Clinical trial results:
A phase IIa, randomized, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of subcutaneously administered BI 655066/ABBV-066 (risankizumab) as add-on therapy over 24 weeks in patients with severe persistent asthma.

Summary

EudraCT number	2014-004932-20
Trial protocol	BE GB HU NL DE PL IT
Global end of trial date	02 February 2018

Results information

Result version number	v1 (current)
This version publication date	17 February 2019
First version publication date	17 February 2019

Trial information

Trial identification

Sponsor protocol code	1311.14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02443298
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	19 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2017
Global end of trial reached?	Yes
Global end of trial date	02 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the study were as follows:
1. Evaluate the safety, efficacy, and pharmacokinetics (PK) of risankizumab as compared to placebo in patients with severe persistent asthma, and
2. Evaluate treatment response as a function of the known clinical phenotypes and exploratory endotypes to inform a companion diagnostic stratification biomarker able to predict treatment response in further clinical studies.

Protection of trial subjects:

Only patients that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All patients were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all patients was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 81
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 64
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	United States: 113
Worldwide total number of subjects	369
EEA total number of subjects	222

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)	300
From 65 to 84 years	69
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomized, double-blind, placebo-controlled, parallel-group multicenter study to assess the efficacy and safety of risankizumab, an IL-23p19 monoclonal antibody, compared to placebo in patients with severe persistent asthma.

Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. Patients attended a specialist sites which ensured that they (the patients) met all strictly implemented inclusion/exclusion criteria. Patients were not to be randomized to trial treatment if any one of the specific entry criteria was violated.

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	Investigator, Monitor, Subject, Assessor

Blinding implementation details:

This was a randomized, double-blind, placebo-controlled, parallel-group multi-center study

Arms

Are arms mutually exclusive?	Yes
Arm title	Risankizumab

Arm description:

Patients received subcutaneous injection of 1 milliliter (mL) prefilled syringe with 90 milligram/ milliliter (mg/mL) risankizumab once every 4 weeks (weeks 0, 4, 8, 12, 16, 20)

Arm type	Experimental
Investigational medicinal product name	Risankizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received subcutaneous injection of 1 milliliter (mL) prefilled syringe with 90 milligram/ milliliter (mg/mL) risankizumab once every 4 weeks (weeks 0, 4, 8, 12, 16, 20)

Arm title	Placebo

Arm description:

Patients received subcutaneous injection of 1 milliliter (mL) prefilled syringe consisting of matching placebo to risankizumab once every 4 weeks (weeks 0, 4, 8, 12, 16, 20)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received subcutaneous injection of 1 milliliter (mL) prefilled syringe consisting of matching placebo to risankizumab once every 4 weeks (weeks 0, 4, 8, 12, 16, 20)

Number of subjects in period 1[1]	Risankizumab	Placebo
Started	105	109
Completed	101	104
Not completed	4	5
Consent withdrawn by subject	1	2
Adverse event, non-fatal	3	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on the patients who had successfully completed the screening and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Risankizumab
Reporting group description:	
Patients received subcutaneous injection of 1 milliliter (mL) prefilled syringe with 90 milligram/ milliliter (mg/mL) risankizumab once every 4 weeks (weeks 0, 4, 8, 12, 16, 20)	
Reporting group title	Placebo
Reporting group description:	
Patients received subcutaneous injection of 1 milliliter (mL) prefilled syringe consisting of matching placebo to risankizumab once every 4 weeks (weeks 0, 4, 8, 12, 16, 20)	

Reporting group values	Risankizumab	Placebo	Total
Number of subjects	105	109	214
Age categorical			
Units: Subjects			
Age Continuous			
Randomized Set (RS): This patient set included all randomized patients, whether treated or not.			
Units: years			
arithmetic mean	54.1	52.3	
standard deviation	± 11.3	± 12.5	-
Sex: Female, Male			
Randomized Set (RS): This patient set included all randomized patients, whether treated or not.			
Units: Subjects			
Female	69	64	133
Male	36	45	81
Race (NIH/OMB)			
Randomized Set (RS): This patient set included all randomized patients, whether treated or not.			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	11	11	22
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	9	8	17
White	84	88	172
More than one race	1	1	2
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Randomized Set (RS): This patient set included all randomized patients, whether treated or not.			
Units: Subjects			
Hispanic or Latino	3	3	6
Not Hispanic or Latino	102	106	208
Unknown or Not Reported	0	0	0
Oral corticosteroid (OCS) use at baseline			
Randomized Set (RS): This patient set included all randomized patients, whether treated or not.			
Units: Subjects			
Use of OCS at baseline - Yes	15	17	32
Use of OCS at baseline - No	90	92	182

