EMA/499801/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fasenra

International non-proprietary name: benralizumab

Procedure No. EMEA/H/C/004433/P46/008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 1/8/2023, the MAH submitted a completed paediatric study for Fasenra, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study D3255C00001, a Multicentre, Randomised, Double-blind, Parallel-group, Placebo-controlled Study to Investigate the Use of Benralizumab for Eosinophilic Esophagitis (MESSINA) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The dosage formulation corresponds to the marketed product, Benralizumab 30 mg/mL solution for injection, 1 mL fill volume, administered as a single injection via the accessorised prefilled syringe (APFS).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study D3255C00001:

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

2.3.2. Clinical study

Clinical study number: D3255C00001

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

Description

Eosinophilic esophagitis (EoE) is a rare chronic allergic inflammatory disorder of the oesophagus influenced by both genetic and environmental risk factors which predispose to allergen sensitisation leading to allergic and eosinophilic inflammation of the oesophageal epithelium, which is normally devoid of eosinophils[1]. Eosinophilic esophagitis is clinically defined by symptoms of oesophageal dysfunction, and histologically by oesophageal inflammation of ≥ 15 eos/hpf, as well as by exclusion of secondary causes of oesophageal eosinophilia. The disease results in progressive transmural inflammation and, in some cases, fibrostenotic complications, which translate in a range of upper GI symptoms that vary with age[1]. Due to the chronic nature of EoE and symptoms recurrency when

[1] O'Shea, K. M., Aceves, S. S., Dellon, E. S., Gupta, S. K., Spergel, J. M., Furuta, G. T., & Rothenberg, M. E. (2018). Pathophysiology of Eosinophilic Esophagitis. *Gastroenterology*, *154*(2), 333–345. https://doi.org/10.1053/j.gastro.2017.06.065

treatments are discontinued, maintenance therapy should be considered in all patients[2]. Most of the current treatment approaches (food elimination diets, oesophageal dilation, and medications) are either burdened with limited efficacy, compliance problems, inadequate availability, or reserved for the treatment of complications.

Benralizumab is a humanised, afucosylated, mAb that binds specifically to the IL-5Rα on the target cell and directly depletes eosinophils through ADCC. The eosinophil-depleting ability of benralizumab which has been shown to be effective in eosinophilic asthma could be also effective in EoE and eosinophilic-driven GI diseases.

Study D3255C00001 (MESSINA) was a randomised, placebo-controlled, double blind, parallel-group, multicentre, Phase III study to compare the efficacy and safety of repeat dosing (Q4W) of subcutaneously administered benralizumab 30 mg versus placebo in male and female patients 12 to 65 years of age with symptomatic and histologically active Eosinophilic Esophagitis.

Methods

The aim of Study D3255C00001 (MESSINA) was to investigate the use of benralizumab as a treatment for patients with EoE. The effect of doses of benralizumab on EoE histologic signs and symptoms were to be assessed over a 52-week treatment period (including a 24-week double-blind placebo-controlled treatment period and a 28-week open-label treatment period). Upon completion of the initial 52-week treatment period, patients were to be offered an additional Open Label Extension period of at least 1 year with benralizumab treatment. The aim of the study was based on the rationale that benralizumab would deplete eosinophils from GI tissue(s), improve the symptoms of dysphagia, and improve endoscopy scores as well as other markers of disease activity.

Study participants

Inclusion Criteria:

Patients 12 to 65 (inclusive) years of age, male or female were eligible for inclusion in study D3255C00001, if they fulfilled the following criteria:

- Diagnosis of EoE documented before randomization by endoscopy (esophageal count of ≥ 15 eos/hpf on at least 1 oesophageal level) and confirmed diagnosis by a centrally read oesophageal biopsy for the purposes of this study (oesophageal count of ≥ 15 eos/hpf at 2 or more oesophageal levels). Two to 4 biopsies were to be obtained from proximal and distal oesophagus and the mid-oesophagus if additional evaluation was necessary.
- Must have been symptomatic at Visit 1 (screening) and Visit 2 (randomisation):
  - A patient-reported average of at least 2 days per week with an episode of dysphagia over the 4 weeks prior to Visit 1.

  AND
  - An average of at least 2 days per week with an episode of dysphagia (daily DSQ ≥ 2) between Visit 1 and Visit 2, and at least 2 days per week with an episode of dysphagia (daily DSQ ≥ 2) in each of the 2 weeks immediately prior to randomisation.
- Must have been adherent to daily diary assessments:
  - Must have completed 70% of daily DSQ diaries between Visit 1 and Visit 2.

[2] Dellon, E. S., Gonsalves, N., Hirano, I., Furuta, G. T., Liacouras, C. A., Katzka, D. A., & American College of Gastroenterology (2013). ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *The American journal of gastroenterology, 108*(5), 679–693. https://doi.org/10.1038/ajg.2013.71

AND

- Must have completed at least 8 of 14 daily DSQ diaries in the 14 days prior to randomisation.

- May have been for at least 4 weeks prior to screening (8 weeks for PPI) on stable background medications for EoE and related treatments without change of medication type or dosage during the run-in period and for the first 52 weeks of the study, unless medically indicated. In case of discontinuation of background medication prior to screening a washout period of at least 8 weeks was necessary.

Exclusion Criteria

Key exclusion criteria were as follows:

- Other GI disorders such as active Helicobacter pylori infection, history of achalasia, oesophageal varices, Crohn's disease, ulcerative colitis, inflammatory bowel disease, or celiac disease.
- Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis during the run-in period, which in the opinion of the Investigator may have put the patient at risk, or influenced the study results, or the patient's ability to complete the study.
- Oesophageal stricture that prevented the easy passage of a standard endoscope or any critical oesophageal stricture that requires dilation during the run-in period.
- Oesophageal dilation performed within 8 weeks prior to screening and prior oesophageal surgery that would have impacted the assessments for EoE.
- Use of a feeding tube or a pattern of not eating solid food daily during the run-in period.
- Hypereosinophilic syndrome, defined by multiple organ involvement and persistent blood eosinophil count > 1500 eos/µL.
- Eosinophilic granulomatosis with polyangiitis vasculitis.
- Eosinophilic gastritis, gastroenteritis, enteritis, or colitis documented by biopsy.

Treatments

	Treatment 1	Treatment 2 (DB Period only)
Study treatment name:	Benralizumab	Placebo
Dosage formulation:	30 mg/mL solution for injection in APFS, 1 mL fill volume	Matching placebo solution for injection in APFS, 1 mL fill volume
	Clear to opalescent, colourless to yellow solution	Clear to opalescent, colourless to yellow solution
Route of administration	SC	SC
Dosing instructions:	Benralizumab active solution was administered SC to patients by healthcare professionals in this clinical study using an APFS.	Placebo solution was administered SC to patients by healthcare professionals in this clinical study using an APFS.
	Each prefilled syringe was designated for single use only and was not administered to more than one patient.	Each prefilled syringe was designated for single use only and was not administered to more than one patient.

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 OL benralizumab treatment period (OL period)
- An additional OLE treatment period (OLE period) (optional)

