Clinical trial results:
A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Lebrikizumab in Adult Patients with Mild-to-Moderate Asthma

Summary

EudraCT number	2013-004625-81
Trial protocol	CZ BG GB SK
Global end of trial date	22 January 2016

Results information

Result version number	v1 (current)
This version publication date	30 March 2017
First version publication date	30 March 2017

Trial information

Trial identification

Sponsor protocol code	WA29249

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02104674
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 Ltd., Roche Trial Information Hotline, 41 616878333, global.trial_information@roche.com
Scientific contact	F.Hoffmann-La Roche Ltd., Roche Trial Information Hotline, 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	18 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A Phase III, randomized, double-blind, placebo-controlled study to evaluate the efficacy of lebrikizumab compared with placebo in improving lung function in adult participants with mild-to-moderate asthma.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation (ICH) E6 guideline for Good Clinical Practice (GCP) and investigators were trained according to applicable Sponsor standard operating procedures (SOPs). Roche and the investigators strictly adhered to the stated provisions in these guidelines. This was documented by the investigator's signature on the protocol agreeing to carry out all of its terms in accordance with the applicable regulations and law and to follow ICH GCP guidelines for good clinical practice.

Background therapy:

Participants could only receive short-acting beta agonists (SABA) therapy for asthma treatment at study entry (less than [<] 10 puffs daily).

Evidence for comparator: -

Actual start date of recruitment	07 June 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	Poland: 36
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	United States: 138
Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	South Africa: 31
Worldwide total number of subjects	313
EEA total number of subjects	95

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)	293
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of 313 enrolled participants, 3 were randomized but not treated during a 12-week treatment period where participants received blinded lebrikizumab/placebo or an open-label active comparator (Montelukast sodium).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lebrikizumab

Arm description:

Lebrikizumab 125 milligrams (mg) administered as subcutaneous (SC) injection on Day 1, 29, and 57 during the 12-week treatment period.

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

Dosage and administration details:

Lebrikizumab administered as SC injection during the 12-week treatment period.

Arm title	Montelukast

Arm description:

Montelukast 10 mg tablet administered orally once daily during the 12-week treatment period.

Arm type	Active comparator
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	Singulair
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Montelukast administered orally during the 12-week treatment period.

Arm title	Placebo

Arm description:

Placebo matched to Lebrikuzimab as SC injection administered on Day 1, 29, and 57 during the 12-week treatment period.

Arm type	Placebo

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

Dosage and administration details:

Placebo matched to Lebrikuzimab as SC injection administered during the 12-week treatment period.

Number of subjects in period 1	Lebrikizumab	Montelukast	Placebo
Started	105	102	106
Completed	98	91	98
Not completed	7	11	8
Consent withdrawn by subject	5	7	4
Adverse Event	1	1	1
Unspecified	1	-	1
Lost to follow-up	-	2	1
Lack of efficacy	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Lebrikizumab
Reporting group description:	
Lebrikizumab 125 milligrams (mg) administered as subcutaneous (SC) injection on Day 1, 29, and 57 during the 12-week treatment period.	
Reporting group title	Montelukast
Reporting group description:	
Montelukast 10 mg tablet administered orally once daily during the 12-week treatment period.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to Lebrikuzimab as SC injection administered on Day 1, 29, and 57 during the 12-week treatment period.	

Reporting group values	Lebrikizumab	Montelukast	Placebo
Number of subjects	105	102	106
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	98	98	97
From 65-84 years	7	4	9
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	64	61	66
Male	41	41	40

Reporting group values	Total		
Number of subjects	313		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	293		
From 65-84 years	20		
85 years and over	0		

Gender categorical Units: Subjects			
Female	191		
Male	122		

End points

End points reporting groups

Reporting group title	Lebrikizumab
Reporting group description:	
Lebrikizumab 125 milligrams (mg) administered as subcutaneous (SC) injection on Day 1, 29, and 57 during the 12-week treatment period.	
Reporting group title	Montelukast
Reporting group description:	
Montelukast 10 mg tablet administered orally once daily during the 12-week treatment period.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to Lebrikuzimab as SC injection administered on Day 1, 29, and 57 during the 12-week treatment period.	
Subject analysis set title	Lebrikizumab-Modified Intent to Treat (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Lebrikizumab 125 mg administered as SC injection on Day 1, 29 and 57 during the 12-week treatment period.	
Subject analysis set title	Montelukast-mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Montelukast 10 mg tablet administered orally once daily during the 12-week treatment period.	
Subject analysis set title	Placebo-mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Placebo matched to Lebrikuzimab administered as SC injection on Day 1, 29 and 57 during the 12-week treatment period.	
Subject analysis set title	Montelukast-Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Montelukast 10 mg tablet administered orally once daily during the 12 week treatment period. Participants were followed up further for 8 weeks during the safety follow-up period.	
Subject analysis set title	Placebo-Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Placebo matched to Lebrikuzimab administered as SC injection on Day 1, 29 and 57 during the 12-week treatment period. Participants were followed up further for 8 weeks during the safety follow-up period.	
Subject analysis set title	Lebrikizumab-Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Lebrikuzimab administered as SC injection on Day 1, 29 and 57 during the 12-week treatment period. Participants were followed up further for 8 weeks during the safety follow-up period.	

Primary: Change From Baseline in Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) at Week 12

End point title	Change From Baseline in Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) at Week 12
End point description:	
FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Modified intent to treat (mITT) population included all randomized participants who received at least one dose of study drug.	
End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Lebrikizumab-Modified Intent to Treat (mITT)	Montelukast-mITT	Placebo-mITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	104	101	105	
Units: Liters				
arithmetic mean (standard error)	0.15 (± 0.033)	0.05 (± 0.032)	0.07 (± 0.03)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The model used absolute change from baseline in pre-bronchodilator in FEV1 as response and the following covariates: Baseline pre-bronchodilator in FEV1, Region, Treatment, Week, and a 4-level categorical variable using Periostin (PERI) and Eosonophil (EOS) levels as (PERI High/EOS High, PERI High/EOS Low, PERI Low/EOS High, and PERI Low/EOS Low)

Comparison groups	Lebrikizumab-Modified Intent to Treat (mITT) v Placebo-mITT
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06 [1]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.044

Notes:

[1] - Mixed effects model for repeated measures (MMRM) was used to model the absolute change from baseline.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The model used absolute change from baseline in pre-bronchodilator in FEV1 as response and the following covariates: Baseline pre-bronchodilator in FEV1, Region, Treatment, Week, and a 4-level categorical variable using PERI and EOS levels as (PERI High/EOS High, PERI High/EOS Low, PERI Low/EOS High, and PERI Low/EOS Low).

Comparison groups	Placebo-mITT v Montelukast-mITT

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6954 [2]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.043

Notes:

[2] - MMRM was used to model the absolute change from baseline.

Secondary: Change From Baseline in Asthma Reliever Medication use at Week 12

End point title	Change From Baseline in Asthma Reliever Medication use at Week 12

End point description:

Participants could only receive SABA therapy for asthma treatment as asthma reliever medication (<10 puffs daily). SABA use was recorded in the eDiary. mITT population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Lebrikizumab-Modified Intent to Treat (mITT)	Placebo-mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102	101		
Units: Puffs/day				
arithmetic mean (standard error)	-0.51 (± 0.108)	-0.55 (± 0.108)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

MMRM was used to model the absolute change from baseline. The model used absolute change from baseline asthma reliever medication (ARM) as response and the following covariates: Baseline ARM, Region, Baseline % of predicted FEV1, Treatment, Week, and a 4-level categorical variable using PERI and EOS levels as (PERI High/EOS High, PERI High/EOS Low, PERI Low/EOS High, and PERI Low/EOS Low)

Comparison groups	Lebrikizumab-Modified Intent to Treat (mITT) v Placebo-mITT

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.32
Variability estimate	Standard error of the mean
Dispersion value	0.144

Secondary: Change From Baseline in the Standardized Asthma Quality of Life Questionnaire (AQLQ[S]) Overall Score at Week 12

End point title	Change From Baseline in the Standardized Asthma Quality of Life Questionnaire (AQLQ[S]) Overall Score at Week 12

End point description:

The AQLQ[S]) was used to assess the participant's asthma-specific health-related quality of life. The 32-item questionnaire contains four domains: activity limitations, symptoms, emotional function, and environmental stimuli. The AQLQ[S]) has a recall specification of 2 weeks. Participants were asked to think about how they had been during the previous 2 weeks and to respond to each of the 32 questions on a 7-point scale (7 = not impaired at all; 1 = severely impaired). An increase in the AQLQ score indicates a better quality of life. The overall AQLQ score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains. mITT population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Lebrikizumab-Modified Intent to Treat (mITT)	Placebo-mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102	102		
Units: Units on scale				
arithmetic mean (standard error)	0.62 (± 0.088)	0.68 (± 0.086)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

MMRM was used to model the absolute change from baseline. The model used absolute change from baseline AQLQ[S]) as response and the following covariates: Baseline AQLQ[S]), Region, Baseline % of predicted FEV1, Treatment, Week, and a 4-level categorical variable using PERI and EOS levels as (PERI High/EOS High, PERI High/EOS Low, PERI Low/EOS High, and PERI Low/EOS Low)

Comparison groups	Lebrikizumab-Modified Intent to Treat (mITT) v Placebo-mITT

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.115

Secondary: Change From Baseline in Fractional Exhaled Nitric Oxide (FeNO) Levels at Week 12

End point title	Change From Baseline in Fractional Exhaled Nitric Oxide (FeNO) Levels at Week 12

End point description:

Safety population included all participants who received at least one dose of study drug and who were grouped according to the treatment they received. Here, number (n)= number of participants evaluable for the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Montelukast-Safety	Placebo-Safety	Lebrikizumab-Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	103	103	104	
Units: parts per billion (ppb)				
arithmetic mean (standard deviation)				
Baseline (n= 103, 103, 104)	65.89 (± 67.81)	50.66 (± 44.49)	52.85 (± 44.98)	
Change at Week 12 (n= 92, 86, 84)	-13.21 (± 33.28)	-10.86 (± 28.41)	-31.85 (± 36.13)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Blood Eosinophil Count at Week 12

End point title	Change From Baseline in Blood Eosinophil Count at Week 12

End point description:

Safety population. Here, number (n)= number of participants evaluable for the specified timepoints.

End point type	Secondary

End point timeframe:
Baseline, Week 12

End point values	Montelukast-Safety	Placebo-Safety	Lebrikizumab-Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	103	103	104	
Units: cells/microliter (cells/mcL)				
arithmetic mean (standard deviation)				
Baseline (n= 103, 103, 104)	262.04 (± 169.84)	233.3 (± 152.61)	230.1 (± 149.9)	
Change at Week 12 (n= 90, 91, 84)	-32.67 (± 165.94)	33.52 (± 173.87)	55.12 (± 215.83)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Periostin at Week 12

End point title	Change From Baseline in Serum Periostin at Week 12

End point description:
Safety population. Here, number (n)= number of participants evaluable for the specified timepoints.

End point type	Secondary

End point timeframe:
Baseline, Week 12

End point values	Montelukast-Safety	Placebo-Safety	Lebrikizumab-Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	103	103	104	
Units: Nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n= 103, 103, 104)	54.6 (± 16.18)	55.37 (± 19.15)	53.85 (± 16.71)	
Change at Week 12 (n= 90, 91, 88)	-1.3 (± 7.72)	0.33 (± 8.13)	-3.92 (± 9.68)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Immunoglobulin E (IgE) Levels at Week 12

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

	at Week 12

End point description:

Safety population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this outcome measure and number (n)= number of participants evaluable for the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Montelukast-Safety	Placebo-Safety	Lebrikizumab-Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	103	102	103	
Units: Microgram (Mcg)/mL				
arithmetic mean (standard deviation)				
Baseline (n= 103, 102, 103)	565.42 (± 1051.63)	868.28 (± 1422.97)	994.46 (± 2032.99)	
Change at Week 12 (n= 89, 89, 86)	26.1 (± 408.43)	-80.28 (± 582.12)	-200.71 (± 643.46)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in C-C Motif Chemokine Ligand 13 (CCL-13) Levels at Week 12

End point title	Change From Baseline in C-C Motif Chemokine Ligand 13 (CCL-13) Levels at Week 12

End point description:

Safety population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this outcome measure and number (n)= number of participants evaluable for the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Montelukast-Safety	Placebo-Safety	Lebrikizumab-Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	103	102	104	
Units: Picogram/mL (pg/mL)				
arithmetic mean (standard deviation)				
Baseline (n= 103, 102, 104)	201.34 (± 81.13)	206.19 (± 91.04)	192.79 (± 87.77)	
Change at Week 12 (n= 90, 90, 88)	0.19 (± 51.31)	4.36 (± 72)	-35.79 (± 57.72)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CCL-17 Levels at Week 12

End point title	Change From Baseline in CCL-17 Levels at Week 12

End point description:

Safety population included all participants who received at least one dose of study drug and who were grouped according to the treatment they received. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this outcome measure and number (n)= number of participants evaluable for the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Montelukast-Safety	Placebo-Safety	Lebrikizumab-Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	103	102	104	
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline (n= 103, 102, 104)	326.09 (± 189.33)	365.48 (± 206.23)	506.49 (± 1476.14)	
Change at Week 12 (n= 90, 90, 87)	5.79 (± 134.93)	23.93 (± 169.01)	-133.93 (± 764.14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Lebrikizumab Concentration After the First Dose (Cmax)

End point title	Maximum Observed Plasma Lebrikizumab Concentration After the First Dose (Cmax)

End point description:

Pharmacokinetic (PK)-evaluable population included participants who had received at least one subcutaneous dose of lebrikizumab and had at least one lebrikizumab PK sample. Here, N (number of participants analyzed) indicates the total number of participants who provided evaluable data for this outcome measure.

End point type	Secondary

End point timeframe:

Postdose on Day 8

End point values	Lebrikizumab-Modified Intent to Treat (mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	103			
Units: Mcg/mL				
arithmetic mean (standard deviation)	14.9 (± 5.91)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Lebrikizumab Concentration After the First Dose (Tmax)

End point title	Time to Reach Maximum Lebrikizumab Concentration After the First Dose (Tmax)

End point description:

PK-evaluable population. Here, N (number of participants analyzed) indicates the total number of participants who provided evaluable data for this outcome measure.

End point type	Secondary

End point timeframe:

Postdose on Day 8

End point values	Lebrikizumab-Modified Intent to Treat (mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	103			
Units: Days				
arithmetic mean (standard deviation)	7.04 (± 1.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Predose Serum Lebrikizumab Concentration (Cmin) at Week 4

End point title	Predose Serum Lebrikizumab Concentration (Cmin) at Week 4

End point description:

PK-evaluable population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this outcome measure.

End point type	Secondary

End point timeframe:

Predose (at Hour 0) on Week 4

End point values	Lebrikizumab-Modified Intent to Treat (mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	101			
Units: Mcg/mL				
arithmetic mean (standard deviation)	9.58 (± 4.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Predose Serum Lebrikizumab Concentration (Cmin) at Week 12

End point title	Predose Serum Lebrikizumab Concentration (Cmin) at Week 12

End point description:

PK-evaluable population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this outcome measure.

End point type	Secondary

End point timeframe:

Predose (at Hour 0) on Week 12

End point values	Lebrikizumab-Modified Intent to Treat (mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: Mcg/mL				
arithmetic mean (standard deviation)	18.1 (± 6.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Elimination Half-Life (t1/2) of Lebrikizumab

End point title	Plasma Elimination Half-Life (t1/2) of Lebrikizumab

End point description:

PK-evaluable population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this outcome measure.

End point type	Secondary

End point timeframe:

Predose (at Hour 0) on Day 57, Days 85, 113, 141

End point values	Lebrikizumab-Modified Intent to Treat (mITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	90			
Units: Days				
arithmetic mean (standard deviation)	23.7 (± 7.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change Fom Baseline in Morning Pre-bronchodilator Peak Expiratory Flow (PEF) at Week 12: Placebo Versus Montelukast

End point title	Change Fom Baseline in Morning Pre-bronchodilator Peak Expiratory Flow (PEF) at Week 12: Placebo Versus Montelukast

End point description:

PEF is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. mITT population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Montelukast-mITT	Placebo-mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	101		
Units: Liters/minute				
arithmetic mean (standard error)	5.92 (± 5.973)	4.69 (± 5.872)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

MMRM was used to model the absolute change from baseline. The model used absolute change from baseline PEF as response and the following covariates: Baseline PEF, Region, Baseline % of predicted FEV1, Treatment, Week, and a 4-level categorical variable using PERI and EOS levels as (PERI High/EOS High, PERI High/EOS Low, PERI Low/EOS High,and PERI Low/EOS Low).

Comparison groups	Montelukast-mITT v Placebo-mITT

Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.57
upper limit	17.04
Variability estimate	Standard error of the mean
Dispersion value	8.012

Secondary: Change From Baseline in Morning Pre-bronchodilator PEF at Week 12: Placebo Versus Lebrikizumab

End point title	Change From Baseline in Morning Pre-bronchodilator PEF at Week 12: Placebo Versus Lebrikizumab

End point description:

PEF is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. mITT population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Lebrikizumab-Modified Intent to Treat (mITT)	Placebo-mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102	101		
Units: Liters/minute				
arithmetic mean (standard error)	1.63 (± 5.551)	5.25 (± 5.565)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

MMRM was used to model the absolute change from baseline. The model used absolute change from baseline PEF as response and the following covariates: Baseline PEF, Region, Baseline % of predicted FEV1, Treatment, Week, and a 4-level categorical variable using PERI and EOS levels as (PERI High/EOS High, PERI High/EOS Low, PERI Low/EOS High, and PERI Low/EOS Low).

Comparison groups	Lebrikizumab-Modified Intent to Treat (mITT) v Placebo-mITT

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.46
upper limit	11.23
Variability estimate	Standard error of the mean
Dispersion value	7.523

Secondary: Number of Participants With Treatment Failure

End point title	Number of Participants With Treatment Failure

End point description:

Treatment failure was defined as a worsening of asthma symptoms (per investigator's assessment of participant report) in association with either relative decline in pre-bronchodilator FEV1 >=20%; or >=20% decline in morning pre-bronchodilator PEF on 2 consecutive days compared with baseline; or use of >=10 puffs of albuterol metered dose inhaler (MDI); or >=2 additional administrations (or any new use) of nebulized short-acting β-agonist (SABA) therapy within any calendar day; or need for any inhaled, oral, or parenteral corticosteroid or for a controller medication. The hazard ratio from the Cox Proportional Hazards model compared the risk of treatment failure for the lebrikizumab-treated and placebo participants. mITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Lebrikizumab-Modified Intent to Treat (mITT)	Placebo-mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	104	105		
Units: Participants with treatment failure	9	11		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Multivariate Cox proportional hazards regression was used to estimate Hazard Ratios. Confidence intervals (CI) calculated according to Wald. Covariates: treatment, region, baseline periostin and eosinophil category, and baseline percentage FEV1 category.

Comparison groups	Placebo-mITT v Lebrikizumab-Modified Intent to Treat (mITT)

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	2.42

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure

End point description:

Treatment failure was defined as a worsening of asthma symptoms (per investigator's assessment of participant report) in association with either relative decline in pre-bronchodilator FEV1 >=20%; or >=20% decline in morning pre-bronchodilator PEF on 2 consecutive days compared with baseline; or use of >=10 puffs of albuterol metered dose inhaler (MDI); or >=2 additional administrations (or any new use) of nebulized short-acting β-agonist (SABA) therapy within any calendar day; or need for any inhaled, oral, or parenteral corticosteroid or for a controller medication. Time to treatment failure was estimated using Kaplan-Meier method. mITT population. Median and corresponding 95% CI could not be estimated due to higher number (>50%) of censored participants who have been reported as 99999.

End point type	Secondary

End point timeframe:

Basleine up to Week 12

End point values	Lebrikizumab-Modified Intent to Treat (mITT)	Placebo-mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	104	105		
Units: Days				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 20	
Adverse event reporting additional description:	
Safety population.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Lebrikizumab-Safety
Reporting group description:	
Lebrikizumab 125 mg SC administered as injection on Day 1, 29 and 57 during the 12-week treatment period. Participants were followed up further for 8 weeks during the safety follow-up period.	
Reporting group title	Montelukast-Safety
Reporting group description:	
Montelukast 10 mg tablet administered orally once daily during the 12-week treatment period. Participants were followed up further for 8 weeks during the safety follow-up period.	
Reporting group title	Placebo-Safety
Reporting group description:	
Placebo matched to lebrikizumab 125 mg SC administered as injection on Day 1, 29 and 57 during the 12-week treatment period. Participants were followed up further for 8 weeks during the safety follow-up period.	

Serious adverse events	Lebrikizumab-Safety	Montelukast-Safety	Placebo-Safety
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 104 (1.92%)	0 / 103 (0.00%)	1 / 103 (0.97%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Lebrikizumab-Safety	Montelukast-Safety	Placebo-Safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 104 (24.04%)	33 / 103 (32.04%)	24 / 103 (23.30%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 104 (2.88%)	5 / 103 (4.85%)	6 / 103 (5.83%)
occurrences (all)	3	6	6
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	6 / 104 (5.77%)	12 / 103 (11.65%)	12 / 103 (11.65%)
occurrences (all)	6	12	15
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 104 (8.65%)	11 / 103 (10.68%)	5 / 103 (4.85%)
occurrences (all)	10	13	5
Upper respiratory tract infection			
subjects affected / exposed	9 / 104 (8.65%)	8 / 103 (7.77%)	5 / 103 (4.85%)
occurrences (all)	9	8	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2015	- Description of completed and ongoing clinical trials with lebrikizumab was updated. - Biomarker subgroups for analysis to include blood eosinophil count was updated. - Secondary efficacy endpoints, pharmacokinetic and pharmacodynamic endpoints, and exploratory efficacy endpoints were updated. - Statistical analyses details were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported