Clinical trial results:
A Phase II, Randomized, Double-blind, Placebo-controlled Bronchoscopy Study to Evaluate the Effects of Lebrikizumab on Airway Eosinophilic Inflammation in Patients with Uncontrolled Asthma on Inhaled Corticosteroids and a Second Controller Medication

Summary

EudraCT number	2014-000275-14
Trial protocol	SE IE GB
Global end of trial date	13 October 2016

Results information

Result version number	v1 (current)
This version publication date	21 October 2017
First version publication date	21 October 2017

Trial information

Trial identification

Sponsor protocol code	GB29260

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02099656
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.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?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate the effect of lebrikizumab in reducing airway eosinophilic inflammation in subjects with uncontrolled asthma, who are using inhaled corticosteroid (ICS) treatment and a second controller medication, as measured by a relative change in the number of airway submucosal eosinophils per surface area of basal lamina (cells per square millimetre [cells/mm^2]) obtained via endobronchial biopsy at Week 12 compared to baseline.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

Subjects continued their ICS controller therapy, as they were receiving prior to screening, throughout the study. ICS therapy included 500–2000 micrograms per day (mcg/day) of fluticasone propionate dry powder inhaler (DPI) or equivalent. Subjects also continued their second asthma controller therapy, as they were receiving prior to screening, throughout the study. The following second controller medications were included in the study: long-acting beta-agonist (LABA), leukotriene receptor antagonist (LTRA), long-acting muscarinic antagonist (LAMA), or theophylline.

Evidence for comparator: -

Actual start date of recruitment	06 November 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	United States: 34
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Sweden: 7
Worldwide total number of subjects	64
EEA total number of subjects	17

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)	0
Adults (18-64 years)	63
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects 18-75 years of age (inclusive) with uncontrolled asthma on inhaled corticosteroid (ICS) therapy and on an eligible second controller medication were recruited. The screening period was three weeks and included four visits (Visits 1, 2, 3, and 4a) and a final assessment of eligibility prior to randomisation at Visit 4b.

Pre-assignment

Screening details:

Asthma had to be diagnosed >/= 12 months before first screening visit. Bronchodilator response, which was defined as >/= 12% relative improvement in forced expiratory volume in 1 second (FEV1) after bronchodilator administration, had to be demonstrated within the 12 months before Visit 1 or at Visit 1, 2, or 3 of screening.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects with uncontrolled asthma on ICS therapy and a second controller medication received subcutaneous (SC) injection of lebrikizumab matching placebo on Days 1 and 8, and on Weeks 4 and 8.

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:

Matching placebo was administered by SC injection on Day 1, Day 8, Week 4, and Week 8.

Arm title	Lebrikizumab

Arm description:

Subjects with uncontrolled asthma on inhaled corticosteroids (ICS) therapy and a second controller medication received SC injection of lebrikizumab on Days 1 and 8, and on Weeks 4 and 8.

Arm type	Experimental
Investigational medicinal product name	Lebrikizumab
Investigational medicinal product code	
Other name	RO5490255
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Lebrikizumab 125 milligrams (mg) was administered by SC injection on Day 1, Day 8, Week 4, and Week 8.

Number of subjects in period 1	Placebo	Lebrikizumab
Started	33	31
Completed	33	30
Not completed	0	1
Refusal to do follow up 2 due to Sponsor info	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects with uncontrolled asthma on ICS therapy and a second controller medication received subcutaneous (SC) injection of lebrikizumab matching placebo on Days 1 and 8, and on Weeks 4 and 8.	
Reporting group title	Lebrikizumab
Reporting group description:	
Subjects with uncontrolled asthma on inhaled corticosteroids (ICS) therapy and a second controller medication received SC injection of lebrikizumab on Days 1 and 8, and on Weeks 4 and 8.	

Reporting group values	Placebo	Lebrikizumab	Total
Number of subjects	33	31	64
Age Categorical Units: Subjects			
Adults (18-64 years)	33	30	63
From 65-84 years	0	1	1
Age Continuous Units: years			
arithmetic mean	43.9	45.9	
standard deviation	± 12.8	± 12.5	-
Gender Categorical Units: Subjects			
Female	14	15	29
Male	19	16	35

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects with uncontrolled asthma on ICS therapy and a second controller medication received subcutaneous (SC) injection of lebrikizumab matching placebo on Days 1 and 8, and on Weeks 4 and 8.	
Reporting group title	Lebrikizumab
Reporting group description:	
Subjects with uncontrolled asthma on inhaled corticosteroids (ICS) therapy and a second controller medication received SC injection of lebrikizumab on Days 1 and 8, and on Weeks 4 and 8.	

Primary: Relative Change From Baseline in the Number of Airway Submucosal Eosinophils per Surface Area of Basal Lamina

End point title	Relative Change From Baseline in the Number of Airway Submucosal Eosinophils per Surface Area of Basal Lamina
End point description:	
To evaluate the effect of lebrikizumab in reducing airway eosinophilic inflammation the relative change from baseline in the number of airway submucosal eosinophils per surface area of basal lamina (cells per square millimetre [cells/mm^2]) was measured after an endobronchial biopsy was performed. Baseline results are presented as 10^9 cells per square metre (10^9 cells/m^2). Relative change was defined as the absolute change from baseline to Week 12, divided by the value at baseline and presented as percentage. The Primary analysis Patients (PP) population was defined as a subset of subjects from the intent-to-treat (ITT) population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (10^9 cells/m^2)	0.439 (± 0.418)	0.224 (± 0.228)		
Week 12, Percentage Change from Baseline	73.9 (± 169.4)	75.6 (± 167.8)		

Statistical analyses

Statistical analysis title	Placebo versus Lebrikizumab
Comparison groups	Placebo v Lebrikizumab

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.5
upper limit	97.6

Secondary: Absolute Change From Baseline in Number of Airway Submucosal Eosinophils per Surface Area of Basal Lamina

End point title	Absolute Change From Baseline in Number of Airway Submucosal Eosinophils per Surface Area of Basal Lamina

End point description:

To evaluate the effect of lebrikizumab on airway eosinophilic inflammation the absolute change in the number of airway submucosal eosinophils per surface area of basal lamina (cells/mm^2) was measured after an endobronchial biopsy was performed. Results are presented as 10^9 cells/m^2. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: 10^9 cells/m^2				
arithmetic mean (standard deviation)				
Baseline, Value at Visit	0.439 (± 0.418)	0.224 (± 0.228)		
Week 12, Change from Baseline	-0.017 (± 0.457)	0.055 (± 0.212)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Change From Baseline in the Number of Airway Epithelial Eosinophils per Surface Area of Basal Lamina

End point title	Relative Change From Baseline in the Number of Airway Epithelial Eosinophils per Surface Area of Basal Lamina

End point description:

To evaluate the effect of lebrikizumab on airway eosinophilic inflammation the relative change in the number of airway epithelial eosinophils per surface area of basal lamina (cells/mm^2) was measured

after an endobronchial biopsy was performed. Baseline results are presented as 10^9 cells/m^2. Relative change was defined as the absolute change from baseline to Week 12, divided by the value at baseline and presented as percentage. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	14		
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (10^9/m^2)	0.054 (± 0.103)	0.045 (± 0.11)		
Week 12, Percentage Change from Baseline	-14.5 (± 61.5)	45.5 (± 171.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Number of Airway Epithelial Eosinophils per Surface Area of Basal Lamina

End point title	Absolute Change From Baseline in Number of Airway Epithelial Eosinophils per Surface Area of Basal Lamina

End point description:

To evaluate the effect of lebrikizumab on airway eosinophilic inflammation the absolute change in the number of airway epithelial eosinophils per surface area of basal lamina (cells/mm^2) was measured after an endobronchial biopsy was performed. Results are presented as 10^9 cells/m^2. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	14		
Units: 10^9 cells/m^2				
arithmetic mean (standard deviation)				
Baseline, Value at Visit	0.054 (± 0.103)	0.045 (± 0.11)		

Week 12, Change from Baseline	-0.031 (± 0.087)	-0.01 (± 0.089)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Change From Baseline in Number of Airway Submucosal Eosinophils per Volume of Submucosa

End point title	Relative Change From Baseline in Number of Airway Submucosal Eosinophils per Volume of Submucosa

End point description:

To evaluate the effect of lebrikizumab on airway eosinophilic inflammation the relative change in the number of airway submucosal eosinophils per volume of submucosa (cells per cubic millimetre [cells/mm^3]) was measured after an endobronchial biopsy was performed. Baseline results are presented as 10^9 cells/litre (L). Relative change was defined as the absolute change from baseline to Week 12, divided by the value at baseline and presented as percentage. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received.The number of subjects analysed is indicated by n for each arm at each time point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (10^9 cells/L)	1.567 (± 1.386)	1.094 (± 1.056)		
Week 12, Percentage Change from Baseline	61.5 (± 157.2)	51.2 (± 134)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Number of Airway Submucosal Eosinophils per Volume of Submucosa

End point title	Absolute Change From Baseline in Number of Airway Submucosal Eosinophils per Volume of Submucosa

End point description:

To evaluate the effect of lebrikizumab on airway eosinophilic inflammation the absolute change in the number of airway submucosal eosinophils per volume of submucosa (cells/mm^3) was measured after an endobronchial biopsy was performed. Results are presented as 10^9 cells/L. The PP population was

defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)				
Baseline, Value at Visit	1.567 (± 1.386)	1.094 (± 1.056)		
Week 12, Change from Baseline	0.259 (± 1.313)	0.198 (± 0.971)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Change From Baseline in Number of Airway Epithelial Eosinophils per Volume of Epithelium

End point title	Relative Change From Baseline in Number of Airway Epithelial Eosinophils per Volume of Epithelium

End point description:

To evaluate the effect of lebrikizumab on airway eosinophilic inflammation the relative change in the number of airway epithelial eosinophils per volume of epithelium (cells/mm^3) was measured after an endobronchial biopsy was performed. Baseline results are presented as 10^9 cells/L. Relative change was defined as the absolute change from baseline to Week 12, divided by the value at baseline and presented as percentage. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	14		
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (10^9 cells/L)	1.051 (± 1.234)	1.283 (± 2.736)		
Week 12, Percentage Change from Baseline	136.1 (± 527.4)	958.4 (± 2349.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Number of Airway Epithelial Eosinophils per Volume of Epithelium

End point title	Absolute Change From Baseline in Number of Airway Epithelial Eosinophils per Volume of Epithelium

End point description:

To evaluate the effect of lebrikizumab on airway eosinophilic inflammation the absolute change in the number of airway epithelial eosinophils per volume of epithelium (cells/mm^3) was measured after an endobronchial biopsy was performed. Results are presented as 10^9 cells/L. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	14		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)				
Baseline, Value at Visit	1.051 (± 1.234)	1.283 (± 2.736)		
Week 12, Change from Baseline	-0.168 (± 1.118)	0.274 (± 3.389)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Blood Eosinophil Count

End point title	Change From Baseline in Blood Eosinophil Count

End point description:

Blood eosinophil counts were performed at multiple time points from baseline (BL) to Week 20. The safety evaluable population was defined as all subjects who received at least one dose of study drug, with subjects grouped according to the actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 4, Week 8, Week 12, Week 16, Week 20

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=33, 31)	0.33 (± 0.235)	0.248 (± 0.142)		
Week 1, Change from BL (n=33, 30)	0.014 (± 0.148)	0.024 (± 0.103)		
Week 4, Change from BL (n=31, 31)	-0.01 (± 0.175)	0.066 (± 0.168)		
Week 8, Change from BL (n=30, 30)	0 (± 0.212)	0.066 (± 0.202)		
Week 12, Change from BL (n=31, 31)	-0.039 (± 0.202)	0.062 (± 0.248)		
Week 16, Change from BL (n=33, 30)	-0.015 (± 0.207)	0.114 (± 0.279)		
Week 20, Change from BL (n=32, 27)	0.022 (± 0.139)	0.07 (± 0.229)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin E (IgE) Levels

End point title	Change From Baseline in Immunoglobulin E (IgE) Levels

End point description:

IgE levels were measured at multiple time points from baseline (BL) to Week 20.The safety evaluable population was defined as all subjects who received at least one dose of study drug, with subjects grouped according to the actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point. Results are presented in International Units per millilitre (IU/mL).

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 12, Week 20

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: IU/mL				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=33, 29)	269 (± 289.7)	265.2 (± 296.5)		
Week 1, Change from BL (n=32, 29)	8.9 (± 22)	-9.1 (± 33.3)		
Week 12, Change from BL, (n=31, 29)	21.1 (± 93.7)	-37.2 (± 63.7)		
Week 20, Change from BL, (n=33, 25)	11.2 (± 73.9)	-44.2 (± 83.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Periostin Levels

End point title	Change From Baseline in Serum Periostin Levels

End point description:

Serum periostin levels were measured at multiple time points from baseline (BL) to Week 20.The safety evaluable population was defined as all subjects who received at least one dose of study drug, with subjects grouped according to the actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point. Results are presented in nanograms per millilitre (ng/mL).

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 12, Week 20

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=33, 31)	51.67 (± 16.01)	52.77 (± 18.93)		
Week 1, Change from BL (n=32, 31)	-2.23 (± 5.11)	-4.33 (± 6.26)		
Week 12, Change from BL (n=31, 31)	0.99 (± 11.37)	-5.08 (± 6.94)		
Week 20, Change from BL (n=33, 28)	0.4 (± 10.8)	-4.53 (± 6.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Chemokine Ligand (CCL)-17 Levels

End point title	Change From Baseline in Chemokine Ligand (CCL)-17 Levels

End point description:

CCL-17 levels were planned to be measured at multiple time points from baseline (BL) to Week 20.The safety evaluable population was defined as all subjects who received at least one dose of study drug, with subjects grouped according to the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 12, Week 20

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: pg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[1] - CCL-17 data were not available for analysis.

[2] - CCL-17 data were not available for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lung Epithelial Cell Chloride Channel Accessory 1 (CLCA1) Gene Expression

End point title	Change From Baseline in Lung Epithelial Cell Chloride Channel Accessory 1 (CLCA1) Gene Expression

End point description:

CLCA1 gene expression at the messenger ribonucleic acid (mRNA) transcript levels in lung epithelial cells was measured by RNA-sequencing at baseline (BL) and Week 12. Change in gene expression levels is reported as reads per kilobase million (RPKM) at Week 12 relative to BL.The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: RPKM				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=21, 20)	2.36 (± 3.72)	7.88 (± 23.83)		
Week 12, Change from BL (n=17, 13)	-0.11 (± 5.76)	-9.66 (± 25.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lung Epithelial Cell SerpinB2 Gene Expression

End point title	Change From Baseline in Lung Epithelial Cell SerpinB2 Gene Expression

End point description:

SerpinB2 gene expression at the mRNA transcript levels in lung epithelial cells was measured by RNA-sequencing at baseline (BL) and Week 12. Change in gene expression levels is reported as RPKM at Week 12 relative to BL.The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: RPKM				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=21, 20)	3.58 (± 3.09)	3.75 (± 3.61)		
Week 12, Change from BL (n=17, 13)	0.37 (± 5.43)	-0.88 (± 6.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lung Epithelial Cell CCL-26 Gene Expression

End point title	Change From Baseline in Lung Epithelial Cell CCL-26 Gene Expression

End point description:

CCL-26 gene expression at the mRNA transcript levels in lung epithelial cells was measured by RNA-sequencing at baseline (BL) and Week 12. Change in gene expression levels is reported as RPKM at Week 12 relative to BL. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: RPKM				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=21, 20)	0.15 (± 0.23)	0.25 (± 0.44)		
Week 12, Change from BL (n=17, 13)	0.09 (± 0.54)	0.01 (± 0.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lung Epithelial Cell Nitric Oxide Synthase 2 (NOS2) Gene Expression

End point title	Change From Baseline in Lung Epithelial Cell Nitric Oxide Synthase 2 (NOS2) Gene Expression

End point description:

NOS2 gene expression at the mRNA transcript levels in lung epithelial cells was measured by RNA-sequencing at baseline (BL) and Week 12. Change in gene expression levels is reported as RPKM at Week 12 relative to BL. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: RPKM				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=21, 20)	5.09 (± 8.92)	5.28 (± 7.1)		
Week 12, Change from BL (n=17, 13)	-0.68 (± 5.16)	-3.26 (± 5.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lung Epithelial Cell Periostin (POSTN) Gene Expression

End point title	Change From Baseline in Lung Epithelial Cell Periostin (POSTN) Gene Expression

End point description:

POSTN gene expression at the mRNA transcript levels in lung epithelial cells was measured by RNA-sequencing at baseline (BL) and Week 12. Change in gene expression levels is reported as RPKM at Week 12 relative to BL. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point.

End point type	Secondary

End point timeframe:
Baseline, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: RPKM				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=21, 20)	6.65 (± 6.5)	7.14 (± 6.65)		
Week 12, Change from BL (n=17, 13)	-0.08 (± 7.53)	-3.54 (± 4.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Change From Baseline in Fractional Exhaled Nitric Oxide (FeNO)

End point title	Relative Change From Baseline in Fractional Exhaled Nitric Oxide (FeNO)

End point description:

Description: FeNO was measured at multiple time points from baseline (BL) to Week 12. At BL FeNO is reported as parts per billion (ppb). Relative change was defined as the absolute change from baseline to each time point, divided by the value at baseline and presented as percentage. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point.

End point type	Secondary

End point timeframe:
Baseline, Week 1, Week 4, Week 8, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=25, 26)	32.3 (± 35.8)	34.5 (± 28)		
Week 1, Change from BL (n=25, 26)	2.5 (± 43.8)	-16.9 (± 37.8)		
Week 4, Change from BL (n=25, 26)	21.2 (± 71.1)	-25.9 (± 45.4)		
Week 8, Change from BL (n=24, 25)	12.1 (± 45.3)	-23.4 (± 37.7)		
Week 12, Change from BL (n=24, 26)	8.8 (± 53.2)	-24.8 (± 40.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1)

End point title	Relative Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1)

End point description:

FEV1 was measured at multiple time points from baseline (BL) to Week 12. At BL FEV1 is reported as volume in litres (L). Relative change was defined as the absolute change from baseline to each time point, divided by the value at baseline and presented as percentage. The PP population was defined as a subset of subjects from the ITT population who received at least one dose of the study drug, and who had evaluable biopsies available for both baseline (Visit 4a) and Week 12 visits. Subjects were grouped according to actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 4, Week 8, Week 12

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=25, 26)	2.352 (± 0.79)	2.15 (± 0.611)		
Week 1, Change from BL (n=25, 26)	2.327 (± 13.949)	5.385 (± 13.584)		
Week 4, Change from BL (n=25, 26)	-0.27 (± 13.39)	0.716 (± 13.956)		
Week 8, Change from BL (n=24, 24)	1.006 (± 12.925)	9.838 (± 22.463)		
Week 12, Change from BL (n=24, 26)	-1.649 (± 16.453)	6.278 (± 19.035)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment-Emergent Adverse Events

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. The safety evaluable population was defined as all subjects who received at least one dose of study drug, with subjects grouped according to the actual treatment received.

End point type	Secondary

End point timeframe:

From Baseline to Week 20

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: percentage of subjects				
number (not applicable)	69.7	67.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Anti-Therapeutic Antibodies (ATAs) to Lebrikizumab

End point title	Percentage of Subjects With Anti-Therapeutic Antibodies (ATAs) to Lebrikizumab

End point description:

Presence of ATAs to lebrikizumab was measured at baseline and up to Week 20. Reported is the percentage of subjects with ATAs to lebrikizumab at baseline and post-baseline. The safety evaluable population was defined as all subjects who received at least one dose of study drug, with subjects grouped according to the actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point.

End point type	Secondary

End point timeframe:

From Baseline up to Week 20

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: percentage of subjects				
number (not applicable)				
Baseline (n=31, 31)	0	3.2		
Post-baseline (n=33, 29)	3	6.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Lebrikizumab Concentration at Week 12

End point title	Serum Lebrikizumab Concentration at Week 12[3]

End point description:

To measure serum lebrikizumab concentration blood samples were taken from subjects in the lebrikizumab arm before dosing at Week 12. The safety evaluable population was defined as all subjects who received at least one dose of study drug, with subjects grouped according to the actual treatment received.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0) at Week 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Serum lebrikizumab concentration was only measured in the arm that received lebrikizumab treatment. Therefore, data are only reported for the lebrikizumab arm.

End point values	Lebrikizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: micrograms per millilitre (mcg/mL)				
arithmetic mean (standard deviation)	13.5 (± 6.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CCL-13 Levels

End point title	Change From Baseline in CCL-13 Levels

End point description:

CCL-13 levels were measured at multiple time points from baseline (BL) to Week 20. The safety evaluable population was defined as all subjects who received at least one dose of study drug, with subjects grouped according to the actual treatment received. The number of subjects analysed is indicated by n for each arm at each time point. Results are presented in picograms per millilitre (pg/mL).

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 12, Week 20

End point values	Placebo	Lebrikizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline, Value at Visit (n=33, 31)	209.2 (± 90.3)	1949.5 (± 9459.5)		
Week 1, Change from BL (n=32, 31)	-3 (± 31.9)	-502.7 (± 2656.9)		
Week 12, Change from BL (n=31, 31)	9.9 (± 33.8)	-1014.6 (± 5419.2)		
Week 20, Change from BL (n=32, 27)	4.1 (± 38)	-1017.3 (± 5116)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to Week 20

Adverse event reporting additional description:

The safety evaluable population was defined as all subjects who received at least one dose of study drug, with subjects grouped according to the actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Lebrikizumab

Reporting group description:

Subjects with uncontrolled asthma on inhaled corticosteroids (ICS) therapy and a second controller medication received SC injection of lebrikizumab on Days 1 and 8, and on Weeks 4 and 8.

Reporting group title	Placebo

Reporting group description:

Subjects with uncontrolled asthma on ICS therapy and a second controller medication received subcutaneous (SC) injection of lebrikizumab matching placebo on Days 1 and 8, and on Weeks 4 and 8.

Serious adverse events	Lebrikizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 31 (19.35%)	1 / 33 (3.03%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lebrikizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 31 (38.71%)	17 / 33 (51.52%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 31 (6.45%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	2 / 31 (6.45%)	2 / 33 (6.06%)	
occurrences (all)	5	5	
Pyrexia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 31 (3.23%)	3 / 33 (9.09%)	
occurrences (all)	1	4	
Vomiting			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 31 (9.68%)	7 / 33 (21.21%)	
occurrences (all)	4	9	
Dyspnoea			
subjects affected / exposed	1 / 31 (3.23%)	4 / 33 (12.12%)	
occurrences (all)	1	4	
Cough			
subjects affected / exposed	1 / 31 (3.23%)	3 / 33 (9.09%)	
occurrences (all)	2	3	
Sinus congestion			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 31 (6.45%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	1 / 31 (3.23%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Sinusitis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2014	Required abstinence or highly effective contraception starting on Visit 1 (Day −21). Removed a duplicate exclusion criterion. Updated Medical Monitor contact information. Clarified who within the Sponsor will be unblinded to eosinophil counts.
29 September 2015	Updated the screening period inhaled corticosteroid (ICS)-compliance requirement from 80% to 70%. Updated the time to re-screening after a subject was deemed non-compliant with ICS during screening from 4 to 6 weeks to at least 1 week. Clarified that the criteria for demonstrating uncontrolled asthma is an Asthma Control Questionnaire-5 score of >/= 1.5 and the presence of asthma symptoms. Corrected an error in the previous Protocol for Appendix 1 visit assessment time windows. Updated Internal Monitoring Committee membership and functioning. Updated the total planned enrollment from 120 to 80 subjects. Updated the analysis plan to include an optional unblinded interim analysis of efficacy and safety. Updated Medical Monitor contact information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported