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Benralizumab does not elicit therapeutic effect in patients with chronic spontaneous urticaria: results from the phase IIb multinational randomized double-blind placebo-controlled ARROYO trial

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Abstract

Background Chronic spontaneous urticaria (CSU) is a relatively common skin disease associated with hives and angio-oedema. Eosinophils play a role in CSU pathogenesis. Benralizumab, an anti-interleukin-5 receptor-α monoclonal antibody, has been shown to induce nearly complete depletion of eosinophils.

Objectives To determine the clinical efficacy and safety of benralizumab in patients with CSU who were symptomatic despite H1 antihistamine treatment.

Methods The 24-week, randomized, double-blind, placebo-controlled, phase IIb portion of the ARROYO trial enrolled adult patients with CSU who were currently on H1 antihistamine treatment. Patients were randomized to one of five treatment groups according to benralizumab dose and regimen for a 24-week treatment period. The primary endpoint was change from baseline in Itch Severity Score (ISS)7 at week 12. The key secondary endpoint was change from baseline in Urticaria Activity Score (UAS)7 at week 12. Additional secondary endpoints included other metrics to assess CSU at week 24, blood eosinophil levels, and pharmacokinetics and immunogenicity assessments. Exploratory subgroup analyses were conducted to explore responses according to demographics, clinical features and biomarkers. Safety was assessed in all treatment groups.

Results Of 155 patients, 59 were randomized to benralizumab 30 mg, 56 to benralizumab 60 mg and 40 to placebo. Baseline and disease characteristics were consistent with what was expected for patients with CSU. There were no significant differences in change from baseline in ISS7 score at week 12 between benralizumab and placebo [benralizumab 30 mg vs. placebo, least-squares mean difference −1.01, 95% confidence interval (CI) −3.28 to 1.26; benralizumab 60 mg vs. placebo, least-squares mean difference −1.79, 95% CI −4.09 to 0.50] nor in change from baseline in UAS7 score at week 12 between benralizumab and placebo (benralizumab 30 mg vs. placebo, $P=0.407$; benralizumab 60 mg vs. placebo, $P=0.082$). Depletion of blood eosinophil levels was observed at week 24 in patients treated with benralizumab. All other secondary endpoints and exploratory/subgroup analyses indicated no significant differences between benralizumab and placebo. Safety results were consistent with the known profile of benralizumab.

Conclusions Although benralizumab resulted in near-complete depletion of blood eosinophils, there was no clinical benefit over placebo.

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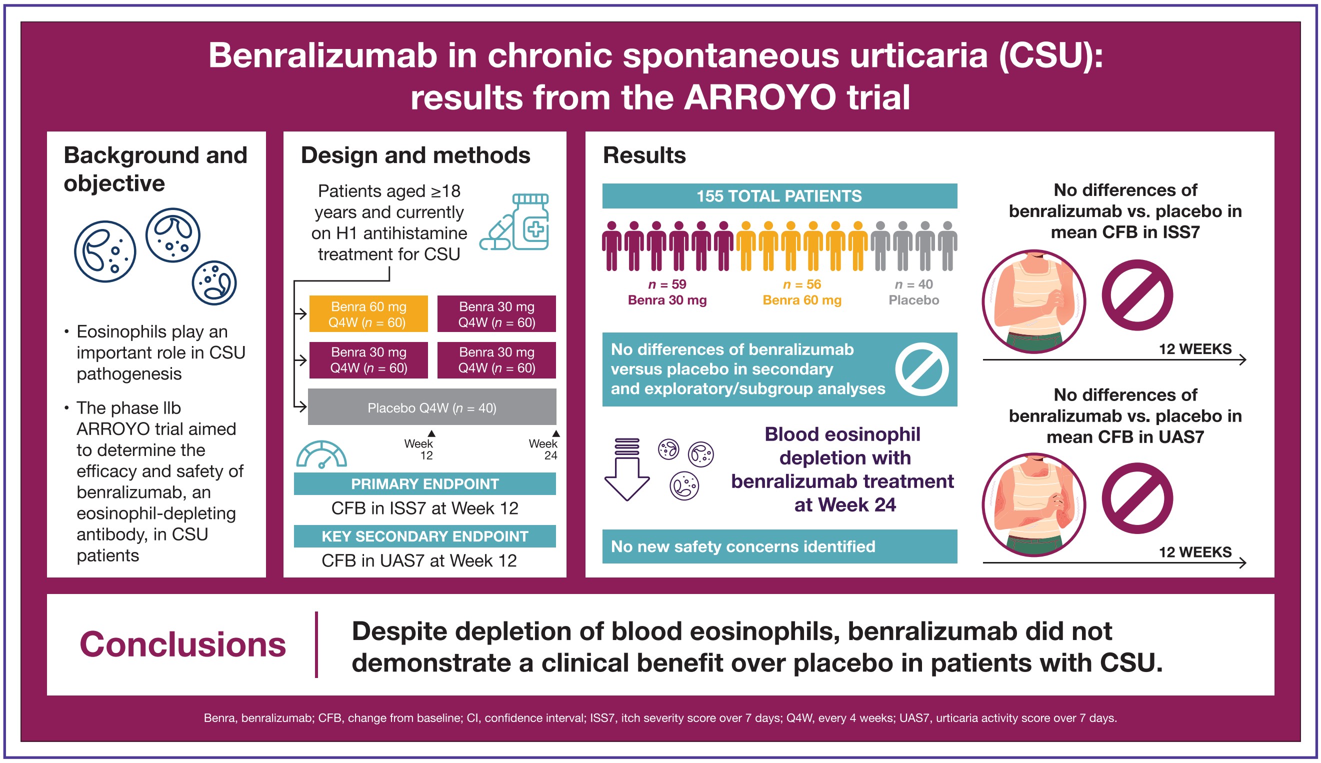
Graphical Abstract



Lay summary

Chronic spontaneous urticaria (CSU) is a common disease characterized by hives, itching and inflammation (swelling) of the skin. CSU is mainly driven by what we call 'mast cells'. 'Eosinophils' are a type of white blood cell that protect the body from infections and allergens. These cells are abundant in skin biopsy samples of people with CSU, especially in the hives that contribute to swelling. Therefore, we thought that reducing eosinophils would be beneficial for treating CSU. Benralizumab is a drug that has been shown to reduce eosinophils in other diseases.

This study, called 'ARROYO', was a 24-week clinical trial that compared benralizumab treatment with a placebo (inactive medicine) in adults with CSU who were taking antihistamines. We aimed to determine whether benralizumab would improve symptoms of CSU over time. Several assessments were used to measure changes in CSU symptoms, including hives, severity of itchiness, swelling of the skin, and other aspects related to overall psychological and physical wellbeing. The characteristics of the 155 people who took part in this study were consistent with what was expected for patients with CSU.

We found that while benralizumab reduced eosinophil levels in people with CSU, there were no differences in symptoms in people receiving benralizumab compared with those receiving placebo. There were no new safety concerns related to benralizumab and no deaths.

Overall, although benralizumab is effective at reducing the number of eosinophils, it is not effective at treating the symptoms of CSU. More studies are needed to uncover potential treatment targets in CSU.

What is already known about this topic?

- Chronic spontaneous urticaria (CSU) is a common dermatological condition that is classically difficult to treat and has substantial impact on patients' quality of life.
- The mast cell-driven aetiology of CSU is highly complex, involving several different types of immune mediators, with significantly increased numbers of immune cells, such as lymphocytes, eosinophils and basophils.
- The anti-interleukin-5Rα monoclonal antibody benralizumab selectively depletes eosinophils and has demonstrated efficacy in other conditions involving this type of white blood cell.

What does this study add?

- Although treatment with benralizumab was shown to effectively deplete eosinophils in patients with CSU, there was no significant clinical efficacy vs. placebo.
- Patient demographics and clinical characteristics were similar to those of previous CSU trials.
- Therefore, results from the ARROYO study suggest the need for further studies to uncover the mechanisms behind CSU pathogenesis to help guide the implementation of improved treatments for this skin condition.

Chronic spontaneous urticaria (CSU) is a debilitating autoimmune skin disease that affects up to 1% of the global population.[1,2] Many patients are affected by CSU over the course of several years.[1,3] Real-world evidence studies show that CSU, as a result of its symptoms, comorbidities and unpredictable disease course, causes substantial impacts on patients' daily activities, mental health and overall health-related quality of life.[2–4]

The pathophysiology of CSU is complex, and the interplay of various cell types and molecular mechanisms defines the immune response in CSU.[5] While it is typically known to be a mast cell-driven disease, eosinophils and other cell types may also play significant roles in the pathogenesis of CSU.[5–11] Two main endotypes of CSU are known: type I is associated with IgE antibodies against autoantigens, and type IIb is driven by autoantibodies, which activate mast cells, including anti-high-affinity IgE receptor-1α (FcεR1α) and anti-IgE.[7] Upon IgE stimulation, mast cells in the skin and, to a lesser extent, basophils in the skin and peripheral blood become degranulated and release histamine.[9,10,12,13] Vasoactive mediators then attract primarily lymphocytes and eosinophils, and somehow neutrophils and basophils, which are prevalent in lesional skin (hives) in CSU.[6,9,13] Mast cells, basophils and eosinophils express activated receptors for interleukin (IL)-4 and IL-5, which play roles in CSU pathogenesis.[9,10,12] Recruitment of eosinophils to sites of inflammation is driven by IL-5, which can prolong the inflammatory manifestations of CSU (i.e. hives and angio-oedema).[6,14]

Treatment options for patients with CSU are limited. The current first-line treatment is second-generation nonsedating antihistamines.[3] Second-line treatment requires the addition of the anti-IgE antibody omalizumab,[15] which has been shown to be effective in many, but not all, patients with CSU. Upon failure, the current third-line treatment option is off-label use of ciclosporin; long-term immunosuppression with treatments like this may be associated with significant side-effects, including lymphoma and other cancers.[3] Other drugs are also under investigation for the treatment of refractory CSU;[14,16–19] however, none of these is approved to date, and there remains a need for new effective treatment options. As the pathophysiology of CSU is associated with the presence of eosinophils in some phenotypes, a direct eosinophil-depleting approach may be beneficial for the treatment of CSU.

Benralizumab is a humanized, afucosylated, anti-IL-5 receptor-α monoclonal antibody that induces direct, rapid and near-complete depletion of eosinophils as well as reductions in basophil counts via enhanced antibody-dependent cell-mediated cytotoxicity.[20–22] In previous studies, benralizumab rapidly depleted eosinophils in the blood, bone marrow, gastrointestinal tissue and lungs.[21–27] Other studies have recently explored treatment of CSU with benralizumab, including a 24-week single-centre single-blind study of 12 patients with CSU, which showed efficacy of benralizumab during and after 12 weeks on active treatment.[28–30] Of the nine patients who received more than one dose of benralizumab, five patients achieved complete response and two patients achieved a partial response upon study completion.[28] A sustained decrease in pruritus severity and weal size was seen at 8 weeks after the last dose of benralizumab; the prolonged effect in patients with a complete response after discontinuation may be due to a modification of biologic pathways that perpetuate the symptoms associated with CSU.[28]

Here, we present findings from the ARROYO trial, which was conducted to determine the clinical efficacy and safety of benralizumab compared with placebo in patients with CSU who were symptomatic despite treatment with an H1 antihistamine.

Patients and methods

Study design

The ARROYO trial (NCT04612725) was a 24-week randomized double-blind placebo-controlled phase IIb clinical trial conducted in 7 countries, with 40 sites participating (ARROYO study investigators listed in Table S1; see Supporting Information).[31] Patients entered a 10-day to 4-week run-in period, which included patients remaining on a stable, locally approved dose of H1 antihistamine treatment throughout the run-in period. The study was designed to evaluate two induction doses of benralizumab (30 mg and 60 mg) vs. placebo in patients with CSU and to compare maintenance dosing regimens [every 4 weeks (Q4W) vs. every 8 weeks (Q8W)] in a 28-week extension period.

Approximately 240 patients were enrolled to ensure that at least 160 patients would be assigned to treatment. With 60 patients in both the benralizumab 60 mg and 30 mg initial dose treatment arms, and 40 patients in the placebo arm, there was 90% power for statistical significance at the two-sided 2.5% level within each induction dose comparison vs. placebo if the assumed effect was a 4.7-point mean difference in change at week 12 in Itch Severity Score over 7 days (ISS7) between benralizumab and placebo, assuming an SD of 6 for the change in ISS7 and a 10% dropout rate. These criteria have been established as per previous CSU trials.[32] After screening for eligibility and completing the run-in period, patients were randomly assigned and stratified by geographic region in a ratio of 3 : 3 : 3 : 3 : 4 to one of five treatment groups (Figure 1) using an interactive voice/web response system. For the first 24 weeks (i.e. prior to the extension period),

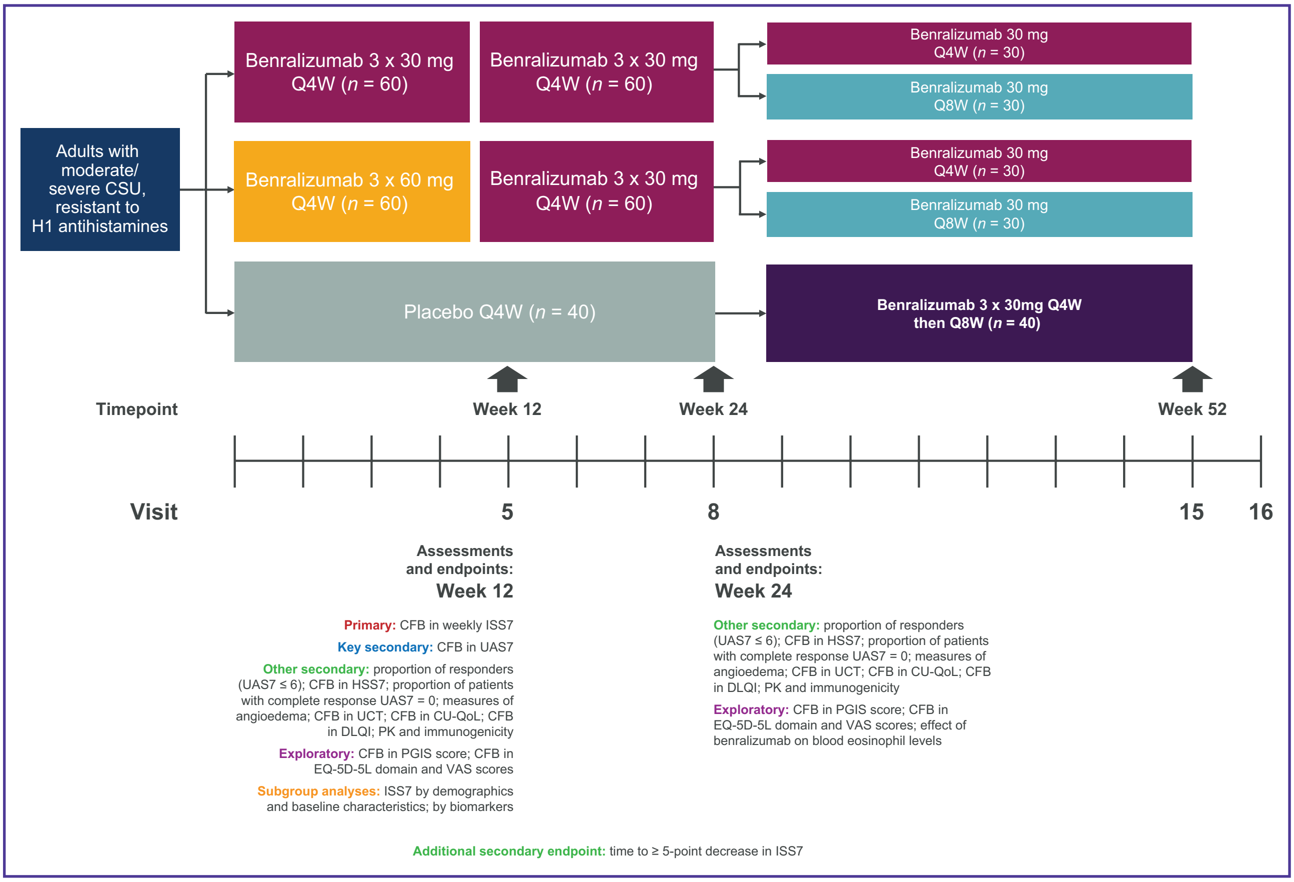


Figure 1 ARROYO phase IIb study design. CFB, change from baseline; CSU, chronic spontaneous urticaria; CU-QoL, Chronic Urticaria Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index; ISS7, Itch Severity Score over 7 days; PGIS, Patient Global Impression of Severity; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; UAS7, 7-day Urticaria Activity Score; UCT, Urticaria Control Test; VAS, visual analogue scale.

the benralizumab 30 mg and benralizumab 60 mg groups were each considered single treatment arms (i.e. prior to evaluation of dosing Q8W). Patients who completed the 24-week period continued to a 28-week extension period up to week 52. Neither patients nor investigators involved in the treatment, clinical evaluations or monitoring of patients were aware of the treatments in either the 24-week or the 28-week study period.

Patients

Full inclusion and exclusion criteria are detailed in File S1 (see Supporting Information). Eligible patients were aged ≥ 18 years (at informed consent) with a physician-confirmed diagnosis of CSU for ≥ 6 months prior to screening; had pruritus and weals for ≥ 6 consecutive weeks prior to screening, despite receiving standard-of-care treatment, including H1 antihistamine therapy; were symptomatic during run-in, defined by an Urticaria Activity Score over 7 days (UAS7) total score of ≥ 16 with an ISS7 of ≥ 8, during the 7 days before randomization; and complied with the locally approved dose of antihistamine that was maintained at randomization. Patients with predominant inducible urticaria or other active dermatological conditions associated with chronic itching and/or skin lesions were excluded.

Study treatment

In the first treatment group, benralizumab 60 mg was administered by subcutaneous (SC) injection every 4 weeks (Q4W) through week 12; the dosage was then decreased to 30 mg Q4W through week 24 (Figure 1). In the second treatment group, benralizumab 30 mg was administered by SC injection Q4W through week 24. In the 28-week extension period, these treatment groups were further divided into two groups each, with the first group receiving benralizumab 30 mg SC injection Q4W and the second group receiving 30 mg SC injection Q8W, through week 52. An additional group received placebo administered by SC injection Q4W through week 24; thereafter, these patients received benralizumab 30 mg Q4W through week 36 followed by benralizumab 30 mg Q8W through week 52.

Assessments and endpoints

Assessments of urticaria disease activity were determined through twice-daily diary entries (morning and evening). The primary endpoint was change from baseline in weekly ISS7 at week 12 (Figure 1). The key secondary endpoint was change from baseline in UAS7 at week 12. Additional secondary endpoints included change from baseline in UAS7 at

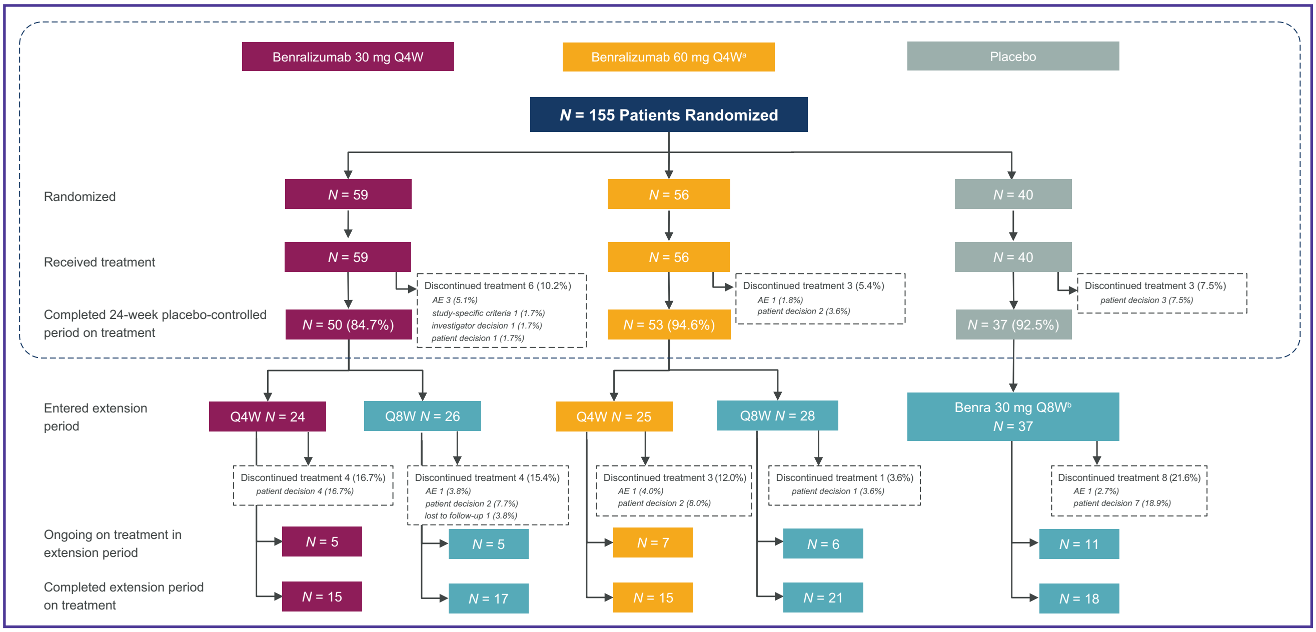


Figure 2 Patient disposition at primary analysis. AE, adverse event; Q4W, every 4 weeks; Q8W, every 8 weeks. [a]Benralizumab 60 mg Q4W group received 3×60 mg Q4W, then 3×30 mg Q4W in 24-week placebo-controlled period. [b]Patients who received placebo switched to the benralizumab asthma regimen in the extension period (3×30 mg Q4W, then 30 mg Q8W).

week 24; proportion of responders (UAS7 $\leq$ 6) at weeks 12 and 24; change from baseline in Hives Severity Score over 7 days (HSS7) at weeks 12 and 24; time to $\geq$ 5-point decrease in ISS7; proportion of patients with complete response UAS7 = 0 at weeks 12 and 24; measures of angio-oedema activity at weeks 12 and 24 in patients with angio-oedema at baseline; change from baseline in Urticaria Control Test at weeks 12 and 24; change from baseline Chronic Urticaria Quality of Life Questionnaire at weeks 12 and 24; change from baseline in Dermatology Life Quality Index at weeks 12 and 24; change from baseline in ISS7 at week 24; and pharmacokinetics and immunogenicity assessments [serum benralizumab concentration and antidrug antibody (ADA)]. Exploratory analyses included change from baseline in Patient Global Impression of Severity score at weeks 12 and 24; change from baseline in EQ-5D-5L scores; rescue medication use; and subgroup analyses of ISS7 at week 12 by demographics and baseline characteristics as well as by biomarkers [blood eosinophils, blood basophils, blood neutrophils, IgG to FcεR1α, total IgE and basophil histamine release assay (BHRA)].

Blood samples were collected at baseline and longitudinally during the double-blind period. These samples were tested for IgG to FcεR1α, total IgE, eosinophil-derived neurotoxin and BHRA levels to evaluate the response of patients with CSU type I and CSU type IIb phenotypes. Blood eosinophils, basophils and neutrophils were also assessed at baseline and longitudinally.

Safety and tolerability were evaluated based on rates of adverse events, vital signs and clinical laboratory measures.

Statistical analysis

The primary endpoint (change from baseline in ISS7 at week 12) was compared between each benralizumab initial treatment group (60 mg and 30 mg) and placebo using a repeated measure analysis of covariance. The secondary endpoints of proportion of responders (UAS7 $\leq$ 6) and of the proportion of patients achieving UAS7 = 0 at weeks 12 and 24 were compared between the active treatment groups and placebo using logistic regression. Subgroup analyses for the primary outcome variable tested for interaction between treatment and covariates for factors such as ISS7, UAS7 and HSS7 at baseline; duration of CSU at enrolment; prior omalizumab use; and baseline blood eosinophils; a mixed-effect model for repeated measures was used for each of these analyses. For the primary and all secondary endpoints, categorical variables were summarized using frequency and percentages, and continuous variables were summarized with descriptive statistics. All point estimates were presented together with 95% confidence intervals (CIs) as measures of precision and nominal two-sided *P*-values.

Results

Patient disposition

The study began enrolling patients on 27 October 2020, and the primary analysis was completed on 12 October 2022. Of 155 randomized and treated patients, 59 were randomly assigned to benralizumab 30 mg, 56 to benralizumab 60 mg and 40 to placebo (Figure 2). Only 12 patients (7.7%) discontinued study treatment during the 24-week placebo-controlled treatment period. Of those who completed the 24-week placebo-controlled treatment period, 50 (84.7%) patients from the benralizumab 30 mg group, 53 patients (94.6%) from the benralizumab 60 mg group and 37 patients (92.5%) from the placebo group entered the 28-week extension period.

Table 1 Key baseline and disease characteristics

Characteristic	Benralizumab 30 mg (*n*=59)	Benralizumab 60 mg (*n*=56)	Placebo (*n*=40)
Age (years), mean (SD)	46.8 (14.4)	45.6 (15.1)	47.1 (14.3)
Age by category (years)			
< 35	11 (18.6)	15 (26.8)	8 (20.0)
35–55	32 (54.2)	25 (44.6)	22 (55.0)
≥ 55	16 (27.1)	16 (28.6)	10 (25.0)
Sex, female	44 (74.6)	45 (80.4)	25 (62.5)
Race			
White	46 (78.0)	42 (75.0)	30 (75.0)
Asian	12 (20.3)	12 (21.4)	8 (20.0)
Other	1 (1.7)	2 (3.6)	2 (5.0)
Region			
North America	14 (23.7)	13 (23.2)	9 (22.5)
Europe	34 (57.6)	33 (58.9)	23 (57.5)
Asia	11 (18.6)	10 (17.9)	8 (20.0)
BMI, mean (SD)	27.7 (5.2)	26.8 (4.7)	28.1 (5.1)
Baseline blood eosinophils (cells per μL), median (range)	120 (10–610)	140 (10–730)	150 (20–500)
Age at first diagnosis, mean (SD)	42.3 (15.2)	39.8 (16.1)	42.7 (16.8)
Time since diagnosis/first appearance (years), mean (SD)	4.6 (6.5)/7.7 (11.1)	5.9 (7.5)/7.8 (10.5)	4.4 (7.8)/7.1 (10.0)
Higher-than-labelled antihistamine dose/combination treatment prior to study entry	5 (8.5)	5 (8.9)	4 (10.0)
Prior omalizumab use	5 (8.5)	5 (8.9)	7 (17.5)
Prior omalizumab use response	4 (6.8)	4 (7.1)	6 (15.0)
Failed – no effect on symptoms	3 (5.1)	4 (7.1)	4 (10.0)
Responder – improved symptoms	1 (1.7)	0	2 (5.0)
Baseline ISS7/HSS7, mean (SD)	15.3 (4.2)/16.5 (4.3)	15.8 (4.1)/16.4 (4.2)	15.5 (3.6)/16.1 (4.6)
Baseline UAS7, mean (SD)	31.8 (7.7)	32.2 (7.4)	31.6 (7.2)
Baseline DLQI, mean (SD)	15.8 (7.2)	14.2 (6.3)	14.8 (7.2)
History of or presence of angio-oedema at baseline	39 (66.1)	29 (51.8)	23 (57.5)

Data are presented as *n* (%) unless otherwise stated. BMI, body mass index; DLQI, Dermatology Life Quality Index; HSS7, Hives Severity Score over 7 days; ISS7, Itch Severity Score over 7 days; UAS7, Urticaria Activity Score over 7 days.

Demographics and baseline characteristics

Key baseline and disease characteristics were consistent with the target population enrolled in other CSU trials (Table 1).[18,19,33–34] The mean age was 46.8 years (SD 14.4) for benralizumab 30 mg, 45.6 years (SD 15.1) for benralizumab 60 mg and 47.1 years (SD 14.3) for placebo groups. Patients were primarily female (benralizumab 30 mg, 74.6%; benralizumab 60 mg, 80.4%; placebo, 62.5%) and White (78.0%, 75.0% and 75.0%, respectively). The proportion of patients receiving higher-than-labelled antihistamine dose/combination treatment prior to study entry was similar among groups (benralizumab 30 mg, 8.5%; benralizumab 60 mg, 8.9%; placebo, 10.0%). Baseline mean ISS7 scores

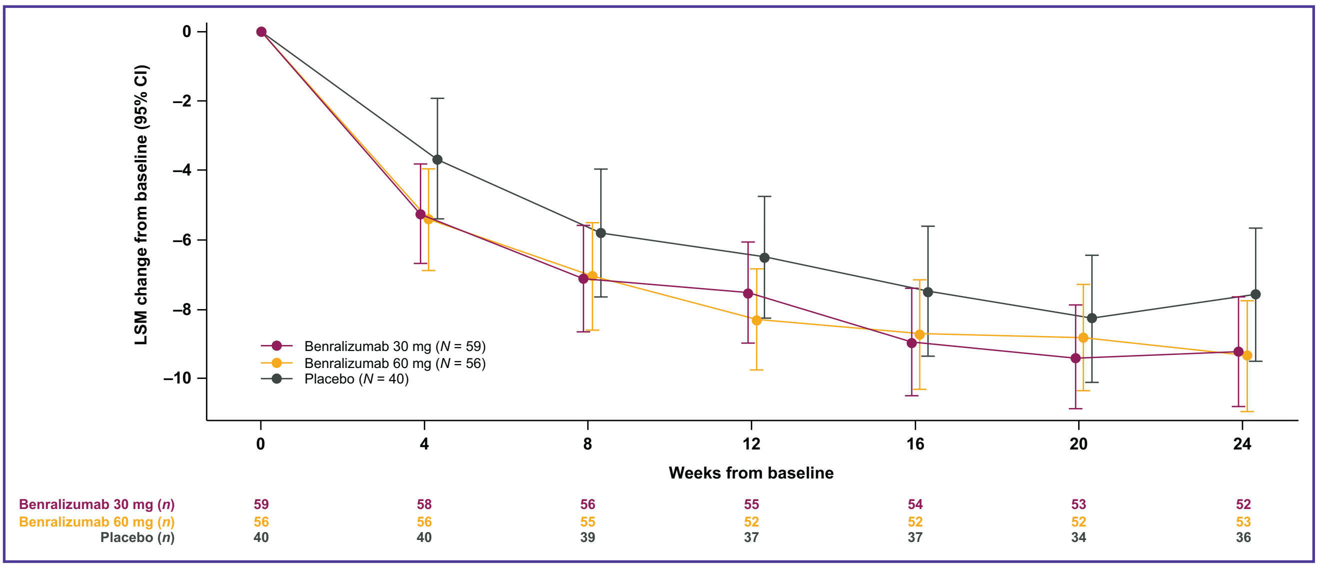


Figure 3 LSM change from baseline in ISS7 up to week 24. CI, confidence interval; LSM, least-squares mean; ISS7, Itch Severity Score over 7 days. ISS7 ranges from 0 (no itch) to 21 (worst itch).

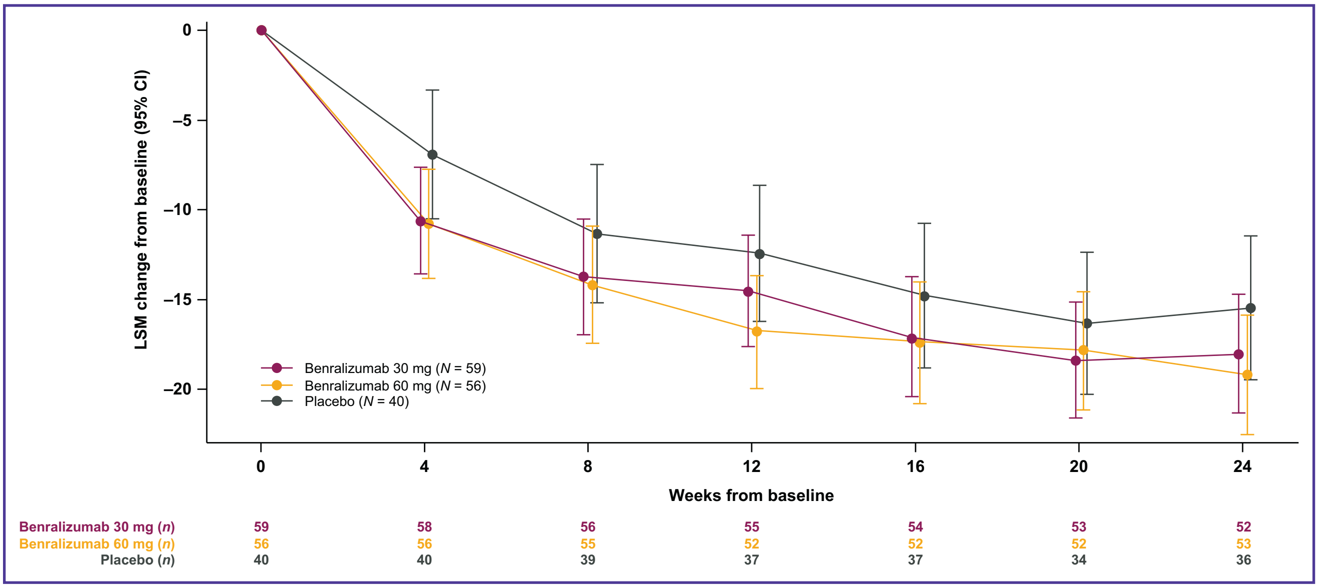


Figure 4 LSM change from baseline in UAS7 up to week 24. LSM, least-squares mean; UAS7, 7-day Urticaria Activity Score. UAS7 ranges from 0 (no urticaria) to 42 (worst urticaria).

were similar across treatment groups [benralizumab 30 mg, 15.3 (SD 4.2); benralizumab 60 mg, 15.8 (SD 4.1); placebo, 15.5 (SD 3.6)].

Primary and secondary endpoints

There was no significant difference in the change from baseline in ISS7 at week 12 between benralizumab (both doses) and placebo [Figure 3; benralizumab 30 mg vs. placebo: least-squares mean difference (LSMD) −1.01 (95% CI −3.28 to 1.26), $P=0.3824$; benralizumab 60 mg vs. placebo: LSMD −1.79 (95% CI −4.09 to 0.50), $P=0.1244$]. There was no significant difference in the key secondary endpoint of change from baseline in UAS7 score at week 12 between benralizumab (both doses) and placebo (Figure 4; benralizumab 30 mg vs. placebo: LSMD −2.07 (95% CI −6.95 to 2.80), $P=0.402$; benralizumab 60 mg vs. placebo: LSMD −4.36 (95% CI −9.28 to 0.56, $P=0.082$). There was no difference in the proportion of responders with UAS7 ≤ 6 or UAS7 = 0 at weeks 12 and 24 [Figure 5; benralizumab 30 mg and benralizumab 60 mg vs. placebo: odds ratio (OR) 2.51, 95% CI 0.75–8.46, and OR 2.36, 95% CI 0.69–8.07 (UAS7 ≤ 6); OR 0.97, 95% CI 0.24–3.93 and OR 0.49, 95% CI 0.11–2.31 (UAS7 = 0) for week 12; OR 1.05, 95% CI 0.43–2.60 and OR 1.54, 95% CI 0.63–3.75 (UAS7 ≤ 6); OR 0.79, 95% CI 0.28–2.26 and OR 1.02, 95% CI 0.36–2.85 (UAS7 = 0) for week 24, respectively]. No between-group differences in UAS7 severity scores were observed.

The changes from baseline in Hives Severity Score over 7 days (HSS7) at weeks 12 and 24 were also not statistically

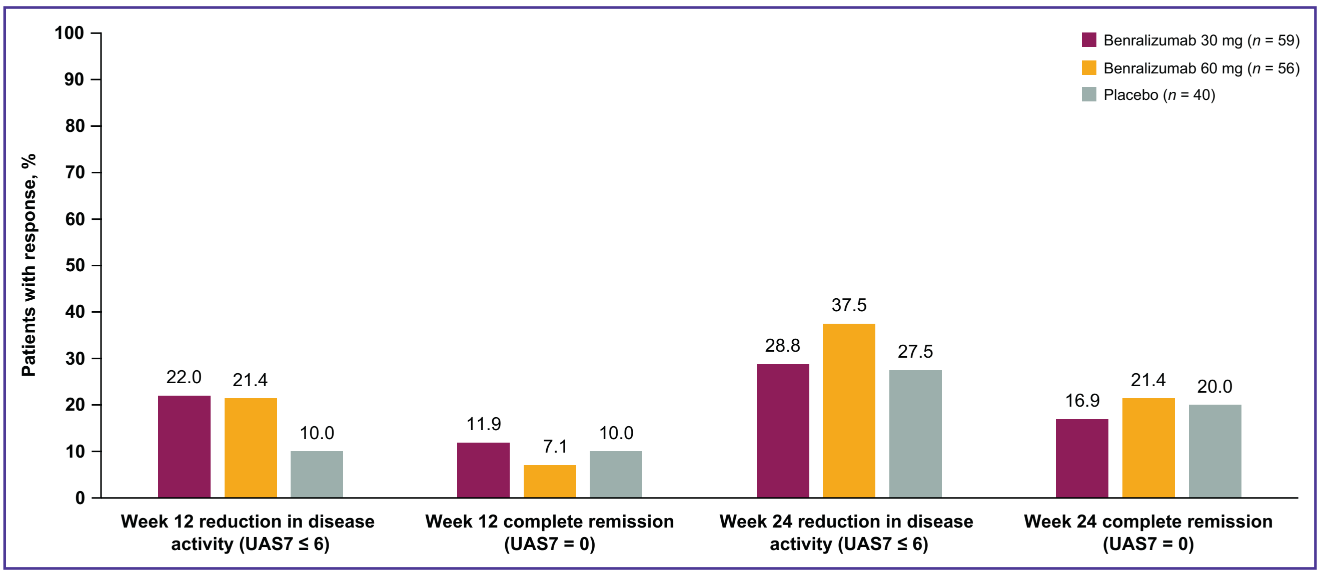


Figure 5 UAS7 unadjusted response rate by treatment group at weeks 12 and 24. UAS7, Urticaria Activity Score over 7 days.

Table 2 Primary and secondary endpoints

Outcome	Benralizumab 30 mg ($n=59$)	Benralizumab 60 mg ($n=56$)	Placebo ($n=40$)
ISS7 at week 12 change from baseline	$n=55$	$n=52$	$n=37$
LSM (95% CI)	–7.50 (–8.94 to –6.05)	–8.28 (–9.76 to –6.80)	–6.49 (–8.24 to –4.74)
LSMD (95% CI) vs. placebo	–1.01 (–3.28 to 1.26)	–1.79 (–4.09 to 0.50)	
P-value vs. placebo	0.382	0.124	
UAS7 score at week 12 change from baseline	$n=55$	$n=52$	$n=37$
LSM (95% CI)	–14.48 (–17.58 to –11.38)	–16.77 (–19.94 to –13.59)	–12.41 (–16.17 to –8.65)
LSMD (95% CI) vs. placebo	–2.07 (–6.95 to 2.80)	–4.36 (–9.28 to 0.56)	
P-value vs. placebo	0.402	0.082	
Proportion of responders (UAS7 ≤ 6) at week 12, *n* (%)	13 (22.0)	12 (21.4)	4 (10.0)
Adjusted response rate (%), (95% CI)[a]	22.04 (13.32–34.22)	21.04 (12.40–33.42)	10.31 (3.95–24.32)
OR (95% CI) vs. placebo	2.51 (0.75–8.46)	2.36 (0.69–8.07)	
HSS7 score week 12 change from baseline	$n=55$	$n=52$	$n=37$
LSM (95% CI)	–7.03 (–8.84 to –5.22)	–8.47 (–10.32 to –6.62)	–5.87 (–8.06 to –3.68)
LSMD (95% CI) vs. placebo[a]	–1.16 (–4.00 to 1.68)	–2.60 (–5.46 to 0.27)	
P-value vs. placebo	0.420	0.075	
Time (weeks) to ≥ 5-point decrease in ISS7, patients with ≥ 5-point decrease, *n* (%)	48 (81.4)	50 (89.3)	33 (82.5)
Mean (SD)	3.58 (4.201)	3.72 (4.329)	7.24 (6.295)
Proportion of patients with complete UAS7 response (UAS7 = 0) at week 12	7 (11.9)	4 (7.1)	4 (10.0)
Adjusted response rate (%), (95% CI)[a]	NC	NC	NC
OR (95% CI) vs. placebo	0.97 (0.24–3.93)	0.49 (0.11–2.31)	
Percentage of angio-oedema-free days over the past 7 days at week 12 in patients with angio-oedema at baseline or history of angio-oedema, mean (SD, *n*)	75.41 (37.705, $n=37$)	82.57 (35.706, $n=28$)	81.93 (34.548, $n=22$)
Patients with angio-oedema in the past 7 days at week 12, M[b] (%, m[c])	14 (35.9%, m[c] = 39)	6 (20.7%, m[c] = 29)	6 (26.1%, m[c] = 23)
UCT at week 12 change from baseline	$n=55$	$n=51$	$n=38$
LSM (95% CI)	4.74 (3.71–5.76)	6.11 (5.05–7.17)	5.02 (3.78–6.26)
LSMD (95% CI) vs. placebo[a]	–0.29 (–1.90 to 1.32)	1.09 (–0.54 to 2.72)	
P-value vs. placebo	0.726	0.189	
CU-Q_2oL score at week 12 change from baseline	$n=55$	$n=51$	$n=38$
LSM (95% CI)	–16.47 (–20.10 to –12.84)	–20.34 (–24.09 to –16.60)	–18.10 (–22.46 to –13.74)
LSMD (95% CI) vs. placebo[a]	1.63 (–4.05 to 7.32)	–2.24 (–7.98 to 3.50)	
P-value vs. placebo	0.570	0.442	
CU-Q_2oL score at week 24 change from baseline	$n=51$	$n=52$	$n=37$
LSM (95% CI)	–17.60 (–21.81 to –13.40)	–22.11 (–26.38 to –17.84)	–19.07 (–24.09 to –14.05)
LSMD (95% CI) vs. placebo[a]	1.47 (–5.09 to 8.02)	–3.04 (–9.62 to 3.54)	
P-value vs. placebo	0.659	0.362	
DLQI score at week 12 change from baseline	$n=55$	$n=51$	$n=38$
LSM (95% CI)	–7.58 (–9.18 to –5.98)	–9.31 (–10.96 to –7.66)	–8.06 (–9.98 to –6.14)
LSMD (95% CI) vs. placebo[a]	0.48 (–2.02 to 2.98)	–1.25 (–3.78 to 1.29)	
P-value vs. placebo	0.7037	0.3320	
DLQI score at week 24 change from baseline	$n=51$	$n=52$	$n=37$
LSM (95% CI)	–8.13 (–9.84 to –6.42)	–10.25 (–11.98 to –8.51)	–9.37 (–11.41 to –7.33)
LSMD (95% CI) vs. placebo[a]	1.24 (–1.42 to 3.90)	–0.88 (–3.56 to 1.80)	
P-value vs. placebo	0.359	0.518	
ISS7 score at week 24 change from baseline	$n=52$	$n=53$	$n=36$
LSM (95% CI)	–9.19 (–10.77 to –7.61)	–9.33 (–10.93 to –7.73)	–7.57 (–9.48 to –5.66)
LSMD (95% CI) vs. placebo[a]	–1.62 (–4.10 to 0.86)	–1.76 (–4.25 to 0.73)	
P-value vs. placebo	0.2	0.165	
UAS7 score at week 24 change from baseline	$n=52$	$n=53$	$n=36$
LSM (95% CI)	–17.99 (–21.29 to –14.68)	–19.17 (–22.51 to –15.83)	–15.43 (–19.43 to –11.44)
LSMD (95% CI) vs. placebo[a]	–2.56 (–7.74 to 2.63)	–3.74 (–8.95 to 1.47)	
P-value vs. placebo	0.331	0.158	
Proportion of responders (UAS7 ≤ 6) at week 24, *n* (%)	17 (28.8)	21 (37.5)	11 (27.5)
Adjusted response rate (%), (95% CI)[a]	28.90 (18.84–41.57)	37.13 (25.63–50.30)	27.87 (16.26–43.45)
OR (95% CI) vs. placebo	1.05 (0.43–2.60)	1.54 (0.63–3.75)	
HSS7 score at week 24 change from baseline	$n=52$	$n=53$	$n=36$
LSM (95% CI)	–8.88 (–10.76 to –7.00)	–9.81 (–11.71 to –7.91)	–7.82 (–10.09 to –5.54)
LSMD (95% CI) vs. placebo[a]	–1.06 (–4.01 to 1.89)	–2.00 (–4.96 to 0.97)	
P-value vs. placebo	0.477	0.185	
Proportion of patients with complete UAS7 response (UAS7 = 0) at week 24, *n* (%)	10 (16.9)	12 (21.4)	8 (20.0)
Adjusted response rate (%), (95% CI)[a]	17.12 (9.54–28.81)	20.83 (12.26–33.12)	20.54 (10.80–35.59)

(*Continued*)

Table 2 (*Continued*)

Outcome	Benralizumab 30 mg (*n*=59)	Benralizumab 60 mg (*n*=56)	Placebo (*n*=40)
OR (95% CI) vs. placebo	0.79 (0.28–2.26)	1.02 (0.36–2.85)	
Percentage of angio-oedema-free days over the past 7 days at week 24 in patients with angio-oedema at baseline or history of angio-oedema, mean (SD, *n*)	78.50 (36.992, *n*=32)	91.33 (27.032, *n*=28)	86.79 (31.798, *n*=20)
Patients with angio-oedema in the past 7 days at week 24, M[b] (%, m[c])	11 (28.2%, m[c]=39)	3 (10.3%, m[c]=29)	4 (17.4%, m[c]=23)
UCT at week 24 change from baseline	*n*=51	*n*=52	*n*=37
LSM (95% CI)	5.24 (4.04–6.45)	6.87 (5.65–8.09)	5.88 (4.44–7.32)
LSMD (95% CI) vs. placebo[a]	–0.63 (–2.51 to 1.24)	0.99 (–0.89 to 2.88)	
P-value vs. placebo	0.505	0.299	

CI, confidence interval; CU-Q$_2$oL, Chronic Urticaria Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index; HSS7, Hives Severity Score over 7 days; ISS7, Itch Severity Score over 7 days; LSM, least-squares mean; LSMD, LSM difference; NC, not calculable; OR, odds ratio; UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test. [a]No significant difference between benralizumab 30 mg and placebo and between benralizumab 60 mg and placebo. Adjusted response rate: adjusted proportions are calculated using the marginal standardization method. [b]The number of participants with angio-oedema in the past 7 days. [c]Number in analysis at visit is the number of participants that could have reached the timepoint of the study.

significant (benralizumab 30 mg and benralizumab 60 mg vs. placebo: LSMD −1.16, 95% CI −4.00 to 1.68 and LSMD −2.60, 95% CI −5.46 to 0.27 for week 12; LSMD −1.06, 95% CI −4.01 to 1.89, and LSMD −2.00, 95% CI −4.96 to 0.97 for week 24, respectively) (Figure S1; see Supporting Information). For all other secondary endpoints, no differences in efficacy outcomes were observed between benralizumab and placebo during the placebo-controlled period (Table 2).

Pharmacokinetic, pharmacodynamic and immunogenicity assessments

At weeks 12 and 24, there was marked depletion of blood eosinophils in those treated with benralizumab, which was in line with the known pharmacodynamic effects of benralizumab (Table 3).[22,35,36] At week 12, serum benralizumab concentrations were about 2.5 times higher in the benralizumab 60 mg group [*n*=53, geometric mean=2490.610 ng mL^{-1}, 0.123% coefficient of variation (CV)] vs. the benralizumab 30 mg group (*n*=52, geometric mean=995.412, 0.305% CV). At week 24, similar serum concentrations of benralizumab in both groups were observed when all patients had been receiving 30 mg for at least three cycles; in the benralizumab 30 mg group (*n*=47, geometric mean=842.988 ng mL^{-1}, 0.6% CV) and the benralizumab 60 mg group (*n*=49, geometric mean=983.387 ng mL^{-1}, 0.591% CV; Figure S2; see Supporting Information). A total of 27.1% of patients in the benralizumab 30 mg and 23.2% of patients in the benralizumab 60 mg group were positive for ADAs at any time through week 24; 24.1% of patients in the benralizumab 30 mg group and 18.5% of patients in the benralizumab 60 mg group had treatment-emergent ADAs detected during this time. This was not associated with reduced eosinophil depletion.

Exploratory/subgroup analyses

While there was reduction in the proportion of patients with rescue medication use over time, similar rates were observed in all arms during the trial (Figure 6). There was no evidence of response in any patient subgroup, including populations identified based on disease characteristics at baseline, such as ISS7, UAS7, HSS7 and duration of CSU at enrolment. There were no remarkable differences between the benralizumab groups and placebo in subgroups either based on medication use prior to study entry (i.e. omalizumab, antihistamines) or by baseline biomarker levels [blood eosinophils (median < 130 cells per μL vs. ≥ 130 cells per μL), blood basophils (median < 40 cells per mL vs. ≥ 40 cells per mL), blood neutrophils (median < 4020 cells per mL vs. ≥ 4020 cells per mL), IgG to FcεR1α, total IgE and BHRA; Figure 7].

Safety

Safety results were similar across the treatment arms and are consistent with the known profile of benralizumab, with no new findings, even at the higher dosage (Table 4). The most common adverse events were COVID-19 (8.5% in

Table 3 Effect of benralizumab on blood eosinophils at week 24

Eosinophils, cells per μL	Benralizumab 30 mg (*n*=59)		Benralizumab 60 mg (*n*=56)		Placebo (*n*=40)	
	Result	Change from baseline	Result	Change from baseline	Result	Change from baseline
Mean (SD)						
Baseline	139.0 (93.03)		165.4 (128.13)		182.3 (115.08)	
Week 24	42.6 (58.85)	–94.3 (100.6)	30.7 (23.42)	–136.5 (135.49)	164.7 (91.93)	–15.3 (83.55)
Median (IQR)						
Baseline	120.0 (90.0–170.0)		140.0 (80.0–210.0)		150.0 (110.0–240.0)	
Week 24	30.0 (20.0–40.0)	–90.0 (–120.0 to –55.0)	20.0 (10.0–40.0)	–105.0 (–190.0 to –40.0)	170.0 (75.0–230.0)	0 (–40.0 to 40.0)

IQR, interquartile range.

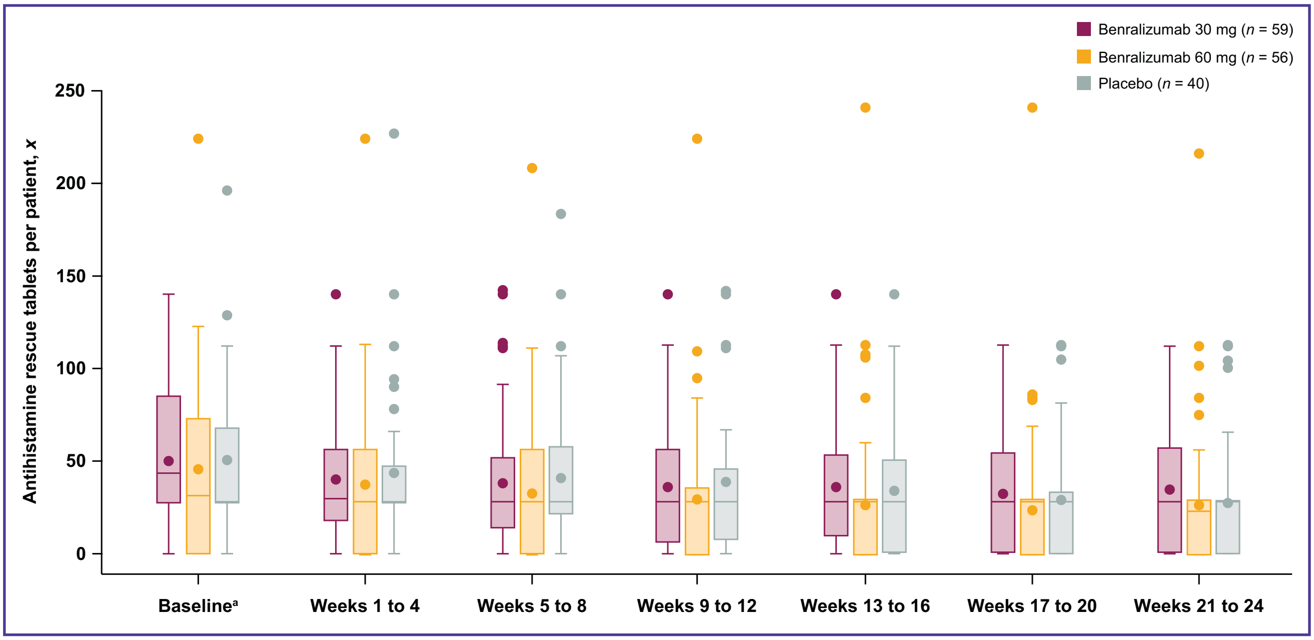


Figure 6 Rescue medication use. [a]Baseline values are based on the 10 days prior to randomization, then scaled up to the equivalent number in a 28-day period to enable comparisons with the postbaseline 28-day periods.

the benralizumab 30 mg group, 8.9% in the benralizumab 60 mg group and 2.5% in the placebo group), headache (5.1%, 5.4% and 5.0%, respectively) and myalgia (5.1%, 1.8% and 2.5%, respectively). All serious adverse events [benralizumab 60 mg, $n=3$ (5.1%); benralizumab 60 mg, $n=1$ (1.8%); placebo, $n=0$] were resolved, and most were reported as not related to benralizumab, with the exception of angio-oedema and urticaria [both $n=1$ (1.8%) in the benralizumab 60 mg group only].

Discussion

It was thought that direct targeting of the IL-5 receptor may be effective in CSU through its effects on immune-mediating cells, such as eosinophils. However, in the 24-week placebo-controlled period of the ARROYO study, changes compared with placebo in the primary and key secondary endpoints were not observed in the overall population, although benralizumab treatment did result in the expected pharmacodynamic effect of blood eosinophil depletion. In light of this, and the fact that no placebo control was available beyond week 24, interpretation of the 28-week extension period data was limited. In addition, the extension period data are incomplete, as the trial was stopped following the primary analysis. Despite these limitations, there was no evidence of further efficacy with longer duration of treatment. Therefore, the results for the 28-week extension period are not reported here. The pathophysiology of CSU is complex, and though eosinophils may contribute to the ongoing immune response in CSU, depletion of eosinophils (and, to a lesser extent, depletion of basophils) alone is not sufficient to control the disease. There was no strong evidence of response in any patient subgroup included in this study, including populations identified based on disease characteristics [ISS7, UAS7 and HSS7 at baseline, as well as duration of CSU at enrolment, prior medication (omalizumab and antihistamines) and biomarkers (blood eosinophils, blood basophils, blood neutrophils, IgG to FcεR1α, total IgE and BHRA)]. Despite a placebo response in ARROYO that was comparable with what was seen in previous CSU trials,[18,19,32,33] biomarker subgroup data support the conclusion of no meaningful efficacy for benralizumab treatment in the current study population. The lack of a statistically significant or clinically meaningful treatment effect of benralizumab suggests that the pathogenesis of this skin disease is more complex than that of respiratory diseases, as eosinophil depletion with benralizumab was demonstrated to deliver clinical efficacy in patients with eosinophilic asthma.[37,38]

This study had several strengths. ARROYO was well designed and well conducted. The measures of disease severity at baseline were similar to those in previous CSU trials, and it was unlikely that patient factors observed would confound interpretation.The study also had a number of limitations. More than half of the patients in this study were recruited from Europe, which resulted in a majority White patient population (> 75% of the total enrolled population). For future studies in CSU, it would be prudent to aim to recruit a more racially diverse representative sample. The study did not exclude patients with eosinopenia, which could have impacted the efficacy findings, as there is a well-described CSU phenotype associated with eosinopenia as well as type IIb autoimmunity, high disease activity and poor response to currently approved biologic treatments.[5]

In conclusion, despite near-complete depletion in blood eosinophils, benralizumab treatment did not demonstrate clinical benefit over placebo for the primary or secondary study endpoints or subgroup analysis. The complexity and as yet not fully characterized heterogeneity of the disease warrant further studies to identify better treatment paradigms for CSU.

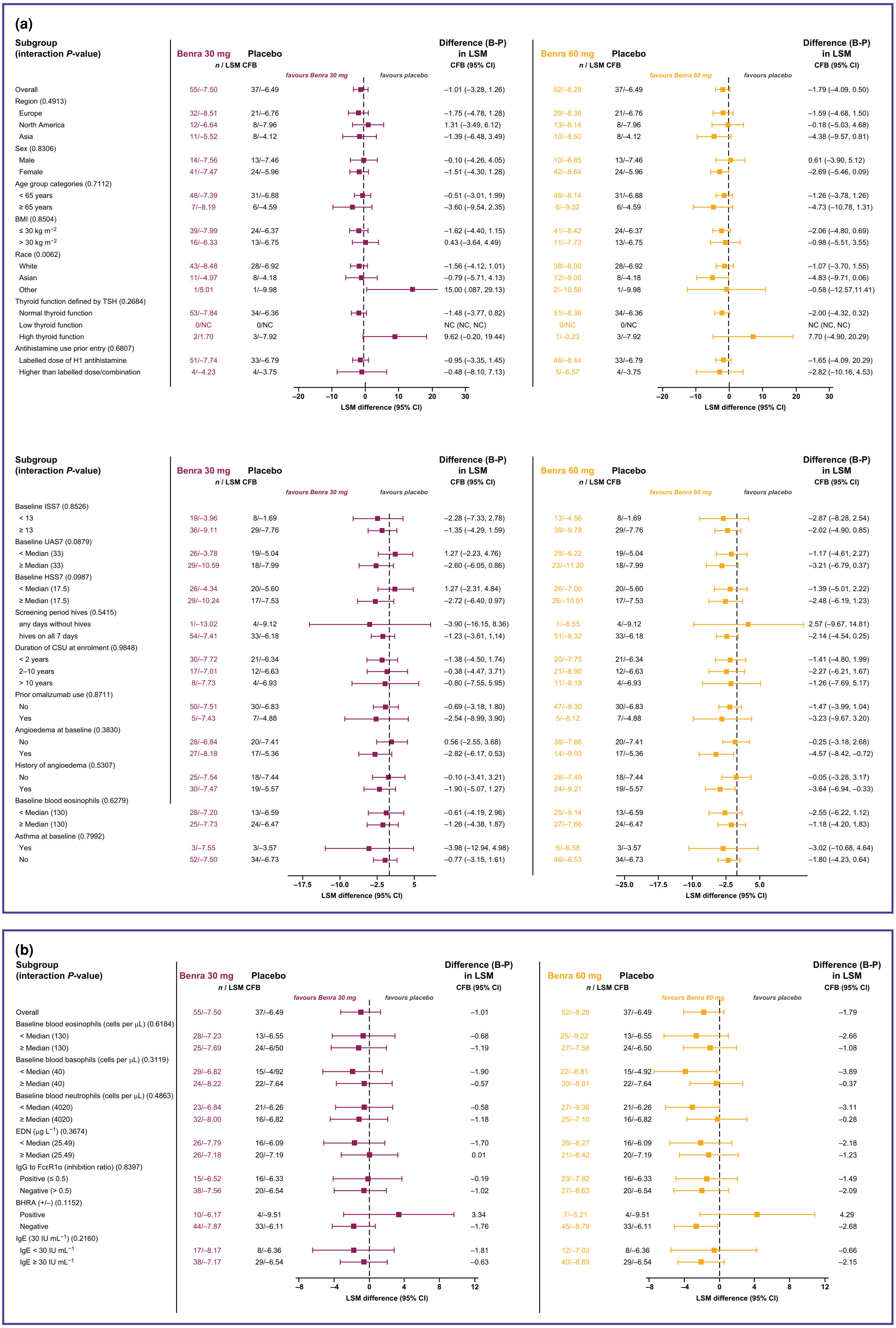


Figure 7 ISS7 at week 12: subgroup analysis. (a) Stratified by baseline demographics and characteristics. (b) Stratified by baseline biomarker levels. Benra, benralizumab; BMI, body mass index; B-P, benra–placebo; CFB, change from baseline; EDN, eosinophil-derived neurotoxin; FcεR1α, high-affinity IgE receptor; ISS7, Itch Severity Score over 7 days; LSM, least-squares mean; NC, not calculable; TSH, thyroid-stimulating hormone.

Table 4 Patients with adverse events (AEs) by category

AEs during the 24-week placebo-controlled period, on treatment	Benralizumab 30 mg (*n*=59)	Benralizumab 60 mg (*n*=56)	Placebo (*n*=40)
Any AE	34 (57.6)	30 (53.6)	23 (57.5)
Most common preferred terms:			
COVID-19	5 (8.5)	5 (8.9)	1 (2.5)
Headache	3 (5.1)	3 (5.4)	2 (5.0)
Myalgia	3 (5.1)	1 (1.8)	1 (2.5)
Arthralgia	2 (3.4)	0	2 (5.0)
Any AE with outcome of death	0	0	0
Any SAE	3 (5.1)	1 (1.8)	0
Hypersensitivity	1 (1.7)	0	0
Subarachnoid haemorrhage	1 (1.7)	0	0
Biliary colic	1 (1.7)	0	0
Angio-oedema	0	1 (1.8)	0
Urticaria	0	1 (1.8)	0
Any AE leading to discontinuation of IP	3 (5.1)	1 (1.8)	0

Data are presented as *n* (%). IP, investigational product; SAE, serious adverse event.

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Conflicts of interest

S.A. is or recently was a speaker and/or advisor for and/or has received research funding from AstraZeneca, BioCryst, Blueprint, CSL Behring, LEO Pharma, Moxie, Novartis, Pfizer, Pharvaris, Sanofi-Regeneron, Takeda and Thermo Fisher Scientific. A.M.G.-A. is or recently was a speaker and/or advisor for and/or has received research funding from Almirall, Amgen, AstraZeneca, Avene, Celldex, Escient Pharmaceuticals, Genentech, GlaxoSmithKline, Instituto Carlos III-FEDER, LEO Pharma, Menarini, Mitsubishi Tanabe Pharma, Novartis, Sanofi-Regeneron, Servier, Thermo Fisher Scientific and Uriach Pharma/Neucor. J.A.B. has been a consultant for Escient Pharmaceuticals, Jasper Therapeutics and Ono Pharmaceutical, and has been a principal investigator and consultant for Amgen, AstraZeneca, Celldex Therapeutics, Genentech, Novartis and Sanofi-Regeneron. M.M. has received honoraria as a speaker and/or consultant for AbbVie, Amgen, argenx, AstraZeneca, Bayer, Beiersdorf, Celldex, Escient Pharmaceuticals, Galderma, GlaxoSmithKline, Incyte, Jasper Therapeutics, Novartis, Pfizer, Pharvaris, Sanofi, Teva, Third Harmonic Bio and Vifor. L. Bahadori, M.B., L.Brooks, C.N.H., P.J., P.B.L., E.R.-S., C.W. and C.J.D. are or were employees of AstraZeneca at the time of the study and may own stock or stock options.

Data availability

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Ethics statement

Independent ethics committees of the trial centres or central institutional review boards approved the trial protocols, amendments, informed consent form, investigator brochure and other relevant documents. The trial was conducted in accordance with the principles of the Declaration of Helsinki and guidelines from the International Council for Harmonisation and Good Clinical Practice. All patients provided written informed consent prior to enrolment.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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