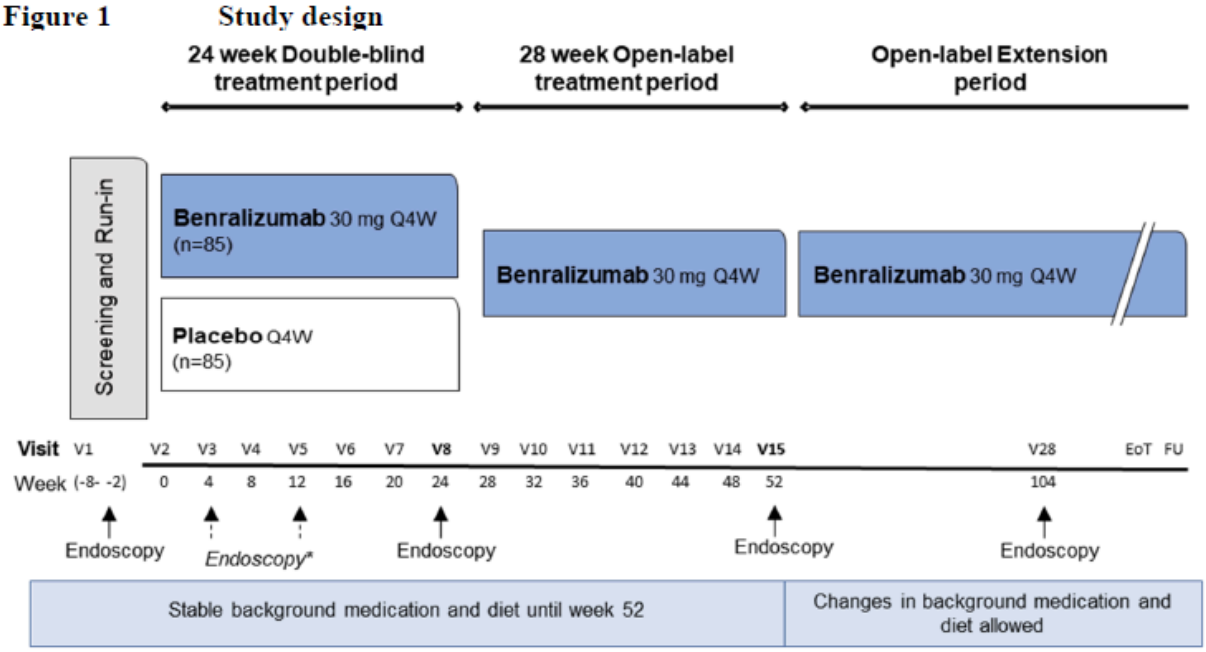
Patients received either benralizumab 30 mg or placebo at 4-week intervals for a 24-week treatment period (DB period). Patients who completed the DB, placebo-controlled treatment period on IP were eligible to continue into an OL treatment period with benralizumab 30 mg Q4W until Week 52 (OL period).

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.

Adult patients were offered the opportunity to participate in an Early Time Point Sub-study, which aimed to generate early time point evidence and demonstrate the impact of eosinophil depletion in tissue and to understand its relationship with endoscopic findings and symptom response.

The flowchart of the study design and the sequence of treatment periods are shown in Figure 1 below:

Figure 1 **Study design**



Q4W every 4 weeks; V Visit; EoT End of Treatment; FU Follow up, *Only for patients in the Early Time Point Sub-study. Note: The first dose of open-label benralizumab occurred at Visit 8 (Week 24), following completion of all double-blind treatment period assessments.

Objective(s)

Primary Objective

The primary objective of the study was 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.

Secondary Objectives

The secondary objectives of the study were to:

- To evaluate the effect of benralizumab 30 mg Q4W on clinical features of EoE and disease activity.
- To evaluate the effect of benralizumab 30 mg Q4W on patient reported QOL measures.
- To evaluate the effect of benralizumab 30 mg Q4W on healthcare resource utilization due to EoE.
- To evaluate the effect of benralizumab 30 mg Q4W on patient reported measures of disease severity and health status.
- To assess the PK and immunogenicity of benralizumab 30 mg Q4W in patients with EoE.

Safety Objective

To assess the safety and tolerability of benralizumab 30 mg Q4W in patients with EoE

Outcomes/endpoints

Dual primary efficacy Endpoints

- 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

Secondary efficacy Endpoints

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
- Changes from baseline in EoE-QoL-A at Week 24
- SF-36-v2 Health Survey at Week 24
- Percent of patients with relevant concomitant procedures and healthcare resource utilisation during the study through Week 24

- PGI-S at Week 24
- PGI-C at Week 24
- 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 highpower 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.

Additional objectives and endpoints were also defined for the longer-term effects (Week 52 efficacy objective & endpoints) of benralizumab 30 mg Q4W in patients with EoE.

Safety Endpoints

- Safety and tolerability were to be evaluated in terms of AEs, vital signs, and clinical laboratory values
- Assessments related to AEs covered:
  - Occurrence/frequency
  - Relationship to IP as assessed by Investigator
  - Intensity
  - Seriousness
  - Death
  - AEs leading to discontinuation of IP
- Vital signs parameters including systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height
- Assessments related to vital signs covered:
  - Observed value
- Absolute and percent change from baseline values over time

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

Sample size

Approximately 170 patients* were planned to be randomly assigned in a 1:1 ratio to benralizumab or matching placebo. This would provide > 95% power for the first primary endpoint (proportion of patients achieving histological response) to demonstrate an increase from 20% or less on placebo, to

50% on benralizumab at the 2-sided 5% significance level (lower placebo rates have been reported in previous EoE studies[3,4]).

*The planned sample size was exceeded as the recruitment period was extended to enrol the targeted number of adolescent patients and adult patients for the Early Time Point Sub-study (see below *Participant Flow*).

The power calculation for the second primary endpoint (change from baseline in DSQ score at Week 24) was based on detecting similar effect sizes (mean difference in change from baseline of the PRO/SD) as seen in previous studies. Assuming an effect size of 0.6, which equates to a 7.2-point difference in change in the DSQ, 85 patients per treatment group would allow > 95% power for statistical significance at the 5% 2-sided level. The high level of power for the primary endpoints ensured stronger statistical evidence could be demonstrated in the Phase III study.

Randomisation and blinding (masking)

All patients were centrally assigned to randomised IP using an interactive web response system. Randomisation for adults was stratified by region (North America versus ROW) and use of swallowed steroids at baseline (categorical, Yes/No). Adolescents were randomly assigned in a separate stratum with no other factors included.

During the first study period of 24 weeks (DB), benralizumab and placebo were not visually distinct from each other. All packaging and labelling of the IP were done in such a way as to ensure blinding for all Sponsor and study centre staff, and all patients. All personnel involved with the analysis of the study remained blinded until the primary database was locked, and CSP deviations were identified. Originally, study centre staff and patients were to remain blinded until the last patient completed Week 52 of the study. However, after the primary analysis was completed and the decision was made to terminate the study, treatment allocations were shared with all study centres to enable unblinding of all randomized patients if needed to inform future treatment options.

Statistical Methods

The Statistical plan of study D3255C00001 followed the general principles mentioned below:

- The primary efficacy analyses were based on the DB period. All efficacy analyses used the FAS (see Results: Number analysed), and patients were analysed according to their randomly assigned treatment, following the ITT 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.
- Hypothesis testing for the dual-primary analyses and key secondary analyses was performed at the 2-sided 5% significance level. If the p-value was less than 0.05, the null hypothesis was rejected and the alternative hypothesis was accepted.

[3] Dellon, E. S., Katzka, D. A., Collins, M. H., Hamdani, M., Gupta, S. K., Hirano, I., & MP-101-06 Investigators (2017). Budesonide Oral Suspension Improves Symptomatic, Endoscopic, and Histologic Parameters Compared With Placebo in Patients With Eosinophilic Esophagitis. *Gastroenterology*, *152*(4), 776–786.e5. https://doi.org/10.1053/j.gastro.2016.11.021

[4] Hirano, I., & Furuta, G. T. (2020). Approaches and Challenges to Management of Pediatric and Adult Patients With Eosinophilic Esophagitis. *Gastroenterology*, *158*(4), 840–851. https://doi.org/10.1053/j.gastro.2019.09.052

- Results of formal statistical comparisons of non-primary or key secondary endpoints were presented with 2-sided 95% CIs and nominal (ie, not multiplicity adjusted) p-values.
- All analyses of Week 52 endpoints used the FAS; analyses were descriptive as no placebo control was available at that time point and therefore no hypothesis testing was performed.

The statistical analysis of the DB period was designed to compare both efficacy and safety of benralizumab to placebo, while the OL period was designed to evaluate the long-term safety, tolerability and persistence of effect of benralizumab in this patient population. The OLE would provide an opportunity to assess long term safety and tolerability.

All safety variables were summarised descriptively using the safety analysis set or the OL benralizumab analysis set (see below: Results, Number analysed). It should be mentioned that the study was not designed or powered to detect differences in any individual AE.

Results

Participant flow

Of the 404 patients enrolled in study D3255C00001, 211 were randomly assigned to study treatment and 210 received treatment during the DB period (103 received benralizumab and 107 received placebo; Table 14.1.1). A total of 207 patients (98.1%) completed the 24-week DB period. The proportions of patients who discontinued study treatment during the DB period were similar between treatment groups (1.9% for the benralizumab group and 1.9% for the placebo group). 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. Patient decision was the most common reason for discontinuation of OL treatment during the OL period (6 patients [2.8%]). Of the 89 patients who completed the OL period, 79 patients enrolled in the optional OLE period (Table 14.1.1).

In the FAS and during the DB period, 34 patients (33.0%) in the benralizumab group and 42 patients (39.3%) in the placebo group had important protocol deviations; during the OL period, 11 patients (11.0%) in the benralizumab group and 11 patients (10.5%) in the placebo/benralizumab group had important protocol deviations.

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).

The first participant enrolled on 13 September 2022. After the primary analysis was completed (primary analysis population consists of the complete population of all patients randomised in the trial, including the complete sub-study population) a decision was made to terminate the study on 25 October 2022, however patients returned to study centres for a follow-up visit 12 weeks (± 7 days) following the last dose of Investigational Product (IP), after which the patient discontinued from the study. The study completion date, as defined by the last patient last visit date, was 6 February 2023. Once the last patient had their last visit, a final analysis was performed (data lock date: 03 March 2023).

Table 14.1.1 Subject disposition (All subjects analysis set)

	Number (%) of subjects		
	Benra 30 mg	Placebo	Total
Subjects enrolled [a]			404
Subjects who were enrolled but not randomized			193
Physician decision			1
Screen failure			182
Withdrawal by subject			9
Other			1
Subjects randomized	104	107	211
Subjects who did not receive treatment with study drug [b]	1 (1.0)	0 (0.0)	1 (0.5)
Failure to meet inclusion/exclusion criteria	1 (1.0)	0 (0.0)	1 (0.5)
Subjects who received treatment with study drug [b]	103 (99.0)	107 (100.0)	210 (99.5)
Subjects who completed DB treatment with study drug [b][d]	101 (97.1)	105 (98.1)	206 (97.6)
Subjects who discontinued DB treatment with study drug [b]	2 (1.9)	2 (1.9)	4 (1.9)
Subject decision	2 (1.9)	2 (1.9)	4 (1.9)
Subjects who discontinued treatment with study drug in DB but completed study follow-up [b]	0 (0.0)	1 (0.9)	1 (0.5)
Subjects who withdrew from study in DB treatment period [b]	2 (1.9)	1 (0.9)	3 (1.4)
Withdrawal by subject	1 (1.0)	1 (0.9)	2 (0.9)
Other	1 (1.0)	0 (0.0)	1 (0.5)
Subjects who completed the DB treatment period [b][e]	101 (97.1)	106 (99.1)	207 (98.1)
Subjects who enrolled in OL treatment period on study drug [b]	100 (96.2)	105 (98.1)	205 (97.2)
Subjects who enrolled in OL treatment period off study drug [b]	1 (1.0)	0 (0.0)	1 (0.5)
Subjects who did not enroll in OL treatment period [b]	0 (0.0)	1 (0.9)	1 (0.5)
Subjects who completed OL treatment with study drug [b]	48 (46.2)	50 (46.7)	98 (46.4)
Subjects who were ongoing on OL treatment with study drug [b]	47 (45.2)	52 (48.6)	99 (46.9)
Subjects who discontinued OL treatment with study drug [b]	5 (4.8)	3 (2.8)	8 (3.8)
Subject decision	5 (4.8)	1 (0.9)	6 (2.8)
Adverse event	0 (0.0)	1 (0.9)	1 (0.5)
Consent withdrawn	0 (0.0)	1 (0.9)	1 (0.5)
Subjects who discontinued treatment with study drug in OL but completed study follow-up [b]	3 (2.9)	1 (0.9)	4 (1.9)
Subjects who withdrew from study in OL treatment period [b]	2 (1.9)	1 (0.9)	3 (1.4)
Withdrawal by subject	2 (1.9)	1 (0.9)	3 (1.4)
Subjects who completed the OL treatment period [b]	43 (41.3)	46 (43.0)	89 (42.2)
Subjects who enrolled in optional OLE treatment period [b]	37 (35.6)	42 (39.3)	79 (37.4)
Subjects who did not enroll in optional OLE treatment period [b]	6 (5.8)	4 (3.7)	10 (4.7)

Benra=Benralizumab. DB=Double blind. OL=Open label. OLE=Open label extension.
[a] Informed consent received.
[b] The percentages are calculated from the number of subjects randomized in each treatment group.
[c] The percentages are calculated from the number of subjects who were enrolled in optional OLE period.
[d] Subjects are considered completed DB treatment with study drug if reached Visit 7 with study drug.
[e] Subjects are considered completed the DB treatment period if reached Visit 8.

\csr\dev\output\tables\t-14-01-01-disp.rtf t_disp.sas 16NOV2022:20:08

Recruitment

Patients were recruited in 12 countries. The majority of patients in the Full Analysis Set were White (93.2%), male (74.8%), and not Hispanic or Latino (92.3%) (Table 15). The median age was 33 years (range: 12 to 62 years). The recruitment of patients under eighteen was markedly lower than adult patients: 28 patients (13.3%) were < 18 years of age whereas 182 patients (86.7%) were ≥ 18 years of age. A total of 160 patients (76.2%) were > 21 years of age.

Demographic characteristics were evenly balanced between treatment groups. The study population was representative of the intended target population. Consistent with the prevalence of EoE, the study recruited more male than female patients.

Table 15 Demographics Characteristics (Full Analysis Set)

Demographic characteristics	Statistics or category	Benra 30 mg (N = 103)	Placebo (N = 107)	Total (N = 210)
Age (years)	n	103	107	210
	Mean (SD)	33.9 (13.49)	33.6 (12.73)	33.7 (13.08)
	Median (min, max)	34.0 (12, 62)	33.0 (12, 61)	33.0 (12, 62)
Age group 1 (years) n (%)	< 18	14 (13.6)	14 (13.1)	28 (13.3)
	18-21	11 (10.7)	11 (10.3)	22 (10.5)
	22-35	32 (31.1)	35 (32.7)	67 (31.9)
	>= 36	46 (44.7)	47 (43.9)	93 (44.3)
	Total	103 (100.0)	107 (100.0)	210 (100.0)
Sex n (%)	Female	31 (30.1)	22 (20.6)	53 (25.2)
	Male	72 (69.9)	85 (79.4)	157 (74.8)
	Total	103 (100.0)	107 (100.0)	210 (100.0)
Race n (%) [a]	Black or African American	1 (1.0)	1 (1.0)	2 (1.0)
	White	97 (94.2)	96 (92.3)	193 (93.2)
	Native Hawaiian or other Pacific Islander	0 (0.0)	1 (1.0)	1 (0.5)
	American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	2 (1.9)	5 (4.8)	7 (3.4)
	Other	3 (2.9)	1 (1.0)	4 (1.9)
	Total	103 (100.0)	104 (100.0)	207 (100.0)
Race group n (%) [a]	White	97 (94.2)	96 (92.3)	193 (93.2)
	Asian	2 (1.9)	5 (4.8)	7 (3.4)
	Other	4 (3.9)	3 (2.9)	7 (3.4)
	Total	103 (100.0)	104 (100.0)	207 (100.0)
Ethnicity group n (%) [a]	Hispanic or Latino	6 (5.8)	10 (9.6)	16 (7.7)
	Non-Hispanic or Latino	97 (94.2)	94 (90.4)	191 (92.3)
	Total	103 (100.0)	104 (100.0)	207 (100.0)
Region group 1 n (%)	North America	47 (45.6)	43 (40.2)	90 (42.9)
	Rest of the World	56 (54.4)	64 (59.8)	120 (57.1)
	Total	103 (100.0)	107 (100.0)	210 (100.0)
Region group 2 n (%)	North America	47 (45.6)	43 (40.2)	90 (42.9)
	European Union	35 (34.0)	41 (38.3)	76 (36.2)
	Rest of the World	21 (20.4)	23 (21.5)	44 (21.0)
	Total	103 (100.0)	107 (100.0)	210 (100.0)

[a] Race and ethnicity are missing for all the French patients due to local regulation rules.

All percentages were based on the number of patients with data.

Benra benralizumab; max maximum; min minimum; N number of patients in treatment group; n number of patients in analysis; SD standard deviation.

Baseline data

Overall, baseline disease characteristics were similar between treatment groups (Table 16). The mean (SD) BMI was 25.67 (5.64) kg/m^2, the median baseline peak oesophageal intraepithelial eosinophil count was 77 eos/hpf, and the median baseline blood eosinophil count was 310 × 10^9 cells/L. At baseline, the majority of patients reported no swallowed steroid use (184 patients [87.6%]) and 113 patients [53.8%] reported presence of strictures.

Table 16 Patient Key Baseline Characteristics (Full Analysis Set)

Variable/category	Statistics or category	Benra 30 mg (N = 103)	Placebo (N = 107)	Total (N = 210)
Body mass index (kg/m^2) [a]	n	103	107	210
	Mean (SD)	25.32 (5.044)	26.01 (6.171)	25.67 (5.643)
	Median (min, max)	24.37 (14.7, 38.4)	24.82 (16.6, 44.6)	24.59 (14.7, 44.6)
Baseline peak oesophageal intraepithelial eosinophil count (eos/hpf)	n	103	107	210
	Mean (SD)	83.83 (42.174)	82.51 (43.490)	83.16 (42.752)
	Median (min, max)	77.00 (3.0, 226.0)	77.00 (18.0, 248.0)	77.00 (3.0, 248.0)
Baseline steroid use [b] n (%)	Yes	12 (11.7)	14 (13.1)	26 (12.4)
	No	91 (88.3)	93 (86.9)	184 (87.6)
	Total	103 (100.0)	107 (100.0)	210 (100.0)
Baseline PPI use n (%)	Yes	45 (43.7)	51 (47.7)	96 (45.7)
	No	58 (56.3)	56 (52.3)	114 (54.3)
	Total	103 (100.0)	107 (100.0)	210 (100.0)
Baseline steroids or PPI use [b] n (%)	Yes	51 (49.5)	56 (52.3)	107 (51.0)
	No	52 (50.5)	51 (47.7)	103 (49.0)
	Total	103 (100.0)	107 (100.0)	210 (100.0)
Presence of strictures at baseline [c]	Yes	49 (47.6)	64 (59.8)	113 (53.8)
	No	54 (52.4)	43 (40.2)	97 (46.2)
	Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)
	Total	103 (100.0)	107 (100.0)	210 (100.0)
Baseline blood eosinophil count (10^9/L)	n	101	104	205
	Mean (SD)	306.040 (168.5947)	354.519 (173.9595)	330.634 (172.6355)
	Median (min, max)	280.000 (50.00, 750.00)	320.000 (50.00, 930.00)	310.000 (50.00, 930.00)

[a] Body mass index = weight(kg)/[height(m)]^2.

[b] Baseline steroid use refers to swallowed topical steroids for EoE background treatment.

[c] Determined by centrally-read Endoscopic Reference Score (EREFS). In case the centrally-read EREFS is not available, local EREFS is used.

Note: All percentages were based on the number of patients with data.

Benra benralizumab; EoE eosinophilic esophagitis; eos eosinophils; hpf high-power field; max maximum; min minimum; N number of patients in treatment group; PPI proton pump inhibitor; SD standard deviation.

Both treatment groups reported similar profile for EoE disease history which was reflective of the protocol-intended patient population having symptomatic and histologically active EoE, with an overall mean time since first EoE symptoms and time from diagnosis of 10.8 and 4.9 years, respectively.

In the benralizumab and placebo groups, 76 and 74 patients, respectively, had 1 or more atopic conditions (defined as current asthma, rhinitis [seasonal or all year round], seasonal conjunctivitis, atopic dermatitis, eczema, and allergy test-based diet).

Overall baseline values of efficacy variables were similar between treatment groups.

Overall medical and surgical history were similar between patients in the benralizumab and placebo groups: a total of 61 patients (29.0%) reported a previous medical history, the most commonly reported being COVID-19 and Helicobacter infections (each reported for 1.9% of patients) and cholecystitis and tonsilitis (each reported for 1.4% of patients). Overall, a total of 143 patients (68.1%) reported a current medical history with food allergy (18.1%) being the most common, followed by anxiety (10.0%), and hypertension (8.6%). Overall, a total of 116 patients (55.2%) reported a surgical history. The most commonly reported surgical history was oesophageal dilation procedure (21.4%).

The most frequently used type of prior MINT (Medications of Interest) were PPIs (21.9%), swallowed ICS (9.0%), and swallowed orodispersible corticosteroids (8.1%%), with a frequency of use similar between the benralizumab and placebo groups.

Number analysed

Six patient populations were defined below:

All subjects analysis set: all subjects screened for the study, and used for the reporting of disposition and screening failures.

Full analysis set (FAS): All randomized subjects who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study. Subjects would be analysed according to their randomized treatments irrespective of whether or not they have been prematurely discontinued, according to the Intent-to-Treat (ITT) principle. Subjects who withdraw consent, or assent when applicable, to participate in the study would be included up to the date of their study termination. All efficacy analyses were to be performed using an ITT approach based on the full analysis set (FAS). For consistency, demographic and baseline characteristics were presented using the FAS.

Safety analysis set: All subjects who have received at least 1 dose of IP. Erroneously treated patients during the DB period (e.g., those randomized to treatment A but actually given treatment B) were accounted for in the treatment group of the treatment they actually received. A subject who had on one or several occasions received active IP was classified as active. Safety summaries and ADA data were based on this analysis set.

Pharmacokinetic analysis set: All subjects who received benralizumab and from whom PK blood samples were assumed not to be affected by factors such as protocol violations (e.g. received wrong dose) and who had at least 1 quantifiable serum PK observation post first dose. All PK summaries would be based on this analysis set.

Open-label benralizumab analysis set: All subjects who started or carried on receiving at least 1 dose of benralizumab after the end of the Week 24 double blind treatment period.

Open-label extension benralizumab analysis set: All subjects who carried on receiving at least 1 dose of benralizumab after the end of the Week 52 double blind + open label treatment periods.

Additionally, *Early time point sub-study analysis set* was defined as all subjects who had Week 4 or Week 12 endoscopy performed.

Table 14 Analysis Sets

Analysis set	Number of patients		
	Benra 30 mg	Placebo	Total
Patients randomized	104	107	211
Patients included in safety analysis set [a]	103	107	210
Patients excluded from safety analysis set [b]	1	0	1
Patients included in full analysis set [c]	103	107	210
Patients excluded from full analysis set [b]	1	0	1
Patients included in PK analysis set [d]	97	96	193
Patients excluded from PK analysis set [b]	7	11	18
Patients included in open label Benralizumab analysis set [e]	100	105	205
Patients excluded from open label Benralizumab analysis set [b]	4	2	6

[a] All patients who received at least 1 dose of IP were included in the safety analysis set.

[b] An individual patient could have been excluded for more than 1 reason.

[c] All patients randomised who received any IP were included in the FAS, irrespective of their protocol adherence and continued participation in the study.

[d] All patients who received benralizumab and from whom PK blood samples were obtained and are assumed not to be affected by factors such as protocol violations and who had at least 1 quantifiable serum PK observation post first dose were included in the PK analysis dataset.

[e] All patients who started or carried on receiving at least 1 dose of benralizumab after the end of the Week 24 DB treatment period.

Benra benralizumab; DB double-blind; FAS Full Analysis Set; IP investigational product; PK pharmacokinetics.

Efficacy results (primary analysis)

Efficacy analyses were performed using the FAS for the DB and the OL periods. Efficacy results are presented for the 24-week DB period for all patients and for all available data up to Week 52 from the OL period (Weeks 24 to 52) by the data cut-off date for the *primary analysis* (19 September 2022). After the primary analysis was completed, the decision was made to terminate the study. 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.

It is clarified that no updated efficacy, PK, PD, or immunogenicity analyses were performed at the final analysis; all analyses for these endpoints in the report relate to the primary analysis data cut-off (19 September 2022).

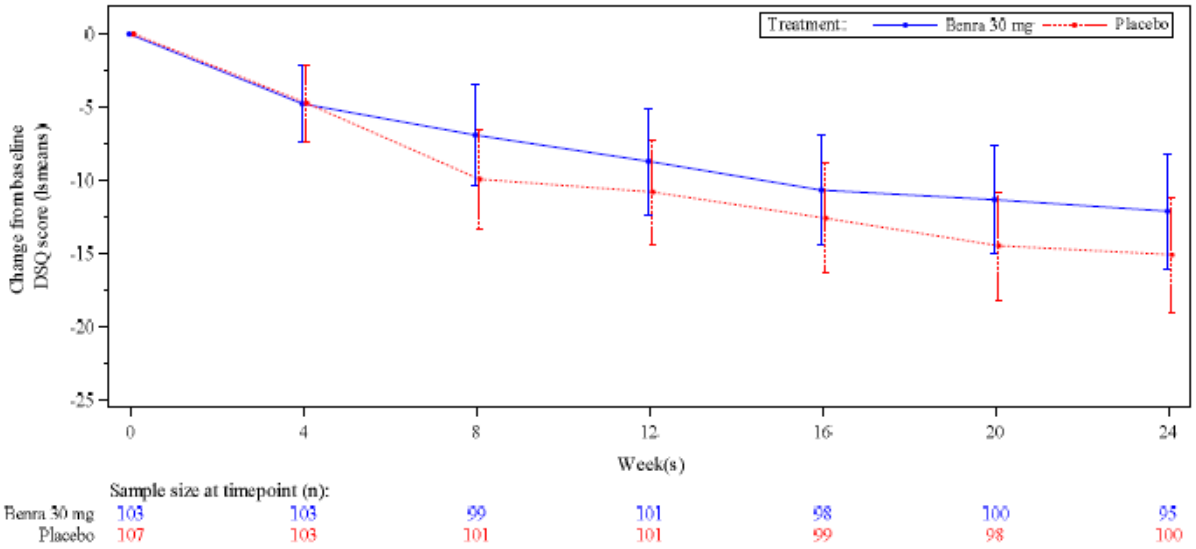
Dual primary endpoints

The proportion of patients who achieved histological response (≤ 6 eos/hpf) at Week 24 was statistically significantly higher in the benralizumab group compared with the placebo group (difference versus placebo: 80.8%, 95% CI: 72.9%, 88.8%; $p < 0.0001$, Table 18) and the robustness of the results were supported by sensitivity analyses.

At baseline, the mean DSQ score was 35.9 and 34.1 in the benralizumab and placebo groups, respectively. *The mean change from baseline in DSQ scores at the primary time point at Week 24* and overall, in the 24-week DB period was similar between treatment groups (LS mean changes from baseline of -12.1 versus -15.1 for benralizumab versus placebo, respectively, Figure 3). The difference

in LS mean change from baseline in DSQ score at Week 24 (3.0) was not statistically significant between treatment groups (95% CI: -1.36, 7.35; p = 0.1770, Table 18). Sensitivity analyses showed consistent results with the primary change in DSQ analysis. Additionally, no clear differences between treatment groups were seen in any of the subgroups assessed.

Figure 3 **Mean Change from Baseline in DSQ Score by Time Point, Line Plot – DB Period (Full Analysis Set)**



* indicates statistical significance with 0.01 ≤ p-value < 0.05 for that time point.

** indicates statistical significance with p-value < 0.01 for that time point.

Baseline was calculated over the 14-day period prior to randomisation.

For any patients with intercurrent events, the DSQ scores after the occurrence of these events were imputed using return-to-baseline MI. Missing data not due to intercurrent events were imputed using MI (MAR).

Error bars indicate the 95% CI.

Benra benralizumab; CI confidence interval; DB double-blind; DSQ Dysphagia Symptom Questionnaire; MAR missing at random; MI multiple imputation; n number of patients with data at that visit (including patients with imputed values post intercurrent events).

Key secondary endpoints

A greater LS mean percent reduction from baseline in tissue eosinophils was observed at Week 24 in the benralizumab group compared with the placebo group with *a difference* between treatment groups which reached nominal statistical significance (-96.2, 95% CI: -114.5, -77.9; p < 0.0001).

A greater *LS mean change from baseline in EoE-HSS total grade score at Week 24* observed in the benralizumab group compared with the placebo group, and the observed difference reached nominal statistical significance (-0.18, 95% CI: -0.21, -0.14; p < 0.0001).

A greater LS *mean reduction from baseline in EoE-HSS total stage score was observed at Week 24* in the benralizumab group compared with the placebo group and the observed difference reached nominal statistical significance (-0.12, 95% CI: -0.16, -0.09; p < 0.0001).

Both scores in EoE Histology Scoring System (EoE-HSS) relate to the presence of eosinophils (eosinophil inflammation, eosinophil abscess, and eosinophil surface layering) in the benralizumab group compared to the placebo group. No clear differences between treatment groups were observed

for features related to epithelium (surface epithelial alteration and dyskeratotic epithelial cells), while a trend for greater improvement in lamina propria was observed for the benralizumab group but was limited by the small number of samples with available lamina propria tissue.

The difference in LS *mean change from baseline in centrally-read EREFS total scores at Week 24* was similar between the two treatment groups (-0.1, 95% CI: -0.52, -0.37; p = 0.7322).

The proportion of patients considered 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]) was greater in the benralizumab group compared to the placebo group driven by the histological response in the benralizumab group, but with no statistically significant or clinically meaningful difference in DSQ between the groups. The difference in treatment responder rate between treatment groups reached nominal statistical significance ((39.0%, 95% CI: 28.6%, 49.4%; p < 0.0001).

The results for the dual-primary and key secondary variables/endpoints are summarized in Table 18:

Table 18 Overview of Primary and Key Secondary Efficacy Results (Full Analysis Set)

Variable	Type of estimate	Analysis model	Comparison	n vs n	Comparison with placebo [a]	95% CI	p-value
Dual primary variables							
Proportion of patients with a histologic response [b] at Week 24	Proportion difference (%)	CMH test	Benra 30 mg (N = 103) vs Placebo (N = 107)	103 vs 107	80.84	(72.89, 88.78)	
	Odds ratio	CMH test	Benra 30 mg (N = 103) vs Placebo (N = 107)	103 vs 107	117.49	(38.17, 361.64)	< 0.0001
Change from baseline in DSQ score at Week 24	Difference in LSMeans	ANCOVA [c]	Benra 30 mg (N = 103) vs Placebo (N = 107)	95 vs 100	2.999	(-1.36, 7.35)	0.1770
Key secondary variables							
Percent change from baseline in peak tissue eosinophil count at Week 24	Difference in LSMeans	ANCOVA [c]	Benra 30 mg (N = 103) vs Placebo (N = 107)	97 vs 100	-96.191	(-114.53, -77.85)	< 0.0001
Change from baseline in EoE-HSS total grade score at Week 24	Difference in LSMeans	ANCOVA [c]	Benra 30 mg (N = 103) vs Placebo (N = 107)	97 vs 100	-0.175	(-0.21, -0.14)	< 0.0001
Change from baseline in EoE-HSS total stage score at Week 24	Difference in LSMeans	ANCOVA [c]	Benra 30 mg (N = 103) vs Placebo (N = 107)	97 vs 100	-0.122	(-0.16, -0.09)	< 0.0001
Change from baseline in centrally-read EREFS total score at Week 24	Difference in LSMeans	ANCOVA [c]	Benra 30 mg (N = 103) vs Placebo (N = 107)	85 vs 84	-0.1	(-0.52, 0.37)	0.7322
Proportion of patients with a treatment response [d] at Week 24	Rate difference (%)	CMH test	Benra 30 mg (N = 103) vs Placebo (N = 107)	103 vs 107	39.02	(28.64, 49.40)	
	Odds ratio	CMH test	Benra 30 mg (N = 103) vs Placebo (N = 107)	103 vs 107	15.86	(5.79, 43.47)	< 0.0001

a A positive result in rate difference, > 1 result in odds ratio, a negative difference in LS means would favour the benralizumab 30 mg group.

b A histologic response was defined as a peak oesophageal intraepithelial eosinophil count ≤ 6 eos/hpf across all available oesophageal levels. Patients with no biopsy data at Week 24 or with intercurrent events prior to Week 24 such as changes to background medications or additional new therapies for EoE were considered non-responders.

c For any patients with intercurrent events, the scores after the occurrence of these events were imputed using return-to-baseline multiple imputation. Missing data not due to intercurrent events were imputed using MI (MAR).

d A treatment response was defined as composite of histologic response and clinically meaningful improvement (30% reduction) from baseline in DSQ score. Patients with missing data at Week 24 or with intercurrent events prior to Week 24 such as changes to background medications or additional new therapies for EoE were considered non-responders.

ANCOVA analysis of covariance; Benra benralizumab; CI confidence interval; CMH Cochran-Maentel-Haenszel; DSQ Dysphagia Symptom Questionnaire; EoE eosinophilic esophagitis; eos eosinophils; EREFS endoscopic reference score; hpf high-power field; HSS histology scoring system; LS means least square means; MAR missing at random; MI multiple imputation; N number of patients in treatment group who could have made it to that time point by the data cut-off; n number of patients with data at that

visit (including patients with imputed values post intercurrent events) for continuous endpoint. For binary endpoints n represents the number of patients in the analysis.

The secondary efficacy variable PEESS was summarized only descriptively since there were not enough paediatric subjects available: the PEESS assessments were completed by the 29 patients who were age ≤ 18 years at the time of Visit 1. The mean change from baseline in PEESS scores at Week 24 was similar between treatment groups.

As statistical significance was not achieved on the DSQ endpoint (at the 5% level), other secondary endpoints in the testing hierarchy could not be formally tested.

Based on the results from the Early Time Point Sub-study (not component of the dual-primary or key secondary endpoints) treatment with benralizumab resulted in a greater LS mean reduction from baseline in peak oesophageal intraepithelial eosinophil counts starting at Week 4 compared with placebo (-69.8 versus +0.07 eos/hpf, respectively), and this greater mean reduction was maintained through Weeks 12 and 24.

PK results (primary analysis)

Serum benralizumab concentrations by time Point during the 24-week DB period and the 28-week OL period were based on the PK analysis set and are summarized in Table 26. Based on geometric mean serum concentrations, PK steady state for patients treated with benralizumab was reached by Week 16 during the DB period. However, the lack of an OL equivalent for the DB Week 16 PK time-point did not allow for a conclusion for the placebo/benralizumab group.

Table 26 Summary of Serum Concentrations (ng/mL) of Benralizumab by Time Point – DB and OL Periods (PK Analysis Set)

Time point	Statistic	Benra 30 mg N = 97	Placebo switched to Benra 30 mg N = 96
Baseline	n	92	-
	n < LLOQ	92	-
	Geometric mean (CV [%]) [a]	BLQ (NA)	-
	Median (Min, Max)	BLQ (BLQ, BLQ)	-
Week 8	n	95	-
	n < LLOQ	0	-
	Geometric mean (CV [%]) [a]	1555.70 (45.03)	-
	Median (Min, Max)	1668.39 (407.51, 4045.43)	-
Week 16	n	91	-
	n < LLOQ	0	-
	Geometric mean (CV [%]) [a]	1582.46 (104.84)	-
	Median (Min, Max)	1753.72 (8.55, 5862.16)	-
Week 24	n	85	91
	n < LLOQ	0	91
	Geometric mean (CV [%]) [a]	1338.65 (187.69)	BLQ (NA)
	Median (Min, Max)	1800.69 (6.08, 5993.92)	BLQ (BLQ,BLQ)
Week 36	n	67	63
	n < LLOQ	2	1
	Geometric mean (CV [%]) [a]	1405.94 (270.24)	1362.27 (136.89)
	Median (Min, Max)	1952.64 (BLQ, 6557.72)	1689.03 (BLQ, 3416.84)
Week 52	n	30	36
	n < LLOQ	0	1
	Geometric mean (CV [%]) [a]	1278.13 (259.61)	1495.61 (198.01)
	Median (Min, Max)	1864.745 (5.68, 4931.18)	2100.8 (BLQ, 5645.74)

[a] Calculated using log-transformed data.

PK serum samples were collected pre-dose at each visit.

If the result is BLQ (Below limit of quantification), the value is set as ½ LLOQ. LLOQ is 3.86 ng/mL.

Baseline is defined as the last valid value prior to first dose of study treatment.

Benra benralizumab; CV coefficient of variation; DB double-blind; LLOQ lower limit of quantification (X ng/mL); N Number of patients in treatment group; n Number of patients in analysis; OL open-label; PK pharmacokinetics; Max maximum; Min minimum; NA not applicable.

Pharmacodynamic results (primary analysis)

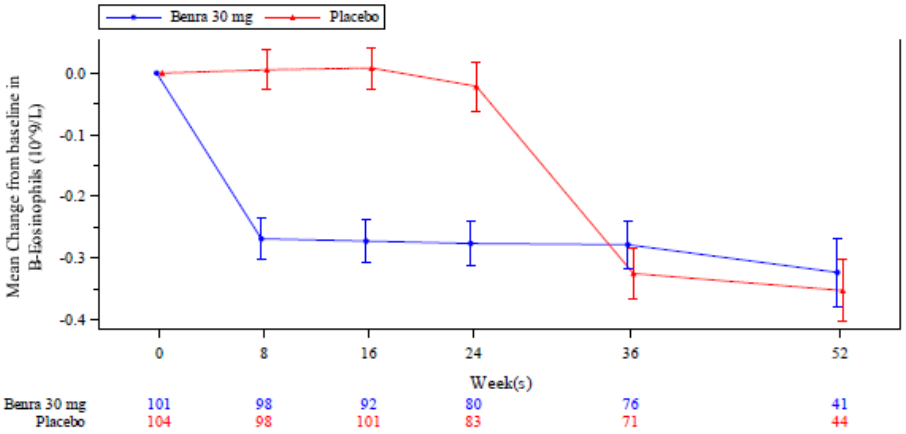
Changes in tissue eosinophil and blood eosinophil counts observed over time during the 24-week DB period and the 28-week OL period were assessed for the primary analysis to evaluate the PD of benralizumab.

Results for the primary analysis showed a greater LS mean percent reduction from baseline in *tissue eosinophils* at Week 24 in the benralizumab group compared with the placebo group and a similar effect was also observed in the Early Time Point Sub-study (Week 4) *(see Efficacy results: Key secondary endpoints)*. For patients in the placebo group who switched to benralizumab in the OL period and had tissue biopsy data available at Week 52, near complete eosinophil depletion was also demonstrated. The mean reduction from baseline in tissue eosinophils in the placebo/benralizumab

group at Week 52 was consistent with the reduction from baseline in the benralizumab group at Week 24.

Benralizumab treatment resulted in near complete depletion of *blood eosinophils* at the first time point assessed (Week 8) following the start of treatment (mean change from baseline: -0.3 × 10^9 cells/L) that was maintained through Week 24 (mean change from baseline: -0.3 × 10^9 cells/L; see Figure 14.3.7.1.1 from Hematology safety testing). Mean changes from baseline in blood eosinophils was 0.0 × 10^9 cells/L in the placebo group over the course of the DB period. Based on available laboratory data at Week 52, the near complete depletion of blood eosinophils was maintained through Week 52 in the benralizumab group (mean change from baseline: -0.3 × 10^9 cells/L).

Figure 14.3.7.1.1 Haematology and clinical chemistry variables, mean change from baseline value by timepoint - line plot - on-study - Double blind and open label period (Safety analysis set)



Benra=Benralizumab.
Baseline is defined as the last valid value prior to first dose of study treatment.
Double blind (DB) period: from the first dose date up to the first dose of open label benralizumab 30 mg, or to the end of the study if the participant does not transition into open label period.
Open label (OL) period: from the first dose of open label benralizumab 30 mg up to the first dose of open label extension benralizumab 30 mg, or to the end of the study if the participant does not transition into open label extension period.
On-study is from date of first dose to last date in study.
Error bar represents the 95% confidence interval, calculated as mean +/- 1.96*standard deviation/sqrt (n).
Reference table: 14.3.7.1.1

Pharmacokinetic/Pharmacodynamic relationship

Exposure-response analyses were performed with PK concentration subgroups, for the dual-primary endpoints (histological response at Week 24 and change from baseline in DSQ score at Week 24). It is clarified that the study was not designed or powered to assess efficacy within any of the pre-defined subgroups and therefore these analyses were considered exploratory: subgroup analyses demonstrated that the proportion of patients with histological response at Week 24 for the benralizumab group for both the > median and the ≤ median benralizumab serum concentration at Week 24 versus placebo subgroups was consistent with the overall analysis results. Subgroup analyses demonstrated that there was no difference in the DSQ score LS mean change from baseline at Week 24 observed for the benralizumab group for both the > median and the ≤ median benralizumab serum concentration at Week 24 versus placebo subgroups. 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.

Immunogenicity results (primary analysis)

Potential impact of ADA on benralizumab PK was investigated by the analysis of serum concentrations in ADA subgroups: benralizumab geometric mean serum concentrations were lower in subgroups of ADA-positive patients compared to ADA-negative patients starting at Week 16 through Week 52, particularly within the subgroup of high-titred ADA-positive patients in the benralizumab group; however, numbers of patients with serum concentration results within each ADA positive subgroup were low.

Assessment of the anti-drug antibody effect on PD showed that: a) median decreases in blood eosinophils were numerically lower in the subgroup of patients with high ADA titre (titre > than the median of the maximum titre), ADA-persistently positive patients, and nAb-positive patients compared to the median decreases in the subgroup of ADA-negative patients and b) median decreases in tissue eosinophils at week 24 were similar in the overall subgroup of ADA-positive patients and ADA-negative patients in the benralizumab group but numerically smaller in the subgroup of high-ADA titre patients.

Additionally, the proportions of patients with histological response were numerically lower in the ADA-positive subgroups compared to the ADA-negative subgroup at Week 24, however no difference was noted at Week 52. Although no marked differences were observed in DSQ between ADA positive and ADA negative subgroup of patients, further interpretation is confounded by the absence of a treatment effect in the overall population.

Safety results

All safety analyses for the DB period and DB + OL + OLE periods were performed using *the safety analysis set*, which included all patients who received at least 1 dose of IP. Safety data were presented for the primary analysis, which included complete data for the 24-week DB period for all patients and all available data for the 28-week OL period and for the OLE period that had accumulated by the primary analysis data cut-off date (19 September 2022). Additionally, cumulative safety data available at the time of the final clinical data lock date (03 March 2023) are referred to as the final analysis. No meaningful differences were identified in safety information based on results for the final analysis compared to the primary analysis.

In line with the balanced disposition between treatment groups, the mean duration of on-treatment exposures to IP during the 24 weeks of the DB period was similar between the benralizumab and placebo groups. Similarly, 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.

Adverse Events

The proportion of patients with AEs with onset during the DB period was similar in the benralizumab group compared with the placebo group. The numbers of patients with SAEs were low in both treatment groups. There were no patients with AEs leading to discontinuation of IP. No deaths were reported during the study (Table 31).

Table 31 Adverse Events in Any Category Reported During the DB Period (Safety Analysis Set)

On-treatment AE category	Number (%) of patients	
	Benra 30 mg (N = 103)	Placebo (N = 107)
Any AE	66 (64.1)	66 (61.7)
Any AE with outcome of death	0 (0.0)	0 (0.0)
Any SAE (including events with outcome of death)	2 (1.9)	1 (0.9)
Any AE leading to discontinuation of IP	0 (0.0)	0 (0.0)

On-treatment includes AEs that occurred from date of first dose to date of EOT visit or IPD visit.

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Percentages are calculated using number of patients in each treatment group (N) as denominator.

AE adverse event; Benra benralizumab; DB double-blind; EOT End of Treatment; IP investigational product; IPD investigational product discontinued; N number of patients in treatment group; SAE serious adverse event

Adverse events with onset during the OL period, by category, were generally similar in the placebo/benralizumab group compared with the benralizumab group (Table 33). SAEs were reported for a total of 5 patients during the OL period (Table 33).

Table 33 Adverse Events in Any Category Reported During the OL Period (OL Benralizumab Analysis Set)

On treatment AE category	Number (%) of patients	
	Benra 30 mg (N = 100)	Placebo switched to Benra 30 mg (N = 105)
Any AE	47 (47.0)	57 (54.3)
Any AE with outcome of death	0 (0.0)	0 (0.0)
Any SAE (including events with outcome of death)	2 (2.0)	3 (2.9)
Any AE leading to discontinuation of IP	0 (0.0)	1 (1.0)

On-treatment includes AEs that occurred from the date of first dose to date of EOT visit or IPD visit.

Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.

Percentages were calculated using number of patients in each treatment group (N) as denominator.

Only events started during OL period are counted.

AE adverse event; Benra benralizumab; EOT End of Treatment; IP investigational product; IPD investigational product discontinued; N number of patients in treatment group; OL open-label; SAE serious adverse event

The most common AEs by Preferred Term with onset during the DB period and OL period are shown in Tables 34 and 37 respectively:

Table 34 Most Common AEs Reported During the DB Period (Frequency of > 3% in Either Treatment Group) (Safety Analysis Set)

	Number (%) of patients [a]	
On-treatment Preferred term	**Benra 30 mg (N = 103)**	**Placebo (N = 107)**
COVID-19	13 (12.6)	13 (12.1)
Headache	9 (8.7)	11 (10.3)
Nasopharyngitis	8 (7.8)	6 (5.6)
Asthma	4 (3.9)	4 (3.7)
Upper respiratory tract infection	2 (1.9)	5 (4.7)
Oropharyngeal pain	4 (3.9)	1 (0.9)
Abdominal pain	0 (0.0)	4 (3.7)

Table 37 Most Common AEs Reported During the OL Period (Frequency of > 3% in Either Treatment Group) (OL Benralizumab Analysis Set)

	Number (%) of patients [a]	
On treatment Preferred term	**Benra 30 mg (N = 100)**	**Placebo switched to Benra 30 mg (N = 105)**
COVID-19	13 (13.0)	10 (9.5)
Nasopharyngitis	6 (6.0)	3 (2.9)
Injection-site erythema	5 (5.0)	2 (1.9)
Diarrhoea	1 (1.0)	4 (3.8)
Hypertension	4 (4.0)	1 (1.0)

[a] Sorted in decreasing frequency of PTs according to total frequency. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

On-treatment includes AEs that occurred from date of first dose to date of EOT visit or IPD visit.

Only events starting during OL period were counted.

Percentages were calculated using number of patients in each treatment group (N) as denominator.

MedDRA Version 25.0.

AE adverse event; Benra benralizumab; COVID-19 coronavirus disease 2019; EOT End of Treatment; IPD investigational product discontinued; MedDRA Medical Dictionary for Regulatory Activities; N number of patients in treatment group; OL open-label; PT preferred term

There were few patients with AEs with onset during the DB period that were assessed as possibly related to IP by the Investigator; there were no notable differences between treatment groups.

For the final analysis, the most common AEs reported during the DB + OL + OLE period were consistent with AEs with onset during the DB period and those with onset during the OL period. There were no notable differences in AEs reported at the time of the final analysis compared to the primary analysis.

Deaths, Serious Adverse Events, Discontinuation of Investigational Product Due to Adverse Events, and Other Significant Adverse Events

No patients had an AE with an outcome of *death* during the study based on the information from both the primary and final analysis.

The *SAEs* reported during the DB and OL periods in all treatment groups are summarized in Tables 38 and 39 below. None of the SAEs with onset in the DB period were assessed by the Investigator as possibly related to IP, none led to discontinuation and all patients recovered.

Of note, four SAEs with onset during the OL period were reported at the time of the primary analysis for 1 *adolescent patient* in the benralizumab group: suicide attempt, affective disorder, depression and oppositional defiant disorder. Although the patient had no prior medical history of psychiatric disorders, an underlying diagnosis of depression was established during hospitalisation for the suicide attempt. All SAEs for this patient were resolved, none were assessed as related to IP and study treatment was continued. However, 2 additional SAEs, suicide attempt and disruptive mood dysregulation disorder were reported for the above patient following the data cut-off for the primary analysis (OLE period). The second suicide attempt included in the final analysis was considered resolved, while the disruptive mood dysregulation disorder was not recovered/not resolved at the time of the final analysis.

In addition, four SAEs with onset during the same period (OL) were reported for 1 *adult patient* in the placebo/benralizumab group: oesophageal food impaction, oesophageal perforation, pneumomediastinum and pneumoperitoneum. Following the endoscopic procedure for food impaction, the patient developed oesophageal perforation, pneumomediastinum and pneumoperitoneum. All SAEs were resolved and assessed as not related to IP, however study treatment was discontinued due to the oesophageal food impaction.

Table 38 SAEs Reported During the DB Period (Safety Analysis Set)

	Number (%) of patients [a]	
On-treatment System Organ Class/ Preferred Term	**Benra 30 mg (N = 103)**	**Placebo (N = 107)**
Patients with any SAE	2 (1.9)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	1 (1.0)	1 (0.9)
Asthma	0 (0.0)	1 (0.9)
Bronchospasm	1 (1.0)	0 (0.0)
Infections and infestations	1 (1.0)	0 (0.0)
Infectious pleural effusion	1 (1.0)	0 (0.0)
Pneumonia bacterial	1 (1.0)	0 (0.0)

Table 39 SAEs Reported During the OL Period (OL Benralizumab Analysis Set)

	Number (%) of patients [a]	
On-treatment System Organ Class/ Preferred Term	**Benra 30 mg (N = 100)**	**Placebo switched to Benra 30 mg (N = 105)**
Patients with any SAE	2 (2.0)	3 (2.9)
Gastrointestinal disorders	1 (1.0)	1 (1.0)
Oesophageal food impaction	1 (1.0)	1 (1.0)
Oesophageal perforation	0 (0.0)	1 (1.0)
Pneumoperitoneum	0 (0.0)	1 (1.0)
Immune system disorders	0 (0.0)	1 (1.0)
Hypersensitivity	0 (0.0)	1 (1.0)
Infections and infestations	0 (0.0)	1 (1.0)
Gastroenteritis	0 (0.0)	1 (1.0)
Psychiatric disorders	1 (1.0)	0 (0.0)
Affective disorder	1 (1.0)	0 (0.0)
Depression	1 (1.0)	0 (0.0)
Oppositional defiant disorder	1 (1.0)	0 (0.0)
Suicide attempt	1 (1.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (1.0)
Pneumomediastinum	0 (0.0)	1 (1.0)

During the DB + OL + OLE periods, a total of 8/208 patients (3.8%) who received benralizumab at any point during the study reported SAEs while receiving benralizumab. After the data cut off for the primary analysis, 1 additional patient in the placebo/benralizumab group reported 1 SAE (anaphylactic reaction) which was resolved.

The analyzed *Adverse Events of interest* included:

- serious infections: for the AEs reported during each study period and the respective treatment groups see Table 38 for the DB period AEs (infectious pleural effusion and pneumonia bacterial and Table 39 for the OL period AEs (gastroenteritis).
- helminth infections: No cases of helminth infections were reported during the DB, OL, or the DB + OL + OLE periods.
- malignancy: an AE of basosquamous carcinoma was reported for 1 patient in the benralizumab group during the OL period and an AE of malignant melanoma in situ was reported for 1 patient in the placebo group during the DB + OL + OLE periods. Neither patient had a medical history of malignancy. Both events were recovered/resolved and did not require treatment.

Hypersensitivity AEs with onset during the DB period were reported in 3.9% of patients in the benralizumab group and for 6.5% patients in the placebo group. The most frequently reported (ie, for ≥ 2 patients) hypersensitivity AEs during the DB period were eczema (3 patients in placebo group), rash (2 patients in benralizumab group), and rhinitis allergic (2 patients in placebo group).

Additional hypersensitivity AEs with onset during the OL period were reported for 2 patients in the benralizumab group (rhinitis allergic and injection site urticaria, reported for 1 patient each) and for 4 patients in the placebo/benralizumab group (hypersensitivity reported for 2 patients, and idiopathic urticaria and injection related reaction, reported for 1 patient, each).

The proportion of patients with *injection-site reaction AEs* reported during the DB period was low and similar for the benralizumab patients (2.9%) and placebo patients (1.9%) groups. At the time of the final analysis, during the DB + OL periods, injection-site reactions were reported for 8.7% of patients in the benralizumab group and for 4.7% of patients in the placebo/benralizumab group, and for a total of 14 patients (6.7%) while receiving benralizumab. None of the additional injection site reactions reported for the final analysis were SAEs and none resulted in discontinuation of IP.

Overall, there was no consistent pattern or trend in the hypersensitivity and injection-site reaction AEs observed in the benralizumab and placebo groups during the study.

Clinical Laboratory Evaluation

Analyses on the *changes in blood eosinophils* are presented in the section of efficacy results.

At the time of the primary analysis, low values for post-baseline *neutrophils* were observed for 20 patients in the benralizumab group and for 11 patients in the placebo/benralizumab group during the DB + OL periods without a pattern for the timing of the mean value decrease. The decreases in neutrophils were transient and resolved over the course of the study for most patients in the study.

There were no clinically meaningful trends in *clinical chemistry values* over time during the DB + OL periods. There were no clinically meaningful trends in *urinalysis* findings over time and no individual clinically important findings were identified in any treatment group during the DB and DB + OL periods.

Few patients reported AEs related to *vital signs*, their incidences were similar between treatment groups, and none were clinically significant.

2.3.3. Discussion on clinical aspects

Study D3255C00001 (MESSINA) 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.

The primary analysis of the MESSINA study performed when all randomised patients completed the 24-week DB period, evaluated the effect of benralizumab on histologic signs and clinical symptoms of EoE at the end of the DB period. In summary for the dual primary efficacy endpoints, treatment with benralizumab resulted in a statistically significant increase in the proportion of patients achieving histological response at Week 24 compared to placebo, yet statistical significance or clinically meaningful difference in DSQ LS mean change from baseline was not demonstrated between benralizumab and placebo treatment groups. Analysis for secondary endpoints supported the dual-primary endpoint results with improvement only in histology-related endpoints and no difference in endoscopic appearance and symptom-related endpoints at Week 24 for benralizumab compared with placebo. Challenges in the interpretation of the OL period data i.e the incomplete follow-up through 52 weeks and the absence of placebo-control did not have a major impact on the overall conclusions of the study.

There was evidence of an effect of ADA on PK, particularly in those patients with high titres, though the number of patients in ADA subgroups were low. Decreases in blood and tissue eosinophil counts were

noted in all ADA-positive subgroups in the benralizumab group; decreases were smaller in the subgroup of high-titred ADA positive patients. There was no effect of ADA on safety.

The safety data presented for the primary analysis and the cumulative data available at the time of the final clinical data lock date are consistent with the known safety profile of benralizumab. No new safety findings associated with benralizumab treatment were identified during the study.

Upon completion of the primary analysis, the decision was made by the sponsor to terminate the study on the grounds of absence of any statistically significant or clinically meaningful difference in clinical symptom endpoints between benralizumab and placebo, despite the demonstration of robust blood and tissue eosinophil depletion.

At the time of study design, the central finding in EoE was eosinophilic inflammation, and the presence of eosinophils in the esophageal epithelium considered pathogenic[1]. The results from the MESSINA study demonstrate that depletion of esophageal eosinophils did not translate to improvements in dysphagia symptoms. A recent review article[5] provides insight into the pathogenesis of EoE, supporting the view that EoE being a Th_2-mediated disease is defined by many more disease features than eosinophilic infiltration. In the same article eosinophil targeting treatments are discussed i.e, IL-5 appears to have a key role in eosinophil trafficking and eosinophil survival, however EoE treatments targeting this cytokine had minor impact on the improvement of clinical symptoms in EoE trials. A possible association between altered neuroimmune activity of cells overexpressed in type 2 inflammation and dysphagia as the major clinical disease presentation in EoE is described in a review article [6] . Both articles suggest a more complex pathophysiological mechanism of esophageal eosinophilia.

3. CHMP's overall conclusion and recommendation

MESSINA was the first clinical study to demonstrate the effect of benralizumab in the depletion of eosinophils in GI tissue, after just 1 dose. Nevertheless, benralizumab did not succeed to reduce dysphagia symptoms or resolve non-eosinophilic histologic or structural features of EoE. Treatment with benralizumab in EoE patients was well tolerated with no new safety findings.

The submitted Phase III study does not change the benefit risk profile for FASENRA. It is agreed that revisions to the Summary of Product Characteristics are not warranted.

☒ Fulfilled:

No regulatory action required.

[5] Salvador Nunes, V. S., Straumann, A., Salvador Nunes, L., Schoepfer, A. M., & Greuter, T. (2023). Eosinophilic Esophagitis beyond Eosinophils - an Emerging Phenomenon Overlapping with Eosinophilic Esophagitis: Collegium Internationale Allergologicum (CIA) Update 2023. *International archives of allergy and immunology*, *184*(5), 411–420. https://doi.org/10.1159/000529910

[6] Kim, B., Rothenberg, M. E., Sun, X., Bachert, C., Artis, D., Zaheer, R., Deniz, Y., Rowe, P., & Cyr, S. (2023). Neuroimmune interplay during type 2 inflammation: symptoms, mechanisms and therapeutic targets in atopic diseases. *The Journal of allergy and clinical immunology*, S0091-6749(23)01070-9. Advance online publication. https://doi.org/10.1016/j.jaci.2023.08.017

Annex. Line listing of all the studies included in the development programme

Clinical study

Product Name: Fasenra Active substance: benralizumab

Study title	Study number	Date of completion	Date of submission of final study report
MESSINA	D3255C00001	6 February 2023	21 July 2023