Baseline Morning peak expiratory flow (PEF)			
Randomized Set (RS): This patient set included all randomized patients, whether treated or not.			
Units: Liter/Minute (L/min)			
arithmetic mean	299.34	309.56	
standard deviation	± 110.50	± 115.34	-
Baseline 24 Hour Rescue Medication Use			
Baseline 24 Hour Rescue Medication Use: Average over the 14 days prior to randomization. Randomized Set (RS): This patient set included all randomized patients, whether treated or not.			
Units: Puff			
arithmetic mean	3.17	3.89	
standard deviation	± 3.81	± 4.78	-
Baseline First 5 questions of the Asthma Control Questionnaire (ACQ5) Score			
Randomized Set (RS): This patient set included all randomized patients, whether treated or not.			
Units: Unit on scale			
arithmetic mean	2.15	2.39	
standard deviation	± 1.15	± 1.17	-

End points

End points reporting groups

Reporting group title	Risankizumab
Reporting group description:	
Patients received subcutaneous injection of 1 milliliter (mL) prefilled syringe with 90 milligram/ milliliter (mg/mL) risankizumab once every 4 weeks (weeks 0, 4, 8, 12, 16, 20)	
Reporting group title	Placebo
Reporting group description:	
Patients received subcutaneous injection of 1 milliliter (mL) prefilled syringe consisting of matching placebo to risankizumab once every 4 weeks (weeks 0, 4, 8, 12, 16, 20)	

Primary: Time to first asthma worsening during the planned 24 week treatment period

End point title	Time to first asthma worsening during the planned 24 week treatment period
End point description:	
Time to first asthma worsening during the planned 24 week treatment period: Asthma worsening was defined as the occurrence of any one of the following four criteria: a) Decrease from baseline of ≥30% in morning peak expiratory flow (PEF) on at least 2 consecutive days. b) Increase from baseline of ≥50% and an increase of least 4 puffs in daily use of rescue medication for at least 2 consecutive days. c) Increase from baseline of ≥0.75 units in ACQ5. d) Severe asthma exacerbations defined as initiation of systemic corticosteroids (prednisone or equivalent) for 3 or more consecutive days for asthma. Additionally, for subjects on maintenance systemic corticosteroids, at least doubling of the maintenance dose resulting in a total daily dose of ≥ 20 mg for three or more consecutive days was considered a severe asthma exacerbation. Full Analysis Set (FAS): All randomized patients who received at least one dose of treatment.	
End point type	Primary
End point timeframe:	
24 weeks	

End point values	Risankizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[1]	109[2]		
Units: Days				
median (confidence interval 80%)	40.00 (30.00 to 52.00)	85.50 (63.00 to 131.00)		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
This was analyzed by using a Cox proportional hazards model that included treatment and the stratification factor of OCS use at baseline as fixed effects. Comparison of Risankizumab to Placebo	
Comparison groups	Risankizumab v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0255
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.46
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.18
upper limit	1.81

Secondary: Time to first asthma worsening during the planned 24 week treatment period according to alternative definition

End point title	Time to first asthma worsening during the planned 24 week treatment period according to alternative definition

End point description:

Time to first asthma worsening during the planned 24 week treatment period according to alternative definition: Asthma worsening was defined as the occurrence of any one of the following four criteria: a) Decrease from baseline of ≥30% in morning peak expiratory flow (PEF) on at least 2 consecutive days. b) Increase from baseline of ≥50% and an increase of least 4 puffs in daily use of rescue medication for at least 2 consecutive days. c) Increase from baseline of ≥0.5 units in ACQ5. d) Severe asthma exacerbations defined as initiation of systemic corticosteroids (prednisone or equivalent) for 3 or more consecutive days for asthma. Additionally, for subjects on maintenance systemic corticosteroids, at least doubling of the maintenance dose resulting in a total daily dose of ≥ 20 mg for three or more consecutive days was considered a severe asthma exacerbation. Full Analysis Set (FAS): All randomized patients who received at least one dose of treatment.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Risankizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[3]	109[4]		
Units: Days				
median (confidence interval 80%)	20.00 (16.00 to 25.00)	37.00 (31.00 to 45.00)		

Notes:

[3] - FAS

[4] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

This was analyzed by using a Cox proportional hazards model that included treatment and the stratification factor of OCS use at baseline as fixed effects. Comparison of Risankizumab to Placebo.

Comparison groups	Risankizumab v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0131
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.47
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.2
upper limit	1.79

Secondary: Annualized rate of asthma worsening during the planned 24 week treatment period

End point title	Annualized rate of asthma worsening during the planned 24 week treatment period

End point description:

Annualized rate of asthma worsening during the planned 24 week treatment period. Asthma worsening was defined as the occurrence of any one of the following four criteria: a) Decrease from baseline of ≥30% in morning peak expiratory flow (PEF) on at least 2 consecutive days. b) Increase from baseline of ≥50% and an increase of least 4 puffs in daily use of rescue medication for at least 2 consecutive days. c) Increase from baseline of ≥0.75 units in ACQ5. d) Severe asthma exacerbations defined as initiation of systemic corticosteroids (prednisone or equivalent) for 3 or more consecutive days for asthma. Additionally, for subjects on maintenance systemic corticosteroids, at least doubling of the maintenance dose resulting in a total daily dose of ≥ 20 mg for three or more consecutive days was considered a severe asthma exacerbation. Mean is Annualized rate. Full Analysis Set (FAS): All randomized patients who received at least one dose of treatment.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Risankizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[5]	109[6]		
Units: Days				
arithmetic mean (standard error)	4.8412 (± 0.577)	3.2410 (± 0.401)		

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Annualized rate is obtained from fitting a negative binomial regression including logarithm of the exposure as an offset, treatment, and OCS use at baseline as covariate. Comparison of Risankizumab to Placebo

Comparison groups	Risankizumab v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065
Method	Negative binomial regression
Parameter estimate	Rate Ratio
Point estimate	1.4937
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.2366
upper limit	1.8044
Variability estimate	Standard error of the mean
Dispersion value	0.22

Secondary: Time to first severe asthma exacerbation during the planned 24 week treatment period

End point title	Time to first severe asthma exacerbation during the planned 24 week treatment period

End point description:

Time to first severe asthma exacerbation during the planned 24 week treatment period. Severe asthma exacerbation was defined as initiation of systemic corticosteroids (prednisone or equivalent) for 3 or more consecutive days for asthma. Additionally, for subjects on maintenance systemic corticosteroids, at least doubling of the maintenance dose resulting in a total daily dose of ≥ 20 mg for three or more consecutive days was considered a severe asthma exacerbation. Full Analysis Set (FAS): All randomized patients who received at least one dose of treatment. 99999 = not estimable due to an insufficient numbers of patient
with an event

End point type	Secondary

End point timeframe:

24 weeks

End point values	Risankizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[7]	109[8]		
Units: Days				
median (confidence interval 80%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[7] - FAS

[8] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Time to first event is obtained from fitting a Cox proportional−hazards model including treatment, and OCS use at baseline as covariate. Comparison of Risankizumab to Placebo.

Comparison groups	Risankizumab v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4619
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.88
upper limit	1.57

Secondary: Annualized rate of severe asthma exacerbation during the planned 24-week treatment period

End point title	Annualized rate of severe asthma exacerbation during the planned 24-week treatment period

End point description:

Annualized rate of severe asthma exacerbation during the planned 24-week treatment period. Severe asthma exacerbation was defined as initiation of systemic corticosteroids (prednisone or equivalent) for 3 or more consecutive days for asthma. Additionally, for subjects on maintenance systemic corticosteroids, at least doubling of the maintenance dose resulting in a total daily dose of ≥ 20 mg for three or more consecutive days was considered a severe asthma exacerbation. Mean is Annualized rate. Full Analysis Set (FAS): All randomized patients who received at least one dose of treatment.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Risankizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[9]	109[10]		
Units: Days				
arithmetic mean (standard error)	1.5901 (± 0.257)	1.4051 (± 0.228)		

Notes:

[9] - FAS

[10] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Annualized rate is obtained from fitting a negative binomial regression including logarithm of the exposure as an offset, treatment, and OCS use at baseline as covariate. Comparison of Risankizumab to Placebo.

