Clinical Study Report Synopsis	
Drug Substance	Benralizumab
Study Code	D3255C00001
Edition Number	1.0
Date	31 May 2023
EudraCT Number	2019-002871-32
NCT Number	04543409

A Multicentre, Randomised, Double-blind, Parallel-group, Placebo-controlled Study to Investigate the Use of Benralizumab for Eosinophilic Esophagitis (MESSINA)

Study dates:

First patient enrolled: 22 September 2020

Last patient last visit: 06 February 2023

Date of early study termination: 25 October 2022

The analyses presented in this report are based on a primary analysis data cut-off date of 19 September 2022 (clinical data lock date: 14 October 2022) and a final analysis (clinical data lock date: 03 March 2023)

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator: [redacted]

Sponsor's Responsible Medical Officer: [redacted]

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study Centres

The study was conducted at 78 study centres in 12 countries.

Publications

Rothenberg ME, Dellon ES, et al. Efficacy and safety of benralizumab in adults and adolescents with eosinophilic esophagitis: results from the 24-week double-blind period of the phase 3 MESSINA trial. Presented at: Digestive Disease Week (DDW); May 7–9, 2023; Chicago, IL, USA, Conference presentation #610.

Objectives and Criteria for Evaluation

Table S1 Dual-primary Objectives and Endpoints

Objectives	Endpoints/variables
Primary	
• To evaluate the effect of benralizumab 30 mg Q4W on histological signs and clinical symptoms of EoE in patients with symptomatic and histologically active EoE	• Proportion of patients with a histological response at Week 24, defined as a peak oesophageal intraepithelial eosinophil count ≤ 6 eos/hpf • Changes from baseline in DSQ score at Week 24

DSQ Dysphagia Symptom Questionnaire; EoE eosinophilic esophagitis; eos eosinophils; hpf high-power field; Q4W every 4 weeks.

Table S2 describes the secondary objectives and endpoints/variables for the double-blind (DB) period through Week 24.

Table S2 Secondary Objectives and Endpoints

Objectives	Endpoints/variables
Secondary	
• To evaluate the effect of benralizumab 30 mg Q4W on clinical features of EoE and disease activity	• Key secondary endpoint: Percent change from baseline in tissue eosinophils at Week 24 • Key secondary endpoint: Changes from baseline in EoE-HSS grade score at Week 24 • Key secondary endpoint: Changes from baseline in EoE-HSS stage score at Week 24 • Key secondary endpoint: Changes from baseline in centrally-read EoE EREFS at Week 24 • Key secondary endpoint: Treatment responder rate at Week 24, defined as a composite of histological response (≤ 6 eos/hpf) and clinically meaningful improvement from baseline in DSQ score (30% improvement). • Centrally-read biopsies for additional histopathology including tissue eosinophil counts at Week 24 • Dysphagia-free days as captured by the DSQ • Frequency of dysphagia episodes as captured by the EoE-3D • Changes from baseline in dysphagia associated pain, discomfort, and overall severity as captured by the EoE-3D at Week 24 • Changes from baseline in abdominal pain and nausea as captured by the daily diary at Week 24 • Changes from baseline in PEESS at Week 24
• To evaluate the effect of benralizumab 30 mg Q4W on patient reported QOL measures	• Changes from baseline in EoE-QoL-A at Week 24 • SF-36-v2 Health Survey at Week 24
• To evaluate the effect of benralizumab 30 mg Q4W on healthcare resource utilisation due to EoE	• Percent of patients with relevant concomitant procedures and healthcare resource utilisation during the study through Week 24
• To evaluate the effect of benralizumab 30 mg Q4W on patient reported measures of disease severity and health status	• PGI-S at Week 24 • PGI-C at Week 24
• To assess the PK and immunogenicity of benralizumab 30 mg Q4W in patients with EoE	• Serum benralizumab concentration • ADA and nAb

ADA anti-drug antibody; DSQ Dysphagia Symptom Questionnaire; EoE eosinophilic esophagitis; EoE-3D Eosinophilic Esophagitis - Daily Dysphagia Diary; EoE-HSS Eosinophilic Esophagitis- Histology Scoring system; EoE-QoL-A Adult Eosinophilic Esophagitis Quality of Life Questionnaire; eos eosinophils; EREFS Endoscopic Reference Score; hpf high-power field; nAb neutralising antibody; PEESS Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2.0, Children and Teens Report; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; PK pharmacokinetics; Q4W every 4 weeks; QOL Quality of Life; SF-36 v2 Short Form-36 Version 2.0.

Table S3 Other Objectives and Endpoints

Other Objectives	Endpoints/variables
• To describe the longer-term effect of benralizumab 30 mg Q4W in patients with EoE	• Proportion of patients with a histological response at Week 52, defined as a peak oesophageal intraepithelial eosinophil count ≤ 6 eos/hpf • Changes from baseline in DSQ score at Week 52 • Changes from baseline in centrally-read EoE EREFS at Week 52 • Centrally-read biopsies for histopathology and tissue eosinophil counts at Week 52 • Dysphagia-free days as captured by the DSQ • Frequency of dysphagia episodes as captured by the EoE-3D • Changes from baseline in dysphagia-associated pain, discomfort, and overall severity as captured by the EoE-3D at Week 52 • Changes from baseline in abdominal pain and nausea as captured by the daily diary at Week 52 • Changes from baseline in PEESS at Week 52 • Changes from baseline in EoE-QoL-A at Week 52 • SF-36-v2 Health Survey at Week 52 • Percent of patients with relevant concomitant procedures and healthcare resource utilisation during the study through Week 52 • PGI-S at Week 52 • PGI-C at Week 52

DSQ Dysphagia Symptom Questionnaire; EoE eosinophilic esophagitis; EoE-3D Eosinophilic Esophagitis - Daily Dysphagia Diary; EoE-QoL-A Adult Eosinophilic Esophagitis Quality of Life Questionnaire; eos eosinophils; EREFS Endoscopic Reference Score; hpf high-power field; PEESS Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2.0, Children and Teens Report; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; Q4W every 4 weeks; SF-36-v2 Short Form-36 Version 2.0.

Table S4 Safety Objectives and Endpoints

Objectives	Endpoints/variables
• To assess the safety and tolerability of benralizumab 30 mg Q4W in patients with EoE	• 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

AE adverse event; EoE eosinophilic esophagitis; IP investigational product; Q4W every 4 weeks.

Exploratory objectives and endpoints are not mentioned in the synopsis. See the Clinical Study Report (CSR) document for those details.

Study Design

This was a randomised, placebo-controlled, DB, parallel-group, multicentre, Phase III study to compare the efficacy and safety of repeat dosing of benralizumab versus placebo in male and female patients 12 to 65 years of age with symptomatic and histologically active eosinophilic esophagitis (EoE).

The clinical study consisted of 4 periods:

- A 2- to 8-week run-in period
- A 24-week placebo-controlled, DB, parallel-group treatment period (DB period)
- A 28-week open-label (OL) benralizumab treatment period (OL period)
- An additional open-label extension (OLE) treatment period (OLE period) (optional)

Patients were randomly assigned in a 1:1 ratio to receive either benralizumab 30 mg or placebo at 4-week intervals (DB period). The randomisation for adults was stratified by region (North America versus rest of world) and use of swallowed steroids at baseline (categorical, Yes/No). Adolescents were randomly assigned in a separate stratum with no other factors included.

Adult patients at participating study centres were offered the opportunity to participate in an Early Time Point Sub-study, [redacted]

The main focus of this CSR is on the primary analysis of the MESSINA study, which was performed when all patients randomised into the study completed the 24-week DB period. The primary analysis included complete data for the 24-week DB period for all patients and all available data for the 28-week OL period that had accumulated by the primary analysis data cut-off date (19 September 2022). Available safety data for the OLE period (after Week 52) at the primary analysis data cut-off date are also presented. The pharmacokinetics (PK) and immunogenicity data cut-off date for the primary analysis was 05 September 2022, prior to the primary analysis data cut-off for the clinical database, due to additional lead time required for analysis of patient samples.

After the primary analysis was performed and interpreted, a decision was made to terminate the study on 25 October 2022. Despite the demonstration of robust blood and tissue eosinophil depletion, no statistically significant or clinically meaningful difference between benralizumab and placebo in symptom endpoints was observed. Patients returned to study

centres for a follow-up visit 12 weeks (± 7 days) after the last dose of Investigational Product (IP), after which the patient discontinued from the study. Once the last patient had their last visit, a final analysis was performed (data lock date: 03 March 2023). Available exposure and safety data from this final analysis are also presented, labelled 'final analysis'. Updated disposition data are also presented, labelled 'final analysis'. No updated efficacy, PK, pharmacodynamics (PD), or immunogenicity analyses were performed at the final analysis; all analyses for these endpoints relate to the primary analysis data cut-off.

Target Population and Sample Size

Patients with symptomatic and histologically active EoE before randomisation, male or female, and aged between 12 and 65 years (inclusive) were eligible for inclusion in this study.

Approximately 170 patients were planned to be randomly assigned in a 1:1 ratio to benralizumab or matching placebo. This goal was exceeded as the recruitment period was extended to enrol the targeted number of adolescent patients as well as adult patients for the Early Time Point Sub-study. Overall, 211 patients were randomly assigned to study treatment and 210 received treatment during the DB period (103 received benralizumab and 107 received placebo).

Investigational Product and Comparator(s): Dosage, Mode of Administration, and Batch Numbers

The (IP) in this study included benralizumab and placebo:

- Benralizumab 30 mg was administered via subcutaneous (SC) injections (accessorised pre-filled syringe [APFS]) every 4 weeks (Q4W).
- Placebo was administered via SC injections (APFS) Q4W.

The batch numbers for benralizumab were: [redacted].

The batch numbers for placebo were: [redacted].

Duration of Treatment

Patients received either benralizumab 30 mg or placebo at 4-week intervals for a 24-week treatment period (DB period). Patients who completed the DB, placebo-controlled treatment period on IP were eligible to continue into an OL treatment period with benralizumab 30 mg Q4W until Week 52 (OL period).

All patients who completed the 52-week treatment period (the 24-week DB treatment period and the 28-week OL treatment period; DB + OL treatment periods) on IP were to be offered the opportunity to continue into an OLE period on benralizumab 30 mg Q4W (OLE), intended to allow each patient at least 1 additional year of treatment with OL benralizumab.

Statistical Methods

The primary analysis, conducted when all randomly assigned patients completed the 24-week DB period, included all available efficacy, safety, PK, and anti-drug antibody (ADA) data; a final analysis was performed for safety data when all patients completed the study. The below mentioned general principles were applied:

- The primary efficacy analyses were based on the DB period and included all randomized patients who received at least one dose of IP (Full Analysis Set [FAS]). Patients were analysed according to their randomly assigned treatment, following the intent-to-treat principle.
- A composite estimand strategy was used for all endpoints that were statistically analysed and included time points up to Week 52.
- To account for multiplicity testing for the dual-primary endpoints and the key secondary endpoints, a hierarchical testing strategy was applied to strongly control the overall type 1 error rate at the 0.05 level.
- Results of formal statistical comparisons of non-primary or key secondary endpoints are presented with 2-sided 95% confidence intervals (CIs) and nominal (ie, not multiplicity adjusted) p-values.
- All analyses of Week 52 endpoints were descriptive as no placebo control was available at that time point and so no hypothesis testing was performed. Week 52 analyses used the FAS.

The proportion of patients with a histological response at Week 24, defined as a peak oesophageal intraepithelial eosinophil count ≤ 6 eos/hpf across all available oesophageal levels, was the first dual-primary endpoint analysed, and was compared between benralizumab and placebo using a Cochran-Maentel-Haenszel (CMH) test stratified by region, baseline steroid use, and presence of strictures at baseline. A composite estimand strategy was used where any patient with missing data at Week 24 or experiencing intercurrent events (randomised treatment discontinuation, increases in background therapy, addition of new EoE therapies, or dilation procedures) was treated as a non-responder at Week 24.

The second dual-primary endpoint analysed, change from baseline in Dysphagia Symptom Questionnaire (DSQ) score at Week 24, was compared between the benralizumab and placebo groups using a composite estimand strategy. Any patient experiencing an intercurrent event had their Week 24 value imputed using a return-to-baseline multiple imputation (MI) method. Patients with missing data not due to intercurrent events had their Week 24 value imputed using missing at random MI. The change from baseline in DSQ score at Week 24 was then analysed using an analysis of covariance (ANCOVA) model for each imputation which included change from baseline in DSQ score at Week 24 as the dependent variable; baseline DSQ score as a continuous covariate; and region, baseline steroid use, and presence of strictures at baseline as categorical covariates. Results were combined across the imputation datasets using Rubin's rule and presented in terms of the least squares (LS) mean change from

baseline at Week 24 for each treatment group and the difference versus placebo, with corresponding 95% CIs. A p-value, corresponding to a 2-sided test, was presented to compare the benralizumab and placebo groups.

Key secondary endpoints are described below in the order they were tested in the multiple testing procedure.

The percent change from baseline in tissue eosinophil counts at Week 24 and the changes from baseline in Eosinophilic Esophagitis - Histology Scoring System (EoE-HSS) total grade score, in EoE-HSS total stage score, and in worst centrally-read EoE - Endoscopic Reference Score (EREFS) score at Week 24 were all compared between the benralizumab and placebo groups using an ANCOVA model. The same composite estimand strategy rules as mentioned for the primary change from baseline in DSQ score endpoint were used.

Treatment response was defined as a composite of histologic response and clinically meaningful improvement (30%) from baseline in DSQ score at Week 24. The proportion of patients who achieved treatment response at Week 24 was compared between benralizumab and placebo using a CMH test controlling for region, baseline steroid use, and presence of strictures at baseline. The same composite estimand strategy as mentioned for the primary endpoint proportion of patients with histological response was used. Other secondary endpoints included efficacy assessments at Week 52 (using the same estimand rules as outlined for the Week 24 endpoints), PK, ADA, PD, and safety. Benralizumab serum trough concentrations were summarised by treatment group at each visit using descriptive statistics for all patients who received benralizumab and had at least 1 quantifiable serum PK observation post first dose not affected by factors. Anti-drug antibodies to benralizumab assessments, from serum samples collected prior to IP administration, were summarised descriptively for both treatment groups using the safety analysis set. The ADA results for each sample were reported as positive or negative; positive samples also reported ADA titre and the presence or absence of neutralising antibody (nAb) using a ligand binding assay. In addition, the effect of ADA on PK, PD, safety, and efficacy was evaluated. Changes in tissue eosinophil and blood eosinophil counts over time were assessed for the primary analysis to evaluate the PD of benralizumab using the FAS and safety analysis sets, respectively. All safety variables were summarised descriptively using the safety analysis set or the OL benralizumab analysis set (including all patients who started or carried on receiving at least one dose of benralizumab after the DB period), and data were presented according to the actual treatment received.

Study Population

Patients were recruited in 12 countries.

A total of 207 patients (98.1%) completed the 24-week DB period. Patient decision was the only reason for discontinuation of DB treatment (4 patients [1.9%]).

Of the 211 patients randomly assigned to study treatment, 206 patients (97.6%) completed DB treatment with study treatment, and 205 patients (97.2%) enrolled in the OL treatment period on study treatment and 1 patient (0.5%) enrolled in the OL period off study treatment. As of the primary analysis data cut-off date, 99 patients (46.9%) were ongoing in the OL period on study treatment, 98 patients (46.4%) completed OL treatment with study treatment, 8 patients (3.8%) discontinued OL treatment with study treatment, and 3 patients (1.4%) withdrew from the study during the OL period. Of the 89 patients who completed the OL period, 79 patients enrolled in the optional OLE period.

A total of 25 adult patients participated in the Early Time Point Sub-study (11 patients in the benralizumab group and 14 patients in the placebo group).

At the final analysis data cut-off date, 161 patients (76.3%) completed OL treatment with study treatment. Of the 93 patients who enrolled in the optional OLE period, 92 patients (98.9%) discontinued optional OLE with study treatment; 1 patient who enrolled and received the first dose in the OLE was incorrectly entered by the investigator as completed. Study terminated by sponsor (88 patients [94.6%]) was the most common reason for discontinuation of OLE treatment during the optional OLE period.

Of the 211 randomly assigned patients, 210 patients were included in the FAS and the safety analysis set; 1 patient in the benralizumab group did not receive at least one dose of study treatment and was excluded. As all patients received the treatment allocated to them, the FAS and safety analysis set were identical.

As of the primary analysis data cut-off date, the OL benralizumab analysis set included 205 patients who started or carried on receiving benralizumab after the end of the 24-week DB treatment period.

Summary of Efficacy Results

For the dual primary endpoints, treatment with benralizumab resulted in a statistically significant increase in the proportion of patients achieving histological response at Week 24 compared to placebo, but no statistically significant or clinically meaningful difference in the DSQ LS mean change from baseline was observed between benralizumab and placebo at Week 24. As statistical significance was not achieved on the DSQ endpoint (at the 5% level), other endpoints in the testing hierarchy could not be formally tested. The following efficacy conclusions were made in patients with symptomatic and histologically active EoE who were administered benralizumab 30 mg Q4W:

<u>Dual-primary Endpoints</u>

- Treatment with benralizumab significantly improved the proportion of patients who achieved histological response (≤ 6 eos/hpf) at Week 24 when compared with placebo (difference versus placebo: 80.8%, 95% CI: 72.9%, 88.8%; $p < 0.0001$).

- The difference between treatment groups in LS mean change from baseline in DSQ score at Week 24 (3.0) was not statistically significant (95% CI: -1.36, 7.35; p = 0.1770).
- Results of sensitivity analyses support the dual-primary endpoint conclusions.
- Consistent results for the dual-primary endpoints were observed across all subgroups including the adolescent subgroup.

Key Secondary Endpoints

- Differences between treatment groups observed for percent change from baseline to Week 24 in tissue eosinophils, change from baseline to Week 24 in EoE-HSS total grade and total stage scores and proportion of treatment responders at Week 24 were considered nominally significant.
- A greater LS mean percent reduction from baseline in tissue eosinophils (-94.8% versus 1.4% respectively) and greater LS mean reduction from baseline in EoE-HSS total grade and total stage score (-0.26 versus -0.09 and -0.20 versus -0.08, respectively) at Week 24 was observed in the benralizumab group compared with the placebo group, respectively.
- The LS mean change from baseline in centrally-read EREFS total scores was similar between the benralizumab and placebo groups at Week 24 (-0.5 versus -0.4, respectively).
- More patients in the benralizumab group were treatment responders at Week 24 (ie, achieved both histological response [≤ 6 eos/hpf] and clinically meaningful improvement in symptom response [≥ 30% improvement in DSQ score from baseline]) compared with the placebo group, driven by the histological response component.

Week 52 Efficacy (all available data from Weeks 24 to 52 up to the primary analysis data cut-off date)

- For histology-based endpoints, results of the dual-primary and key secondary endpoints were maintained up to Week 52 in patients randomised to benralizumab who continued into the OL period.
- For endoscopic appearance (centrally-read EREFS total score) and symptom-based endpoints, no evidence of meaningful improvements with up to 52 weeks of benralizumab treatment were observed.

Summary of Pharmacokinetic Results

Based on data available at the time of the primary analysis, benralizumab trough serum concentrations reached steady-state by Week 16 during the DB period for the benralizumab group.

Summary of Pharmacodynamic Results

Based on the primary analysis, depletion in oesophageal tissue eosinophils was observed at Week 24 and was maintained through Week 52 in patients randomly assigned to benralizumab.

Depletion of oesophageal tissue eosinophils following benralizumab treatment was also seen in patients who participated in the Early Time Point Sub-study, at Week 4 and persisted to Weeks 12 and 24. Patients in the placebo/benralizumab group showed similar results as early as Week 36 and was maintained to Week 52.

For patients in the benralizumab group, treatment resulted in near complete depletion of blood eosinophils that was maintained through Week 52, consistent with the mechanism of action and results in previous asthma studies. Patients in the placebo/benralizumab group showed similar results at Week 52.

Summary of Pharmacokinetic/Pharmacodynamic Relationships

Based on the primary analysis, substantial overlap in the 95% CIs of the PK concentration subgroups for each of the dual primary endpoints support that there is no clear evidence of a difference in effect by benralizumab serum concentration subgroups.

Summary of Immunogenicity Results

- Based on data available at the time of the primary analysis, the incidence of treatment-emergent ADA was 17.6% in patients with EoE in the benralizumab group at Week 24. At Week 52, the incidence of treatment-emergent ADA was 18.6%.
- Treatment-emergent ADA responses were generally persistently positive and nAb positive in the benralizumab group.
- Seroconversion occurred by Week 24 in the benralizumab group. No patients seroconverted at Week 52.
- The peak median titre was seen at Week 16 in patients in the benralizumab group.
- Geometric mean serum trough benralizumab concentrations were generally lower in ADA-positive patients, particularly in high-titred ADA-positive patients, compared with ADA-negative patients.
- Decreases in blood and tissue eosinophil counts were seen in all ADA-positive subgroups in the benralizumab group. Median reductions in blood and tissue eosinophils were numerically smaller in the subgroup of high-titred ADA-positive patients compared with ADA-negative patients. In ADA-positive subgroups in the benralizumab group, numerically smaller proportions of patients achieved histological response compared with ADA-negative patients at Week 24; no difference was noted at Week 52. There was no consistent trend in terms of an effect of ADA on DSQ across the ADA subgroups.

Summary of Safety Results

Treatment with benralizumab for up to 52 weeks in patients with EoE was well tolerated and displayed adverse event (AE) data that was consistent with the known safety profile of benralizumab, with no new safety findings. The safety profile of adolescents (< 18 years old) was consistent with that of adults (≥ 18 years old).

No patients had an AE with an outcome of death during the study. There were no AEs leading to discontinuation of IP during the DB period.

In line with the similar disposition between the treatment groups, the mean durations of on-treatment exposures to IP during the DB period were similar between the benralizumab and placebo groups (169.4 days and 169.3 days, respectively), based on the primary analysis. Based on the primary analysis, the mean durations of on-treatment exposures to IP during the 28-week OL period, when all patients received benralizumab, were similar between the benralizumab and placebo/benralizumab groups (126.7 days and 129.1 days, respectively). Based on the final analysis, the mean duration of exposure to benralizumab during the DB + OL periods for those initially randomised to benralizumab was 311.1 days and 229.1 days in patients who received benralizumab at any point during the DB + OL periods, including patients initially assigned to placebo who switched to benralizumab at Week 24.

The following safety results were based on all patients in the safety analysis set:

Double-blind Period (Primary Analysis)

- The proportion of patients with AEs with onset during the DB period was similar between the benralizumab group (64.1%) and placebo group (61.7%).
- The 2 most common AEs by preferred term (PT) during the DB period were coronavirus disease 2019 (12.6%) and headache (8.7%) in the benralizumab group, which were generally similar to the placebo group (12.1% and 10.3%, respectively).
- Bronchospasm, infectious pleural effusion, and pneumonia bacterial were the only serious AEs (SAEs) reported for the benralizumab group during the DB period (2 patients). Asthma was the only SAE reported for the placebo group.
- [redacted] were reported for 1 patient in the benralizumab group, only. No events of helminth parasitic infection or malignant neoplasms were reported during the study.
- There were few patients with hypersensitivity AEs during the DB period (benralizumab, 4 patients; placebo, 7 patients) One patient in the benralizumab group had a serious hypersensitivity AE of [redacted]. No events of anaphylaxis/anaphylactic reactions were reported during the DB period.
- The overall proportion of patients with injection-site reaction AEs (high level term and PT) reported during the DB period was low and similar for both treatment groups. All of the injection-site reaction AEs reported during the DB period were nonserious; none resulted in discontinuation of IP.
- There were no clinically meaningful trends in laboratory parameters and no notable differences were observed between treatment groups during the DB or DB + OL periods.
- There were no clinically meaningful changes in vital signs over time and no notable differences were observed between treatment groups during the DB or DB + OL periods.

Open-label and Open-label Extension Periods (Primary Analysis)

- Results for safety during the OL and OLE periods were consistent with the known safety profile of benralizumab, with no new safety findings.
- One AE leading to discontinuation ([redacted]) with onset during the OL period and 1 AE leading to discontinuation ([redacted]) with onset during the OLE period were reported for 1 patient, each, in the placebo/benralizumab group.
- There were few patients with SAEs with onset during the OL period (benralizumab, 2 patients; placebo/benralizumab, 3 patients). No SAEs with onset during the OLE were reported.
- In the placebo/benralizumab group, there was 1 patient with an SAE of [redacted] ([redacted]) with onset during the OL period. There were no cases with onset during the OLE period reported.
- There were no cases of helminth infections or malignant neoplasms with onset during the OL or OLE periods.
- Few hypersensitivity AEs were reported. There was no consistent pattern or trend in hypersensitivity AEs with onset during the DB + OL periods in the benralizumab and placebo/benralizumab groups.
- Overall, few injection site reaction AEs were reported. There was no consistent pattern or trend in the injection-site reaction AEs observed in the benralizumab and placebo/benralizumab groups during the DB + OL period.

Final Analysis

There were no meaningful differences in safety information based on results for the final analysis compared with the primary analysis.

Conclusions

- Treatment with benralizumab 30 mg Q4W significantly improved histological response ($\leq$ 6 eos/hpf) at Week 24 compared with placebo (87.4% versus 6.5% of patients, respectively; $p < 0.0001$) (dual-primary endpoint).
- The mean change from baseline in DSQ scores was similar between the treatment groups over the 24-week DB period. The difference in LS mean change from baseline in DSQ score at Week 24 (3.0) was not statistically significant (95% CI: -1.36, 7.35; $p = 0.1770$) (dual-primary endpoint).
- Consistent results for the dual-primary endpoints were observed across all subgroups including the adolescent subgroup.
- Results for the secondary endpoints supported the dual-primary endpoints with improvement in histology-related endpoints but no difference in endoscopic appearance and symptom-related endpoints at Week 24 for benralizumab compared with placebo.

- Analysis of available data at Week 52 showed consistency with Week 24 for histology-related endpoints. For endoscopic appearance and symptom-related endpoints, no further meaningful improvements were observed.
- Treatment with benralizumab in EoE patients was generally well tolerated and safety data were consistent with the known safety profile of benralizumab, with no new safety findings.
- There was evidence of an effect of ADA on PK, particularly in those patients with high titres, however, the numbers of patients in ADA subgroups were low. Decreases in blood and tissue eosinophil counts were seen in all ADA-positive subgroups in the benralizumab group; however, the decreases were smaller in the subgroup of high-titred ADA positive patients. There was no effect of ADA on safety.