Synoptic Clinical Study Report	
Drug Substance	Benralizumab
Study Code	D3256C00001
Edition Number	1
Date	24 January 2023
EudraCT Number	2020-000285-42
NCT Number	NCT04605094

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)

Study dates: First participant enrolled: 12 November 2020 (first participant screened); 10 December 2020 (first participant randomised)

Last participant last visit: 13 September 2022

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator:

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Sponsor's Responsible Medical Officer:

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

2. SYNOPSIS

The study sponsor, AstraZeneca (AZ), has made the determination that the results of the D3256C00001 (HILLIER) study 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 to be presented in the format of a synoptic clinical study report (CSR) per the AZ company standard process. Results presented in this report include those from the primary analysis of the study, performed when follow-up of the placebo-controlled period of the study was complete, and the final safety update analysis which was performed when the last participant completed the study follow-up visit after the study was terminated.

Study centre(s)

A total of 48 study centres in 8 countries (Bulgaria, Czech Republic, Spain, France, Poland, the United States, Australia, and Korea) consented at least 1 participant.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Estimand description / Endpoints
Primary	
To compare the clinical efficacy of benralizumab 30 mg with placebo in patients with AD despite treatment with topical medications [a].	• Population: Full analysis set • 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 • Intercurrent events: Participants who withdraw from the study will be considered as non-responders from the time these events occur up to Week 16. Patients who require rescue therapy [b] from Day 29 up to Week 16 will be considered as non-responders from the time of this rescue use up to Week 16. • Summary measure: Odds ratio and difference in proportions between benralizumab and placebo at Week16
Secondary	
To compare the effect of benralizumab with placebo on supportive measures of clinical efficacy in patients with AD despite treatment with topical medications [a].	• 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
To compare benralizumab with placebo on patient-reported health-related quality of life measures in patients with AD despite treatment with topical medications [a].	• Change from baseline in DLQI and CDLQI at Week 16
To estimate the PK and immunogenicity of benralizumab 30 mg in patients with AD despite treatment with topical medications [a].	• Serum benralizumab concentration • ADA
To 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].	• 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	

Objectives	Estimand description / Endpoints
To compare the safety and tolerability of benralizumab with placebo in patients with AD despite treatment with topical medications [a].	Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory values. Assessments related to AEs cover: • Occurrence/frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP Vital signs parameters include systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height. Assessments related to vital signs cover: • Observed value • Absolute and percent change from baseline values over time
Tertiary/exploratory	
To explore the effect of benralizumab compared to placebo on healthcare resource utilization due to AD.	Rate of AD-related healthcare resource utilization during the study
To explore the effect of benralizumab compared to placebo on patient-reported health-related quality of life measures in patients with AD despite treatment with topical medications [a].	Change from baseline in scores for: • HADS • PGI-S • SF-36v2 Health Survey • EQ-5D-5L • CCI • Patient-reported experience (free text entry)
CCI [redacted]	

[a] The locally approved regimen of topical medication.

[b] Rescue therapy is defined in Section 6.5.3 of the CSP (Appendix16.1.1).

[c] The key secondary endpoints used the same estimand as outlined for the primary endpoint. For all other endpoints, the estimands are detailed in the SAP (Appendix 16.1.9).

AD, atopic dermatitis; 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; PK, pharmacokinetics; POEM, Patient-Oriented Eczema Measure; Q4W, every 4 weeks; Q8W, every 8 weeks; SAP, Statistical Analysis Plan; SCORAD, SCORing Atopic Dermatitis.

Study design

This was a Phase 2 multinational, randomized, double-blind, parallel-group, 16-week placebo-controlled study with a 36-week extension. The study evaluated the efficacy and safety of benralizumab 30 mg in male and female participants ≥ 12 years of age with moderate to severe atopic dermatitis (AD) who remained symptomatic despite treatment with standard of care treatment with topical medications. The study was designed to compare the safety and efficacy of benralizumab 30 mg every 4 weeks (Q4W) with placebo and identify the appropriate maintenance administration frequency (Q4W versus every 8 weeks [Q8W]).

This 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 informed consent/assent, all eligible participants entered a run-in period of 1 to 4 weeks during which inclusion/exclusion criteria was assessed, medical history was taken, and complete physical exam was conducted (Visit 1, See Table 3 in the Clinical Study Protocol [CSP] in Appendix 16.1.1). Potentially eligible participants entered a 7-day washout period during which all topical medications for AD except the stable emollient moisturizer regimen were discontinued. Participants were provided with a handheld device to respond to patient-reported outcomes (PRO) questionnaires during the study.

Target population and sample size

Approximately 270 participants were expected to be enrolled/screened in order 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. Enrolled study participants were then also stratified based on age and blood eosinophil levels for analysis purposes.

Informed Consent/Assent/age/gender/weight

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

2 Male and female participants ≥ 12 years of age at the time of signing the Informed Consent Form.

Type of Participants and Disease

3 Physician-confirmed diagnosis of AD (according to American Academy of Dermatology Consensus Criteria) that was not adequately controlled with topical medications.

4 Eczema Area and Severity Index (EASI) score of ≥ 12 at screening and ≥ 16 at randomization.

5 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.

6 AD involvement of ≥ 8% body-surface area at screening and ≥ 10% body-surface area at randomization.

7 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.

8 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).

9 Participants that had applied a stable dose of topical emollient (moisturizer) twice daily for ≥ 7 consecutive days immediately before the randomization visit (note: See CSP [Appendix 16.1.1] for exclusion criterion 11 for limitations regarding emollients).

10 Participants must have been willing and able to complete daily PRO 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.

Reproduction

11 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 (note: See CSP [Appendix 16.1.1] for inclusion criterion 11 for details).

12 Females not of childbearing potential (note: See CSP [Appendix 16.1.1] for inclusion criterion 12 for details).

See Section 5.2 of the CSP [Appendix 16.1.1] for exclusion criteria.

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

Benralizumab:

- CCI [redacted]
- Route of administration: Subcutaneous injection.
- Batch numbers: a by-participant listing of batch numbers is presented in Listing 16.1.6.

Placebo

- CCI [redacted]
- Route of administration: Subcutaneous injection.
- Batch numbers: a by-participant listing of batch numbers is presented in Listing 16.1.6.

Duration of treatment

This study consisted of the following consecutive periods:

- A 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.

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. Analysis sets are defined in Section 2.2 of the statistical analysis plan (SAP) in Appendix 16.1.9. The study was terminated after the primary analysis and all ongoing participants were required to complete a final follow-up visit regardless of where they had reached in the extension period of the study. The final analysis was performed once all final follow-up visits were completed and included updated safety data presentations; no efficacy analyses were performed at the final analysis.

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

Study population

A total of 244 participants were screened and 194 participants were randomized from 48 study centres in 8 countries. 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.

A total of 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 of age ≥ 35 years; mean (standard deviation [SD]) age at screening was 29.6 (15.90) years.

A total of 175 participants (90.2%) entered the extension period, all but 1 of which received treatment and 72 (37.1%) completed extension period treatment by the primary analysis data cut-off. Sixty-four participants (33.0%) were withdrawn when the extension period of the study was terminated by the sponsor due to lack of evidence of treatment benefit. There were 62 participants (32.0%) with at least 1 important protocol deviation at any point during the study, the incidence of which was similar across treatment groups.

Summary of efficacy results at the primary analysis

The primary endpoint of the study was a binary response giving the proportion of participants with an IGA 0/1 and a decrease in IGA of ≥ 2 points at Week 16 relative to baseline. The primary endpoint of the study was not met. There was no significant difference between benralizumab and placebo in the proportion of participants with response at Week 16 relative

to baseline (treatment difference -8.62% [95% confidence interval {95%CI}: -17.94%, 0.71%], p = 0.080).

There were no clear differences in secondary endpoints. Results were as follows:

- Key secondary endpoint: There was 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% [95%CI -16.67%, 6.36%], p = 0.384).
- Key secondary endpoint: There was no significant difference between benralizumab and placebo in the proportion of participants achieving an improvement of ≥ 4 points in peak pruritis NRS score at Week 16 (treatment difference: 0.69% [95%CI -8.93%, 10.32%], p = 0.889).
- Key secondary endpoint: There was 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% [95%CI -16.94%, 0.59%], p = 0.078).
- There was 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% [95%CI -19.87%, 6.99%], p = 0.350).
- There was 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% [95%CI -9.04%, 2.68%], p = 0.301).
- There was 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 (95% CI: -0.86, 7.24), p = 0.121).
- There was 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 [95% CI: -0.28, 0.75], p = 0.372).
- There was 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 [95% CI: -0.63, 4.42], p = 0.140).
- There was 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 [95% CI: -3.78, 10.42], p = 0.357).
- Change from baseline in Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI) at Week 16:
  - There was 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 [95% CI: -1.28, 3.44], p = 0.365).

  - There was 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 [95% CI: -3.38, 5.78], p = 0.593.

- Despite not meeting primary or secondary endpoints, blood eosinophils were depleted (see eosinophils in summary of safety results) and significant reductions in CCI [redacted] were observed. At week 16, mean (SD) change from baseline in CCI [redacted] in the benralizumab group and CCI [redacted] in the placebo group.

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

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

Table S-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
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
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)	

Outcome	Benralizumab N = 96	Placebo N = 98	P-value
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
Peak Pruritus NRS score W2 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)	
CCI [redacted]	[redacted]	[redacted]	

[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; CCI [redacted]; 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.

Sources: Table 14.2.1p, Table 14.2.2.3.2p, Table 14.2.2.3.1p, Table 14.2.2.4p, Table 14.2.2.3.3p, Table 14.2.2.3.4p, Table 14.2.3.4p, Table 14.2.4.2p, Table 14.2.5.2p, Table 14.2.6.2p, Table 14.2.7.2p, Table 14.1.14.1p, Table 14.2.18.1, Table 14.3.7.1.

CCI

[redacted]

Summary of pharmacokinetics results at the primary analysis

In the 16-week, placebo-controlled treatment period, pharmacokinetics (PK) results in participants with AD were reported as being in line with those previously reported with benralizumab in participants with asthma and nasal polyps.

CCI

[redacted]

Summary of safety results at the primary analysis

In the 16-week, placebo-controlled treatment period, the following safety results were reported:

- 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 were reported for 3 participants (3.1%) in the benralizumab group (cardiac failure congestive, paranasal sinus inflammation and dermatitis atopic) and no participants in the placebo group. Adverse events 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.
- 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.

- A total of 3 participants [3.1%] reported severe AEs in the benralizumab groups: dermatitis atopic (2 participants [2.1%]) and dermatitis exfoliative generalised (1 participants [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.
- Adverse events 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 (1 participant [1.0%] reported for each preferred term). Adverse events being possibly related to the study drug were reported for 8 participants (8.2%) in the placebo group: alopecia, chalazion, chest discomfort, diarrhoea, lymphadenopathy, seborrhoea, torticollis, and upper respiratory tract infection (1 participant [1.0%] reported for each AE).
- No AEs with the outcome of death were reported for any participant in the benralizumab groups or placebo group during the 16-week treatment period.
- 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. As expected, and in line with the known pharmacodynamic effects of benralizumab, mean eosinophils had a greater decrease from baseline to Week 16 in the benralizumab group (baseline: 0.482×10^9/L, Week 16: 0.040×10^9/L; change from baseline -0.457×10^9/L) than in the placebo group (baseline: 0.464×10^9/L, Week 16: 0.355×10^9/L; change from baseline -0.129×10^9/L).

In the overall study including the 36-week extension period, the following safety results were reported:

- No AEs with a fatal outcome were reported. In addition to the benralizumab participants with SAEs reported during the 16-week placebo-controlled treatment period, 2 participants (2.3%) who switched to benralizumab in the extension period after receiving placebo had SAEs (Hodgkin's disease, migraine). 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.
- 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.
- During the extension period, 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 (2 participants [2.3%]), and diarrhoea, eczema herpeticum, lymphadenopathy,

neutropenia, oedema peripheral, thrombocytopenia, and upper respiratory tract infection (each in 1 participant [1.1%]). Adverse events being possibly related to the study drug were reported for 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 urticaria (1 participant [1.1%] each).

- All other AEs observed during the extension period were reported as not related to study drug.
- The most common AE over the course of the study was COVID-19 (benralizumab: 21.9%, placebo/benralizumab: 19.4%); 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.

Conclusion

This was a Phase 2 multinational, randomized, double-blind, parallel-group, 16-week placebo-controlled study with a 36-week extension. The study was terminated by sponsor decision following primary analysis of the results from 16-week placebo-controlled phase which indicated that participants were not benefiting from treatment.

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

The PK results from Study D3256C00001 were in line with those reported previously with benralizumab.

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.