Comparison groups	Risankizumab v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.555
Method	Negative binomial regression
Parameter estimate	Rate Ratio
Point estimate	1.1317
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.8652
upper limit	1.4803
Variability estimate	Standard error of the mean
Dispersion value	0.237

Secondary: Trough forced expiratory volume in 1 second (FEV1) in-clinic change from baseline at week 24

End point title	Trough forced expiratory volume in 1 second (FEV1) in-clinic change from baseline at week 24

End point description:

Trough forced expiratory volume in 1 second (FEV1) in-clinic change from baseline at week 24. Full Analysis Set (FAS): All randomized patients who received at least one dose of treatment. One patient not included in the analysis due to missing baseline value. Number of patients with either baseline or on-treatment data at the respective week and does not require having both.

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	Risankizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[11]	109[12]		
Units: Liter (L)				
least squares mean (standard error)	-0.052 (± 0.036)	-0.013 (± 0.035)		

Notes:

[11] - FAS

[12] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect repeated measures (MMRM) model including treatment, OCS use at baseline, test day, treatment−by−test day interaction, baseline, and baseline−by−test day interaction as covariates patient as a random effect. Unstructured covariance structure for within−patient variation. Comparison of Risankizumab to Placebo.

Comparison groups	Risankizumab v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4423
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.039
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.104
upper limit	0.026
Variability estimate	Standard error of the mean
Dispersion value	0.051

Secondary: Post-bronchodilator forced expiratory volume in 1 second (FEV1) in-clinic change from baseline at week 24

End point title	Post-bronchodilator forced expiratory volume in 1 second (FEV1) in-clinic change from baseline at week 24

End point description:

Post-bronchodilator forced expiratory volume in 1 second (FEV1) in-clinic change from baseline at week 24. FAS: All randomized patients who received at least one dose of treatment. One patient not included in the analysis due to missing baseline value and one patient not included in the analysis due to missing on-treatment data. Number of patients with either baseline or on-treatment data at the respective week and does not require having both.

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	Risankizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[13]	109[14]		
Units: Liter (L)				
least squares mean (standard error)	-0.097 (± 0.032)	-0.030 (± 0.032)		

Notes:

[13] - FAS

[14] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect repeated measures (MMRM) model including treatment, OCS use at baseline, test day, treatment−by−test day interaction, baseline, and baseline−by−test day interaction as covariates patient as a random effect. Unstructured covariance structure for within−patient variation. Comparison of Risankizumab to Placebo.

Comparison groups	Risankizumab v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1377
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.068
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.126
upper limit	-0.009
Variability estimate	Standard error of the mean
Dispersion value	0.045

Secondary: Weekly Asthma Control Questionaire score at week 24

End point title	Weekly Asthma Control Questionaire score at week 24

End point description:

Weekly Asthma Control Questionaire score at week 24. Full Analysis Set (FAS): All randomized patients who received at least one dose of treatment. Ten patients excluded from the analysis due to missing data at week 24.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Risankizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[15]	109[16]		
Units: Unit on Scale				
least squares mean (standard error)	1.857 (± 0.099)	1.708 (± 0.099)		

Notes:

[15] - FAS

[16] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an analysis of covariance (ANCOVA) model separately for each week including treatment, OCS use at baseline, and baseline as covariates. The weekly averages of daily measurements are calculated before fitting the model. Comparison of Risankizumab to Placebo.

Comparison groups	Risankizumab v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1985
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.149
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0
upper limit	0.297
Variability estimate	Standard error of the mean
Dispersion value	0.115

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the administration of first dose of study medication until 16 weeks after last dose of study medication, up to 40 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Risankizumab

Reporting group description:

Patients received subcutaneous injection of 1 milliliter (mL) prefilled syringe with 90 milligram/ milliliter (mg/mL) risankizumab once every 4 weeks (weeks 0, 4, 8, 12, 16, 20)

Reporting group title	Placebo

Reporting group description:

Patients received subcutaneous injection of 1 milliliter (mL) prefilled syringe consisting of matching placebo to risankizumab once every 4 weeks (weeks 0, 4, 8, 12, 16, 20)

Serious adverse events	Risankizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 105 (13.33%)	21 / 109 (19.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Dyskinesia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 105 (0.95%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
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			
Asthma			
subjects affected / exposed	6 / 105 (5.71%)	5 / 109 (4.59%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			

subjects affected / exposed	1 / 105 (0.95%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 105 (0.95%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 105 (0.95%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 105 (0.95%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar spinal stenosis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 105 (0.95%)	0 / 109 (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			
Appendicitis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 105 (0.95%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 105 (0.95%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 105 (0.95%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 109 (0.92%)	
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	Risankizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 105 (80.00%)	80 / 109 (73.39%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	9 / 105 (8.57%)	3 / 109 (2.75%)	
occurrences (all)	10	4	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 105 (6.67%)	6 / 109 (5.50%)	
occurrences (all)	10	13	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	65 / 105 (61.90%)	58 / 109 (53.21%)	
occurrences (all)	153	145	
Dyspnoea			

subjects affected / exposed	6 / 105 (5.71%)	7 / 109 (6.42%)	
occurrences (all)	9	18	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 105 (0.00%)	6 / 109 (5.50%)	
occurrences (all)	0	6	
Infections and infestations			
Bronchitis			
subjects affected / exposed	11 / 105 (10.48%)	9 / 109 (8.26%)	
occurrences (all)	11	10	
Nasopharyngitis			
subjects affected / exposed	11 / 105 (10.48%)	22 / 109 (20.18%)	
occurrences (all)	12	31	
Sinusitis			
subjects affected / exposed	6 / 105 (5.71%)	3 / 109 (2.75%)	
occurrences (all)	6	5	
Upper respiratory tract infection			
subjects affected / exposed	9 / 105 (8.57%)	10 / 109 (9.17%)	
occurrences (all)	10	13	
Urinary tract infection			
subjects affected / exposed	5 / 105 (4.76%)	6 / 109 (5.50%)	
occurrences (all)	6	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2015	Total number of patients changed from 300 to 270; total number of patients in each arm changed from 150 to 135. Converted Visit 11 at week 36 to a phone visit. Removed Asthma Quality of Life Questionnaire (AQLQ) administration and endpoints related to AQLQ. Decreased frequency of blood collection for biomarkers and genotyping. Decreased number of patients to be enrolled in the Bronchoscopy Sub-study from approximately 25 patients in each group to 15 patients in each group. Added serum pregnancy test at Visit 1B. Inclusion Criterion 6 (severe asthma exacerbation) changed to be consistent with American Thoracic Society/European Respiratory Society (ATS/ERS) definitions. Exclusion Criterion 12 (description of birth control use) changed to align with local regulations. Added Exclusion Criterion 20 (exclusion of patients at high risk for allergy/hypersensitivity). Added criterion for investigator to discontinue patients from study for unexpected medical conditions that could compromise patient safety. Added that patients on anticoagulation therapy were not to undergo bronchoscopy procedures. Bronchial wash added to bronchoscopy procedure and storage/shipping conditions clarified. Clarifications on the planned assessments taken during the bronchoscopy procedure. Brief description of biomarker analyses added. Additional revisions included administrative updates and clarifications.
04 December 2015	Clarification in Exclusion Criterion 12 (description of birth control use)
11 July 2016	BI 655066 changed to risankizumab throughout document. Clarification of Screening Period. Total number of patients entered changed from 270 to 200; patients in each treatment group changed from 135 to 100. Modified reversibility criteria to align with current Global Initiative for Asthma guidelines and current practice for reversibility testing. Changed requirement for stable medication prior to screening from 6 weeks to 4 weeks. Changed Inclusion Criterion 6 to allow entry of patients with history of less than 2 asthma exacerbations in previous year but having asthma that was not adequately controlled. Additional instructions provided for reversibility testing. Additional revisions included administrative updates and clarifications.
13 October 2016	Product name changed to reflect change in license agreement with new US sponsor, AbbVie. Changes in reference to Sponsor from BI to AbbVie in US and BI for all other participating countries.
17 August 2017	Addition of alternative definitions 1 and 2 for asthma worsening. Addition of secondary and further endpoints. Asthma worsening criteria modified from increase of 0.5 units to 0.75 units. Statistical model for analysis of primary, secondary, and further endpoints was modified to only include one stratification factor: OCS use at baseline as a fixed effect. Revisions to reflect updates to the Investigator's Brochure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported