |
| Median                                                | -2.2                | -5.3                             |
| Range                                                 | -19.0 to 2.7        | -19.8 to 8.0                     |
| 90% CI of the mean                                    | -6.4 to -1.2        | -10.1 to -3.4                    |
| Treatment difference in LSMs†<br>(vs placebo)         |                     | <b>-3.3</b>                      |
| 90% CI of the LSMs difference                         |                     | -7.2 to 0.7                      |
| <b>Secondary outcomes</b>                             |                     |                                  |
| <b>Placebo</b>                                        |                     |                                  |
| <b>Quilizumab<br/>450 mg</b>                          |                     |                                  |
| <b>Weekly ISS* (at week 4)</b>                        |                     |                                  |
| Mean ± SD                                             | -5.3 ± 5.8          | -6.4 ± 6.6                       |
| Range                                                 | -20.0 to 1.2        | -19.8 to 2.8                     |
| 90% CI of the mean                                    | -7.7 to -2.8        | -9.3 to -3.4                     |
| Treatment difference in LSMs†<br>(vs placebo)         |                     | <b>-1.5</b>                      |
| 90% CI of the LSMs difference                         |                     | -4.9 to 2.0                      |
| <b>UAS7* (at week 20)</b>                             |                     |                                  |
| Mean ± SD                                             | -7.4 ± 13.4         | -12.9 ± 14.8                     |
| Median                                                | -2.0                | -11.0                            |
| Range                                                 | -38.0 to 9.3        | -37.0 to 16.0                    |
| 90% CI of the mean                                    | -13.1 to -1.8       | -19.6 to -6.2                    |
| Treatment difference in LSMs†<br>(vs placebo)         |                     | <b>-5.8</b>                      |
| 90% CI of the LSMs difference                         |                     | -14.1 to 2.5                     |
| <b>Additional outcome</b>                             |                     |                                  |
| <b>Placebo</b>                                        |                     |                                  |
| <b>Quilizumab<br/>450 mg</b>                          |                     |                                  |
| <b>Weekly number of hives score*<br/>(at week 20)</b> |                     |                                  |
| Mean ± SD                                             | -3.6 ± 7.6          | -6.0 ± 7.8                       |
| Median                                                | 0.0                 | -3.5                             |
| Range                                                 | -19.0 to 8.2        | -19.0 to 8.0                     |
| 90% CI of the mean                                    | -6.8 to -0.4        | -9.6 to -2.5                     |
| Treatment difference in LSMs†<br>(vs placebo)         |                     | <b>-2.5</b>                      |
| 90% CI of the LSMs difference                         |                     | -6.9 to 2.0                      |

Boldface values indicate the point change from baseline relative to placebo for each of the scores listed.

LSM, Least-squares mean.

\*Missing week 4 and week 20 weekly scores were imputed by the worst weekly score up to weeks 4 and 20, respectively.

†LSM was estimated using an analysis of covariance model controlling for baseline ISS, baseline number of hives, and baseline UAS7, respectively, and country.

immunogenicity. For details on study flow (Fig E1), patients' demographic characteristics and disposition (see Table E1 and Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)), and all assessments, see this article's **Methods** and **Results** sections in the Online Repository at [www.jacionline.org](http://www.jacionline.org).

The primary efficacy outcome was the absolute change from baseline to week 20 in the weekly ISS. In patients treated with quilizumab, we observed a decrease from baseline of -3.3 points (90% CI, -7.2 to 0.7; *P* = .17) relative to the placebo group (Table I; see Fig E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)) at week 20. At week 4, there was a decrease

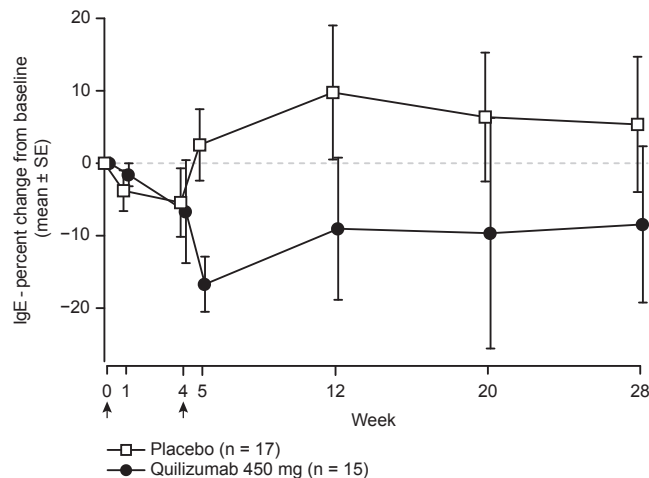


**FIG 1.** Effect of quilizumab on serum total IgE level from baseline to week 28. One patient from the quilizumab group had baseline and week 28 IgE values of 88 and 1991 IU/mL, respectively (a 2163% change from baseline). Because of the large effect on the mean and SE, we removed this value. Arrows indicate quilizumab doses at weeks 0 and 4. SE, Standard error.

from baseline of  $-1.5$  points (90% CI,  $-4.9$  to  $2.0$ ;  $P = .47$ ) relative to the placebo group (Table I; Fig E2). Neither of these decreases fell within the minimally important difference (MID) range of 4.5 to 5.

The observed decrease from baseline in the urticaria activity score over 7 days (UAS7) at week 20 for the quilizumab group was  $-5.8$  points (90% CI,  $-14.1$  to  $2.5$ ;  $P = .24$ ) relative to placebo (Table I; see Fig E3, A, in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)), a difference that fell short of the MID range of 9.5 to 10.5. No statistically or clinically meaningful difference in the hives score between quilizumab and placebo was observed at week 20 ( $-2.5$ -point change from baseline; 90% CI,  $-6.9$  to  $2.0$ ;  $P = .35$ ; MID range, 5.0-5.5; Table I; Fig E3, B). Sensitivity analysis to adjust for imbalances in patient disease characteristics had a negligible impact on efficacy outcomes (see Table E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). When patients were stratified by UAS7 (see Figs E4 and E5 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)) or baseline IgE levels (see Fig E6 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)), we did not observe a consistent treatment effect for quilizumab in either the weekly ISS (Fig E4) or the UAS7 (Figs E5 and E6) because of the large variance and the small sample sizes in the subgroups.

Quilizumab treatment reduced mean serum total IgE level approximately 17% from baseline by week 5, when it reached its lowest level (Fig 1). Median serum total IgE level decreased by approximately 30% from baseline at week 20, when it reached its lowest median level. By week 28, the mean and median levels of IgE had not yet returned to baseline. Quilizumab pharmacokinetics were consistent with that observed in previous studies,<sup>8</sup> and no antitherapeutic antibodies or new safety issues were observed (see this article's Results section; also see Table E3 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

Although the pathogenesis of CSU is not fully understood, IgE is clearly a key player in the disease given that omalizumab treatment reduced the levels of soluble serum IgE effectively in patients with asthma (89% to 98%)<sup>9</sup> and

significantly improved the weekly ISS in patients with CSU.<sup>3</sup> Because our previous studies indicated that quilizumab targets IgE switching and blocks newly produced, specific IgE, our objective was to evaluate quilizumab as a therapy for CSU. Although quilizumab reduced median serum IgE level approximately 30% in patients with CSU, it did not cause clinically meaningful improvements in the weekly ISS or the UAS7. We therefore hypothesize that the remaining serum IgE that mediates CSU pathology is produced by long-lived IgE plasma cells that are not targeted by quilizumab because of their lack of membrane IgE.

We acknowledge that this was a small, signal-seeking study, and perhaps there were biases in the study sample of patients that affected the outcomes. Patients enrolled into this study may have been more resistant to quilizumab or anti-IgE mechanisms. Furthermore, it is possible that higher doses or a longer treatment duration with quilizumab may have resulted in a treatment effect. Although the data from omalizumab trials strongly support a role for soluble IgE in CSU pathogenesis, our data indicate that ongoing IgE switching and stimulation of B-cell memory may not be key disease drivers, and additional studies will be required to fully understand the etiology of this disease.

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Jeffrey M. Harris, MD, PhD<sup>a</sup>  
Christopher R. Cabanski, PhD<sup>a</sup>  
Heleen Scheerens, PhD<sup>a</sup>  
Divya Samineni, PhD<sup>a</sup>  
Mary S. Bradley, MS<sup>a</sup>  
Colette Cochran, BSN<sup>a</sup>  
Petra Staubach, MD<sup>b</sup>  
Martin Metz, MD<sup>c</sup>  
Gordon Sussman, MD, FRCPC<sup>d</sup>  
Marcus Maurer, MD<sup>c</sup>

From <sup>a</sup>Genentech, Inc, South San Francisco, Calif; <sup>b</sup>the Department of Dermatology, University Medical Center Mainz, Mainz, Germany; <sup>c</sup>the Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité-Universitätsmedizin Berlin, Berlin, Germany; and <sup>d</sup>the Division of Clinical Immunology and Allergy, Department of Medicine, University of Toronto, Toronto, Ontario, Canada. E-mail: [harris.jeffrey@gene.com](mailto:harris.jeffrey@gene.com).

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**A randomized trial of quilizumab in adults with refractory chronic spontaneous urticaria**

Jeffrey M. Harris, MD, PhD,<sup>a\*</sup> Christopher R. Cabanski, PhD,<sup>a</sup> Heleen Scheerens, PhD,<sup>a</sup> Divya Samineni, PhD,<sup>a</sup> Mary S. Bradley, MS,<sup>a</sup> Colette Cochran, BSN,<sup>a</sup> Petra Staubach, MD,<sup>b</sup> Martin Metz, MD,<sup>c</sup> Gordon Sussman, MD, FRCPC,<sup>d</sup> and Marcus Maurer, MD<sup>c</sup>

<sup>a</sup>Genentech, Inc., South San Francisco, CA USA

<sup>b</sup>Department of Dermatology, University Medical Center Mainz, Mainz, Germany

<sup>c</sup>Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité-Universitätsmedizin Berlin, Berlin, Germany

<sup>d</sup>Division of Clinical Immunology and Allergy, Department of Medicine, University of Toronto, Toronto, Canada

**\*Corresponding author:**

Jeffrey M. Harris

Genentech, Inc.

1 DNA Way

South San Francisco, CA 94080-4990 USA

Email: [harris.jeffrey@gene.com](mailto:harris.jeffrey@gene.com)

Tel: 650-467-7154

Fax : 866-858-7006

Email: [harris.jeffrey@gene.com](mailto:harris.jeffrey@gene.com)

**27 Abbreviations:**

28 AE: adverse event; ANCOVA: analysis of covariance; ATA: anti-therapeutic antibody; BMI: body  
29 mass index; CI: confidence interval;  $C_{max}$ : maximum observed serum concentration;  $C_{min}$ :  
30 minimum observed serum concentration; CSU: chronic spontaneous urticaria; ELISA: enzyme-  
31 linked immunosorbent assay; Ig: immunoglobulin; ISS: itch-severity score; ITT: intention-to-  
32 treat; LSM: least-squares mean; LTRA: leukotriene receptor antagonist; MID: minimally  
33 important difference;  $T_{max}$ , time of maximum observed serum concentration;  $t_{1/2}$ : terminal  
34 elimination half-life; TPO, thyroperoxidase; UAS: urticaria activity score: UAS7: urticaria activity  
35 score over 7 days; WOCF: worst observation carried forward.

## **METHODS**

### **Trial design**

The QUAIL study (NCT01987947, ClinicalTrials.gov) was a randomized, double-blinded, placebo-controlled trial of quilizumab in the treatment of refractory CSU, conducted at three centers in Canada and Germany. Thirty-two CSU patients, who remained symptomatic despite treatment with H<sub>1</sub>-antihistamines (at up to four times the approved doses), with or without LTRAs, were randomly allocated to 450 mg quilizumab or placebo at a 1:1 ratio by an interactive web response system. The study consisted of a screening period (Days -7 to -14), a 20-week treatment period, and an 8-week follow-up period.

### **Ethics and consent**

The study was conducted under the approval of the institutional review board or ethics committee at each study center, in accordance with US Food and Drug Administration regulations, the International Conference on Harmonization Guidelines for Good Clinical Practice, and any other applicable country laws. Written and informed consent was obtained from each patient or the patient's legally authorized representative before his or her participation in the study.

### **Participants**

#### **Inclusion criteria**

The trial included adults, 18–75 years old, with a diagnosis of chronic spontaneous urticaria (CSU) refractory to H<sub>1</sub>-antihistamines, with or without leukotriene receptor antagonists (LTRAs), for 6 months or longer. Patients were required to have itch and hives for longer than 6 consecutive weeks, despite H<sub>1</sub>-antihistamine, and an urticaria activity score over 7 days (UAS7)  $\geq 16$ , with the itch component of the UAS7  $\geq 8$  during the 7 days prior to randomization (Day 1). Patients were required to have daily, stable doses of H<sub>1</sub>-antihistamine (up to 4 times the

approved dosage), with or without an LTRA, for at least 3 consecutive days before the screening visit. Patients must have been willing and able to complete a daily symptom diary for the duration of the study.

#### Exclusion criteria

Patients who had received previous treatment with omalizumab, or any other monoclonal antibody therapies for 9 months prior to screening, were excluded from the trial. Patients who received routine doses (daily or every other day during 5 or more consecutive days) of the following medications within 30 days prior to screening were also excluded: systemic or cutaneous (topical) corticosteroids (prescription or over the counter), hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide. Other patients excluded were those who had received intravenous immunoglobulin or plasmapheresis within 30 days prior to screening.

#### Outcomes

The primary efficacy outcome was the absolute change from baseline in the weekly itch-severity score (ISS) at Week 20. The ISS was recorded once daily in an electronic patient diary, on a scale of 0 (none) to 3 (severe), with a total score range of 0–21, and a minimally important difference (MID) of 4.5–5, deemed to be the smallest change in the score that represents a meaningful difference to the patient.<sup>E1</sup> The baseline weekly score was calculated as the sum of the daily ISS over the 7 days prior to randomization (Day 1). The Week 20 ISS was calculated as the sum of the daily ISS over 7 days prior to the Week 20 visit (Day 141).

Secondary efficacy outcomes were the absolute change from baseline in the weekly ISS at Week 4 and the absolute change from baseline in the UAS7 at Week 20. The daily UAS is a diary-based, combined score of itch severity (0=none, to 3=severe) and number of hives (0=none; 1= 1 to 19 hives; 2= 20 to 50 hives; 3= greater than 50 hives). The UAS7 is the sum of

the daily UAS for 7 days, for a total score range of 0–42<sup>E2</sup> and a MID of 9.5–10.5.<sup>E1</sup> An additional outcome was the change from baseline to Week 20 in the weekly number of hives score, which has a MID of 5.0–5.5.<sup>E1</sup> Safety outcomes, including the incidence and severity of treatment-emergent adverse events (AEs) were analyzed throughout the study.

### **Serum IgE**

Blood draws for serum immunoglobulin E (IgE) analyses were collected on Day 1 (pre-dose and 1 hour post-dose), Week 4 (pre-dose), and on Weeks 5, 12, 20, and 28. Total IgE levels were measured by ImmunoCap (ViraCor-IBT Laboratories; Lee's Summit, MO) and the change in serum total IgE was assessed from baseline to Week 28.

### **Pharmacokinetics and immunogenicity**

Serum levels of quilizumab for pharmacokinetic assessments were measured using a validated enzyme-linked immunosorbent assay (ELISA) developed by Genentech, Inc. (South San Francisco, CA). The pharmacokinetic outcomes included serum concentrations prior to dosing at Weeks 0 and 4 ( $C_{\min, \text{wk}4}$ ), maximum observed serum concentrations following drug administration at Weeks 0 and 4 ( $C_{\max, \text{wk}0}$ ,  $C_{\max, \text{wk}4}$ ); time of maximum observed serum concentration ( $T_{\max, \text{wk}0}$ ,  $T_{\max, \text{wk}4}$ ) and terminal elimination half-life ( $t_{1/2}$ ). Immunogenicity, as measured by the presence of serum anti-therapeutic antibodies (ATAs) was assessed in samples at Weeks 0, 12, 20, and 28 using a validated bridging ELISA.

### **Statistical methods**

The analysis of the primary endpoint, the absolute change from baseline in the weekly ISS at Week 20, consisted of the treatment comparison between the 450 mg quilizumab group and the placebo group using analysis of covariance (ANCOVA), controlling for baseline weekly ISS and

study center. Missing weekly ISS scores were imputed by carrying forward the worst post-baseline observation (WOCF, worst observation carried forward).

Similar analysis methods were used to evaluate the secondary endpoints of the absolute change from baseline in the weekly ISS at Week 4, weekly number of hives score at Week 20, and UAS7 at Week 20.

After observing imbalances for several disease characteristics between the two treatment groups, sensitivity analysis was performed where the following covariates were added to the ANCOVA model: IgE level at screening, duration of CSU, and presence of angioedema.

Similar methods, including adjustment for disease characteristic imbalances, were also used for additional post hoc exploratory analyses, which included the absolute change from baseline between the quilizumab group and the placebo group in the weekly ISS and UAS7 at Week 20 when stratified by baseline UAS7 ( $< 28$ ,  $\geq 28$ ) and baseline IgE ( $< 75$  IU/mL,  $\geq 75$  IU/mL). P-values for post hoc analyses were not adjusted for multiple comparisons.

#### Determination of sample size

Under the assumption of a common standard deviation (SD) of the change from baseline to Week 20 in the weekly ISS of approximately 6, we estimated that approximately 30 patients (15 per arm) would need to be enrolled for the study to yield an approximately 90% probability that the halfwidth (i.e., precision) of the 90% confidence interval (CI) is  $\leq 4.5$ , which represents the expected treatment effect.

## RESULTS

### Study flow and patient disposition

Enrollment for the study occurred from December 2013 to March 2014, and the study was completed in October 2014. Thirty-two patients were randomized: 17 patients to placebo and 15 patients to 450 mg quilizumab. Among the patients randomized, 16 (94%) in the placebo group and 15 (100%) in the quilizumab group completed the study treatment at Week 4, while 13 (77%) patients in the placebo group and 13 (87%) patients in the quilizumab group completed the study through Week 28 (Figure E1). The mean age was  $43 \pm 12.6$  years, and 72% of the patients were female (Table E1). We observed minor imbalances between the treatment groups in baseline characteristics or CSU symptom scores. Patients in the placebo group had a longer history of CSU (mean of 14.3 years versus 8.3 years in the quilizumab group), lower IgE levels (mean of 111 IU/mL versus 155 IU/mL in the quilizumab group), and a larger proportion of patients had angioedema at baseline (77% versus 60% in the quilizumab group) than the quilizumab-treated group (Table E1).

### Efficacy: Sensitivity analysis

To determine whether observed imbalances in patient disease characteristics between treatment groups had any impact on the analysis of the primary or secondary efficacy endpoints, a sensitivity analysis was performed to adjust for these imbalances. This adjustment had negligible impact on analysis results (Table E2) and did not change the interpretation of the study findings.

### Efficacy: Post hoc analyses

To determine whether patients with worse symptoms responded better to quilizumab than those with milder symptoms, we divided the patients into two groups determined by their baseline UAS7. We set the cutoff score at 28, the median UAS7 at baseline, to have adequate numbers

in each subgroup. We found that both placebo and quilizumab-treated, UAS7-high groups similarly improved until Week 5 for the weekly ISS (Figure E4B) and until approximately Week 7 for the UAS7 (Figure E5B). After those time points, the UAS7-high quilizumab group continued to show a slight improvement in both measures out to Week 20, while the placebo group scores began to return to baseline levels. At Week 20, we observed a treatment difference for the weekly ISS of -3.9 (90% CI: -9.9 to 2.1,  $P = .27$ ; Figure E4B) and for the UAS7 of -8.9 (90% CI: -22.6 to 5.1,  $P = .28$ ; Figure E5B). For the UAS7-low subgroups, quilizumab treatment showed no benefit to patients over placebo (Figures E4A and E5A).

We also investigated if there was linkage between patient baseline IgE levels and the level of clinical response to quilizumab as measured by the UAS7 (Figure E6) and the weekly ISS. For patients with high IgE ( $\geq 75$  IU/mL), there was no difference in UAS7 scores between placebo and quilizumab groups by Week 20 (Figure E6B). However, patients with low baseline IgE ( $< 75$  IU/mL) showed a 19.1-point mean improvement (90% CI: -34.1 to -4.1;  $P = .05$ ) by Week 20 (Figure E6A). A similar pattern was observed for the weekly ISS; there was no difference in weekly ISS scores between placebo and quilizumab groups by Week 20 in patients with high IgE, but patients with low IgE showed a 7.4-point mean improvement (90% CI: -13.0 to -1.8;  $P = .04$ ) by Week 20.

### Pharmacokinetics

The mean  $\pm$  SD  $C_{\max, \text{wk1}}$  and  $C_{\max, \text{wk4}}$  values were  $43 \pm 15$  and  $58 \pm 23$   $\mu\text{g/mL}$ , which occurred at  $T_{\max, \text{wk1}}$  and  $T_{\max, \text{wk4}}$  of  $7.4 \pm 1.1$  and  $35.2 \pm 1.5$  days, respectively, after Week 0 and 4, following the drug administration. Based on non-compartmental analysis, the mean  $t_{1/2}$  value of quilizumab was  $19.0 \pm 1.5$  days, as expected for an IgG1 monoclonal antibody, and consistent with the pharmacokinetic characteristics seen in other quilizumab studies.<sup>E3</sup>

**188 Safety**

189 Quilizumab was well tolerated. No large imbalances in adverse event (AE) rates were observed  
190 among the treatment groups, no patients withdrew from the study due to AEs, and no serious  
191 AEs or deaths were reported (Table E3). No quilizumab-induced ATAs were detected in this  
192 study.

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206 **Table E1.** Patient demographics and baseline disease characteristics

| Patient demographics                    | Placebo<br>(n = 17) | Quilizumab<br>450 mg<br>(n = 15) | All patients<br>(N = 32) |
|-----------------------------------------|---------------------|----------------------------------|--------------------------|
| Age (y), mean (SD)                      | 41.8 (12.3)         | 44.7 (13.2)                      | 43.2 (12.6)              |
| Age group (y)                           |                     |                                  |                          |
| 18–40                                   | 9 (53%)             | 5 (33%)                          | 14 (44%)                 |
| 41–64                                   | 8 (47%)             | 8 (53%)                          | 16 (50%)                 |
| ≥ 65                                    | 0                   | 2 (13%)                          | 2 (6%)                   |
| Sex                                     |                     |                                  |                          |
| Female                                  | 13 (77%)            | 10 (67%)                         | 23 (72%)                 |
| Race                                    |                     |                                  |                          |
| Asian                                   | 1 (6%)              | 2 (13%)                          | 3 (9%)                   |
| Black                                   | 0                   | 2 (13%)                          | 2 (6%)                   |
| White                                   | 16 (94%)            | 11 (73%)                         | 27 (84%)                 |
| Country                                 |                     |                                  |                          |
| Canada                                  | 8 (47%)             | 7 (47%)                          | 15 (47%)                 |
| Germany                                 | 9 (53%)             | 8 (53%)                          | 17 (53%)                 |
| Weight (kg), mean (SD)                  | 81.6 (24.8)         | 76.2 (20.5)                      | 79.1 (22.8)              |
| BMI (kg/m <sup>2</sup> ), mean (SD)     | 29.1 (9.7)          | 25.4 (5.2)                       | 27.4 (8.1)               |
| <b>Baseline disease characteristics</b> |                     |                                  |                          |
| Duration of CSU (y)                     |                     |                                  |                          |
| Mean (SD)                               | 14.3 (19.0)         | 8.3 (13.0)                       | 11.5 (16.5)              |
| Median                                  | 6.8                 | 2.3                              | 4.2                      |
| IgE level at screening (IU/mL)*         |                     |                                  |                          |
| Mean (SD)                               | 111.6 (158.1)       | 155.0 (132.8)                    | 132.6 (145.7)            |
| Median                                  | 62.0                | 81.0                             | 75.0                     |
| Weekly ISS, mean (SD)                   | 14.6 (3.5)          | 14.2 (3.4)                       | 14.4 (3.4)               |
| Weekly number of hives score, mean (SD) | 14.6 (4.5)          | 14.5 (4.9)                       | 14.6 (4.6)               |
| UAS7, mean (SD)                         | 29.3 (7.2)          | 28.7 (7.1)                       | 29.0 (7.1)               |
| Presence of angioedema                  | 13 (77%)            | 9 (60%)                          | 22 (69%)                 |

207 BMI, body mass index; SD, standard deviation.

208 \*IgE levels were available for n = 16 patients in the placebo group.

209

**Table E2.** Efficacy outcomes (ITT population) adjusted for imbalances in patient disease characteristics

| Primary outcome                                        | Quilizumab 450 mg |
|--------------------------------------------------------|-------------------|
| Weekly ISS <sup>†</sup> (at Week 20)                   |                   |
| Treatment difference in LSMs* (vs. placebo)            | <b>-2.9</b>       |
| 90% CI of the LSMs difference                          | (-7.1 to 1.3)     |
| P-value                                                | 0.26              |
| <b>Secondary outcomes</b>                              |                   |
| Weekly ISS <sup>†</sup> (at Week 4)                    |                   |
| Treatment difference in LSMs* (vs. placebo)            | <b>-1.4</b>       |
| 90% CI of the LSMs difference                          | (-5.0 to 2.3)     |
| P-value                                                | 0.53              |
| UAS7 <sup>†</sup> (at Week 20)                         |                   |
| Treatment difference in LSMs* (vs. placebo)            | <b>-4.7</b>       |
| 90% CI of the LSMs difference                          | (-13.5, 4.0)      |
| P-value                                                | 0.37              |
| <b>Additional outcome</b>                              |                   |
| Weekly number of hives score <sup>†</sup> (at Week 20) |                   |
| Treatment difference in LSMs* (vs. placebo)            | <b>-1.8</b>       |
| 90% CI of the LSMs difference                          | (-6.5 to 2.9)     |
| P-value                                                | 0.51              |

212

213 CI, confidence interval; ITT, intention-to-treat; LSM, least-squares mean; SD, standard  
214 deviation.

215 <sup>†</sup>Missing Week 4 and Week 20 weekly scores were imputed by the worst weekly score up to  
216 Weeks 4 and 20, respectively.

217 \*LSM was estimated using an ANCOVA model controlling for baseline value (ISS, number of  
218 hives, and UAS7, respectively), country, IgE level at screening (<75, 75 to <200, ≥200 IU/mL),  
219 duration of CSU (<1, 1 to <2, 2 to <10, ≥10 years), and presence of angioedema (yes, no).

220

221 **Table E3.** Safety

|                                                      | <b>Placebo<br/>(n = 17)</b> | <b>Quilizumab<br/>450 mg<br/>(n = 15)</b> |
|------------------------------------------------------|-----------------------------|-------------------------------------------|
| Patients with at least one AE                        | 7 (41%)                     | 8 (53%)                                   |
| Number of events                                     | 15                          | 19                                        |
| Number of deaths                                     | 0                           | 0                                         |
| Number of patients withdrawn from study due to an AE | 0                           | 0                                         |
| Number of patients with at least one:                |                             |                                           |
| Serious AE                                           | 0                           | 0                                         |
| AE leading to withdrawal from treatment              | 0                           | 0                                         |
| Treatment-related AE                                 | 0                           | 1 (6.7%)                                  |
| Grade 2 AE or higher                                 | 5 (29%)                     | 2 (13%)                                   |
| Grade 3 AE or higher                                 | 1 (6%)                      | 0                                         |
| AE within 24 hours of dose                           | 2 (12%)                     | 3 (20%)                                   |
| Treatment-related AE within 24 hours of dose         | 0                           | 1 (7%)                                    |
| Medical concepts-patients with:                      |                             |                                           |
| Anaphylaxis (narrow)                                 | 0                           | 0                                         |
| Serious infections                                   | 0                           | 0                                         |
| Parasitic infections                                 | 0                           | 0                                         |
| Malignancies                                         | 0                           | 0                                         |
| Injection site reactions                             | 0                           | 0                                         |

222

223 AE, adverse event.

**Figure legends**

**Figure E1.** Study flow and patient disposition. All 17 patients assigned to placebo and all 15 patients assigned to 450 mg quilizumab were included in the analyses.

**Figure E2.** Mean weekly ISS in the intention-to-treat (ITT) population from baseline to Week 20. Arrows indicate quilizumab doses at Week 0 and Week 4. Missing weekly scores were imputed using the worst post-baseline weekly score up to Week 20. SE, standard error.

**Figure E3.** Additional outcomes. **A**, Mean UAS7 from baseline to Week 20. **B**, Mean weekly number of hives score (ITT population). Arrows indicate quilizumab doses at Week 0 and Week 4. Missing weekly scores were imputed using the worst post-baseline weekly score up to Week 20. SE, standard error.

**Figure E4.** Mean change from baseline in weekly ISS by baseline UAS7 subgroup. **A**, UAS7-low ( $< 28$ ) patient subgroup. **B**, UAS7-high ( $\geq 28$ ) patient subgroup. Missing values were imputed by WOCF. Arrows indicate quilizumab doses at Week 0 and Week 4. Gray dashed lines indicate baseline. SE, standard error.

**Figure E5.** Mean change from baseline in UAS7 by baseline UAS7 subgroup. **A**, UAS7-low ( $< 28$ ) patient subgroup. **B**, UAS7-high ( $\geq 28$ ) patient subgroup. Missing values were imputed by WOCF. Arrows indicate quilizumab doses at Week 0 and Week 4. Gray dashed lines indicate baseline. SE, standard error.

**Figure E6.** Mean UAS7 score by baseline IgE. **A**, IgE-low ( $< 75$  IU/ml) subgroup. **B**, IgE-high ( $\geq 75$  IU/mL) subgroup. Missing values were imputed by WOCF. Arrows indicate quilizumab doses at Week 0 and Week 4. SE, standard error.

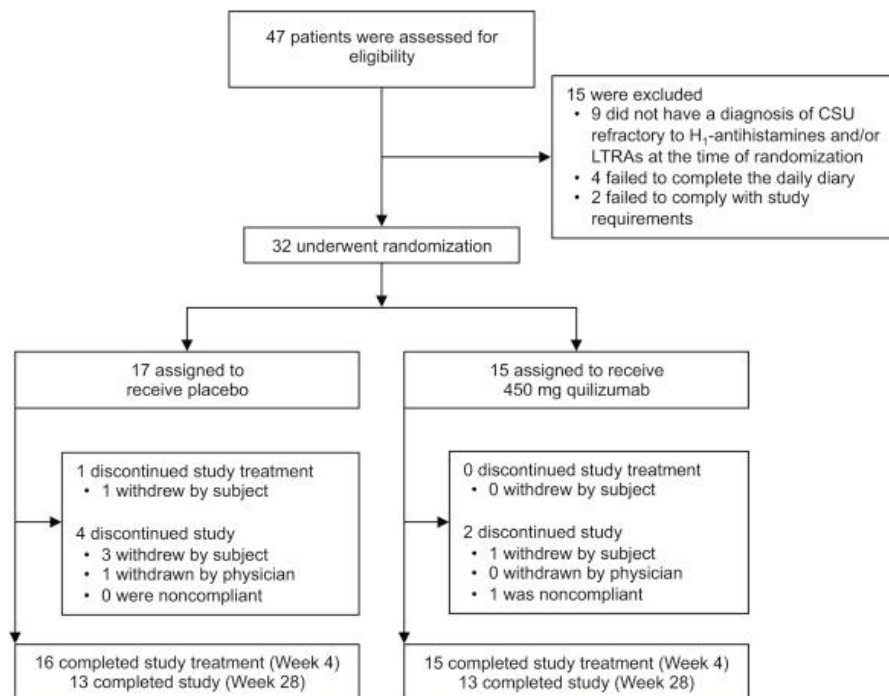


Fig E1.

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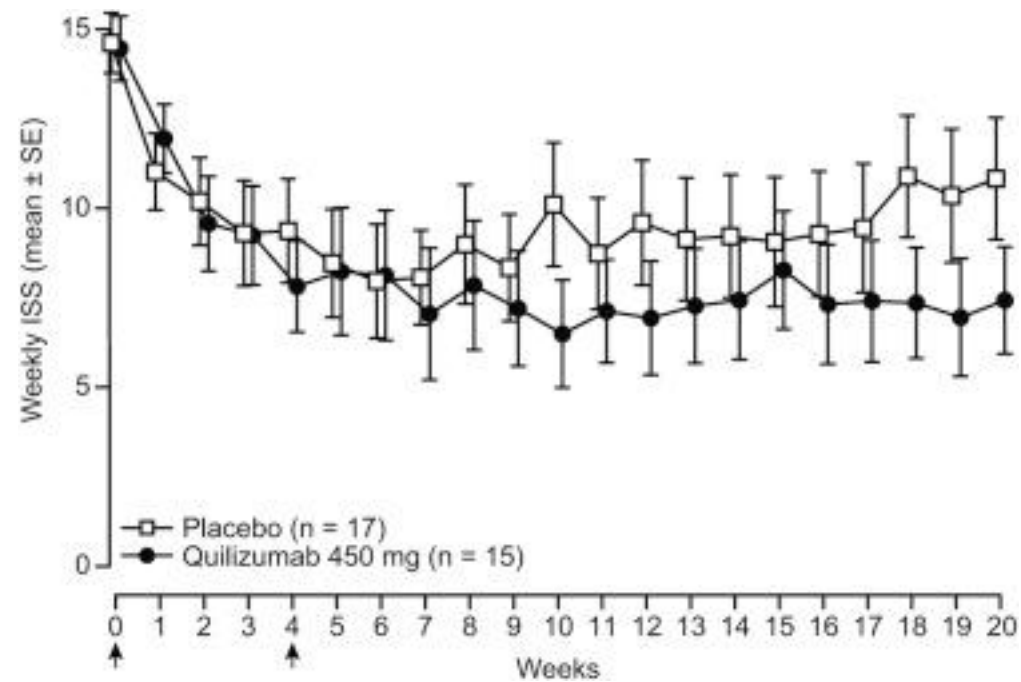


Fig E2.

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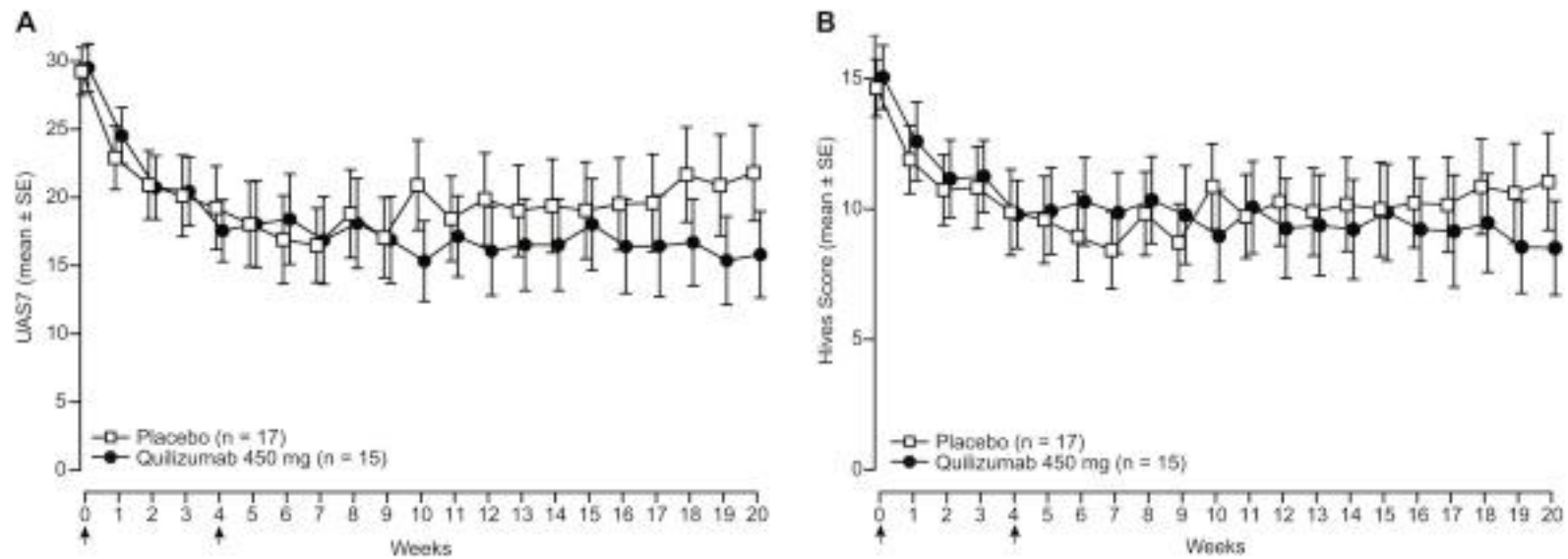


Fig E3.

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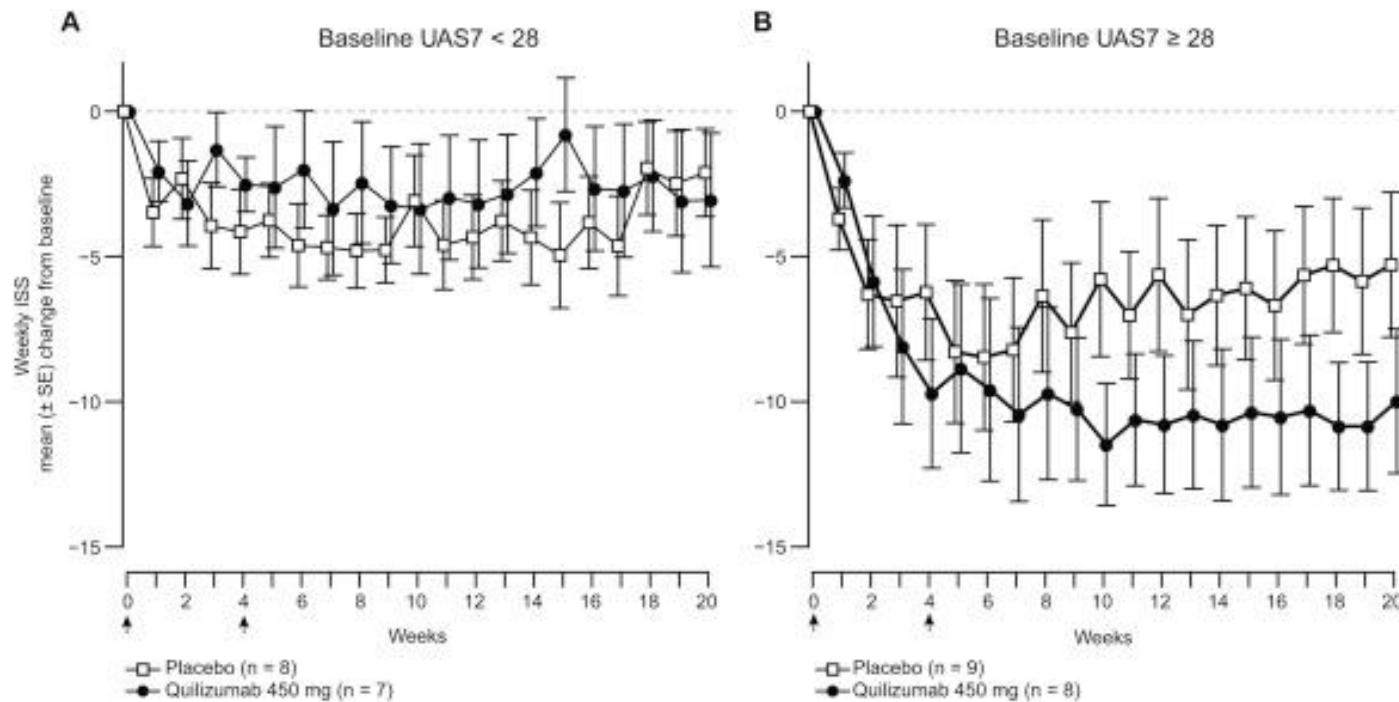


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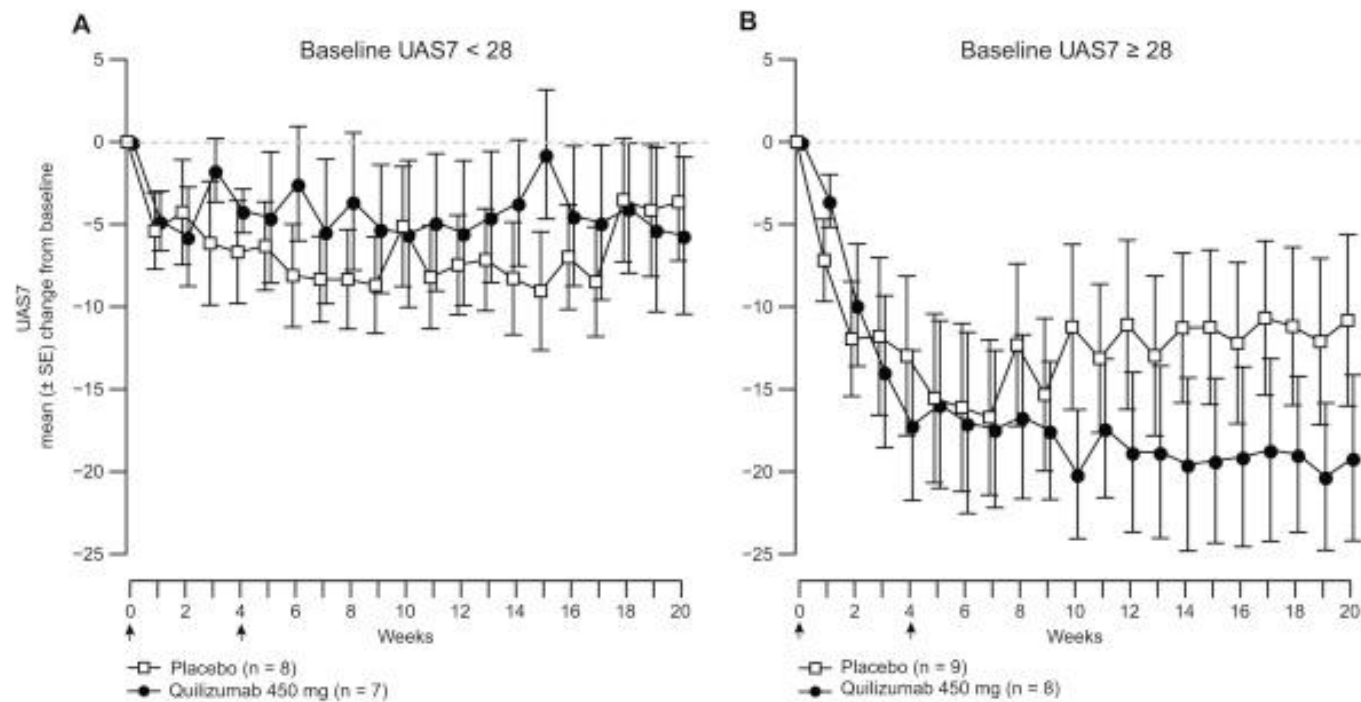


Fig E5.

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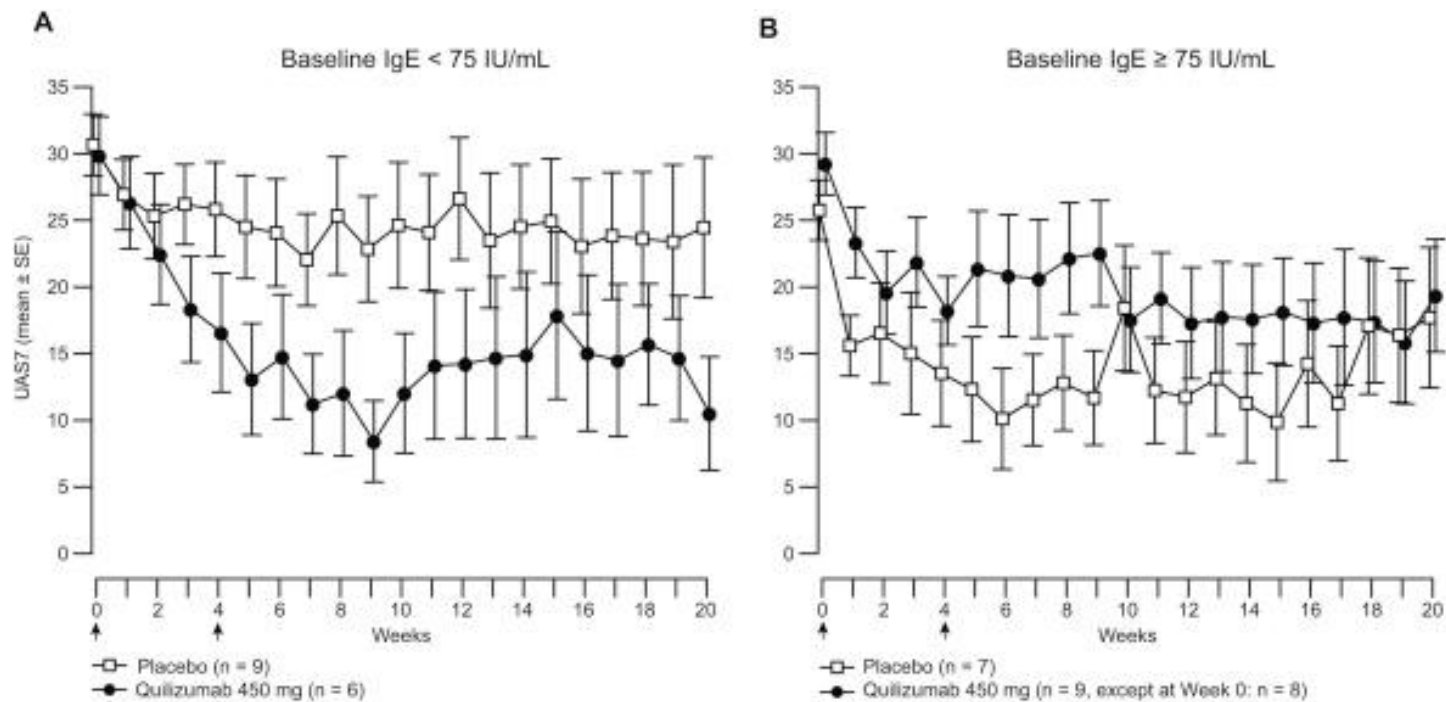


Fig E6.

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