Clinical trial results:
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)

Summary

EudraCT number	2020-000285-42
Trial protocol	CZ BG FR PL
Global end of trial date	13 September 2022

Results information

Result version number	v1 (current)
This version publication date	28 March 2023
First version publication date	28 March 2023

Trial information

Trial identification

Sponsor protocol code	D3256C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04605094
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Karlebyhusentren, B674 Astraallen, Södertälje, Sweden, 151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 September 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to compare the clinical efficacy of benralizumab 30 milligram (mg) with placebo in participants with atopic dermatitis (AD) despite treatment with topical medications.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Czechia: 28
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Korea, Republic of: 38
Worldwide total number of subjects	194
EEA total number of subjects	105

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	53
Adults (18-64 years)	133
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 2, double-blind, placebo-controlled study was conducted in participants with moderate to severe AD at 48 study centers in 8 countries.

Pre-assignment

Screening details:

This study consisted of a screening period (up to 4 weeks), placebo-controlled double-blind treatment period (up to 16 weeks) and an extension period (up to 36 weeks). A total of 194 participants were randomized and received treatment in this study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Benralizumab

Arm description:

Participants received benralizumab 30 mg subcutaneous (SC) injection on Day 1 visit for every 4 weeks (Q4W) until Week 16 visit. In extension phase, participants received benralizumab 30 mg SC injection for either Q4W or every 8 weeks (Q8W) until Week 52 visit.

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Benralizumab was administered as a SC injection of 1 milliliter (mL) volume containing 30 mg dose to participants by health care professionals in arms, abdominal wall and thighs in rotation.

Arm title	Placebo

Arm description:

Participants received placebo matching benralizumab on Day 1 visit for Q4W until Week 16. In extension phase, participants received benralizumab 30 mg SC injection for Q4W until Week 28 visit and then followed by benralizumab 30 mg SC injection for Q8W until Week 52 visit.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

A matching placebo was administered as a SC injection to participants by health care professionals in arms, abdominal wall and thighs in rotation.

Number of subjects in period 1	Benralizumab	Placebo
Started	96	98
Completed	37	37
Not completed	59	61
Consent withdrawn by subject	22	19
Physician decision	2	2
Study terminated by Sponsor	31	33
Adverse event, non-fatal	2	2
Unspecified	1	1
Lost to follow-up	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Benralizumab
Reporting group description:	
Participants received benralizumab 30 mg subcutaneous (SC) injection on Day 1 visit for every 4 weeks (Q4W) until Week 16 visit. In extension phase, participants received benralizumab 30 mg SC injection for either Q4W or every 8 weeks (Q8W) until Week 52 visit.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching benralizumab on Day 1 visit for Q4W until Week 16. In extension phase, participants received benralizumab 30 mg SC injection for Q4W until Week 28 visit and then followed by benralizumab 30 mg SC injection for Q8W until Week 52 visit.	

Reporting group values	Benralizumab	Placebo	Total
Number of subjects	96	98	194
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	29.8	29.5	
standard deviation	± 15.87	± 16.00	-
Gender Categorical Units: Subjects			
Female	40	32	72
Male	56	66	122
Race Units: Subjects			
Black or African American	6	6	12
Asian	24	20	44
White	65	70	135
Other	1	2	3
Ethnicity Units: Subjects			
Hispanic or Latino	11	13	24
Not Hispanic or Latino	85	85	170

End points

End points reporting groups

Reporting group title	Benralizumab

Reporting group description:

Participants received benralizumab 30 mg subcutaneous (SC) injection on Day 1 visit for every 4 weeks (Q4W) until Week 16 visit. In extension phase, participants received benralizumab 30 mg SC injection for either Q4W or every 8 weeks (Q8W) until Week 52 visit.

Reporting group title	Placebo

Reporting group description:

Participants received placebo matching benralizumab on Day 1 visit for Q4W until Week 16. In extension phase, participants received benralizumab 30 mg SC injection for Q4W until Week 28 visit and then followed by benralizumab 30 mg SC injection for Q8W until Week 52 visit.

Subject analysis set title	Benralizumab Q4W -> Q4W
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received benralizumab 30 mg SC injection on Day 1 visit Q4W until Week 16 visit. In extension phase, these participants again received benralizumab 30 mg SC injection Q4W until Week 52 visit.

Subject analysis set title	Benralizumab Q4W -> Q8W
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received benralizumab 30 mg SC injection on Day 1 visit Q4W until Week 16 visit. In extension phase, these participants received benralizumab 30 mg SC injection Q8W until Week 52 visit.

Primary: Percentage of Participants With an Investigator Global Assessment (IGA) 0/1 and a Decrease in IGA of ≥2 Points at Week 16 Relative to Baseline

End point title	Percentage of Participants With an Investigator Global Assessment (IGA) 0/1 and a Decrease in IGA of ≥2 Points at Week 16 Relative to Baseline

End point description:

The IGA is an instrument used in clinical studies to rate the severity of atopic dermatitis globally, based on a 5-point scale ranging from 0 = clear; 1 = almost clear; 2 = mild disease; 3 = moderate disease; 4 = severe disease. The IGA used clinical characteristics of erythema, infiltration, papulation, oozing, and crusting as guidelines for the overall severity assessment. A higher score indicated greater severity. A responder at Week 16 was defined as having IGA 0/1 and a decrease in IGA of ≥2 points at Week 16 relative to baseline. Participants who withdrew from the study/required rescue therapy after Day 28 were considered as non-responders from the time these events occurred. Baseline was defined as the last recorded value on or prior to the date of randomization. The Full Analysis set (FAS) consisted of all randomized participants who received at least 1 dose of study drug, irrespective of their protocol adherence and continued participation in the study.

End point type	Primary

End point timeframe:

Baseline (Week 0) and at Week 16

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	98		
Units: percentage of participants				
number (confidence interval 95%)	9.4 (3.36 to 14.93)	17.3 (10.40 to 25.12)		

Statistical analyses

Statistical analysis title	Treatment difference in IGA responders

Statistical analysis description:

Estimates were from a logistic regression model that included treatment group, age as recorded on electronic case report form (eCRF) at screening (>=12 to <18 years; >=18 years), blood eosinophils as recorded on eCRF at screening (<300 cells/microliters [µL]; >=300 cells/µL) and baseline value of IGA score.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.08
Method	Regression, Logistic
Parameter estimate	Difference in response rate
Point estimate	-8.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.94
upper limit	0.71

Secondary: Percentage of Participants Who Experienced 75/90% Reduction From Baseline in Eczema Area and Severity Index (EASI-75/90) at Week 16

End point title	Percentage of Participants Who Experienced 75/90% Reduction From Baseline in Eczema Area and Severity Index (EASI-75/90) at Week 16

End point description:

The EASI assessed the severity and extent of AD. Severity of 4 AD disease characteristics (erythema, induration/papulation, excoriation [scratching], lichenification) each were assessed on a scale of 0 (absent) to 3 (severe) in each of 4 body regions (head/neck, trunk, upper limbs, and lower limbs). Total body total score=sum of the region total scores; ranged from 0 to 72. Participants were classified as responders if they achieved at least 75/90% reduction from baseline in their EASI total score at Week 16. Participants who withdrew from study/required rescue therapy after Day 28 were non-responders from the time these events occurred. Higher scores indicated a more severe or more extensive condition. Baseline was defined as the last recorded value on or prior to the date of randomization. The FAS consisted of all randomized participants who received at least 1 dose of study drug, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and at Week 16

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	98		
Units: percentage of participants				
number (confidence interval 95%)				
EASI-75	19.8 (11.71 to 27.45)	24.5 (16.27 to 33.19)		
EASI-90	7.3 (2.05 to 12.42)	15.3 (8.33 to 22.50)		

Statistical analyses

Statistical analysis title	Treatment difference in EASI-75 responders

Statistical analysis description:

Estimates were from a logistic regression model that included treatment group, age as recorded on eCRF at screening (>=12 to < 18 years; >=18 years), blood eosinophils as recorded on eCRF at screening (<300 cells/µL; >=300 cells/µL) and baseline EASI total score.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.384
Method	Regression, Logistic
Parameter estimate	Difference in response rate
Point estimate	-5.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.67
upper limit	6.36

Statistical analysis title	Treatment difference in EASI-90 responders

Statistical analysis description:

Estimates were from a logistic regression model that included treatment group, age as recorded on eCRF at screening (>=12 to < 18 years; >=18 years), blood eosinophils as recorded on eCRF at screening (<300 cells/µL; >=300 cells/µL) and baseline EASI total score.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.078
Method	Regression, Logistic
Parameter estimate	Difference in response rate
Point estimate	-8.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.94
upper limit	0.59

Secondary: Percentage of Participants With an Improvement of ≥4 or More Points in Peak Pruritus Weekly Score

End point title	Percentage of Participants With an Improvement of ≥4 or More Points in Peak Pruritus Weekly Score

End point description:

The Peak Pruritus numeric rating scale (NRS) was a 1-item daily assessment of the worst itch the participant experienced over the past 24 hours. The score ranged from 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable." and so a reduction in score was considered an improvement. A responder was defined as having an improvement of 4 or more points relative to baseline. Participants who withdrew from the study/required rescue therapy after Day 28 were considered as non-responders from the time these events occurred. The Week 16 weekly scores were defined as the average of the daily scores for the 7 days prior to the weekly score. The FAS consisted of all randomized participants who received at least 1 dose of study drug, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

At Week 16

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	98		
Units: percentage of participants				
number (confidence interval 95%)	14.6 (7.87 to 21.70)	14.3 (7.28 to 20.90)		

Statistical analyses

Statistical analysis title	Treatment difference in Peak Pruritus NRS

Statistical analysis description:

Estimates were from a logistic regression model that included treatment group, age as recorded on eCRF at screening (>=12 to < 18 years; >=18 years), blood eosinophils as recorded on eCRF at screening (<300 cells/µL; >=300 cells/µL) and baseline Peak Pruritus score.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.889
Method	Regression, Logistic
Parameter estimate	Difference in response rate
Point estimate	0.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.93
upper limit	10.32

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events in the on-study period were reported from the first dose of study treatment (Day 1) up to end of follow-up, approximately a maximum up to Week 60

Adverse event reporting additional description:

The Safety Analysis set consisted of all participants who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Benralizumab

Reporting group description:

Participants received benralizumab 30 mg SC injection on Day 1 visit for Q4W until Week 16 visit. In extension phase participants received benralizumab 30 mg SC injection for either Q4W or Q8W until Week 52 visit.

Reporting group title	Placebo

Reporting group description:

Participants received placebo matching benralizumab on Day 1 visit for Q4W until Week 16. In extension phase participants received benralizumab 30 mg SC injection for Q4W until Week 28 visit and then followed by benralizumab 30 mg SC injection for Q8W until Week 52 visit.

Serious adverse events	Benralizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 96 (3.13%)	2 / 98 (2.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hodgkin's disease			
subjects affected / exposed	0 / 96 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 96 (1.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			

subjects affected / exposed	0 / 96 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Paranasal sinus inflammation			
subjects affected / exposed	1 / 96 (1.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 96 (1.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Benralizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 96 (39.58%)	39 / 98 (39.80%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 96 (4.17%)	6 / 98 (6.12%)	
occurrences (all)	4	13	
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 96 (5.21%)	5 / 98 (5.10%)	
occurrences (all)	5	6	
COVID-19			
subjects affected / exposed	21 / 96 (21.88%)	19 / 98 (19.39%)	
occurrences (all)	23	20	
Nasopharyngitis			
subjects affected / exposed	9 / 96 (9.38%)	7 / 98 (7.14%)	
occurrences (all)	10	9	
Upper respiratory tract infection			

subjects affected / exposed	9 / 96 (9.38%)	6 / 98 (6.12%)	
occurrences (all)	12	8	
Conjunctivitis			
subjects affected / exposed	3 / 96 (3.13%)	9 / 98 (9.18%)	
occurrences (all)	4	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2020	The primary rationale for this amendment was to add study mitigation language to provide sites with measures that were implemented if a participant was not able to visit a study site to ensure that the clinical trial could continue while minimizing risk to the participant, maintaining compliance with GCP, and minimize risks to the study integrity. Photography at some site visits was added to support the potential for use during study mitigation and as a tool for future trials. Other changes were made as points of clarification and correction of minor errors or omissions.
04 May 2021	The primary rationale for amendment was to align the contents of the clinical study protocol with the updated project specific safety requirements for benralizumab studies. Other changes were made as points of clarification, alignment with the updated protocol template, and correction of minor errors or omissions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated as the study did not support the continued development of benralizumab for the indication of AD.

Notes: