EU Clinical Trials Register

Clinical trial results:
A Phase II, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Lebrikizumab in Patients with Chronic Obstructive Pulmonary Disease and a History of Exacerbations

Summary

EudraCT number	2015-001122-42
Trial protocol	HU DK PL
Global end of trial date	25 November 2016

Results information

Result version number	v1 (current)
This version publication date	19 November 2017
First version publication date	19 November 2017

Trial information

Trial identification

Sponsor protocol code	WB29804

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02546700
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	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, 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	25 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of lebrikizumab compared with placebo in improving lung function, as measured by the absolute change in pre-bronchodilator forced expiratory volume in one second (FEV1) in participants with chronic obstructive pulmonary disease (COPD) and a history of exacerbations in the biomarker-high group (elevated serum periostin or blood eosinophils) and biomarker-low group.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol. The sponsor and investigators strictly adhered to the stated provisions in the 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 International Council for Harmonisation (ICH) GCP guidelines. Approval from the Institutional Review Board (IRB)/Ethics Committee (EC) was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. Sponsor also obtained approval from the relevant Competent Authority prior to starting the study.

Background therapy:

Participants continued on stable doses of their standard-of-care therapy for the duration of the 24-week placebo-controlled period that must have included inhaled corticosteroids (ICS) and at least one long-acting bronchodilator inhaler medication (long-acting beta agonist [LABA] and/or long-acting muscarinic antagonist [LAMA]).

Evidence for comparator: -

Actual start date of recruitment	17 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 63
Country: Number of subjects enrolled	Poland: 45
Country: Number of subjects enrolled	Bulgaria: 41
Country: Number of subjects enrolled	Russian Federation: 47
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Denmark: 17
Worldwide total number of subjects	309
EEA total number of subjects	166

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)	144
From 65 to 84 years	165
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 391 participants were screened of which 309 participants were randomized.

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo matched to lebrikizumab was administered subcutaneously once in every 4 weeks for a total of 6 doses.

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:

Placebo was administered as per the schedule mentioned in arm description.

Arm title	Lebrikizumab

Arm description:

Lebrikizumab 125 milligrams (mg) was administered subcutaneously once in every 4 weeks for a total of 6 doses.

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

Dosage and administration details:

Lebrikizumab was administered as per the schedule mentioned in arm description.

Number of subjects in period 1	Placebo	Lebrikizumab
Started	154	155
Completed	144	146
Not completed	10	9
Consent withdrawn by subject	8	2
Adverse Event	-	2
Death	1	1
Lost to follow-up	1	-
Lack of efficacy	-	4

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	

Placebo matched to lebrikizumab was administered subcutaneously once in every 4 weeks for a total of 6 doses.

Reporting group title	Lebrikizumab
Reporting group description:	

Lebrikizumab 125 milligrams (mg) was administered subcutaneously once in every 4 weeks for a total of 6 doses.

Reporting group values	Placebo	Lebrikizumab	Total
Number of subjects	154	155	309
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	64.6	64.5	
standard deviation	± 7.1	± 7.1	-
Gender Categorical			
Units: Subjects			
Female	58	58	116
Male	96	97	193

Subject analysis sets

Subject analysis set title	Placebo: Biomarker-High
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	

Placebo matched to lebrikizumab was administered subcutaneously once in every 4 weeks for a total of 6 doses to the participants considered as biomarker-high. Biomarker-high participants were defined as the participants with baseline (Day -14) periostin greater than or equal to (>=) 50 nanograms per milliliter (ng/mL) or blood eosinophils >=300 cells per microliter (cells/mcL).

Subject analysis set title	Lebrikizumab: Biomarker-High
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	

Lebrikizumab 125 mg was administered subcutaneously once in every 4 weeks for a total of 6 doses to the participants considered as biomarker-high. Biomarker-high participants were defined as the participants with baseline (Day -14) periostin >=50 ng/mL or blood eosinophils >=300 cells/mcL.

Subject analysis set title	Placebo: Biomarker-Low
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	

Placebo matched to lebrikizumab was administered subcutaneously once in every 4 weeks for a total of 6 doses to the participants considered as biomarker-low. Biomarker-low participants were defined as the participants with baseline (Day -14) periostin less than (<) 50 ng/mL and blood eosinophils <300 cells/mcL.

Subject analysis set title	Lebrikizumab: Biomarker-Low
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	

Lebrikizumab 125 mg was administered subcutaneously once in every 4 weeks for a total of 6 doses to

the participants considered as biomarker-low. Biomarker-low participants were defined as the participants with baseline (Day -14) periostin <50 ng/mL and blood eosinophils <300 cells/mcL.

Reporting group values	Placebo: Biomarker-High	Lebrikizumab: Biomarker-High	Placebo: Biomarker-Low
Number of subjects	80	86	74
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	65.8	65.2	63.2
standard deviation	± 7.4	± 6.9	± 6.6
Gender Categorical Units: Subjects			
Female	33	25	25
Male	47	61	49

Reporting group values	Lebrikizumab: Biomarker-Low		
Number of subjects	69		
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	63.6		
standard deviation	± 7.4		
Gender Categorical Units: Subjects			
Female	33		
Male	36		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo matched to lebrikizumab was administered subcutaneously once in every 4 weeks for a total of 6 doses.	
Reporting group title	Lebrikizumab
Reporting group description:	
Lebrikizumab 125 milligrams (mg) was administered subcutaneously once in every 4 weeks for a total of 6 doses.	
Subject analysis set title	Placebo: Biomarker-High
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Placebo matched to lebrikizumab was administered subcutaneously once in every 4 weeks for a total of 6 doses to the participants considered as biomarker-high. Biomarker-high participants were defined as the participants with baseline (Day -14) periostin greater than or equal to (>=) 50 nanograms per milliliter (ng/mL) or blood eosinophils >=300 cells per microliter (cells/mcL).	
Subject analysis set title	Lebrikizumab: Biomarker-High
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Lebrikizumab 125 mg was administered subcutaneously once in every 4 weeks for a total of 6 doses to the participants considered as biomarker-high. Biomarker-high participants were defined as the participants with baseline (Day -14) periostin >=50 ng/mL or blood eosinophils >=300 cells/mcL.	
Subject analysis set title	Placebo: Biomarker-Low
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Placebo matched to lebrikizumab was administered subcutaneously once in every 4 weeks for a total of 6 doses to the participants considered as biomarker-low. Biomarker-low participants were defined as the participants with baseline (Day -14) periostin less than (<) 50 ng/mL and blood eosinophils <300 cells/mcL.	
Subject analysis set title	Lebrikizumab: Biomarker-Low
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Lebrikizumab 125 mg was administered subcutaneously once in every 4 weeks for a total of 6 doses to the participants considered as biomarker-low. Biomarker-low participants were defined as the participants with baseline (Day -14) periostin <50 ng/mL and blood eosinophils <300 cells/mcL.	

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

End point title	Change from Baseline in Pre-bronchodilator Forced Expiratory Volume in One Second (FEV1) at Week 12
End point description:	
Adjusted mean change from baseline in pre-bronchodilator FEV1 (assessed using spirometry) at Week 12 was calculated. Modified intent-to-treat (mITT) population included participants who were randomized and received at least one dose of any study drug, grouped according to the treatment assigned at randomization within biomarker-high and biomarker-low subgroups.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo: Biomarker-High	Lebrikizumab: Biomarker-High	Placebo: Biomarker-Low	Lebrikizumab: Biomarker-Low
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	86	74	69
Units: milliliters (mL)				
least squares mean (confidence interval 95%)	46.4 (1.5 to 91.2)	51.7 (8.2 to 95.1)	-20.1 (-68.0 to 27.8)	-8.1 (-56.8 to 40.5)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.	
Comparison groups	Placebo: Biomarker-High v Lebrikizumab: Biomarker-High
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.867
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Difference
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57
upper limit	67.6
Variability estimate	Standard error of the mean
Dispersion value	31.7

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.	
Comparison groups	Placebo: Biomarker-Low v Lebrikizumab: Biomarker-Low
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7308
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Difference
Point estimate	12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.4
upper limit	80.3

Variability estimate	Standard error of the mean
Dispersion value	34.7

Secondary: Rate of Moderate or Severe COPD Exacerbation

End point title	Rate of Moderate or Severe COPD Exacerbation

End point description:

A moderate COPD exacerbation was defined as new or increased COPD symptoms (for example, dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to treatment with systemic corticosteroids and/or antibiotics. A severe COPD exacerbation was defined as new or increased COPD symptoms (for example, dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to hospitalization. Adjusted exacerbation rate per year was calculated. mITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Placebo: Biomarker-High	Lebrikizumab: Biomarker-High	Placebo: Biomarker-Low	Lebrikizumab: Biomarker-Low
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	86	74	69
Units: exacerbations/year				
number (not applicable)	0.78	1.07	0.93	1.14

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Rate ratio was calculated as rate for lebrikizumab group/rate for placebo group.

Comparison groups	Placebo: Biomarker-High v Lebrikizumab: Biomarker-High
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Rate Ratio
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.36

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Rate ratio was calculated as rate for lebrikizumab group/rate for placebo group.

Comparison groups	Placebo: Biomarker-Low v Lebrikizumab: Biomarker-Low
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Rate Ratio
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.15

Secondary: Change from Baseline in Post-bronchodilator FEV1 at Week 24

End point title	Change from Baseline in Post-bronchodilator FEV1 at Week 24

End point description:

Adjusted mean change from baseline in post-bronchodilator FEV1 at Week 24 was calculated. mITT population. 'Number of Subjects Analysed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo: Biomarker-High	Lebrikizumab: Biomarker-High	Placebo: Biomarker-Low	Lebrikizumab: Biomarker-Low
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	76	83	71	65
Units: mL				
least squares mean (confidence interval 95%)	20.6 (-24.5 to 65.6)	31.2 (-12.0 to 74.5)	-8.3 (-56.5 to 39.9)	-10.7 (-60.2 to 38.8)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.

Comparison groups	Placebo: Biomarker-High v Lebrikizumab: Biomarker-High

Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Mean Difference
Point estimate	10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.6
upper limit	72.9

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.

Comparison groups	Placebo: Biomarker-Low v Lebrikizumab: Biomarker-Low
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Mean Difference
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-71.5
upper limit	66.6

Secondary: Change from Baseline in Pre-bronchodilator FEV1 at Week 24

End point title	Change from Baseline in Pre-bronchodilator FEV1 at Week 24

End point description:

Adjusted mean change from baseline in pre-bronchodilator FEV1 at Week 24 was calculated. mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo: Biomarker-High	Lebrikizumab: Biomarker-High	Placebo: Biomarker-Low	Lebrikizumab: Biomarker-Low
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	86	74	69
Units: mL				
least squares mean (confidence interval 95%)	17.5 (-26.4 to 61.5)	46.8 (4.3 to 89.3)	-31.4 (-78.3 to 15.5)	1.9 (-46.1 to 49.9)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.	
Comparison groups	Placebo: Biomarker-High v Lebrikizumab: Biomarker-High
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Mean Difference
Point estimate	29.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.8
upper limit	90.3

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.	
Comparison groups	Placebo: Biomarker-Low v Lebrikizumab: Biomarker-Low
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Mean Difference
Point estimate	33.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.8
upper limit	100.4

Secondary: Time to First COPD Exacerbation

End point title	Time to First COPD Exacerbation

End point description:

COPD exacerbation was defined as new or increased COPD symptoms (for example, dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days. Time to first COPD exacerbation was estimated using Kaplan-Meier analysis. mITT population. '99999' indicates that data could not be estimated due to higher number of censored participants.

End point type	Secondary
End point timeframe:	
Baseline up to Week 24	

End point values	Placebo: Biomarker-High	Lebrikizumab: Biomarker-High	Placebo: Biomarker-Low	Lebrikizumab: Biomarker-Low
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	86	74	69
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)	25.9 (24.9 to 99999)	99999 (25.0 to 99999)	24.9 (24.0 to 99999)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo: Biomarker-High v Lebrikizumab: Biomarker-High
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5233
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	2.1

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo: Biomarker-Low v Lebrikizumab: Biomarker-Low
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3085
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	2.28

Secondary: Change from Baseline in Health-Related Quality of Life as Assessed by the Overall Score of the Saint George's Respiratory Questionnaire for COPD (SGRQ-C) at Week 24

End point title	Change from Baseline in Health-Related Quality of Life as Assessed by the Overall Score of the Saint George's Respiratory Questionnaire for COPD (SGRQ-C) at Week 24

End point description:

SGRQ-C was assessed by asking participants to recall their COPD-related experiences and to respond to 40 questions included within three domains: symptoms (7 items), activity (13 items), and impacts (20 items). Overall SGRQ-C score ranged from 0 to 100, where lower score indicated better health-related quality of life. Change from baseline in overall SGRQ-C score at Week 24 was reported. mITT population. 'Number of Subjects Analysed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo: Biomarker-High	Lebrikizumab: Biomarker-High	Placebo: Biomarker-Low	Lebrikizumab: Biomarker-Low
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	76	83	70	64
Units: units on a scale				
least squares mean (confidence interval 95%)	-5.4 (-8.3 to -2.4)	-4.6 (-7.5 to -1.7)	-8.8 (-11.9 to -5.7)	-2.4 (-5.6 to 0.9)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.

Comparison groups	Placebo: Biomarker-High v Lebrikizumab: Biomarker-High
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	4.8

	Statistical Analysis 2

Statistical analysis title	
Statistical analysis description:	
Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.	
Comparison groups	Placebo: Biomarker-Low v Lebrikizumab: Biomarker-Low
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Mean Difference
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	10.9

Secondary: Change from Baseline in COPD Symptoms as Measured by the Overall Score of the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) at Week 24

End point title	Change from Baseline in COPD Symptoms as Measured by the Overall Score of the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) at Week 24
End point description:	
EXACT comprised of 14-item questionnaire containing four domains: breathlessness (5 items), cough and sputum (3 items), chest symptoms (3 items), and additional attributes (3 items). Overall EXACT score was the average of domain scores. It ranged from 0 to 100, where higher score indicated a more severe condition. Change from baseline in overall EXACT score at Week 24 was reported. mITT population. 'Number of Subjects Analysed' = participants evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo: Biomarker-High	Lebrikizumab: Biomarker-High	Placebo: Biomarker-Low	Lebrikizumab: Biomarker-Low
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64	60	51	48
Units: units on a scale				
least squares mean (confidence interval 95%)	-2.4 (-4.4 to -0.4)	-2.4 (-4.5 to -0.3)	-1.9 (-4.2 to 0.4)	-1.4 (-3.7 to 1.0)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.	
Comparison groups	Placebo: Biomarker-High v Lebrikizumab: Biomarker-High

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Mean Difference
Point estimate	0
Confidence interval	

	level	95 %
	sides	2-sided
	lower limit	-2.9
	upper limit	2.9

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.

Comparison groups	Placebo: Biomarker-Low v Lebrikizumab: Biomarker-Low
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Mean Difference
Point estimate	0.5
Confidence interval	

	level	95 %
	sides	2-sided
	lower limit	-2.8
	upper limit	3.8

Secondary: Change from Baseline in Cough and Sputum as Measured by the Cough and Sputum Domain Score of the EXACT at Week 24

End point title	Change from Baseline in Cough and Sputum as Measured by the Cough and Sputum Domain Score of the EXACT at Week 24

End point description:

EXACT comprised of 14-item questionnaire containing four domains: breathlessness (5 items), cough and sputum (3 items), chest symptoms (3 items), and additional attributes (3 items). Cough and Sputum domain score ranged from 0 to 100, where higher score indicated a more severe condition. Change from baseline in cough and sputum domain EXACT score at Week 24 was reported. mITT population. 'Number of Subjects Analysed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo: Biomarker-High	Lebrikizumab: Biomarker-High	Placebo: Biomarker-Low	Lebrikizumab: Biomarker-Low
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64	60	51	48
Units: units on a scale				
least squares mean (confidence interval 95%)	-4.0 (-6.9 to -1.2)	-5.2 (-8.2 to -2.2)	-5.6 (-8.9 to -2.3)	-2.2 (-5.7 to 1.2)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.	
Comparison groups	Placebo: Biomarker-High v Lebrikizumab: Biomarker-High
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	3

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Adjusted mean difference was calculated as difference between adjusted mean values of lebrikizumab group minus placebo group.	
Comparison groups	Placebo: Biomarker-Low v Lebrikizumab: Biomarker-Low
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted Mean Difference
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	8.2

Secondary: Change from Baseline in Dyspnea as Assessed by the Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) at Week 24

End point title	Change from Baseline in Dyspnea as Assessed by the Baseline

	Dyspnea Index/Transition Dyspnea Index (BDI/TDI) at Week 24

End point description:

The BDI scores ranged from 0 (very severe impairment) to 4 (no impairment) for each of 3 domains (functional impairment, magnitude of task, and magnitude of effort) and were summed to determine the BDI total score (0 to 12). The TDI scores ranged from -3 (major deterioration) to +3 (major improvement) for each of the 3 domains (functional impairment, magnitude of task, and magnitude of effort). The sum of all domains yielded the TDI total score (-9 to +9). Change from baseline in BDI/TDI at Week 24 was reported. mITT population. 'Number of Subjects Analysed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo: Biomarker-High	Lebrikizumab: Biomarker-High	Placebo: Biomarker-Low	Lebrikizumab: Biomarker-Low
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	72	76	66	62
Units: ratio				
arithmetic mean (standard deviation)	1.0 (± 2.9)	1.4 (± 2.9)	2.3 (± 2.8)	1.6 (± 3.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-Therapeutic Antibody (ATA) to Lebrikizumab

End point title	Percentage of Participants with Anti-Therapeutic Antibody (ATA) to Lebrikizumab[1]

End point description:

This outcome measure was planned to be analyzed only in overall lebrikizumab arm. Safety evaluable population included participants who received at least one dose of study treatment, grouped according to the actual treatment received. 'Number of Subjects Analysed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 36

Notes:

[1] - 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: This endpoint was planned to be evaluated for lebrikizumab group only.

End point values	Lebrikizumab			
Subject group type	Reporting group			
Number of subjects analysed	154			
Units: percentage of participants				
number (not applicable)	13.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Trough Concentration (Cmin) of Lebrikizumab

End point title	Minimum Observed Serum Trough Concentration (Cmin) of Lebrikizumab[2]

End point description:

This outcome measure was planned to be analyzed only in overall lebrikizumab arm. Pharmacokinetic (PK) population included participants who received at least one dose of lebrikizumab, and had available PK data. 'n' = participants evaluable for this endpoint at given timepoints.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0) at Weeks 4 and 12, at Week 24

Notes:

[2] - 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: This endpoint was planned to be evaluated for lebrikizumab group only.

End point values	Lebrikizumab			
Subject group type	Reporting group			
Number of subjects analysed	155			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Week 4 (n=152)	9.09 (± 3.64)			
Week 12 (n=147)	14.7 (± 6.68)			
Week 24 (n=143)	15.2 (± 8.10)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Elimination Half-Life (t1/2) of Lebrikizumab[3]

End point description:

Elimination half-life was defined as the time measured for the serum concentration to decrease by one half. This outcome measure was planned to be analyzed only in overall lebrikizumab arm. PK population. 'Number of Subjects Analysed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0) on Day 1 (Baseline) and Weeks 1, 4, 12, 24, 28, and 36

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: This endpoint was planned to be evaluated for lebrikizumab group only.

End point values	Lebrikizumab			
Subject group type	Reporting group			
Number of subjects analysed	136			
Units: days				
arithmetic mean (standard deviation)	25.1 (± 7.26)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 36

Adverse event reporting additional description:

Safety evaluable population

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo matched to lebrikizumab was administered subcutaneously once in every 4 weeks for a total of 6 doses.

Reporting group title	Lebrikizumab

Reporting group description:

Lebrikizumab 125 milligrams (mg) was administered subcutaneously once in every 4 weeks for a total of 6 doses.

Serious adverse events	Placebo	Lebrikizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 154 (14.94%)	21 / 155 (13.55%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Road traffic accident			

subjects affected / exposed	1 / 154 (0.65%)	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 1	0 / 0		
Chest injury				
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intentional overdose				
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Rib fracture				
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Congenital, familial and genetic disorders				
Exomphalos				
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac arrest				
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Coronary artery occlusion				
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Myocardial infarction			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Metabolic encephalopathy			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	
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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	10 / 154 (6.49%)	15 / 155 (9.68%)	
occurrences causally related to treatment / all	0 / 12	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	2 / 154 (1.30%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary granuloma			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary necrosis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

	3 / 154 (1.95%)	3 / 155 (1.94%)	
subjects affected / exposed	3 / 154 (1.95%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 154 (0.65%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 154 (0.00%)	1 / 155 (0.65%)	
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	Placebo	Lebrikizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 154 (42.86%)	57 / 155 (36.77%)	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	55 / 154 (35.71%)	51 / 155 (32.90%)	
occurrences (all)	74	76	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 154 (6.49%)	7 / 155 (4.52%)	
occurrences (all)	10	7	
Bronchitis			

subjects affected / exposed	7 / 154 (4.55%)	9 / 155 (5.81%)	
occurrences (all)	7	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2015	The primary and secondary efficacy objectives were updated to reflect that these objectives will be evaluated within the biomarker-high and biomarker-low subgroups. The primary efficacy endpoint "absolute change in pre-bronchodilator FEV1 (liters) from baseline to Week 24" was changed to "absolute change in pre-bronchodilator FEV1 (liters) from baseline to Week 12". Inclusion and exclusion criteria were modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported