Synoptic Clinical Study Report	
Drug Substance	Benralizumab
Study Code	D3259C00001
Edition Number	1.0
Date	06 June 2023
EudraCT Number	2020-000169-17
NCT Number	NCT04612725

A Phase 2b Multinational, Randomised, Double-blind, Parallel-group, 24-week Placebo-controlled Study with 28-week Extension to Investigate the Use of Benralizumab in Patients with Chronic Spontaneous Urticaria Who are Symptomatic Despite the Use of Antihistamines (ARROYO)

Study dates:
First participant enrolled: 27 October 2020
Last participant last visit: 28 March 2023
The analyses presented in this report are based on a clinical data lock date of 12 October 2022 and an update from final clinical data lock of 24 April 2023.

Phase of development:
Therapeutic exploratory (II)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

The study Sponsor, AstraZeneca (AZ), has made the determination that the results of the D3259C00001 (ARROYO) study do not support the continued development of benralizumab for the indication of chronic spontaneous urticaria (CSU). For this reason, the study was terminated after the primary analysis and results of the study are presented in the format of a synoptic clinical study report (CSR) per the AZ company standard process. Results presented in this CSR include those from the primary analysis of the study, performed when follow-up of the placebo-controlled period of the study was complete, and the final safety update analysis which was performed when the last participant completed the study follow-up visit after the study was terminated.

Study centre(s)

A total of 46 study centres in 7 countries (Bulgaria, Poland, Spain, Germany, the United States, Japan, and Korea) consented at least 1 participant.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary	
• To determine the clinical efficacy of benralizumab compared to placebo in patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	• Population: Full Analysis Set • Endpoint: Change from baseline in ISS7 at Week 12 • Intercurrent events: All data up to Week 12 will be included regardless of randomised treatment adherence or rescue medication received • Summary measure: difference in least squares mean change from baseline in ISS7 at Week 12 between benralizumab and placebo
Secondary	
• To evaluate the effect of benralizumab compared to placebo on supportive measures of clinical efficacy in patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	• Key secondary endpoint: Change from baseline in UAS7 at Week 12 [a] • Change from baseline in UAS7 at Week 24 • Proportion of responders (UAS7 $\leq$ 6) at Week 12 • Change from baseline in HSS7 at Week 12 • Time to $\geq$ 5 point decrease (clinically relevant decrease) in ISS7 • Proportion of participants with complete UAS7 response (UAS7 = 0) at Week 12 • Measures of angioedema activity at Week 12 in participants with angioedema at baseline • Change from baseline in UCT at Week 12
• To evaluate the effect of benralizumab on patient-reported health-related quality of life measures in patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	• Change from baseline in CU-Q_2oL at Weeks 12 and 24 • Change from baseline in DLQI at Weeks 12 and 24
• To assess the PK and immunogenicity of benralizumab 30 mg and 60 mg in patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	• Serum benralizumab concentration • ADA
• To evaluate the longer-term effect of benralizumab compared to placebo at Week 24 on measures of clinical efficacy in patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	• Change from baseline in ISS7 at Week 24 • Change from baseline in UAS7 at Week 24 • Proportion of responders (UAS7 $\leq$ 6) at Week 24 • Change from baseline in HSS7 at Week 24 • Proportion of participants with complete UAS7 response (UAS7 = 0) at Week 24 • Measures of angioedema activity at Week 24 in participants with angioedema at baseline • Change from baseline in UCT at Week 24

Objectives	Estimand description/Endpoints
• To evaluate the efficacy of administration of benralizumab Q8W versus Q4W up to Week 52 in patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	• Change from baseline in ISS7 at Week 52 • Other supportive efficacy assessments at Week 52 in participants on a Q8W dosing regimen compared to those on a Q4W dosing regimen.
Safety	
• To assess the safety and tolerability of benralizumab in patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory values. Assessments related to AEs cover: • Occurrence/frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP Vital signs parameters include systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height. Assessments related to vital signs cover: • Observed value • Absolute and percent change from baseline values over time
Tertiary/exploratory	
• To evaluate the effect of benralizumab compared to placebo on healthcare resource utilisation due to CSU in patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	• Rate of CSU-related healthcare resource utilisation during the study
• To evaluate the effect of benralizumab compared to placebo on overall severity of disease patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	• Change from baseline in PGI-S score at Week 12 and at Week 24
• To evaluate the mechanism of action of benralizumab in patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	CCI [redacted]
CCI [redacted]	
• To evaluate the effect of benralizumab compared to placebo on general health status in patients with CSU who are symptomatic despite the use of H_1 antihistamine treatment.	• Change from baseline in EQ-5D-5L domain and VAS scores

[a] The key secondary endpoint used the same treatment policy strategy estimand as outlined for the primary endpoint. All other estimands are detailed fully in the SAP (Appendix 16.1.9).

ADA, anti-drug antibodies; AE, adverse event; CU-Q_2oL, Chronic Urticaria Quality of Life Questionnaire; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; EQ-5D-5L, European Quality of Life-5 Dimensions; HSS7, hives severity score over 7 days; ISS7, itch severity score over 7 days; IP, investigational product; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; RNA, ribonucleic acid; SAP, Statistical Analysis Plan; UAS7, urticaria activity score over 7 days; UCT, Urticaria Control Test; VAS, visual analogue scale.

Study design

This was a Phase 2b multinational, randomised, double-blind, parallel-group, 24-week placebo-controlled study with 28-week extension. The study evaluated the efficacy and safety of benralizumab in male and female participants ≥ 18 years of age with CSU refractory to standard of care treatment which included second generation H_1 antihistamines (at approved or up to 4 times approved doses) as monotherapy or in combination with leukotriene receptor antagonists (LTRAs) and/or H_2 blockers. The study was designed to evaluate 2 induction doses of benralizumab (60 mg and 30 mg) compared to placebo, and a comparison of maintenance dosing regimens (Q8W versus Q4W) in the 28-week extension period.

This study consisted of the following consecutive periods:

- A 10-day to 4-week run-in period.
- A 24-week placebo-controlled, double-blind treatment period (comprising an initial 12-week ‘induction dose’ period followed by an additional 12-week dosing period).
- A 28-week blinded-to-dosing regimen extension period for maintenance treatment.

During the 24-week placebo-controlled period, the benralizumab 30 mg group received 30 mg of benralizumab throughout until Week 24, whereas the benralizumab 60 mg group received 60 mg of benralizumab until Week 12, and 30 mg of benralizumab until Week 24.

Following informed consent, all eligible participants entered a run-in period of 10 days to 4 weeks during which inclusion/exclusion criteria were assessed, medical history taken, and complete physical exam was conducted (Visit 1, see Table 2 in the Clinical Study Protocol [CSP] in Appendix 16.1.1). Potentially eligible participants remained on a stable, locally-approved dose of their H_1 antihistamine treatment throughout the run-in period. Participants were provided with a handheld device to respond to patient-reported outcomes (PRO) questionnaires during the study.

Target population and sample size

Approximately 240 participants were expected to be enrolled/screened in order to achieve 160 eligible study participants randomly assigned to study treatment. Randomisation of study participants was stratified by region.

Inclusion Criteria

Participants were eligible to be included in the study only if all of the following criteria applied:

Informed consent/age/gender

1 Provision of the signed and dated written informed consent of the participant prior to any mandatory study-specific procedures, sampling, and analyses. The informed consent process is described in the CSP Appendix A 3 (Appendix 16.1.1).

2 Adult participants ≥ 18 years of age at the time of signing the Informed Consent Form.

Type of participants and disease

3 Physician-confirmed diagnosis of CSU (also known as chronic idiopathic urticaria) for at least 6 months prior to screening (Visit 1).

4 Presence of pruritus and wheals for at least 6 consecutive weeks prior to screening (Visit 1), despite receiving standard of care, which may have included second generation H_1 antihistamines (at approved or up to 4-times approved doses) as monotherapy or in combination with LTRAs and/or H_2 blockers.

5 Symptomatic during run-in, defined by the following:
   (a) Urticaria activity score over 7 days (UAS7) total score of ≥ 16 with an itch severity score over 7 days (ISS7) of ≥ 8, during the 7 days prior to randomisation (Visit 2).
   (b) In-clinic UAS total score of ≥ 4 on at least one of the screening days.

6 Willing to use a second-generation H_1 antihistamine at the approved dose and as monotherapy (Section 6.5.1 in the CSP [Appendix 16.1.1]) from the screening visit (Visit 1) until the end of the study.

7 Participants had to complete daily PRO assessments and met the following compliance criteria:
   (a) Complete at least 80% of daily PRO assessments between Visit 1 and Visit 2 and
   (b) Complete at least 6 of 7 daily PRO assessments in the 7 days prior to Visit 2.

8 Compliance with the locally-approved dose of antihistamine (Section 6.5.1 in the CSP [Appendix 16.1.1]), maintained at randomisation.

Reproduction

9 Females of childbearing potential had to agree to use a highly effective method of birth control (confirmed by the Investigator) from randomisation, throughout the study duration, and within 12 weeks after last dose of IP and have a negative serum pregnancy test result on Visit 1 (note: See CSP [Appendix 16.1.1] for inclusion criterion 9 for details).

10 Females not of childbearing potential (note: See CSP [Appendix 16.1.1] for inclusion criterion 10 for details).

Exclusion Criteria

Participants were excluded from the study if any of the following criteria applied:

Medical Conditions

1 Participants with predominant inducible urticaria, ie, urticaria that was predominantly due to a clearly defined stimulus (eg, pressure [dermographism], delayed pressure, cold, heat, sunlight, vibration, water, physical exercise, or increased body temperature [cholinergic]).

2 Participants with diseases, other than chronic urticaria, with urticaria or angioedema symptoms such as urticaria vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa) and hereditary or acquired angioedema (eg, due to C1-inhibitor deficiency). Additionally, any other skin disease associated with chronic itching and/or skin lesions that, in the investigators opinion, might have influenced the study evaluations and results (eg, atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus, etc.).

See Section 5.2 of the CSP (Appendix 16.1.1) for the exclusion criteria.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Benralizumab

- Dosage formulation: Benralizumab 30 mg/mL solution (20 mM L-histidine/L-histidine hydrochloride monohydrate, 0.25 M trehalose dihydrate and 0.006% [w/v] polysorbate 20, pH 6.0) for injection in accessorised prefilled syringe (APFS), 1 mL fill volume.
- Route of administration: Subcutaneous injection.
- Batch numbers: A by-participant listing of batch numbers is presented in Listing 16.1.6.

Placebo

- Dosage formulation: Matching placebo solution (20 mM L-histidine/L-histidine hydrochloride monohydrate, 0.25 M trehalose dihydrate and 0.006% [w/v] polysorbate 20, pH 6.0) for injection in an APFS, 1 mL fill volume.
- Route of administration: Subcutaneous injection.
- Batch numbers: A by-participant listing of batch numbers is presented in Listing 16.1.6.

Duration of treatment

This study consisted of the following consecutive periods:

- A 10-day to 4-week run-in period.
- A 24-week placebo-controlled, double-blind treatment period (comprising an initial 12-week ‘induction dose’ period followed by an additional 12-week dosing period).
- A 28-week blinded-to-dosing regimen extension period for maintenance treatment.

Statistical methods

The primary efficacy analyses were based on the double-blind, 24-week placebo-controlled induction period. Available data from the extension period of the study up to Week 52 were also presented at the primary analysis. Efficacy endpoints were analysed using the Full Analysis Set, the analysis of safety endpoints was based on the Safety Analysis Set. Analysis sets are defined in Section 2.2 of the statistical analysis plan in Appendix 16.1.9. The study was terminated after the primary analysis and all ongoing participants were required to complete a final follow-up visit regardless of where they had reached in the extension period of the study. The final analysis was performed once all final follow-up visits were completed and included updated safety data presentations; no efficacy analyses were performed at the final analysis.

The primary endpoint, change from baseline in ISS7 at Week 12, was compared between each benralizumab initial treatment group (30 mg and 60 mg) with placebo using a Mixed-effect Model for Repeated Measures. The dependent variable in this model was the change from baseline in ISS7 at post-baseline protocol-specified visits (up to the Week 24 visit). Treatment group was included as an explanatory variable along with the baseline ISS7 score, region, visit and treatment-by-visit interaction as fixed effects. An unstructured covariance structure was used to model the within-patient errors. If the model failed to converge, the following structures were attempted in the specified order: Toeplitz, first-order autoregressive, compound symmetric, and variance components. Least squares (LS) mean estimates for change from baseline at Week 12 and differences in LS mean estimates between the treatment groups and placebo were obtained from this model.

Study population

A total of 221 participants were screened and 155 participants were randomised and treated. Twelve participants (7.7%) discontinued study treatment during the 24-week placebo-controlled treatment period, and 143 participants (92.3%) completed treatment in the 24-week placebo-controlled treatment period of the study.

A total of 140 participants (90.3%) entered the extension period. Twenty participants (12.9%) discontinued study treatment during the extension period, and 100 participants (64.5%) completed treatment in the extension period by the primary analysis data cut-off (12 October 2022). As of the final clinical data lock date (24 April 2023), 35 participants (22.6%) discontinued study treatment during the extension period, and 105 participants (67.7%) completed treatment in the extension period.

Overall, 41 participants (26.5%) were male, and 114 participants (73.5%) were female. A total of 34 participants (21.9%) were of age < 35 years, 79 (51.0%) were between the age of ≥ 35 and ≤ 55 years, and 42 (27.1%) were of age > 55 years; mean (standard deviation [SD]) age at screening was 46.5 (14.53) years.

There were 34 participants (21.9%) with at least 1 important protocol deviation at any point during the study, the incidence of which was similar across treatment groups. The most commonly reported important protocol deviation overall was: “did not meet daily PRO completion compliance up to Visit 2”.

Summary of efficacy results

The primary endpoint was the change from baseline in ISS7 score at Week 12, which was compared between each benralizumab initial treatment group (30 mg and 60 mg) with placebo. The primary endpoint of the study was not met. There was no significant difference in the change from baseline in ISS7 score at Week 12 between benralizumab 30 mg and placebo (difference in LS means: −1.01 [95% confidence interval {95%CI}: −3.28, 1.26], p = 0.3824), and between benralizumab 60 mg and placebo (difference in LS means: −1.79 [95%CI: −4.09, 0.50], p = 0.1244).

There were no clear differences between treatment groups in secondary efficacy endpoints. Results for primary and secondary efficacy endpoints for the 24-week placebo-controlled treatment period are presented in the table below.

There was no evidence of differential treatment effects across the pre-defined subgroup analyses.

As no difference in efficacy outcomes between benralizumab and placebo were observed during the placebo-controlled period, and no placebo control was available beyond Week 24, interpretation of the available efficacy data from the extension period of the study is limited.

Table S2 Summary of Efficacy Endpoints (Full Analysis Set)

Outcome	Benralizumab 30 mg Total N = 59	Benralizumab 60 mg Total N = 56	Placebo N = 40
Primary Efficacy Endpoint			
ISS7 score W12 change from baseline	n = 55	n = 52	n = 37
LSM (95% CI)	-7.50 (-8.94, -6.05)	-8.28 (-9.76, -6.80)	-6.49 (-8.24, -4.74)
LSM difference (95% CI) vs. placebo	-1.01 (-3.28, 1.26)	-1.79 (-4.09, 0.50)	
P-value vs. placebo	0.3824	0.1244	
Key Secondary Efficacy Endpoint			
UAS7 score W12 change from baseline	n = 55	n = 52	n = 37
LSM (95% CI)	-14.48 (-17.58, -11.38)	-16.77 (-19.94, -13.59)	-12.41 (-16.17, -8.65)
LSM difference (95% CI) vs. placebo	-2.07 (-6.95, 2.80)	-4.36 (-9.28, 0.56)	
P-value vs. placebo	0.4016	0.0819	
Secondary Efficacy Endpoints			
ISS7 score W24 change from baseline	n = 52	n = 53	n = 36
LSM (95% CI)	-9.19 (-10.77, -7.61)	-9.33 (-10.93, -7.73)	-7.57 (-9.48, -5.66)
LSM difference (95% CI) vs. placebo	-1.62 (-4.10, 0.86)	-1.76 (-4.25, 0.73)	
P-value vs. placebo	0.1995	0.1654	

Outcome	Benralizumab 30 mg Total N = 59	Benralizumab 60 mg Total N = 56	Placebo N = 40
UAS7 score W24 change from baseline	n = 52	n = 53	n = 36
LSM (95% CI)	-17.99 (-21.29, -14.68)	-19.17 (-22.51, -15.83)	-15.43 (-19.43, -11.44)
LSM difference (95% CI) vs. placebo	-2.56 (-7.74, 2.63)	-3.74 (-8.95, 1.47)	
P-value vs. placebo	0.3314	0.1582	
Proportion of responders (UAS7 ≤ 6) at W12, n (%)	13 (22.0)	12 (21.4)	4 (10.0)
Response rate (%), (95% CI)	22.04 (13.32, 34.22)	21.04 (12.40, 33.42)	10.31 (3.95, 24.32)
Difference (%) (95% CI) vs. placebo [a]	11.72 (-2.37, 25.82)	10.73 (-3.42, 24.88)	
P-value vs. placebo	0.1373	0.1697	
Proportion of responders (UAS7 ≤ 6) at W24, n (%)	17 (28.8)	21 (37.5)	11 (27.5)
Response rate (%), (95% CI)	28.90 (18.84, 41.57)	37.13 (25.63, 50.30)	27.87 (16.26, 43.45)
Difference (%) (95% CI) vs. placebo [a]	1.03 (-16.90, 18.96)	9.27 (-9.37, 27.90)	
P-value vs. placebo	0.9105	0.3389	
Proportion of participants with complete UAS7 response (UAS7 = 0) at W12			
Unadjusted response rate, n (%) [b]	7 (11.9)	4 (7.1)	4 (10.0)
P-value vs. placebo	0.9678	0.3689	
Proportion of participants with complete UAS7 response (UAS7 = 0) at W24, n (%)	10 (16.9)	12 (21.4)	8 (20.0)
Response rate (%), (95% CI)	17.12 (9.54, 28.81)	20.83 (12.26, 33.12)	20.54 (10.80, 35.59)
Difference (%) (95% CI) vs. placebo [a]	-3.43 (-18.96, 12.11)	0.28 (-15.84, 16.40)	
P-value vs. placebo	0.6624	0.9726	
HSS7 score W12 change from baseline	n = 55	n = 52	n = 37
LSM (95% CI)	-7.03 (-8.84, -5.22)	-8.46 (-10.31, -6.62)	-5.87 (-8.06, -3.68)
LSM difference (95% CI) vs. placebo	-1.16 (-4.00, 1.68)	-2.60 (-5.46, 0.27)	
P-value vs. placebo	0.4203	0.0754	
HSS7 score W24 change from baseline	n = 52	n = 53	n = 36
LSM (95% CI)	-8.88 (-10.76, -7.00)	-9.81 (-11.71, -7.91)	-7.81 (-10.09, -5.54)
LSM difference (95% CI) vs. placebo	-1.06 (-4.01, 1.89)	-2.00 (-4.96, 0.97)	
P-value vs. placebo	0.4772	0.1851	
Time (weeks) to ≥ 5-point decrease in ISS7, participants with ≥ 5-point decrease, n (%)	48 (81.4)	50 (89.3)	33 (82.5)
Median time to decrease (95% CI)	3.0 (2.0, 5.0)	2.0 (2.0, 3.0)	8.0 (3.0, 11.0)
Participants with angioedema at baseline or history of angioedema, N	39	29	23
Percentage of angioedema-free days over the past 7 days at W12, mean (SD, n)	77.50 (35.990, n = 36)	85.63 (32.435, n = 27)	81.93 (34.548, n = 22)
Participants with angioedema in the past 7 days at W12, M (%)	14 (35.9%)	6 (20.7%)	6 (26.1%)
Participants with angioedema at baseline or history of angioedema, N	39	29	23
Percentage of angioedema-free days over the past 7 days at W24, mean (SD, n)	78.50 (36.992, n = 32)	91.33 (27.032, n = 28)	86.79 (31.798, n = 20)

Outcome	Benralizumab 30 mg Total N = 59	Benralizumab 60 mg Total N = 56	Placebo N = 40
Participants with angioedema in the past 7 days at W24, M (%)	11 (28.2%)	3 (10.3%)	4 (17.4%)
UCT at W12 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)
LSM difference (95% CI) vs. placebo	-0.29 (-1.90, 1.32)	1.09 (-0.54, 2.72)	
P-value vs. placebo	0.7256	0.1890	
UCT at W24 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)
LSM difference (95% CI) vs. placebo	-0.63 (-2.51, 1.24)	0.99 (-0.89, 2.88)	
P-value vs. placebo	0.5048	0.2991	
CU-Q2oL score at W12 change from baseline	n = 55	n = 51	n = 38
LSM (95% CI)	-16.47 (-20.10, -12.84)	-20.34 (-24.09, -16.60)	-18.10 (-22.46, -13.74)
LSM difference (95% CI) vs. placebo	1.63 (-4.05, 7.32)	-2.24 (-7.98, 3.50)	
P-value vs. placebo	0.5704	0.4416	
CU-Q2oL score at W24 change from baseline	n = 51	n = 52	n = 37
LSM (95% CI)	-17.60 (-21.81, -13.40)	-22.11 (-26.38, -17.84)	-19.07 (-24.09, -14.05)
LSM difference (95% CI) vs. placebo	1.47 (-5.09, 8.02)	-3.04 (-9.62, 3.54)	
P-value vs. placebo	0.6591	0.3624	
DLQI score at W12 change from baseline	n = 55	n = 51	n = 38
LSM (95% CI)	-7.58 (-9.18, -5.98)	-9.31 (-10.96, -7.66)	-8.06 (-9.98, -6.14)
LSM difference (95% CI) vs. placebo	0.48 (-2.02, 2.98)	-1.25 (-3.78, 1.29)	
P-value vs. placebo	0.7037	0.3320	
DLQI score at W24 change from baseline	n = 51	n = 52	n = 37
LSM (95% CI)	-8.13 (-9.84, -6.42)	-10.25 (-11.98, -8.51)	-9.37 (-11.41, -7.33)
LSM difference (95% CI) vs. placebo	1.24 (-1.42, 3.90)	-0.88 (-3.56, 1.80)	
P-value vs. placebo	0.3590	0.5175	

[a] Treatment difference results are calculated from the logistic regression model.

[b] Unadjusted response rates are presented due to the low n.

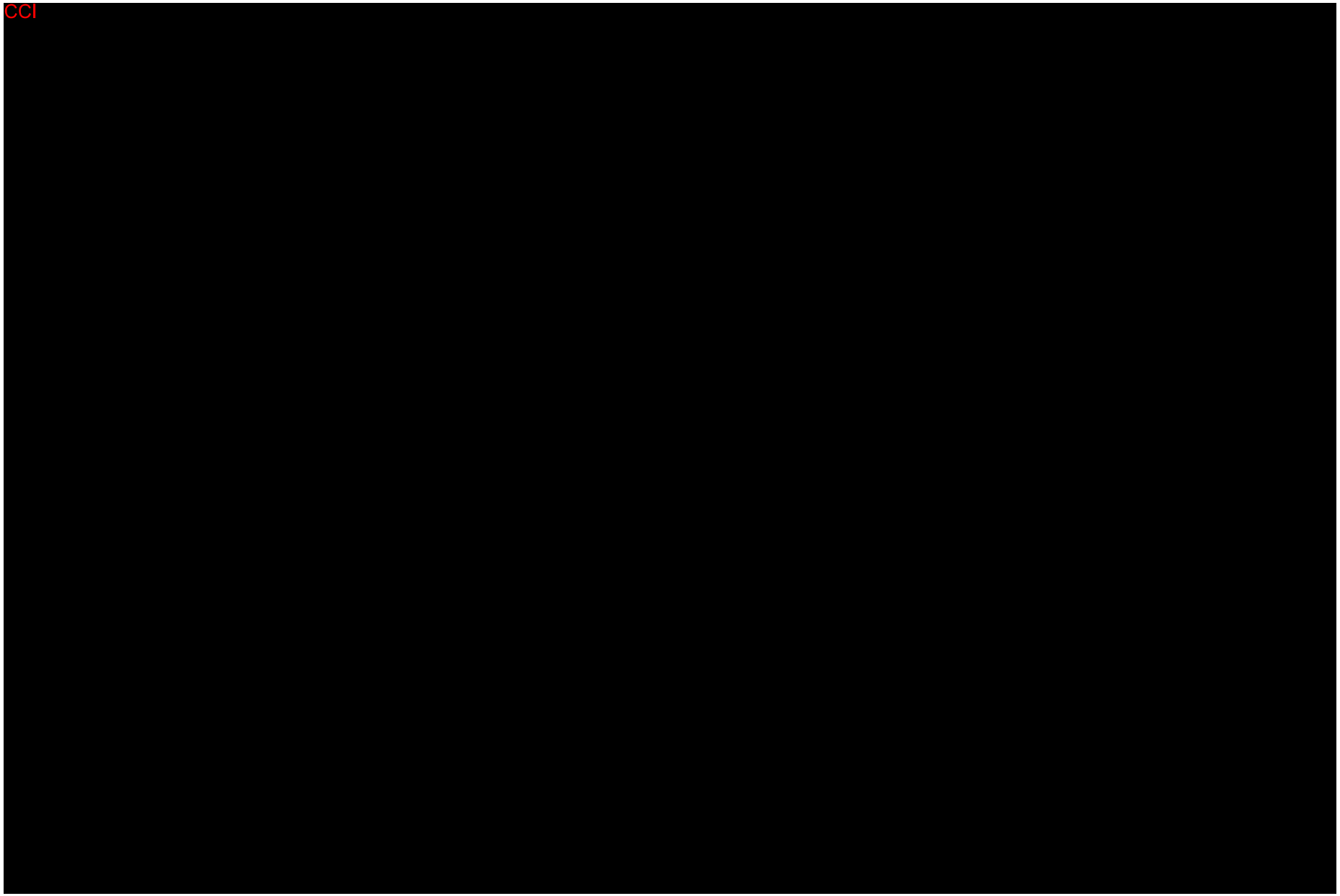
CI, confidence interval; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index; HSS7, hives severity score over 7 days; ISS7, itch severity score over 7 days; LSM, least squares mean; M, number of participants with angioedema in the past 7 days; N, number of participants in treatment group; n, number of participants included in analysis; SD, standard deviation; UAS7, urticaria activity score over 7 days; UCT, Urticaria Control Test; W, week.

Sources: Table 14.2.1.1p, Table 14.2.1.3p, Table 14.2.2.3p, Table 14.2.2.5.1p, Table 14.2.2.5.2p, Table 14.2.2.6.1p, Table 14.2.2.6.2p, Table 14.2.3.2p, Table 14.2.1.10p, Table 14.2.4.2, Table 14.2.5.3p, Table 14.2.6.2p, Table 14.2.7.2p.

- Despite not meeting primary or secondary endpoints for efficacy, blood eosinophils were depleted in line with the known pharmacodynamic effects of benralizumab. Median eosinophils had a greater decrease from baseline to Week 24 in the benralizumab 30 mg group and the benralizumab 60 mg group than in the placebo group.

- Reductions in serum levels of eosinophil-derived neurotoxin (EDN) were observed at Week 24. The median changes from baseline in EDN were larger in the benralizumab 30 mg group and the benralizumab 60 mg group than in the placebo group.
- The median changes from baseline in basophils were similar in the benralizumab 30 mg group, the benralizumab 60 mg group and the placebo group.
- Median neutrophils had a greater decrease from baseline to Week 24 in the benralizumab 30 mg group and the benralizumab 60 mg group than in the placebo group.

CCI



Summary of anti-drug antibody results

Anti-drug antibody (ADA) prevalence: A total of 27.1% of participants in the benralizumab 30 mg, and 23.2% of participants in the benralizumab 60 mg group were ADA-positive at any time during the 24-week placebo-controlled treatment period. None of the participants in the placebo group were ADA-positive at any time during the 24-week placebo-controlled period.

Anti-drug antibody incidence: ADA incidence is defined as ADA-negative at baseline and post-baseline ADA-positive, or ADA-positive at baseline and boosted the pre-existing titre by > 4-fold during the study period. A total of 24.1% of participants in the benralizumab 30 mg group, and 18.5% of participants in the benralizumab 60 mg group had treatment-emergent ADA detected during the 24-week placebo-controlled treatment period. None of the participants in the placebo group had treatment-emergent ADA detected during the 24-week placebo-controlled period.

Anti-drug antibody persistently positive: Persistently positive is defined as ADA-negative at baseline and positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment. A total of 24.1% of participants in the benralizumab 30 mg, and 13.0% of participants in the benralizumab 60 mg group were persistently ADA-positive during the 24-week placebo-controlled treatment period. The majority of post-baseline ADA responses were persistently ADA-positive.

Summary of pharmacokinetic results

A Week 12, higher serum concentrations of benralizumab were observed in the benralizumab 60 mg group (n = 52, geometric mean 2490.610 ng/mL, 0.123% coefficient of variation [CV]) than in the benralizumab 30 mg group (n = 53, geometric mean 995.412 ng/mL, 0.305% CV).

At Week 24, by which point the 60 mg group had received three × 4-weekly doses of 60 mg followed by three × 4-weekly doses of 30 mg, similar serum concentrations of benralizumab were observed in the benralizumab 60 mg group (n = 49, geometric mean 983.387 ng/mL, 0.591% CV) and the benralizumab 30 mg group (n = 47, geometric mean 842.988 ng/mL, 0.600% CV).

At Week 12, the mean change from baseline in ISS7 scores were similar between the serum concentration tertiles (T) for benralizumab 30 mg (T1: mean [SD]: −8.88 [7.429], n = 16; T2: mean [SD] = −7.88 [5.985], n = 18; T3: mean [SD] = −7.02 [7.299], n = 18) and benralizumab 60 mg (T1: mean [SD] = −9.78 [7.804], n = 16; T2: mean [SD] = −8.15 [4.227], n = 17; T3: mean [SD] = −8.51 [5.692], n = 18).

Within the benralizumab 30 mg group, serum concentrations were numerically higher in ADA-negative participants at Week 24 (n = 32, geometric mean 1058.437 ng/mL, 0.338% CV) than in ADA-persistently positive participants (n = 8, geometric mean 221.426 ng/mL,

6.498% CV) and the ADA-positive with titre > median of maximum participants (n = 6, geometric mean 125.903 ng/mL, 13.777% CV).

Within the benralizumab 60 mg group, serum concentrations were numerically higher in ADA-negative participants at Week 24 (n = 37, geometric mean 1134.143 ng/mL, 0.441% CV) than in ADA-persistently positive participants (n = 3, geometric mean 302.918 ng/mL, 2.340% CV) and the ADA-positive with titre > median of maximum participants (n = 5, geometric mean 175.315 ng/mL, 11.855% CV).

Summary of safety results

In the 24-week placebo-controlled treatment period, the following safety results were reported:

- A total of 34 participants (57.6%) in the benralizumab 30 mg group, 30 participants (53.6%) in the benralizumab 60 mg group, and 23 participants (57.5%) in the placebo group reported AEs.

Table S4 Number of Participants with Adverse Events in any Category Reported in the On-Treatment Period - 24-Week Placebo-Controlled Treatment Period (Safety Analysis Set)

	Number (%) of participants [a]		
AE category	Benralizumab 30mg Total (N = 59)	Benralizumab 60mg Total (N = 56)	Placebo (N = 40)
Any AE	34 (57.6)	30 (53.6)	23 (57.5)
Any AE with outcome = death	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	3 (5.1)	1 (1.8)	0 (0.0)
Any AE leading to discontinuation of IP	3 (5.1)	1 (1.8)	0 (0.0)
Any AE leading to dose interruption	2 (3.4)	1 (1.8)	2 (5.0)
Any AE leading to withdrawal from study	3 (5.1)	1 (1.8)	0 (0.0)

[a] Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

Includes adverse events with an onset date between the day of first dose of IP treatment and the day prior to first dose in extension period, or last dose in placebo-controlled period + 30 days for those who do not enter the extension period.

Percentages are based on the total numbers of participants in the treatment group (N).

AE, adverse event; IP, investigational product; N, number of participants in treatment group; SAE, serious adverse event.

Source: Table 14.3.2.1p.

- The most commonly reported AEs by preferred term (PT) (> 5% in either group) were coronavirus disease 2019 (COVID-19), headache, and myalgia.

Table S5 Number of Participants with Adverse Events Reported in the On-Treatment Period by Preferred Term with a Cut-off of > 5% in Either Treatment Group for Preferred Terms – 24-Week Placebo-Controlled Treatment Period (Safety Analysis Set)

	Number (%) of participants [a]		
Preferred term	Benralizumab 30 mg Total (N = 59)	Benralizumab 60 mg Total (N = 56)	Placebo (N = 40)
Participants with any AE	34 (57.6)	30 (53.6)	23 (57.5)
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)
Nasopharyngitis	1 (1.7)	4 (7.1)	2 (5.0)

[a] Number (%) of participants with AEs, sorted by descending frequency of preferred term in benralizumab 30 mg group.

Participants with multiple events in the same preferred term are counted only once in that preferred term. Participants with events in more than 1 preferred term are counted once in each of those preferred terms.

Includes adverse events with an onset date between the day of first dose of IP treatment and the day prior to first dose in extension period, or last dose in placebo-controlled period + 30 days for those who do not enter the extension period.

Percentages are based on the total numbers of participants in the treatment group (N).

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AE, adverse event; COVID-19, Coronavirus disease 2019; IP, investigational product; N, number of participants in treatment group.

Source: Table 14.3.2.3p.

- Adverse events assessed by the Investigator as possibly related to the study treatment were reported for 3 AEs in the benralizumab 30 mg group: dermatitis acneiform, menstruation irregular, and rhinorrhoea (each PT was reported by 1 distinct participant [1.7%]), and 8 AEs in the benralizumab 60 mg group: injection site erythema (2 participants [3.6%]), angioedema, headache, injection site pruritus, injection site reaction, injection site swelling, urticaria (each PT was reported by 1 distinct participant [1.8%]). Adverse events possibly related to the study treatment were reported for 2 AEs in the placebo group: oedema and pruritus (1 participant [2.5%]).
- Injection site reactions, injection site swelling, and injection site erythema reported in the benralizumab 60 mg group were all of mild intensity. No injection site reactions were reported for the benralizumab 30 mg group or placebo group.
- No AEs with the outcome of death were reported for any participant in the benralizumab 30 mg and 60 mg groups or the placebo group during the 24-week treatment period.
- Serious adverse events (SAEs) were reported for 3 participants (5.1%) in the benralizumab 30 mg group (hypersensitivity, subarachnoid haemorrhage and biliary colic; each PT was reported by 1 distinct participant [1.7%]), 1 participant (1.8%) in the benralizumab 60 mg group (angioedema and urticaria), and no participants in the placebo group.

- During the 24-week placebo-controlled treatment period, most AEs were reported as mild or moderate in intensity. Severe AEs were reported for 1 participant (1.7%) in the benralizumab 30 mg group (subarachnoid haemorrhage), and 1 participant (1.8%) in the benralizumab 60 mg group (angioedema and urticaria). No severe AEs were reported for participants in the placebo group during this treatment period.
- Three participants (5.1%) in the benralizumab 30 mg group, 1 participant (1.8%) in the benralizumab 60 mg group and no participants in the placebo group experienced AEs leading to discontinuation of study treatment during the 24-week placebo-controlled treatment period.
- There were no clinically meaningful changes in mean values from baseline for haematology variables, clinical chemistry laboratory variables, or urinalysis variables within the benralizumab 30 mg and 60 mg or placebo groups. As expected, and in line with the known pharmacodynamic effects of benralizumab, median eosinophils had a greater decrease from baseline to Week 24 in the benralizumab 30 mg and 60 mg groups than in the placebo group (see eosinophils in the summary of efficacy results).

In the 28-week extension period, the following safety results were reported as of the primary analysis data cut-off (12 October 2022):

Table S6 Number of Participants with Adverse Events in any Category Reported in the On-Treatment Period - 28-Week Extension Period (Extension Period Analysis Set)

	Number (%) of participants [a]		
AE category	Placebo/ Benralizumab (N = 37)	Benralizumab/ Q4W Total (N = 49)	Benralizumab/ Q8W Total (N = 54)
Any AE	15 (40.5)	26 (53.1)	24 (44.4)
Any AE with outcome = death	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	1 (2.7)	0 (0.0)	3 (5.6)
Any AE leading to discontinuation of IP	0 (0.0)	1 (2.0)	1 (1.9)
Any AE leading to dose interruption	1 (2.7)	1 (2.0)	1 (1.9)
Any AE leading to withdrawal from study	0 (0.0)	1 (2.0)	1 (1.9)

[a] Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

Includes adverse events with an onset date on or after day of first dose in extension period up to day of the last dose + 30 days.

Percentages are based on the total numbers of participants in the treatment group (N).

AE, adverse event; IP, investigational product; N, number of participants in treatment group; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event.

Source: Table 14.3.2.1e.

- During the 28-week extension period, the most commonly reported AEs by PT (> 5% in either group) were nasopharyngitis, COVID-19, and ligament sprain. As of the final clinical data lock date (24 April 2023), at least one AE was reported by 18 (48.6%) participants who switched to benralizumab after receiving placebo, 27 (55.1%) participants in the benralizumab/Q4W group, and 26 (48.1%) participants in the benralizumab/Q8W group. The proportion of participants who reported any AE leading to discontinuation of IP increased to 2 (3.7%) participants. The most commonly reported AEs by PT (> 5% in either group) during the 28-week extension period were nasopharyngitis, COVID-19, ligament sprain, back pain, sinusitis, and arthralgia.

Table S7 Number of Participants with Adverse Events Reported in the On-Treatment Period by Preferred Term with a Cut-off of > 5% in Either Treatment Group for Preferred Terms – 28-Week Extension Period (Safety Analysis Set)

	Number (%) of participants [a]		
Preferred term	Placebo/ Benralizumab (N = 37)	Benralizumab/ Q4W Total (N = 49)	Benralizumab/ Q8W Total (N = 54)
Participants with any AE	15 (40.5)	26 (53.1)	24 (44.4)
Nasopharyngitis	2 (5.4)	5 (10.2)	2 (3.7)
COVID-19	4 (10.8)	3 (6.1)	4 (7.4)
Ligament sprain	0 (0.0)	3 (6.1)	0 (0.0)
Dizziness	0 (0.0)	2 (4.1)	0 (0.0)
Back pain	0 (0.0)	1 (2.0)	3 (5.6)
Sinusitis	3 (8.1)	1 (2.0)	0 (0.0)
Arthralgia	3 (8.1)	0 (0.0)	0 (0.0)

[a] Number (%) of participants with AEs, sorted by descending frequency of preferred term in benralizumab/Q4W Total group.

Participants with multiple events in the same preferred term are counted only once in that preferred term. Participants with events in more than 1 preferred term are counted once in each of those preferred terms.

Includes adverse events with an onset date on or after day of first dose in extension period up to day of the last dose + 30 days.

Percentages are based on the total numbers of participants in the treatment group (N).

MedDRA version 25.0.

AE, adverse event; COVID-19, Coronavirus disease 2019; IP, investigational product; N, number of participants in treatment group; Q4W, every 4 weeks; Q8W, every 8 weeks.

Source: Table 14.3.2.3e.

- During the 28-week extension period, AEs considered by the Investigator to be possibly related to the study treatment were reported for 3 AEs in the benralizumab/Q4W group: dry mouth, dry eye (1 participant [2.0%]), and dyspnoea (1 participant [2.0%]) and no participants in the benralizumab/Q8W group. Adverse events possibly related to the study treatment were reported for 3 AEs in the group of participants who switched to benralizumab after receiving placebo: asthma and hypoaesthesia (each PT was reported

by 1 distinct participant [2.7%]). All other AEs observed during the extension period were reported as not related to study treatment. As of the final clinical data lock date (24 April 2023), AEs considered by the Investigator to be possibly related to the study treatment remained unchanged in the in the benralizumab/Q4W group and benralizumab/Q8W group. In the group of participants who switched to benralizumab after receiving placebo, an additional participant reported AE of asthma that was considered by the Investigator to be possibly related to the study treatment (total of 2 distinct participants [5.4%]).

- No AEs of injection site reactions were reported during the 28-week extension period.
- No AEs with the outcome of death were reported.
- In the 28-week extension period, 3 participants (5.6%) in the benralizumab/Q8W group reported SAEs (bladder cancer, ureterolithiasis, and meniscus injury: each PT was reported by 1 distinct participant [1.9%]), and 1 participant (2.7%) who switched to benralizumab in the extension period after receiving placebo had an SAE of asthma. The SAE of asthma was entered twice in the CRF. The duplicate entry is not an error and was done in order to enter additional event details.
- During the 28-week extension period, most AEs were reported as mild or moderate in intensity. Severe AEs were reported by 1 participant (2.0%) in the benralizumab/Q4W group (urticaria) and PPD , and no participants who switched to benralizumab after receiving placebo during the 28-week extension period.
- Four participants (6.8%) who had received benralizumab 30 mg, 2 participants (3.6%) who had received benralizumab 60 mg and 1 participant (2.5%) who had received placebo during the 24-week placebo-controlled treatment period experienced AEs leading to discontinuation of study treatment at any point during the study. Of those, 1 participant (2.0%) in the benralizumab/Q4W group and 1 participant (1.9%) in the benralizumab/Q8W group, discontinued study treatment due to AEs during the 28-week extension period. The proportion of participants who reported AEs leading to discontinuation of study treatment at any point during the study remained unchanged as of the final clinical data lock date (24 April 2023) except for one additional participant who had received benralizumab 60 mg (total of 3 participants [5.4%]). Subsequently, 3 participants (5.2%) in the benralizumab/Q4W group and 4 participants (7.0%) in the benralizumab/Q8W group, discontinued study treatment due to AEs during the 28-week extension period by final data lock.
- There were no clinically meaningful changes in mean values from baseline for haematology, clinical chemistry laboratory or urinalysis variables in the benralizumab/Q4W group, the benralizumab/Q8W group or the group who switched to benralizumab after receiving placebo during the 28-week extension period.

Conclusion(s)

Benralizumab did not demonstrate clinical benefit over placebo with respect to any of the primary or secondary efficacy endpoints in this study, and no sub-population with evidence of clinically meaningful benralizumab efficacy was identified, despite the observed blood eosinophil depletion.

The PK and immunogenicity results from this study were consistent with those reported previously for benralizumab.

During the 24-week, placebo-controlled treatment period, in participants with CSU who remained symptomatic despite treatment with standard of care treatment with antihistamines, the safety and tolerability findings were consistent with the known profile of benralizumab and no new safety concerns were observed.