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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Fasenra

benralizumab

Procedure no: EMEA/H/C/004433/P46/007

Note

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

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1. Introduction

On 13/2/2023, the MAH submitted a completed paediatric study for Fasenra, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The MAH determined that the results of the study D3256C00001 (HILLIER) do not support the continued development of benralizumab for the indication of atopic dermatitis (AD), and for this reason the study was terminated after the primary analysis and results of the study are presented in the format of a synoptic clinical study report (CSR).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study D3256C00001, titled "A Phase 2 Multinational, Randomized, Double-blind, Parallel group, 16-week Placebo-controlled Study with a 36–week Extension to Investigate the Use of Benralizumab for Patients with Moderate to Severe Atopic Dermatitis Despite Treatment with Topical Medications (The HILLIER Study)" 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 in accessorized prefilled syringe (APFS) with 1 mL fill volume.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a synoptic clinical report for:

Study D3256C00001, titled "A Phase 2 Multinational, Randomized, Double-blind, Parallel group, 16-week Placebo-controlled Study with a 36–week Extension to Investigate the Use of Benralizumab for Patients with Moderate to Severe Atopic Dermatitis Despite Treatment with Topical Medications (The HILLIER Study)".

2.3.2. Clinical study

Clinical study number: D3256C00001

Title: "A Phase 2 Multinational, Randomized, Double-blind, Parallel group, 16-week Placebo-controlled Study with a 36–week Extension to Investigate the Use of Benralizumab for Patients with Moderate to Severe Atopic Dermatitis Despite Treatment with Topical Medications (The HILLIER Study)".

Description

Benralizumab (MEDI-563) is a humanised, afucosylated, monoclonal antibody (immunoglobulin G1 kappa) that binds to the human alpha chain of the IL-5 receptor, which is expressed on the surface of

eosinophils and basophils (Takatsu et al 1994, Toba et al 1999). Benralizumab depletes eosinophils and basophils by inducing apoptosis via enhanced antibody-dependent cell-mediated cytotoxicity (Kolbeck et al 2010).

Benralizumab is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists. The recommended dose is 30 mg administered by subcutaneous (SC) injection every 4 weeks (Q4W) for the first 3 doses, followed by every 8 weeks (Q8W) thereafter.

Study D3256C00001 is submitted as part of the MAH's investigation on the clinical utility of benralizumab across a range of indications involving eosinophil-driven pathology. Data from the approved severe asthma indication demonstrate that benralizumab 30 mg Q4W is safe and well tolerated among adolescent patients.

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, affecting between 2.1% and 4.9% of adults (Barbarot et al 2018), and up to 20% of children in some countries (Nutten 2015).

Blood eosinophilia though variable in the general population of patients with AD, increases with disease severity, thereby supporting the eosinophilic nature of the disease (Jenerowicz et al 2007). Eosinophils are more likely to be present in acutely diseased skin samples than in chronically diseased samples. However, the markers of eosinophil activation and degradation (e.g., eosinophil peroxidase, major basic protein [MBP], eosinophil cationic protein and eosinophil-derived neurotoxin [EDN]), as revealed by immunofluorescence and eosinophil membrane disruption by electron microscopy, are prominent within AD skin samples providing further evidence of eosinophil involvement in the pathophysiology of AD. According to the rationale proposed by the MAH, this evidence for a role of eosinophils in the pathophysiology of AD suggests that a direct eosinophil-depleting approach, as provided by benralizumab, may prove beneficial in the treatment of AD by improving symptoms and AD-related quality of life.

Methods

Study D3256C00001 was a phase 2 multinational, randomized, double-blind, placebo-controlled, parallel-group study to compare the efficacy and safety of benralizumab 30 mg monotherapy vs placebo in patients ≥ 12 years of age with moderate to severe AD who remain symptomatic despite treatment with standard of care treatment with topical medications. Benralizumab 30 mg was administered subcutaneously (SC) every 4 weeks (Q4W) for comparison with placebo for a period of 16 weeks and identification of the appropriate maintenance dosing frequency (Q4W vs Q8W) during a 36-week extension period.

Study participants

The target population consisted of male and female patients ≥ 12 years of age with moderate to severe AD who remained symptomatic despite standard of care treatment with topical medications.

Inclusion Criteria:

- Physician-confirmed diagnosis of AD (according to American Academy of Dermatology Consensus Criteria) that was not adequately controlled with topical medications.
- Eczema Area and Severity Index (EASI) score of ≥ 12 at screening and ≥ 16 at randomization.
- Investigator Global Assessment (IGA) score of ≥ 3 (on a scale of 0 to 4, in which 3 was moderate and 4 was severe) at screening and at randomization.

- AD involvement of ≥ 8% body-surface area at screening and ≥ 10% body-surface area at randomization.
- A pruritus numerical rating scale average score for maximum itch intensity of ≥ 4, based on the average of daily pruritus numerical rating scale scores for maximum itch intensity reported during the 7 days prior to randomization.
- Documented recent history (within 6 months prior to screening) of inadequate response to treatment with topical medications, or participants for whom topical treatments were otherwise medically inadvisable (eg, because of important side effects or safety risks).
- Participants that had applied a stable dose of topical emollient (moisturizer) twice daily for ≥ 7 consecutive days immediately before the randomization visit.
- Participants must have been willing and able to complete daily PRO (patient reported outcome) assessments:

  a) complete at least 70% of daily PRO assessments between Visit 1 and Visit 2 and

  b) complete at least 5 of 7 daily PRO assessments in the 7 days prior to Visit 2.
- Females of childbearing potential must agree to use a highly effective method of birth control (confirmed by the Investigator) from randomization, throughout the study duration, and within 12 weeks after last dose of IP and have a negative serum pregnancy test result on Visit 1.
- Females not of childbearing potential

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

- medical conditions: active dermatological conditions other than AD, malignancies, active helminth parasitic infections, history of known immunodeficiency disorder incl. positive HIV test, active liver disease and other disorders that could affect the safety of the participant throughout the study, influence the findings of the studies and their interpretations or impede the participant's ability to complete the entire duration of study.
- prior/concomitant therapy: AD treatment with TCS, TCI or topical PDE-4 inhibitors, initiation of AD treatment with prescription moisturizers or moisturizers containing specific additives, regular use of tanning booth or phototherapy for AD, use of immunosuppressive medication, known history of allergy or reaction to any component of the formulation.
- other criteria

Treatments

The study consisted of the following consecutive periods:

- A 1- to 4-week run-in period, including a 7-day washout period of topical medications prior to randomization.
- A 16-week placebo-controlled, double-blind treatment period.
- A 36-week blinded-to-dosing regimen extension period for maintenance treatment.

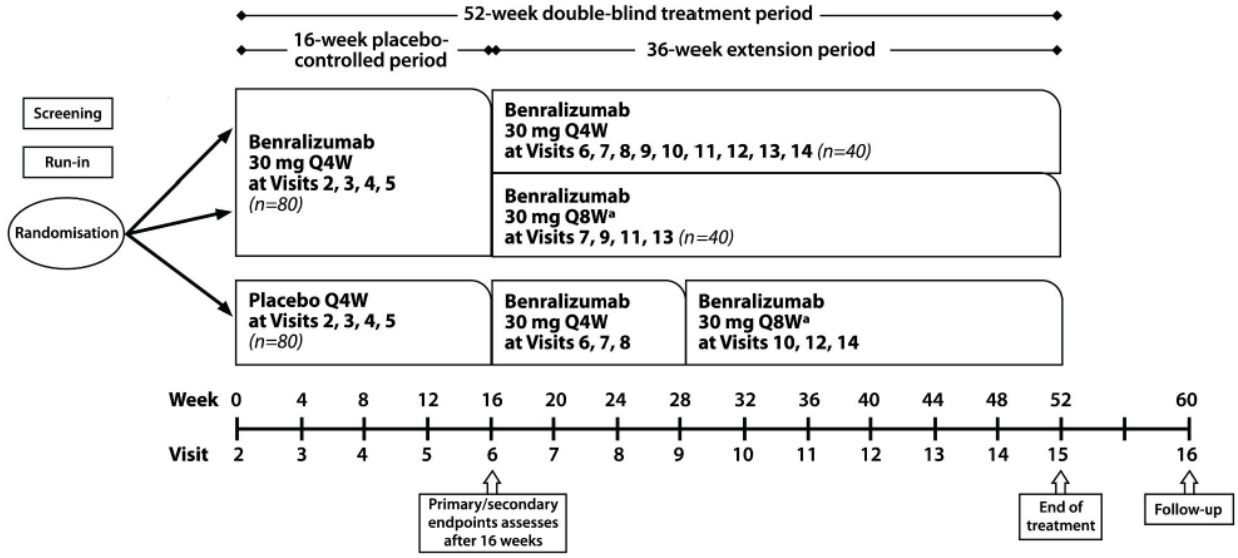
Following the 1- to 4-week run-in period, patients were randomized in a ratio of 1:1:2 to one of the three treatment sequences:

- Benralizumab 30 mg Q4W until Week 16, followed by an extension period with benralizumab 30 mg Q4W administered until Week 52

- Benralizumab 30 mg Q4W until Week 16, followed by an extension period with benralizumab 30 mg Q8W administered until Week 52
- Placebo Q4W until Week 16, followed by an extension period with benralizumab 30 mg Q4W administered until Week 28, and then benralizumab 30 mg Q8W administered until Week 52.

The general study design is summarized in Figure 2:

Figure 2 **Study Design**



[a] To maintain blinding, patients will receive investigational product every Q4W during the extension period. Placebo will be administered Q8W, occurring 4 weeks after each benralizumab administration.

n, number; Q4W, every 4 weeks; Q8W, every 8 weeks.

The approved dosing regimen of benralizumab in severe asthma is 30 mg Q4W for the first 3 doses, followed by 30 mg Q8W thereafter. In adult and adolescent patients with severe asthma (SIROCCO [Bleecker et al 2016] and CALIMA [FitzGerald et al 2016]), treatment with benralizumab 30 mg Q8W and Q4W resulted in near complete blood eosinophil depletion for both the Q8W and Q4W dosing regimens. Since the PK/PD relationship of adolescents with asthma has been shown to be consistent with those of adults (SIROCCO and CALIMA) and given that PK/PD relationships are consistent across disease populations, the same benralizumab treatment regimen was administered to adults and adolescents in this study.

Throughout the study, participants were required to maintain a stable regimen of their topical emollient (moisturizer) for AD. If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD was to be provided to study participants at the discretion of the investigator.

Objective(s)

Primary Objective

The primary objective of the study was to:

- compare the clinical efficacy of benralizumab 30 mg with placebo in patients with AD despite treatment with topical medications [a].

Secondary Objective

The secondary objectives of the study were to:

- compare the effect of benralizumab with placebo on supportive measures of clinical efficacy in patients with AD despite treatment with topical medications [a].
- compare benralizumab with placebo on patient-reported health-related quality of life measures in patients with AD despite treatment with topical medications [a].
- estimate the PK and immunogenicity of benralizumab 30 mg in patients with AD despite treatment with topical medications [a].
- compare long-term treatment with benralizumab 30 mg Q8W versus benralizumab 30 mg Q4W up to Week 52 in patients with AD despite treatment with topical medications [a].

Safety

- to compare the safety and tolerability of benralizumab with placebo in patients with AD despite treatment with topical medications [a].

[a] The locally approved regimen of topical medication.

AD, atopic dermatitis; PK, pharmacokinetics

Outcomes/endpoints

Primary Endpoint:

- A binary response giving the proportion of patients with an IGA 0/1 and a decrease in IGA of ≥ 2 points at Week 16 relative to baseline.

Secondary Endpoints:

- Key secondary endpoint [c]: proportion of patients with skin clearance (EASI-75) at Week 16
- Key secondary endpoint [c]: proportion of patients with an improvement of ≥ 4 or more points in peak pruritus weekly score at Week 16
- Key secondary endpoint [c]: proportion of patients with skin clearance (EASI-90) at Week 16
- Proportion of patients with skin clearance (EASI-50) at Week 16
- Proportion of patients with skin clearance (EASI-100) at Week 16
- Change from baseline in EASI score at Week 16
- Change from baseline in peak pruritus score at Week 2
- Change from baseline in POEM score at Week 16
- Change from baseline in SCORAD at Week 16
- Change from baseline in DLQI and CDLQI at Week 16
- Serum benralizumab concentration
- ADA
- Change from baseline in EASI total score at Week 52.
- Proportion of patients with an IGA 0/1 and a decrease in IGA of ≥ 2 points at Week 52 relative to baseline
- Proportion of patients with EASI-75 at Week 52
- Other supportive efficacy assessments at Week 52 as appropriate

- Safety and tolerability evaluated in terms of AEs, vital signs, and clinical laboratory values.

c The key secondary endpoints used the same estimand as outlined for the primary endpoint.

ADA, anti-drug antibodies; AE, adverse event; CDLQI, The Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IP, investigational product; POEM, Patient-Oriented Eczema Measure; Q4W, every 4 weeks; Q8W, every 8 weeks; SAP, Statistical Analysis Plan; SCORAD, SCORing Atopic Dermatitis.

Additional objectives (tertiary/exploratory) were also defined for comparison of benralizumab effect vs placebo on: healthcare resource utilization due to AD, patient-reported health-related quality of life measures, AD patients with comorbid asthma and chronic rhinosinusitis with nasal polyps, predictive value of baseline and early post dose biomarker data with clinical efficacy outcomes, the mechanism of action of benralizumab in AD and use of skin photography to inform clinical efficacy assessments in patients with AD.

Sample size

Approximately 270 participants were expected to be enrolled/screened to achieve at least 160, and a maximum of 200, eligible study participants randomly assigned to study intervention to ensure that a broad distribution of participants was recruited across the range of ages and blood eosinophil levels to allow potential identification of responding subpopulations and appropriate cut-offs for future studies, if necessary. The sample size calculations were based on the primary endpoint (proportion of patients with an IGA 0/1 and a decrease in IGA of $\geq$ 2 points relative to baseline). The calculations were associated with differences between benralizumab 30 mg Q4W and placebo at Week 16 during the initial double-blind, placebo-controlled phase of the study.

For the primary analysis, the sample size calculation would power the study to detect a difference between benralizumab 30 mg Q4W and placebo in the overall population. Additional calculations have been provided to ensure that the study was adequately powered to detect treatment differences and consistency of effect in potential subgroups, should efficacy be limited to a subset of the population.

Randomisation and blinding (masking)

Randomization was stratified by baseline blood eosinophils (< 300 cells/μL; $\geq$ 300 cells/μL), and age (12 to < 18 years; $\geq$ 18 years) into the following strata:

- $\geq$ 12 years to < 18 years and < 300 cells/μL
- $\geq$ 12 years to < 18 years and $\geq$ 300 cells/μL
- $\geq$ 18 years and < 300 cells/μL
- $\geq$ 18 years and $\geq$ 300 cells/μL

Neither the participant nor any of the Investigators or AstraZeneca staff involved in the treatment, clinical evaluation, and monitoring of the participants were aware of the treatment received.

Blinded IP (benralizumab or placebo) was administered by SC injection at the investigational site Q4W for up to 48 weeks. Participants randomized to receive benralizumab Q8W in the extension period also received Q8W placebo injections at intervening visits (Figure 2) to maintain blinding to the benralizumab Q4W treatment regimen.

Statistical Methods

The primary efficacy analyses were based on the double-blind, 16-week placebo-controlled treatment period. Available data from the extension period of the study up to Week 52 were also presented at the primary analysis. Efficacy endpoints were analysed using the Full Analysis Set; the analysis of safety endpoints was based on the Safety Analysis Set. Continuous variables were summarized using the following descriptive summary statistics: number of observations (n), mean, SD, SE, median, minimum, maximum value, and quartiles where more appropriate.

For the primary Week 16 analyses of binary endpoints, after the use of rescue medication from Day 29 onwards, participants were considered as non-responders from the point of the rescue medication use onwards. Any participants with missing visits (including data after withdrawal of study at any time) or missing Week 16 endpoint results were also considered as non-responders. For the primary Week 16 analyses of continuous repeated measures endpoints, any data after the use of rescue medication from Day 29 onwards or after withdrawal from study at any time were treated as missing and the mixed model repeat measurements analyses fitted on the remaining available data.

Intercurrent events were withdrawal from the study at any time or needing rescue therapy from Day 29 onwards. However, participants who started on placebo and switched to benralizumab in the extension phase were additionally permitted rescue therapy for 28 days from starting benralizumab, and thus additionally any rescue therapy use from Day 141 (ie, 29 days after first dose of benralizumab) onwards was considered as an intercurrent event for these participants.

Participants after withdrawal from the study at any time were considered as non-responders. Similarly, for change from baseline analyses, those intercurrent events were considered as missing data.

Results

Participant flow

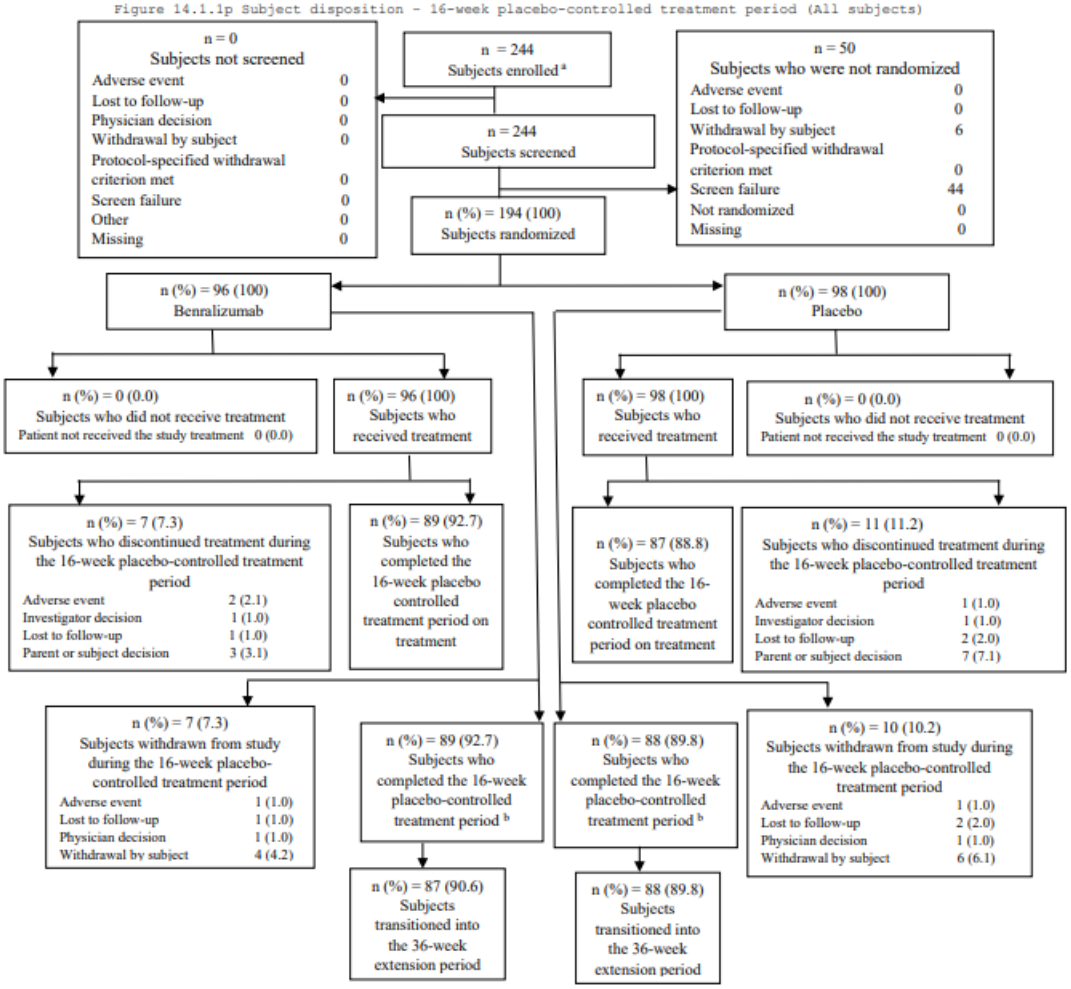
A total of 244 participants were screened and 194 participants were randomized allocated at treatment groups as follows:

Table 14.1.1 Subject disposition - Overall (All subjects)

	Number (%) of subjects				
	Benralizumab Q4W -> Q4W	Benralizumab Q4W -> Q8W	Benralizumab Total	Placebo -> Benralizumab	Total
Subjects enrolled[a]					244
Subjects screened					244
Subjects randomized	47 (100.0)	49 (100.0)	96 (100.0)	98 (100.0)	194 (100.0)
Subjects who were not randomized[*]					50 (100.0)
Screen failure					44 (88.0)
Withdrawal by subject					6 (12.0)

Eighteen participants (9.3%) discontinued study treatment during the 16-week placebo-controlled treatment period, and 177 participants (91.2%) completed the 16-week placebo-controlled treatment period of the study (Table 14.1.1p).

Figure 14.1.1p Subject disposition - 16-week placebo-controlled treatment period (All subjects)



Source: Table 14.1.1
n Number of subjects.
[a] Informed consent received.
[b] Includes subjects who discontinued treatment but remained in the study for all visits up to and including follow-up visit.

A total of 175 participants (90.2%) entered the extension period, all but 1 of which received treatment.

Participant disposition data from the 36-week extension period are shown in Table 14.1.1. A similar proportion of participants from benralizumab and placebo/benralizumab groups discontinued treatment in extension period. The most frequently reported reason for participant withdrawal was "withdrawal by subject" which was reported equally by both treatment groups.

The study was terminated after the primary analysis and all ongoing participants were required to complete a final follow-up visit regardless of where they had reached in the extension period of the study. The final analysis was performed once all final follow-up visits were completed and included updated safety data presentations; no efficacy analyses were performed at the final analysis.

Table 14.1.1 Subject disposition - Overall (All subjects)

	Number (%) of subjects				
	Benralizumab Q4W -> Q4W	Benralizumab Q4W -> Q8W	Benralizumab Total	Placebo -> Benralizumab	Total
Subjects who entered extension period	41 (87.2)	46 (93.9)	87 (90.6)	88 (89.8)	175 (90.2)
Subjects who did not enter extension period	1 (2.1)	1 (2.0)	2 (2.1)	0	2 (1.0)
Parent or subject decision	1 (2.1)	1 (2.0)	2 (2.1)	0	2 (1.0)
Subjects who completed treatment in extension period	17 (36.2)	16 (32.7)	33 (34.4)	30 (30.6)	63 (32.5)
Subjects who discontinued treatment in extension period	6 (12.8)	13 (26.5)	19 (19.8)	18 (18.4)	37 (19.1)
Adverse event	0	1 (2.0)	1 (1.0)	3 (3.1)	4 (2.1)
Condition under investigation worsened	0	0	0	3 (3.1)	3 (1.5)
Investigator decision	0	1 (2.0)	1 (1.0)	1 (1.0)	2 (1.0)
Other	0	0	0	1 (1.0)	1 (0.5)
Parent or subject decision	5 (10.6)	11 (22.4)	16 (16.7)	10 (10.2)	26 (13.4)
Protocol violation	1 (2.1)	0	1 (1.0)	0	1 (0.5)
Due to COVID-19 pandemic[b]	0	0	0	0	0
Subjects who discontinued treatment but completed study follow-up	0	1 (2.0)	1 (1.0)	0	1 (0.5)
Subjects ongoing on treatment in extension period	18 (38.3)	17 (34.7)	35 (36.5)	39 (39.8)	74 (38.1)
Subjects ongoing in study in extension period	33 (70.2)	30 (61.2)	63 (65.6)	68 (69.4)	131 (67.5)
Subjects who completed study	5 (10.6)	4 (8.2)	9 (9.4)	7 (7.1)	16 (8.2)
Subjects withdrawn from study	9 (19.1)	15 (30.6)	24 (25.0)	23 (23.5)	47 (24.2)
Adverse event	1 (2.1)	0	1 (1.0)	2 (2.0)	3 (1.5)
Lost to follow-up	0	1 (2.0)	1 (1.0)	3 (3.1)	4 (2.1)
Physician decision	1 (2.1)	1 (2.0)	2 (2.1)	1 (1.0)	3 (1.5)
Withdrawal by subject	7 (14.9)	13 (26.5)	20 (20.8)	17 (17.3)	37 (19.1)
Due to COVID-19 pandemic[b]	0	0	0	0	0

COVID-19 Corona Virus Disease 2019.
[a]Informed consent received.
[b]Representing any reasons caused by the COVID-19 pandemic, counts are to be considered independent of all other given reasons and are not part of the overall total for each column.
Percentages are based on the total numbers of subjects randomized in the treatment group or overall.
[f]Percentages are based on the total numbers of subjects not randomized.

The first participant enrolled (screening) on 12 November 2020 and the study completion date, as defined by the last patient last visit date, was 13 September 2022.

Recruitment

48 study centres from 8 countries contributed the study participants. A total of 54.1% of all participants were enrolled in Europe, 20.1% in North America and 25.8% in the Rest of the World (table 14.1.7):

Table 14.1.7 Demographic characteristics - Overall (Full analysis set)

		Number (%) of subjects				
Demographic characteristic		Benralizumab Q4W -> Q4W (N=47)	Benralizumab Q4W -> Q8W (N=49)	Benralizumab Total (N=96)	Placebo -> Benralizumab (N=98)	Total (N=194)
Ethnic group n (%)	n	47 (100.0)	49 (100.0)	96 (100.0)	98 (100.0)	194 (100.0)
	Hispanic or Latino	5 (10.6)	6 (12.2)	11 (11.5)	13 (13.3)	24 (12.4)
	Not Hispanic or Latino	42 (89.4)	43 (87.8)	85 (88.5)	85 (86.7)	170 (87.6)
Region n (%)	n	47 (100.0)	49 (100.0)	96 (100.0)	98 (100.0)	194 (100.0)
	Europe	25 (53.2)	28 (57.1)	53 (55.2)	52 (53.1)	105 (54.1)
	North America	9 (19.1)	8 (16.3)	17 (17.7)	22 (22.4)	39 (20.1)
	Rest of the World	13 (27.7)	13 (26.5)	26 (27.1)	24 (24.5)	50 (25.8)
Country n (%)	n	47 (100.0)	49 (100.0)	96 (100.0)	98 (100.0)	194 (100.0)
	AUS	3 (6.4)	4 (8.2)	7 (7.3)	5 (5.1)	12 (6.2)
	BGR	2 (4.3)	2 (4.1)	4 (4.2)	8 (8.2)	12 (6.2)
	CZE	6 (12.8)	11 (22.4)	17 (17.7)	11 (11.2)	28 (14.4)
	ESP	4 (8.5)	6 (12.2)	10 (10.4)	12 (12.2)	22 (11.3)
	FRA	1 (2.1)	1 (2.0)	2 (2.1)	3 (3.1)	5 (2.6)
	KOR	10 (21.3)	9 (18.4)	19 (19.8)	19 (19.4)	38 (19.6)
	POL	12 (25.5)	8 (16.3)	20 (20.8)	18 (18.4)	38 (19.6)
	USA	9 (19.1)	8 (16.3)	17 (17.7)	22 (22.4)	39 (20.1)

Max Maximum. Min Minimum. N Number of subjects in treatment group. n Number of subjects included in analysis. SD Standard deviation.
[a] Including Black or African American, Native Hawaiian or other Pacific Islander, American indian or Alaska Native, Not Reported and Other.
AUS Australia. BGR Bulgaria. CZE Czech Republic. ESP Spain. FRA France. KOR South Korea. POL Poland. USA United States.
Percentages are based on the total number of subjects in the treatment group or overall (N).

The majority of participants were White (69.6%), followed by Asian (22.7%). 62.9% of patients were men and 37.1% were women with a mean age at screening, 29.6±15.90 years and the following age

distribution: 53 participants (27.3%) were between the age of ≥ 12 to < 18 years, 22 (11.3%) were between the age of ≥ 18 and < 21 years, 62 (32.0%) were between the age of ≥ 21 and < 35 years and 57 (29.4%) were ≥ 35 years of age.

The mean weight, height, and BMI of all participants were 71.86±21.827 kg, 169.07±8.82 cm, and 24.94±6.5 kg/m2 without differences between treatment groups.

Baseline data

The majority (56.2%) of patients in the placebo and benralizumab groups were diagnosed with AD before the age of 6 years old. The proportion of patients with a family history of AD was similar between treatment groups.

49,5% of participants in any treatment group had been previously or currently diagnosed with allergy to airborne substances, 49% with Rhinitis, 41.2% with Food Allergies, 40.7% with Asthma, 20.1% with Conjunctivitis Allergic and 12.9% with Staph. aureus colonization. All other comorbidities were reported by <10% of participants.

Table 14.1.12.1 Stratification factors recorded at randomization by IVRS - Overall (Full analysis set)

		Number (%) of subjects				
Blood eosinophils at screeening	Age at screening	Benralizumab Q4W -> Q4W (N=47)	Benralizumab Q4W -> Q8W (N=49)	Benralizumab Total (N=96)	Placebo -> Benralizumab (N=98)	Total (N=194)
< 300 cells/µL	>= 12 to < 18 years	4 (8.5)	5 (10.2)	9 (9.4)	9 (9.2)	18 (9.3)
	>= 18 years	16 (34.0)	17 (34.7)	33 (34.4)	34 (34.7)	67 (34.5)
>= 300 cells/µL	>= 12 to < 18 years	9 (19.1)	8 (16.3)	17 (17.7)	18 (18.4)	35 (18.0)
	>= 18 years	18 (38.3)	19 (38.8)	37 (38.5)	37 (37.8)	74 (38.1)

IVRS Interactive Voice Response System. N Number of subjects in treatment group.
Percentages are based on the total number of subjects in the treatment group or overall (N).
One adolecent was randomized to >= 300 cells/µL, but had levels < 300 cells/µL.

Participant baseline data (Full analysis set) for efficacy variables IGA score, EASI total score and Peak pruritus NRS were adequately balanced across treatment groups:

		Number (%) of subjects				
Variable	Statistics	Benralizumab Q4W -> Q4W (N=47)	Benralizumab Q4W -> Q8W (N=49)	Benralizumab Total (N=96)	Placebo -> Benralizumab (N=98)	Total (N=194)
Investigator Global Assessment (IGA) score	n	47	49	96	98	194
	0 - Clear	0	0	0	0	0
	1 - Almost clear	0	0	0	0	0
	2 - Mild	0	0	0	0	0
	3 - Moderate	33 (70.2)	36 (73.5)	69 (71.9)	60 (61.2)	129 (66.5)
	4 - Severe	14 (29.8)	13 (26.5)	27 (28.1)	38 (38.8)	65 (33.5)
Eczema Area and Severity Index (EASI) total score	n	47	49	96	98	194
	Mean	28.00	29.16	28.59	29.54	29.07
	SD	11.909	11.851	11.831	10.836	11.320
	Median	24.40	25.00	24.80	27.35	26.25
	Min	16.0	16.5	16.0	16.0	16.0
	Max	70.5	64.8	70.5	57.9	70.5
Peak pruritus numeric rating scale (NRS)	n	47	49	96	98	194
	Mean	7.40	7.74	7.57	7.82	7.70
	SD	1.392	1.416	1.407	1.363	1.387
	Median	7.43	7.80	7.59	7.86	7.82
	Min	4.1	5.1	4.1	1.8	1.8
	Max	10.0	10.0	10.0	10.0	10.0

Stratification factors, baseline blood eosinophils (< 300 cells/μL; $\geq$ 300 cells/μL) and age (12 to < 18 years; $\geq$ 18 years) recorded at randomization (IVRS) are summarized below:

		Number (%) of subjects				
Blood eosinophils at screeening	Age at screening	Benralizumab Q4W -> Q4W (N=47)	Benralizumab Q4W -> Q8W (N=49)	Benralizumab Total (N=96)	Placebo -> Benralizumab (N=98)	Total (N=194)
< 300 cells/µL	>= 12 to < 18 years	4 (8.5)	5 (10.2)	9 (9.4)	9 (9.2)	18 (9.3)
	>= 18 years	16 (34.0)	17 (34.7)	33 (34.4)	34 (34.7)	67 (34.5)
>= 300 cells/µL	>= 12 to < 18 years	9 (19.1)	8 (16.3)	17 (17.7)	18 (18.4)	35 (18.0)
	>= 18 years	18 (38.3)	19 (38.8)	37 (38.5)	37 (37.8)	74 (38.1)

IVRS Interactive Voice Response System. N Number of subjects in treatment group.
Percentages are based on the total number of subjects in the treatment group or overall (N).
One adolecent was randomized to >= 300 cells/µL, but had levels < 300 cells/µL.

Participants had a history of the following disease-related medications (sorted in decreasing frequency of use) topical corticosteroids (87.1%), topical calcineurin inhibitors (44.3%), H1 antihistamines (29.9%) and systemic corticosteroids (23.7%).

Numbers analysed

The Full Analysis Set included all 194 randomized patients who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study. The analysis was performed according to their randomized treatment irrespective of whether they were prematurely discontinued.

The Safety Analysis Set included all patients who received at least one dose of IP (194 patients). Erroneously treated participants were accounted for in the analysis set by assigning them to the treatment they actually received. A participant who received at least one dose of active IP was classified as active and included in the active IP treatment group/sequence. Safety and ADA data were based on this analysis set and for whom any post-dose data were available.

Pharmacokinetic analysis set (143 patients) included all participants who received benralizumab and from whom PK blood samples were assumed not to be affected by factors such as protocol violations (eg. wrong dose) and who had at least one quantifiable serum PK observation post first dose. All PK summaries were based on this analysis set.

The *extension period analysis* set included all participants who started or continued receiving at least one dose of benralizumab after the end of Week 16 placebo-controlled period, and thus entering the extension period (174 patients).

The study was terminated after the primary analysis and all ongoing participants were required to complete a final follow-up visit regardless of where they had reached in the extension period of the study. The final analysis was performed once all final follow-up visits were completed and included only updated safety data presentations.

Efficacy results

Primary endpoint

No significant difference between benralizumab and placebo in the proportion of participants with a binary response of IGA 0/1 and a decrease in IGA of ≥ 2 points at Week 16 relative to baseline (treatment difference -8.62%).

Table 1 Summary of Efficacy Endpoints (Double-Blind 16 Week Treatment Period, Full Analysis Set)

Outcome	Benralizumab N = 96	Placebo N = 98	P-value
Primary Efficacy Endpoint			
IGA score of 0/1 and change ≥2 from baseline, n (%)	9 (9.4)	17 (17.3)	
Response rate (%), (95% CI)[a]	9.1 (3.36, 14.93)	17.8 (10.40, 25.12)	
Difference (%) (95% CI) vs. placebo[a,b]	-8.62 (-17.94, 0.71)		0.080

Secondary endpoints

- Key Secondary endpoint: No significant difference between benralizumab and placebo in the proportion of participants achieving 75% reduction in EASI total score at Week 16 relative to baseline (treatment difference: -5.15%).
- Key Secondary endpoint: No significant difference between benralizumab and placebo in the proportion of participants achieving 90% reduction in EASI total score at Week 16 relative to baseline (treatment difference -8.18%).
- Key Secondary endpoint: No significant difference between benralizumab and placebo in the proportion of participants achieving an improvement of ≥ 4 points in peak pruritus NRS score at Week 16 (treatment difference: 0.69%).

Table 1 (cont'd)

Outcome	Benralizumab N = 96	Placebo N = 98	P-value
Key Secondary Efficacy Endpoints			
EASI score ≥75% improvement from baseline, n (%)	19 (19.8)	24 (24.5)	
Response rate (%), (95% CI)[a]	19.6 (11.71, 27.45)	24.7 (16.27, 33.19)	
Difference (%) (95% CI) vs. placebo[a,b]	-5.15 (-16.67, 6.36)		0.384
EASI score ≥90% improvement from baseline, n (%)	7 (7.3)	15 (15.3)	
Response rate (%), (95% CI)[a]	7.2 (2.05, 12.42)	15.4 (8.33, 22.50)	
Difference (%) (95% CI) vs. placebo[a,b]	-8.18 (-16.94, 0.59)		0.078
Peak pruritus NRS score improvement ≥4 from baseline, n (%)	14 (14.6)	14 (14.3)	
Response rate (%), (95% CI)[a]	14.8 (7.87, 21.70)	14.1 (7.28, 20.90)	
Difference (%) (95% CI) vs. placebo[a,b]	0.69 (-8.93, 10.32)		0.889

- No significant difference between benralizumab and placebo in the proportion of participants achieving 50% reduction in EASI total score at Week 16 relative to baseline (treatment difference -6.44%).
- No significant difference between benralizumab and placebo in the proportion of participants achieving 100% reduction in EASI total score at Week 16 relative to baseline (treatment difference -3.18%).
- No significant difference in LS mean change from baseline in EASI score at Week 16 between benralizumab and placebo (difference in LS means: 3.19).

- No significant difference in LS mean change from baseline in peak pruritus NRS score at Week 2 between benralizumab and placebo (difference in LS means: 0.23).
- No significant difference in LS mean change from baseline in Patient-Oriented Eczema Measure (POEM) score (higher score=more severe eczema) at Week 16 between benralizumab and placebo (difference in LS means: 1.90).
- No significant difference in LS mean change from baseline in SCORing Atopic Dermatitis (SCORAD) score at Week 16 between benralizumab and placebo (difference in LS means: 3.32).
- Change from baseline in Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI) at Week 16:
  - No significant difference in LS mean change from baseline in DLQI score at Week 16 between benralizumab and placebo (difference in LS means: 1.08)
  - No significant difference in LS mean change from baseline in CDLQI score at Week 16 between benralizumab and placebo (difference in LS means: 1.20).
- Mean blood eosinophils had a greater decrease from baseline to Week 16 in the benralizumab group compared to placebo group. Mean (SD) change from baseline in EDN (eosinophil-derived neurotoxin) was -68.859 (70.6398) µg/L in the benralizumab group and -9.706 (48.0460) µg/L in the placebo group.

Table S-1 (cont'd)

Outcome	Benralizumab N = 96	Placebo N = 98	P-value
Secondary Efficacy Endpoints			
EASI score change from baseline, LSM (95% CI)[b]	-11.24 (-14.10, -8.38)	-14.43 (-17.30, -11.57)	
LSM difference (95% CI) vs. placebo[a]	3.19 (-0.86, 7.24)		0.121
EASI score ≥50% improvement from baseline, n (%)	35 (36.5)	41 (41.8)	
Response rate (%), (95% CI)[a]	35.9 (26.43, 45.44)	42.4 (32.77, 51.97)	
Difference (%) (95% CI) vs. placebo[a,b]	-6.44 (-19.87, 6.99)		0.350
EASI score 100% improvement from baseline, n (%)	3 (3.1)	6 (6.1)	
Response rate (%), (95% CI)[a]	3.1 (0.0, 6.53)	6.2 (1.52, 10.96)	
Difference (%) (95% CI) vs. placebo[a,b]	-3.18 (-9.04, 2.68)		0.301

Outcome	Benralizumab N = 96	Placebo N = 98	P-value
Peak Pruritus NRS score Week 2 change from baseline	n = 95	n = 98	
LSM (95% CI)[a]	-1.76 (-2.18, -1.35)	-2.09 (-2.51, -1.66)	
LSM difference (95% CI) vs. placebo[a]	0.23 (-0.28, 0.75)		0.372
POEM score change from baseline	n = 80	n = 70	
LSM (95% CI)[a]	-4.04 (-5.81, -2.28)	-5.94 (-7.75, -4.13)	
LSM difference (95% CI) vs. placebo[a]	1.90 (-0.63, 4.42)		0.140
SCORAD score change from baseline	n = 86	n = 85	
LSM (95% CI)[a]	-21.28 (-26.31, -16.25)	-24.60 (-29.62, -19.59)	
LSM difference (95% CI) vs. placebo[a]	3.32 (-3.78, 10.42)		0.357
DLQI score change from baseline	n = 64	n = 56	
LSM (95% CI)[a]	-5.15 (-6.79, -3.51)	-6.23 (-7.92, -4.54)	
LSM difference (95% CI) vs. placebo[a]	1.08 (-1.28 to 3.44)		0.365
CDLQI score change from baseline	n = 17	n = 15	
LSM (95% CI)[a]	-3.92 (-7.17, -0.67)	-5.12 (-8.33, -1.92)	
LSM difference (95% CI) vs. placebo[a]	1.20 (-3.38, 5.78)		0.593
Rescue medication use, n (%)	24 (25.0)	20 (20.4)	
Eosinophils mean (SD) W16 change from baseline (10^9/L)	-0.457 (0.3989)	-0.129 (0.4316)	
EDN mean (SD) W16 change from baseline (µg/L)	-68.859 (70.6398)	-9.706 (48.0460)	

a No significant difference between benralizumab and placebo. Adjusted response rate: adjusted proportions are calculated using the marginal standardization method. b Treatment difference results are calculated from the logistic regression model. CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EDN eosinophil-derived neurotoxin; IGA, Investigator Global Assessment; LSM, least squares mean; n, number; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; W2 Week2; W16 Week 16.

The primary analysis of efficacy results indicates that the primary endpoint of the study i.e., the proportion of participants with an investigator global assessment (IGA) 0/1 and a decrease in IGA of ≥ 2 points at Week 16 relative to baseline, was not met.

Additionally, there was no statistically significant difference in the effect of benralizumab compared to placebo on secondary endpoints. Of note, mean blood eosinophils had a greater decrease from baseline to Week 16 in the benralizumab group compared to placebo group and significant reductions in serum levels of eosinophil-derived neurotoxin (EDN) were observed.

Interpretation of the available efficacy data from the extension period of the study is limited on the grounds that no difference in efficacy outcomes between benralizumab and placebo were observed during the placebo-controlled period, and no placebo control was available beyond Week 16.

Safety results

16-week, placebo-controlled treatment period (results from primary analysis):

- A total of 39 participants (40.6%) in the benralizumab groups and 40 participants (40.8%) in the placebo group reported AEs.
- Serious adverse events (SAEs) were reported for 3 participants (3.1%) in the benralizumab group (cardiac failure congestive, paranasal sinus inflammation and dermatitis atopic, see also Table 14.3.4.1) and no participants in the placebo group.
- No AEs with a fatal outcome were reported for any participant in the benralizumab groups or placebo group during the 16-week treatment period.

Table 14.3.2.7p Number of subjects with adverse events reported in the on-treatment period in any category, by relationship as assessed by investigator and severity - 16-week placebo-controlled treatment period (Safety analysis set)

	Total number of AEs[a]			
AE category	Benralizumab Q4W -> Q4W (N=47)	Benralizumab Q4W -> Q8W (N=49)	Benralizumab Total (N=96)	Placebo -> Benralizumab (N=98)
Any AE	17 (36.2)	22 (44.9)	39 (40.6)	40 (40.8)
Any possibly[b] related AE	2 (4.3)	4 (8.2)	6 (6.3)	8 (8.2)
Any AE of severe intensity	1 (2.1)	2 (4.1)	3 (3.1)	0
Any possibly[b] related AE of severe intensity	0	1 (2.0)	1 (1.0)	0
Any AE with outcome = death	0	0	0	0
Any possibly[b] related AE with outcome = death	0	0	0	0
Any AE of severe intensity with outcome = death	0	0	0	0
Any possibly[b] related AE of severe intensity with outcome = death	0	0	0	0
Any SAE (including events with outcome = death)	1 (2.1)	2 (4.1)	3 (3.1)	0
Any SAE with outcome other than death[c]	1 (2.1)	2 (4.1)	3 (3.1)	0
Any possibly[b] related SAE	0	0	0	0
Any SAE of severe intensity	0	1 (2.0)	1 (1.0)	0
Any possibly[b] related SAE of severe intensity	0	0	0	0
Any SAE related to study procedures	0	1 (2.0)	1 (1.0)	0

AE Adverse event. IP Investigational product. N Number of subjects in treatment group. SAE Serious adverse event.
[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.
[b] As assessed by the investigator.
[c] All subjects experiencing an SAE with non-fatal outcome (regardless if they later had a fatal SAE).
[d] Action taken, Drug Permanently Discontinued.
Includes adverse events with an onset date between the day of first dose of IP treatment and the day prior to first dose in extension period, or last dose in placebo-controlled period + 30 days for those who do not enter the extension period.

- AEs leading to discontinuation of the IP were reported for 4 participants (4.2%) in the benralizumab groups and 1 participant (1.0%) in the placebo group.

Table 14.3.5.1p Number of subjects with adverse events leading to discontinuation of investigational product and event rate reported in the on-treatment period, by system organ class and preferred term - 16-week placebo-controlled treatment period (Safety analysis set)

	Benralizumab Q4W -> Q4W (N=47)		Benralizumab Q4W -> Q8W (N=49)		Benralizumab Total (N=96)		Placebo -> Benralizumab (N=98)	
System organ class / Preferred term	Number (%) of subjects[a]	Event rate (per 100 pt years)[b]	Number (%) of subjects[a]	Event rate (per 100 pt years)[b]	Number (%) of subjects[a]	Event rate (per 100 pt years)[b]	Number (%) of subjects[a]	Event rate (per 100 pt years)[b]
Subjects with any AE leading to discontinuation	2 (4.3)	20.17	2 (4.1)	17.67	4 (4.2)	18.83	1 (1.0)	4.76
Infections and infestations	1 (2.1)	10.08	0	0	1 (1.0)	4.71	0	0
Eczema infected	1 (2.1)	10.08	0	0	1 (1.0)	4.71	0	0
Skin and subcutaneous tissue disorders	1 (2.1)	10.08	2 (4.1)	17.67	3 (3.1)	14.13	0	0
Dermatitis atopic	0	0	2 (4.1)	17.67	2 (2.1)	9.42	0	0
Dermatitis exfoliative generalised	1 (2.1)	10.08	0	0	1 (1.0)	4.71	0	0
General disorders and administration site conditions	0	0	0	0	0	0	1 (1.0)	4.76
Chest discomfort	0	0	0	0	0	0	1 (1.0)	4.76

AE Adverse event. IP Investigational product. N Number of subjects in treatment group.
[a] Number (%) of subjects with AEs, sorted by international order for system organ class and alphabetically for preferred term.
[b] Number of subjects with AEs divided by the total number of days at risk for AEs across all subjects in given group, multiplied by 365.25 multiplied by 100.
Subjects with multiple events in the same preferred term are counted only once in that preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred terms.
The total period at risk for each subject was the duration of the on-treatment period.
The number of years at risk of AE across all subjects in benralizumab Q4W -> Q4W group = 9.92 years; in benralizumab Q4W -> Q8W group = 11.32 years; in benralizumab Total group = 21.24 years; in placebo -> benralizumab group = 21.02 years.
Includes adverse events with an onset date between the day of first dose of IP treatment and the day prior to first dose in extension period, or last dose in placebo-controlled period + 30 days for those who do not enter the extension period.
Percentages are based on the total number of subjects in the treatment group (N).
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- A total of 3 participants (3.1%) reported severe AEs in the benralizumab groups: dermatitis atopic (2 participants [2.1%]) and dermatitis exfoliative generalized (1 participant [1.0%]). No severe AEs were reported for participants in the placebo group during this treatment period. All other AEs for participants in the benralizumab groups or placebo group were reported as mild or moderate in severity.
- AEs assessed by the Investigator as possibly related to the study drug were reported for 6 participants (6.3%) in the benralizumab groups (chills, dermatitis atopic, headache, injection site reaction, lymphadenopathy, and palpitations) and 8 participants (8.2%) in the placebo group (alopecia, chalazion, chest discomfort, diarrhoea, lymphadenopathy, seborrhoea, torticollis, and upper respiratory tract infection).
- The most commonly reported AEs (> 5% in either group) were COVID-19 (benralizumab: 9 participants [9.4%]; placebo: 4 participants [4.1%]), upper respiratory infection (benralizumab: 5 participants [5.2%]; placebo: 2 participants [2.0%]), and headache (benralizumab: 3 participants [3.1%]; placebo: 5 participants [5.1%]). All other individual AEs were reported in ≤ 5% of participants in either group.
- One participant (1.0%) reported an injection site reaction of mild intensity in the benralizumab group. No other injection site reactions were reported for the benralizumab group or placebo group.
- There were no clinically meaningful changes in mean values from baseline for haematology variables, clinical chemistry laboratory variables, or urinalysis variables within the benralizumab or placebo groups. Mean eosinophils had a greater decrease from baseline to Week 16 in the benralizumab group (Table 1).

36-week extension period (results from primary analysis):

- A total of 46 participants (52.9%) in the benralizumab groups and 49 participants (56.3%) who had received placebo during the 16-week placebo-controlled treatment period reported AEs.
- SAEs (Hodgkin's disease, migraine) were reported for 2 participants (2.3%) who switched from placebo to benralizumab in the extension period.
- No AEs with a fatal outcome were reported.
- Seven participants (7.3%) who had received benralizumab and 6 participants (6.1%) who had received placebo during the 16-week placebo-controlled treatment period experienced AEs leading to discontinuation of study treatment at any point during the study, of which 3 participants (3.4%) and 4 participants (4.6%), respectively, discontinued IP due to AEs during the extension period.

Table 14.3.2.1e Number of subjects with adverse events in any category reported in the on-treatment period - 36-week extension period (Extension period analysis set)

	Overall			
	Number (%) of subjects[a]			
AE category	Benralizumab Q4W -> Q4W (N=41)	Benralizumab Q4W -> Q8W (N=46)	Benralizumab Total (N=87)	Placebo -> Benralizumab (N=87)
Any AE	21 (51.2)	25 (54.3)	46 (52.9)	49 (56.3)
Any AE with outcome = death	0	0	0	0
Any SAE (including events with outcome = death)	0	0	0	2 (2.3)
Any AE leading to discontinuation of IP	3 (7.3)	0	3 (3.4)	4 (4.6)

AE Adverse event. IP Investigational product. N Number of subjects in treatment group. SAE Serious adverse event.
[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
Includes adverse events with an onset date on or after day of first dose in extension period up to day of end of treatment visit or last dose + 30 days.
Percentages are based on the total number of subjects in the treatment group (N).

- No participants in the benralizumab groups reported severe AEs. One participant (1.1%) who switched to benralizumab after receiving placebo reported a severe AE of Hodgkin's disease. All other AEs were reported as mild or moderate in severity.
- AEs considered by the Investigator to be possibly related to the study drug were reported for 8 participants (9.2%) in the benralizumab group (fatigue, diarrhoea, eczema herpeticum, lymphadenopathy, neutropenia, oedema peripheral, thrombocytopenia, and upper respiratory tract infection) and 5 participants (5.7%) in the group of participants who switched to benralizumab after receiving placebo (chalazion, conjunctivitis, depression, herpes zoster, upper respiratory tract infection, and urticarial).
- The most common AE (> 5% in either group) were: COVID-19 (benralizumab: 12 participants [13.8%]; placebo/benralizumab: 12 participants [14.9%]), Nasopharyngitis (benralizumab 8 participants [9.2%]; placebo/benralizumab: 7 participants [8.0%]), Bronchitis (benralizumab 5 participants [5.7]; placebo/benralizumab: 4 participants [4.6%]), Conjunctivitis (benralizumab: 2 participants [2.3%]; placebo/benralizumab: 6 [6.9%]), Upper respiratory tract infection (benralizumab: 4 participants [4.6%]; placebo/benralizumab: 5 participants [5.7%]). All other AEs had an incidence of < 10%, which was generally similar between groups.
- There were no clinically meaningful changes in mean values from baseline for haematology, clinical chemistry laboratory or urinalysis variables within the benralizumab or placebo groups during the 36-week extension period.

Serious Adverse Events

The total number of participants with SAEs in the overall study (52 weeks), reported by SOC and PT, are shown in Table 14.3.4.1:

Table 14.3.4.1 Number of subjects with serious adverse events and event rate reported in the on-study period, by system organ class and preferred term - Overall (Safety analysis set)

	Benralizumab Q4W -> Q4W (N=47)		Benralizumab Q4W -> Q8W (N=49)		Benralizumab Total (N=96)		Placebo -> Benralizumab (N=98)	
System organ class / Preferred term	Number (%) of subjects[a]	Event rate (per 100 pt years)[b]	Number (%) of subjects[a]	Event rate (per 100 pt years)[b]	Number (%) of subjects[a]	Event rate (per 100 pt years)[b]	Number (%) of subjects[a]	Event rate (per 100 pt years)[b]
Subjects with any SAE	1 (2.1)	3.48	2 (4.1)	6.55	3 (3.1)	5.06	2 (2.0)	3.30
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	0	1 (1.0)	1.65
Hodgkin's disease	0	0	0	0	0	0	1 (1.0)	1.65
Nervous system disorders	0	0	0	0	0	0	1 (1.0)	1.65
Migraine	0	0	0	0	0	0	1 (1.0)	1.65
Cardiac disorders	0	0	1 (2.0)	3.27	1 (1.0)	1.69	0	0
Cardiac failure congestive	0	0	1 (2.0)	3.27	1 (1.0)	1.69	0	0
Respiratory, thoracic and mediastinal disorders	1 (2.1)	3.48	0	0	1 (1.0)	1.69	0	0
Paranasal sinus inflammation	1 (2.1)	3.48	0	0	1 (1.0)	1.69	0	0
Skin and subcutaneous tissue disorders	0	0	1 (2.0)	3.27	1 (1.0)	1.69	0	0
Dermatitis atopic	0	0	1 (2.0)	3.27	1 (1.0)	1.69	0	0

IP Investigational product. N Number of subjects in treatment group. SAE Serious adverse event.
[a] Number (%) of subjects with SAEs, sorted by international order for system organ class and alphabetically for preferred term.
[b] Number of subjects with SAEs divided by the total number of days at risk for SAEs across all subjects in given group, multiplied by 365.25 multiplied by 100.
Subjects with multiple events in the same preferred term are counted only once in that preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred terms.
The total period at risk for each subject was the duration of the on-study period.
The number of years at risk of SAE across all subjects in benralizumab Q4W group = 28.77 years; in benralizumab Q8W group = 30.55 years; in benralizumab Total group = 59.32 years; in placebo group = 60.58 years.
Includes serious adverse events with an onset date on or after the day of first dose of IP treatment.
Percentages are based on the total number of subjects in the treatment group (N).
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Immunogenicity results (primary analysis)

Anti-drug antibodies to benralizumab were summarized using descriptive statistics at each visit by treatment group based on the safety analysis set.

- *ADA prevalence:* At the time of the primary analysis, a total of 22.9% of participants in the benralizumab group and 8.2% of participants in the placebo group were ADA positive at any time during the 16-week treatment period.

ADA category	Statistics	Benralizumab Total (N=96)	Placebo -> Benralizumab (N=98)
ADA prevalence (positive at baseline and/or post-baseline)	n/N (%)[a, b]	22/96 (22.9%)	8/97 (8.2%)
	Min	0	50
	1st quartile	50.0	50.0
	Median	200.0	75.0
	3rd quartile	800.0	100.0
	Max	6400	200

- *ADA incidence:* At the time of the primary analysis, a total of 16.5% of participants in the benralizumab group and 3.4% of participants in the placebo group were ADA positive at any time during the 16-week treatment period.

ADA category	Statistics	Benralizumab Total (N=96)	Placebo -> Benralizumab (N=98)
ADA incidence [f]	n/N (%) [a, c]	15/91 (16.5%)	3/87 (3.4%)
	Min	0	50
	1st quartile	50.0	50.0
	Median	200.0	50.0
	3rd quartile	800.0	100.0
	Max	6400	100

ADA incidence is defined as ADA-negative at baseline and post-baseline ADA positive, or ADA positive at baseline and boosted the pre-existing titre by > 4-fold during the study period.

– *ADA positive with maximum titre > median of maximum titres:* At the time of the primary analysis, a total of 8.3% of participants in the benralizumab group and 4.1% of participants in the placebo group were ADA positive with maximum titre > median of maximum titres at any time during the 16-week treatment period.

ADA category	Statistics	Benralizumab Total (N=96)	Placebo -> Benralizumab (N=98)
ADA positive with maximum titre > median of maximum titres [j]	n/N (%) [a, b]	8/96 (8.3%)	4/97 (4.1%)
	Min	400	100
	1st quartile	800.0	100.0
	Median	1200.0	100.0
	3rd quartile	1600.0	150.0
	Max	6400	200

Calculation of the median of maximum titres was based on the maximum titre for each ADA positive subject within each treatment group (incl. both baseline and post-baseline measurements).

PK results (primary analysis)

Serum benralizumab concentration were summarized using descriptive statistics at each visit by treatment group based on the PK analysis set.

Within the benralizumab group, serum concentrations (geometric mean) were higher in ADA-negative participants at the end of the 16-week treatment period than in ADA-positive participants as shown in table 14.2.16.4:

		Benralizumab Total (N=95)	
Time point	Summary statistic	ADA Negative	ADA Positive
Week 16	n	62	25
	n<LLOQ	0	1
	Geometric mean[a]	1613.724	489.406
	95% CI[a]	1433.4915 - 1816.6169	239.9449 - 998.2204
	CV (%)[a]	49.3	432.7
	Arithmetic mean	1770.742	966.944
	SD	713.7640	735.3376
	Min	335.60	1.93
	1st quartile	1321.220	300.390
	Median	1699.080	1128.160
	3rd quartile	2099.900	1454.310
	Max	3621.37	2307.96

ADA Anti-Drug Antibodies. CI Confidence interval. CV Coefficient of variation. LLOQ Lower limit of quantification (3.86 ng/mL). Max Maximum. Min Minimum. N Number of subjects in treatment group. n number of subjects in analysis. SD Standard deviation.
[a] Calculated using log transformed data.
PK serum samples were collected pre-dose at each visit.
A subject is defined as ADA positive if a positive result is available at any time (including baseline and all post-baseline measurements); otherwise ADA negative.

2.3.3. Discussion on clinical aspects

This was a Phase 2 multinational, randomized, double-blind, parallel-group, 16-week placebo-controlled study with a 36-week extension. The main objective of the study was to compare the clinical efficacy of benralizumab 30 mg with placebo in the target population of AD patients who remained symptomatic despite treatment with topical medications. Secondary objectives included the comparison of the effect of benralizumab with placebo on supportive measures of clinical efficacy in the above target population. The choice of the primary endpoint (a binary response that classifies a participant's skin clearance at Week 16 using the IGA score) is adequately documented: IGA is used for the evaluation of the overall inflammatory signs of AD (erythema, induration/papulation, lichenification, oozing/crusting) based on a 5-point scale (range from 0-clear to 4 severe). IGA is recommended by international guidelines to be used in clinical practice for the determination of disease activity and response to treatment. It has also been used in clinical trials for the registration of other products for the treatment of AD.

The analysis of efficacy results provided solid evidence that benralizumab did not demonstrate clinical advantage over placebo in any of the primary or secondary efficacy endpoints, and no sub-population with clinically meaningful benralizumab efficacy was identified, despite the observed blood eosinophil depletion. The study was terminated by sponsor decision following primary analysis of the results from 16-week placebo-controlled phase, which indicated that study participants were not benefiting from treatment.

During the 16-week, placebo-controlled treatment period, in participants with moderate to severe AD who remained symptomatic despite treatment with standard of care treatment with topical medications, the safety and tolerability findings were consistent with the known profile of benralizumab and no new safety concerns were observed.

3. CHMP overall conclusion and recommendation

Study D3256C00001 primary and key secondary endpoints were not met in the overall population, and there were no efficacy signals in subpopulations of interest. No safety concerns were raised. The submitted study does not influence the benefit risk for benralizumab and immediate revisions to the Summary of Product Characteristics are not warranted.

☒ **Fulfilled**