Clinical trial results:
A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Brodalumab in Subjects With Inadequately Controlled Asthma and High Bronchodilator Reversibility

Summary

EudraCT number	2012-003351-11
Trial protocol	DE IE IT GR PL
Global end of trial date	15 May 2015

Results information

Result version number	v1 (current)
This version publication date	27 May 2016
First version publication date	27 May 2016

Trial information

Trial identification

Sponsor protocol code	20120141

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01902290
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info - Clinical Trials, Amgen (EUROPE) GmbH, MedinfoInternational@amgen.com
Scientific contact	IHQ Medical Info - Clinical Trials, Amgen (EUROPE) GmbH, MedinfoInternational@amgen.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	15 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 May 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of brodalumab compared with placebo as measured by the change in asthma control (based on the Asthma Control Questionnaire [ACQ]) from baseline at week 24 in subjects with inadequately controlled asthma and high reversibility despite standard of care.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and other applicable regulations/guidelines.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 May 2013
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	Poland: 64
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 2
Country: Number of subjects enrolled	United States: 212
Worldwide total number of subjects	421
EEA total number of subjects	130

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)	382
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 157 centers in Asia, Australia, Canada, Europe, and the United States.

Pre-assignment

Screening details:

Eligible subjects completed 3 run-in visits over 4 weeks after all eligibility criteria were met. After completion of the run-in visits, subjects returned to the clinic for randomization and the baseline visit. Randomization was stratified based on the current use of long-acting β-agonist (LABA) and number of prior exacerbations in the past year.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo subcutaneous injections on day 1 and weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.

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:

Administered by subcutaneous injection

Arm title	Brodalumab 210 mg

Arm description:

Participants received brodalumab 210 mg administered by subcutaneous injection on day 1 and weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.

Arm type	Experimental
Investigational medicinal product name	Brodalumab
Investigational medicinal product code	AMG 827
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Brodalumab 210 mg administered by subcutaneous injection

Number of subjects in period 1	Placebo	Brodalumab 210 mg
Started	210	211
Received treatment	207	208
Completed	162	158
Not completed	48	53
Consent withdrawn by subject	19	27
Death	1	-
Lost to follow-up	2	2
Decision by sponsor	26	24

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneous injections on day 1 and weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.	
Reporting group title	Brodalumab 210 mg
Reporting group description:	
Participants received brodalumab 210 mg administered by subcutaneous injection on day 1 and weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.	

Reporting group values	Placebo	Brodalumab 210 mg	Total
Number of subjects	210	211	421
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	47.2	47.2	
standard deviation	± 13.3	± 13.9	-
Gender categorical Units: Subjects			
Female	122	124	246
Male	88	87	175
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	10	13	23
Black or African American	30	20	50
Multiple	1	1	2
Native Hawaiian or Other Pacific Islander	1	1	2
White	164	176	340
Other	3	0	3
Ethnicity Units: Subjects			
Hispanic or Latino	8	13	21
Not Hispanic or Latino	202	198	400
Randomized Strata Units: Subjects			
LABA -No; ≤ 2 asthma exacerbation prior year	32	37	69
LABA -No; > 2 asthma exacerbation prior year	0	1	1
LABA -Yes; ≤ 2 asthma exacerbation prior year	161	156	317
LABA -Yes; > 2 asthma exacerbation prior year	17	17	34

Duration of Asthma			
Data were available for 210 subjects in each treatment group.			
Units: years			
arithmetic mean	22.14	23.05	
standard deviation	± 14.8	± 14.45	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneous injections on day 1 and weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.	
Reporting group title	Brodalumab 210 mg
Reporting group description:	
Participants received brodalumab 210 mg administered by subcutaneous injection on day 1 and weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.	

Primary: Change From Baseline in the Asthma Control Questionnaire (ACQ) Composite Score at Week 24

End point title	Change From Baseline in the Asthma Control Questionnaire (ACQ) Composite Score at Week 24
End point description:	
The ACQ is an instrument to evaluate asthma control/impairment. It is a validated composite score that assesses disease control by evaluating 7 questions: night time awakenings, asthma symptoms upon wakening, activity limitation, shortness of breath, wheeze frequency, short-acting bronchodilator use, and forced expiratory volume in 1 second (FEV1). The total score is the mean of the responses to the 7 questions, and ranges between 0 (totally-controlled) and 6 (extremely poorly controlled). The full analysis set consists of all randomized subjects who received at least 1 dose of study treatment.	
End point type	Primary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147[1]	137[2]		
Units: units on a scale				
least squares mean (standard error)	-0.815 (± 0.073)	-0.865 (± 0.074)		

Notes:

[1] - Participants in the full analysis set with available data

[2] - Participants in the full analysis set with available data

Statistical analyses

Statistical analysis title	Analysis of ACQ Change From Baseline at Week 24
Statistical analysis description:	
Change in the ACQ score from baseline at week 24 was tested for treatment effect (brodalumab versus placebo) using a mixed effects model with repeated measures at the significance level of 0.05 (2-sided).	
Comparison groups	Placebo v Brodalumab 210 mg

Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5219 [3]
Method	Mixed-effect model
Parameter estimate	Difference from placebo
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.203
upper limit	0.103

Notes:

[3] - The model included treatment group, study week as a categorical variable, stratification factors, interaction of treatment group by week and baseline ACQ with random intercept, assuming first-order autoregressive covariance structure.

Secondary: Asthma Exacerbation Rate From Baseline to Week 24

End point title	Asthma Exacerbation Rate From Baseline to Week 24

End point description:

The asthma exacerbation event rate is defined as the number of events per subject year during the 24 week treatment period. An asthma exacerbation was defined as an asthma worsening that requires systemic corticosteroids for at least 3 days during the study; distinct asthma exacerbations were defined as events with start dates more than 10 days apart from each other.

End point type	Secondary

End point timeframe:

Baseline to week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[4]	205[5]		
Units: exacerbations per subject year				
number (not applicable)	0.57	0.81		

Notes:

[4] - Full analysis set

[5] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of Asthma Exacerbation Rate
Comparison groups	Brodalumab 210 mg v Placebo
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.102 [6]
Method	Generalized Linear Model
Parameter estimate	Rate ratio
Point estimate	1.41

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	2.12

Notes:

[6] - P-value was from a generalized linear model under a negative binomial distribution assumption adjusting for stratification factors.

Secondary: Change From Baseline in the ACQ Composite Score at Week 24 in the LABA Strata

End point title	Change From Baseline in the ACQ Composite Score at Week 24 in the LABA Strata

End point description:

The ACQ is an instrument to evaluate asthma control/impairment. It is a validated composite score that assesses disease control by evaluating 7 questions: night time awakenings, asthma symptoms upon wakening, activity limitation, shortness of breath, wheeze frequency, short-acting bronchodilator use, and FEV1. The total score is the mean of the responses to the 7 questions, and ranges between 0 (totally-controlled) and 6 (extremely poorly controlled).

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121[7]	108[8]		
Units: units on a scale				
least squares mean (standard error)	-0.793 (± 0.084)	-0.831 (± 0.088)		

Notes:

[7] - Participants in the full analysis set in the LABA strata with available data

[8] - Participants in the full analysis set in the LABA strata with available data

Statistical analyses

Statistical analysis title	Analysis of ACQ in LABA Strata
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6632 [9]
Method	Mixed effect model
Parameter estimate	Difference from placebo
Point estimate	-0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.134

Notes:

[9] - The model includes treatment group, study week as a categorical variable, stratification factors, interaction of treatment group by week and baseline ACQ with random intercept assuming first-order autoregressive covariance structure.

Secondary: Asthma Exacerbation Rate From Baseline to Week 24 in LABA Strata

End point title	Asthma Exacerbation Rate From Baseline to Week 24 in LABA Strata

End point description:

The asthma exacerbation event rate is defined as the number of events per subject year during the 24 week treatment period. An asthma exacerbation was defined as an asthma worsening that requires systemic corticosteroids for at least 3 days during the study; distinct asthma exacerbations were defined as events with start dates more than 10 days apart from each other.

End point type	Secondary

End point timeframe:

From baseline to week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[10]	167[11]		
Units: exacerbations per subject year				
number (not applicable)	0.6	0.89		

Notes:

[10] - Participants in the full analysis set in the LABA strata with available data

[11] - Participants in the full analysis set in the LABA strata with available data

Statistical analyses

Statistical analysis title	Analysis of Exacerbation Rate in LABA Strata
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096 [12]
Method	Generalized Linear Model
Parameter estimate	Rate ratio
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	2.24

Notes:

[12] - P-value was from a generalized linear model under a negative binomial distribution assumption adjusting for stratification factors.

Secondary: Change From Baseline in Daily Asthma Symptoms Score at Week 24

End point title	Change From Baseline in Daily Asthma Symptoms Score at Week 24

End point description:

The Asthma Symptom Diary is comprised of 23 questions answered on a hand held device. There are 10

items completed in the Morning and 13 items completed in the evening. Subjects were asked to rate the severity of their symptoms, activity limitations and nighttime awakening due to symptoms and use of rescue medication and nebulizer each day. Five symptom related items in the morning and five symptom related items in the evening are used to compute a daily asthma symptom score that is aggregated over days to compute a 7 day average asthma symptom score. The range of the score is 0 to 4.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121[13]	117[14]		
Units: units on a scale				
least squares mean (standard error)	-0.397 (± 0.042)	-0.443 (± 0.043)		

Notes:

[13] - Full analysis set with available data

[14] - Full analysis set with available data

Statistical analyses

Statistical analysis title	Analysis of Daily Asthma Symptom Score
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.329 [15]
Method	Mixed effect model
Parameter estimate	Difference from placebo
Point estimate	-0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.137
upper limit	0.046

Notes:

[15] - Includes treatment group, study week as a categorical variable, stratification factors, interaction of treatment group by week and baseline daily asthma symptom score with random intercept, assuming first-order autoregressive covariance structure.

Secondary: Change From Baseline in Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) at Week 24

End point title	Change From Baseline in Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) at Week 24

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148[16]	137[17]		
Units: L/sec				
least squares mean (standard error)	0.207 (± 0.045)	0.237 (± 0.046)		

Notes:

[16] - Full analysis set with available data

[17] - Full analysis set with available data

Statistical analyses

Statistical analysis title	Analysis of Pre-bronchodilator FEV1
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4549 [18]
Method	Mixed effect model
Parameter estimate	Difference from placebo
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.049
upper limit	0.109

Notes:

[18] - Includes treatment group, study week as categorical variable, stratification factors, interaction of treatment group by week and baseline age, gender, pooled race, height & pre-FEV1 with random intercept assuming first-order autoregressive structure.

Secondary: Change From Baseline in Daily Rescue Short-acting Beta-agonist Use at Week 24

End point title	Change From Baseline in Daily Rescue Short-acting Beta-agonist Use at Week 24

End point description:

Participants recorded daily rescue short-acting beta-agonist (SABA) use in the asthma symptom diary. The daily rescue medication score was assigned based on daytime and night time rescue beta agonist use (rescue inhaler and nebulizer). Each use of the nebulizer was counted as 4 puffs.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121[19]	117[20]		
Units: units on a scale				
least squares mean (standard error)	-1.359 (± 0.243)	-1.231 (± 0.246)		

Notes:

[19] - Full analysis set with available data

[20] - Full analysis set with available data

Statistical analyses

Statistical analysis title	Analysis of Rescue Short-acting β-agonist Use
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6317 [21]
Method	Mixed effect model
Parameter estimate	Difference from placebo
Point estimate	0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.396
upper limit	0.653

Notes:

[21] - Includes treatment group, study week as categorical variable, stratification factors, interaction of treatment group by week and baseline daily rescue SABA use with random intercept assuming first-order autoregressive covariance structure.

Secondary: Time to First Asthma Exacerbation

End point title	Time to First Asthma Exacerbation

End point description:

An asthma exacerbation is defined as an asthma worsening that requires systemic corticosteroids for at least 3 days during the study. Median time to first asthma exacerbation could not be estimated, the percentage of participants with an asthma exacerbation is reported.

End point type	Secondary

End point timeframe:

Baseline to week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[22]	205[23]		
Units: percentage of participants				
number (not applicable)	20.1	23.9		

Notes:

[22] - Full analysis set

[23] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of Time to First Asthma Exacerbation
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.238 [24]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.277
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.843
upper limit	1.936

Notes:

[24] - Log rank test stratified for baseline stratification factors.

Secondary: Number of Participants with Asthma Exacerbations From Baseline to Week 24

End point title	Number of Participants with Asthma Exacerbations From Baseline to Week 24

End point description:

An asthma exacerbation is defined as an asthma worsening that requires systemic corticosteroids for at least 3 days during the study.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[25]	205[26]		
Units: participants	41	49		

Notes:

[25] - Full analysis set

[26] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of Asthma Exacerbations
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.351 [27]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.01

Notes:

[27] - Testing of treatment effect in logistic regression and adjusted for stratification factors.

Secondary: Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) Overall Score at Week 24

End point title	Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) Overall Score at Week 24

End point description:

The AQLQ is an asthma-specific instrument and includes evaluations of both symptom and quality of life measures. The 32-item instrument measures 4 domains affected by asthma including activity limitations, emotional function, exposure to environmental stimuli, and symptoms. Patients are asked to recall their experiences during the last 2 weeks and to respond to each question on a 7-point scale (7=no impairment, 1=severe impairment). The overall score was calculated as the mean of the responses to the 32 questions.

End point type	Secondary

End point timeframe:

Baseline and week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147[28]	137[29]		
Units: units on a scale				
least squares mean (standard error)	0.804 (± 0.085)	0.803 (± 0.087)		

Notes:

[28] - Full analysis set with available data

[29] - Full analysis set with available data

Statistical analyses

Statistical analysis title	Analysis of AQLQ Overall Score
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.987 [30]
Method	Mixed effect model
Parameter estimate	Difference from placebo
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.174
upper limit	0.171

Notes:

[30] - The model includes treatment group, study week as a categorical variable, stratification factors, interaction of treatment group by week and baseline AQLQ with random intercept assuming first-order autoregressive covariance structure.

Secondary: Change From Baseline in Peak Expiratory Flow Rate (PEFR) at Week 24

End point title	Change From Baseline in Peak Expiratory Flow Rate (PEFR) at Week 24

End point description:

PEFR was measured by the participant twice daily at approximately the same time each day, once in the morning and once in the evening.

End point type	Secondary

End point timeframe:

Baseline and week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146[31]	129[32]		
Units: L/min				
least squares mean (standard error)				
Morning peak flow	0.072 (± 5.813)	0.706 (± 5.885)		
Evening peak flow	-10.008 (± 5.719)	-4.089 (± 5.771)		

Notes:

[31] - Full analysis set with available data = 146 for morning and 135 for evening data

[32] - Full analysis set with available data

Statistical analyses

Statistical analysis title	Analysis of Morning Peak Flow
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9053 [33]
Method	Mixed effect model
Parameter estimate	Difference from placebo
Point estimate	0.635
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.82
upper limit	11.089

Notes:

[33] - Includes treatment group, study week, stratification factors, interaction of treatment group by week and baseline age, gender, pooled race, height, am peak flow with random intercept assuming first-order autoregressive covariance structure.

Statistical analysis title	Analysis of Evening Peak Flow
Comparison groups	Placebo v Brodalumab 210 mg

Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2661 [34]
Method	Mixed effect model
Parameter estimate	Difference from placebo
Point estimate	5.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.515
upper limit	16.354

Notes:

[34] - Includes treatment group, study week, stratification factors, interaction of treatment group by week and baseline age, gender, pooled race, height, am peak flow with random intercept assuming first-order autoregressive covariance structure.

Secondary: Change From Baseline in PEFR Variation at Week 24

End point title	Change From Baseline in PEFR Variation at Week 24

End point description:

The variation of peak flow is defined as the absolute value of the difference between the A.M. and P.M. peak flow in one day for an individual patient.

End point type	Secondary

End point timeframe:

Baseline and week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121[35]	115[36]		
Units: L/min				
least squares mean (standard error)	-0.872 (± 2.135)	-4.892 (± 2.169)		

Notes:

[35] - Full analysis set with available data

[36] - Full analysis set with available data

Statistical analyses

Statistical analysis title	Analysis of Variation of Peak Flow
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0871 [37]
Method	Mixed effect model
Parameter estimate	Difference from placebo
Point estimate	-4.021

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.627
upper limit	0.586

Notes:

[37] - Includes treatment group, study week, stratification factors, interaction of treatment group by week and baseline age, gender, pooled race, height & variation of peak flow with random intercept assuming first-order autoregressive covariance structure

Secondary: Proportion of Asthma Symptom-Free Days in 4-Weeks Intervals

End point title	Proportion of Asthma Symptom-Free Days in 4-Weeks Intervals

End point description:

The number of asthma symptom-free days was derived from the asthma symptom diary, and defined as days that a patient has a score of zero in their daily asthma symptom diary score. Proportion of asthma symptom-free days is calculated from the number of days the subject completed the diary in the corresponding 4-week interval during the treatment period.

End point type	Secondary

End point timeframe:

4-week intervals from baseline to week 24

End point values	Placebo	Brodalumab 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[38]	205[39]		
Units: proportion of days				
least squares mean (standard error)				
Week 4 (n = 204, 203)	0.111 (± 0.021)	0.09 (± 0.021)		
Week 8 (n = 193, 192)	0.153 (± 0.029)	0.138 (± 0.029)		
Week 12 (n = 185, 184)	0.168 (± 0.032)	0.166 (± 0.032)		
Week 16 (n = 176, 174)	0.194 (± 0.036)	0.201 (± 0.036)		
Week 20 (n = 167, 162)	0.207 (± 0.038)	0.211 (± 0.039)		
Week 24 (n = 160, 153)	0.223 (± 0.04)	0.214 (± 0.04)		

Notes:

[38] - Full analysis set

[39] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of Asthma Symptom-free Days at Week 4
Comparison groups	Brodalumab 210 mg v Placebo
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2765 [40]
Method	ANCOVA
Parameter estimate	Difference from placebo
Point estimate	-0.021

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.059
upper limit	0.017

Notes:

[40] - Testing of treatment effect in analysis of covariance test and adjusted for baseline daily asthma symptom score and stratification factors

Statistical analysis title	Analysis of Asthma Symptom-free Days at Week 8
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5805 [41]
Method	ANCOVA
Parameter estimate	Difference from placebo
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.067
upper limit	0.037

Notes:

[41] - Testing of treatment effect in analysis of covariance test and adjusted for baseline daily asthma symptom score and stratification factors

Statistical analysis title	Analysis of Asthma Symptom-free Days at Week 12
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9466 [42]
Method	ANCOVA
Parameter estimate	Difference from placebo
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.056

Notes:

[42] - Testing of treatment effect in analysis of covariance test and adjusted for baseline daily asthma symptom score and stratification factors

Statistical analysis title	Analysis of Asthma Symptom-free Days at Week 16
Comparison groups	Placebo v Brodalumab 210 mg

Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8179 [43]
Method	ANCOVA
Parameter estimate	Difference from placebo
Point estimate	0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.057
upper limit	0.072

Notes:

[43] - Testing of treatment effect in analysis of covariance test and adjusted for baseline daily asthma symptom score and stratification factors

Statistical analysis title	Analysis of Asthma Symptom-free Days at Week 20
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9139 [44]
Method	ANCOVA
Parameter estimate	Difference from placebo
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.066
upper limit	0.073

Notes:

[44] - Testing of treatment effect in analysis of covariance test and adjusted for baseline daily asthma symptom score and stratification factors

Statistical analysis title	Analysis of Asthma Symptom-free Days at Week 24
Comparison groups	Placebo v Brodalumab 210 mg
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8316 [45]
Method	ANCOVA
Parameter estimate	Difference from placebo
Point estimate	-0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.083
upper limit	0.067

Notes:

[45] - Testing of treatment effect in analysis of covariance test and adjusted for baseline daily asthma symptom score and stratification factors

Secondary: Serum Brodalumab Concentration

End point title	Serum Brodalumab Concentration[46]

End point description:

Serum brodalumab concentrations were measured using an enzyme-linked immunosorbent assay (ELISA).
The lower limit of quantification (LLOQ) = 0.0500 µg/mL; values below the LLOQ were set to zero.

End point type	Secondary

End point timeframe:

Day 1 to week 22, day 14

Notes:

[46] - 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: Brodalumab concentration was only measured in subjects in the Brodalumab treatment group.

End point values	Brodalumab 210 mg			
Subject group type	Reporting group			
Number of subjects analysed	196			
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 1 predose (n = 196)	0 (± 0)			
Week 1 predose (n = 196)	8.48 (± 5.55)			
Week 2 predose (n = 178)	16.8 (± 9.85)			
Week 2 day 3 (n = 50)	24.9 (± 15.8)			
Week 4 predose (n = 174)	14.5 (± 9.28)			
Week 8 predose (n = 174)	11.1 (± 9.03)			
Week 12 predose (n = 161)	10.6 (± 9.86)			
Week 16 predose (n = 150)	8.93 (± 9.06)			
Wee 22 predose (n = 136)	8.94 (± 9.32)			
Week 22 day 3 (n = 46)	18 (± 15.4)			
Week 22 day 7 (n = 46)	14.8 (± 13.3)			
Week 22 day 10 (n = 43)	12.5 (± 12.2)			
Week 22 day 14 (n = 146)	9.06 (± 9.78)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug until 30 days after last dose; median duration of treatment was 155 days.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneous injections on day 1 and weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.	
Reporting group title	Brodalumab 210 mg
Reporting group description:	
Participants received brodalumab 210 mg administered by subcutaneous injection on day 1 and weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.	

Serious adverse events	Placebo	Brodalumab 210 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 207 (3.86%)	7 / 208 (3.37%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bile duct adenocarcinoma			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (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			
Pneumothorax traumatic			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (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	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Microcytic anaemia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
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			
Acute respiratory failure			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			

subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Brodalumab 210 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	132 / 207 (63.77%)	156 / 208 (75.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Flushing			

subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
Haemorrhage			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	4 / 207 (1.93%)	0 / 208 (0.00%)	
occurrences (all)	4	0	
Pallor			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Thrombophlebitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Asthma prophylaxis			
subjects affected / exposed	2 / 207 (0.97%)	1 / 208 (0.48%)	
occurrences (all)	2	1	
Endodontic procedure			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Mammoplasty			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 207 (0.48%)	2 / 208 (0.96%)	
occurrences (all)	1	2	
Application site pain			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	6	0	
Chest discomfort			

subjects affected / exposed	0 / 207 (0.00%)	3 / 208 (1.44%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	5 / 207 (2.42%)	2 / 208 (0.96%)	
occurrences (all)	7	2	
Induration			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	2 / 207 (0.97%)	3 / 208 (1.44%)	
occurrences (all)	2	5	
Injection site bruising			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	3	
Injection site erythema			
subjects affected / exposed	3 / 207 (1.45%)	6 / 208 (2.88%)	
occurrences (all)	13	16	
Injection site haemorrhage			
subjects affected / exposed	2 / 207 (0.97%)	1 / 208 (0.48%)	
occurrences (all)	3	1	
Injection site induration			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	3	
Injection site nodule			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	2	
Injection site pain			
subjects affected / exposed	1 / 207 (0.48%)	4 / 208 (1.92%)	
occurrences (all)	12	16	
Injection site paraesthesia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	2	
Injection site pruritus			
subjects affected / exposed	0 / 207 (0.00%)	4 / 208 (1.92%)	
occurrences (all)	0	5	
Injection site swelling			

subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	2	
Injection site urticaria			
subjects affected / exposed	1 / 207 (0.48%)	2 / 208 (0.96%)	
occurrences (all)	7	5	
Malaise			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	2 / 207 (0.97%)	1 / 208 (0.48%)	
occurrences (all)	2	1	
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Hypersensitivity			
subjects affected / exposed	0 / 207 (0.00%)	4 / 208 (1.92%)	
occurrences (all)	0	5	
Seasonal allergy			
subjects affected / exposed	2 / 207 (0.97%)	0 / 208 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Breast mass			

subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Menorrhagia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Menstrual disorder			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Oedema genital			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	63 / 207 (30.43%)	72 / 208 (34.62%)	
occurrences (all)	88	108	
Bronchospasm			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	6 / 207 (2.90%)	11 / 208 (5.29%)	
occurrences (all)	7	11	
Dry throat			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	3 / 207 (1.45%)	7 / 208 (3.37%)	
occurrences (all)	3	7	
Epistaxis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	3 / 207 (1.45%)	3 / 208 (1.44%)	
occurrences (all)	4	3	
Nasal polyps			

subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	3 / 207 (1.45%)	1 / 208 (0.48%)	
occurrences (all)	3	1	
Productive cough			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Respiratory tract congestion			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Rhinitis allergic			
subjects affected / exposed	5 / 207 (2.42%)	3 / 208 (1.44%)	
occurrences (all)	6	3	
Rhinorrhoea			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Sinus congestion			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	1 / 207 (0.48%)	8 / 208 (3.85%)	
occurrences (all)	2	9	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 207 (0.97%)	1 / 208 (0.48%)	
occurrences (all)	2	2	
Apathy			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	

Confusional state			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	3 / 207 (1.45%)	3 / 208 (1.44%)	
occurrences (all)	3	3	
Insomnia			
subjects affected / exposed	1 / 207 (0.48%)	2 / 208 (0.96%)	
occurrences (all)	1	2	
Mood swings			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Somnambulism			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Investigations			
Bilirubin conjugated increased			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
White blood cells urine positive			

subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Animal scratch			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Back injury			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Arthropod sting			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Chest injury			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Ear canal injury			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Face injury			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	2 / 207 (0.97%)	0 / 208 (0.00%)	
occurrences (all)	2	0	
Facial bones fracture			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Foot fracture			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
Hand fracture			

subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Joint dislocation			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	2	
Ligament sprain			
subjects affected / exposed	3 / 207 (1.45%)	1 / 208 (0.48%)	
occurrences (all)	3	1	
Meniscus injury			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	3 / 207 (1.45%)	0 / 208 (0.00%)	
occurrences (all)	4	0	
Rib fracture			
subjects affected / exposed	2 / 207 (0.97%)	1 / 208 (0.48%)	
occurrences (all)	2	1	
Skeletal injury			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Scratch			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Upper limb fracture			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Cardiac disorders			

Angina pectoris			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Supraventricular tachycardia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Aphonia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Burning sensation			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	2	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Cervical radiculopathy			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	1 / 207 (0.48%)	2 / 208 (0.96%)	
occurrences (all)	1	3	
Dysgeusia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	11 / 207 (5.31%)	8 / 208 (3.85%)	
occurrences (all)	12	13	
Hypersomnia			

subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
Migraine			
subjects affected / exposed	2 / 207 (0.97%)	0 / 208 (0.00%)	
occurrences (all)	3	0	
Nerve compression			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Peroneal nerve palsy			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Radiculitis lumbosacral			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
Sinus headache			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Lymphopenia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	

Neutrophilia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	1 / 207 (0.48%)	3 / 208 (1.44%)	
occurrences (all)	1	4	
Tinnitus			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 207 (0.48%)	2 / 208 (0.96%)	
occurrences (all)	1	2	
Chalazion			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Macular oedema			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Abdominal discomfort			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Abdominal pain lower			
subjects affected / exposed	2 / 207 (0.97%)	0 / 208 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			

subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	8	
Dry mouth			
subjects affected / exposed	3 / 207 (1.45%)	0 / 208 (0.00%)	
occurrences (all)	4	0	
Diarrhoea			
subjects affected / exposed	4 / 207 (1.93%)	4 / 208 (1.92%)	
occurrences (all)	4	16	
Gastritis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Gastrointestinal disorder			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 207 (0.48%)	2 / 208 (0.96%)	
occurrences (all)	1	2	
Gingival pain			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Inguinal hernia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	3 / 207 (1.45%)	6 / 208 (2.88%)	
occurrences (all)	7	7	
Loose tooth			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Oedema mouth			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Pancreatitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	3	0	
Stomatitis			

subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Salivary gland enlargement			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 207 (1.45%)	2 / 208 (0.96%)	
occurrences (all)	4	2	
Toothache			
subjects affected / exposed	3 / 207 (1.45%)	0 / 208 (0.00%)	
occurrences (all)	3	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Acne			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Dermatitis contact			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Dermatitis atopic			
subjects affected / exposed	1 / 207 (0.48%)	3 / 208 (1.44%)	
occurrences (all)	1	3	
Erythema			
subjects affected / exposed	2 / 207 (0.97%)	4 / 208 (1.92%)	
occurrences (all)	2	6	
Eczema			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
Pruritus			

subjects affected / exposed	1 / 207 (0.48%)	2 / 208 (0.96%)	
occurrences (all)	2	3	
Papule			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Pruritus generalised			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
Rash pruritic			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 207 (0.00%)	4 / 208 (1.92%)	
occurrences (all)	0	6	
Rash vesicular			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
Transient acantholytic dermatosis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Urticaria papular			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 207 (0.97%)	8 / 208 (3.85%)	
occurrences (all)	2	10	
Back pain			
subjects affected / exposed	5 / 207 (2.42%)	6 / 208 (2.88%)	
occurrences (all)	5	7	
Muscle spasms			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Muscular weakness			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 207 (0.97%)	0 / 208 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal disorder			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 207 (0.48%)	2 / 208 (0.96%)	
occurrences (all)	1	2	
Myalgia			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Neck pain			
subjects affected / exposed	3 / 207 (1.45%)	0 / 208 (0.00%)	
occurrences (all)	4	0	
Pain in extremity			
subjects affected / exposed	0 / 207 (0.00%)	4 / 208 (1.92%)	
occurrences (all)	0	4	
Rotator cuff syndrome			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Senile ankylosing vertebral hyperostosis			

subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Synovial cyst			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	2 / 207 (0.97%)	1 / 208 (0.48%)	
occurrences (all)	2	1	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	3 / 207 (1.45%)	1 / 208 (0.48%)	
occurrences (all)	3	1	
Bronchitis			
subjects affected / exposed	14 / 207 (6.76%)	13 / 208 (6.25%)	
occurrences (all)	16	14	
Bronchitis bacterial			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Candida infection			
subjects affected / exposed	0 / 207 (0.00%)	3 / 208 (1.44%)	
occurrences (all)	0	4	
Cellulitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 207 (0.48%)	3 / 208 (1.44%)	
occurrences (all)	1	3	
Diverticulitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	2 / 207 (0.97%)	1 / 208 (0.48%)	
occurrences (all)	2	1	
Folliculitis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	

Gastroenteritis			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Gastroenteritis viral			
subjects affected / exposed	1 / 207 (0.48%)	3 / 208 (1.44%)	
occurrences (all)	1	3	
Genital herpes			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Genital infection fungal			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Gingivitis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Hordeolum			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Incision site abscess			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 207 (0.48%)	8 / 208 (3.85%)	
occurrences (all)	1	8	
Lower respiratory tract infection			
subjects affected / exposed	3 / 207 (1.45%)	1 / 208 (0.48%)	
occurrences (all)	3	1	
Lung infection			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	19 / 207 (9.18%)	24 / 208 (11.54%)	
occurrences (all)	22	29	

Oral candidiasis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	1 / 207 (0.48%)	3 / 208 (1.44%)	
occurrences (all)	1	3	
Otitis externa			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	4 / 207 (1.93%)	3 / 208 (1.44%)	
occurrences (all)	4	3	
Pharyngitis streptococcal			
subjects affected / exposed	2 / 207 (0.97%)	0 / 208 (0.00%)	
occurrences (all)	2	0	
Pneumonia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Post procedural infection			
subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	
Respiratory tract infection viral			
subjects affected / exposed	2 / 207 (0.97%)	1 / 208 (0.48%)	
occurrences (all)	2	1	
Rhinitis			
subjects affected / exposed	2 / 207 (0.97%)	3 / 208 (1.44%)	
occurrences (all)	2	3	
Sinusitis			
subjects affected / exposed	10 / 207 (4.83%)	5 / 208 (2.40%)	
occurrences (all)	11	5	
Tonsillitis			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	

Tonsillitis bacterial			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
Tooth infection			
subjects affected / exposed	1 / 207 (0.48%)	2 / 208 (0.96%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	19 / 207 (9.18%)	24 / 208 (11.54%)	
occurrences (all)	21	25	
Urinary tract infection			
subjects affected / exposed	2 / 207 (0.97%)	3 / 208 (1.44%)	
occurrences (all)	2	4	
Viral infection			
subjects affected / exposed	2 / 207 (0.97%)	0 / 208 (0.00%)	
occurrences (all)	2	0	
Viral pharyngitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 207 (2.90%)	4 / 208 (1.92%)	
occurrences (all)	6	4	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Gout			

subjects affected / exposed	0 / 207 (0.00%)	1 / 208 (0.48%)	
occurrences (all)	0	1	
Hypercholesterolaemia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 208 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 207 (0.48%)	1 / 208 (0.48%)	
occurrences (all)	1	1	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 207 (0.00%)	2 / 208 (0.96%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2012	Major changes included: - Corrected an error in the list of proscribed medications in Section 6. - Section 8.1 was amended to remove reasons for removal of a subject from the study (investigator decision, withdrawal of partial consent, pregnancy, ineligibility, protocol deviations, noncompliance, and > 3 asthma exacerbations); 2 of these items (pregnancy and > 3 asthma exacerbations) were added to the reasons for a subject to stop investigational product (IP), but remain in the study.
04 December 2013	- Consistent with the intent of the protocol and rest of the brodalumab program, a follow-up assessment was added to collect safety information 4 weeks after the last dose of IP for those subjects who were terminated early from the study.
26 March 2014	- Based on the identification of suicidal behavior and suicidal ideation as a potential risk and after discussion with regulatory agencies, the Columbia Suicide Severity Rating Scale and the Patient Health Questionnaire depression scale were added as instruments to assess eligibility and monitor subject safety (ie, stopping rules). - Other minor editorial corrections and clarifications were made.
03 October 2014	- Included details about interim analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported