EU Clinical Trials Register

Clinical trial results:
A 48 weeks study of three different dose regimens of BI 655066 administered subcutaneously in patients with moderate to severe chronic plaque psoriasis (randomised, dose-ranging, active-comparator-controlled (ustekinumab), double-blind within dose groups of BI 655066)

Summary

EudraCT number	2012-004384-48
Trial protocol	FI SE DE NO
Global end of trial date	31 July 2015

Results information

Result version number	v1 (current)
This version publication date	14 August 2016
First version publication date	14 August 2016

Trial information

Trial identification

Sponsor protocol code	1311.2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02054481
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, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 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	15 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 November 2014
Global end of trial reached?	Yes
Global end of trial date	31 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall purpose of this trial is to assess clinical efficacy and safety of different subcutaneous doses of BI 655066 in adult patients with chronic plaque psoriasis in order to select doses for further clinical trials.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

Ustekinumab (Stelara®) administered by subcutaneous injection plus two saline injections at Week 0, Stelara® injection plus one saline injection at Weeks 4 and 16. Stelara® dose was 45 mg for patients with body weight ≤100 kg at randomisation or 90 mg for patients with body weight >100 kg at randomisation.

Actual start date of recruitment	26 February 2014
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	Canada: 37
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United States: 120
Worldwide total number of subjects	231
EEA total number of subjects	74

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	210
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

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

Blinding implementation details:

The different dose groups of BI 655066 were double-blind. Patients, investigators, and efficacy assessors were blinded to treatment. Stelara® was open-label to investigators and blinded to patients and efficacy assessors.

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 655066 18 mg

Arm description:

18 mg BI 655066 administered by subcutaneous injection plus two placebo matching BI 655066 injections at Week 0, followed by two placebo matching BI 655066 injections each at Weeks 4 and 16.

Arm type	Experimental
Investigational medicinal product name	BI 655066 18 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

18 mg BI 655066 administered by subcutaneous injection at Week 0.

Investigational medicinal product name	Placebo matching BI 655066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Two placebo matching BI 655066 injections administered each at Weeks 0, 4 and 16.

Arm title	BI 655066 90 mg

Arm description:

90 mg BI 655066 administered by subcutaneous injection plus two placebo matching BI 655066 injections at Week 0, followed by 90 mg BI 655066 plus one placebo matching BI 655066 injection at Weeks 4 and 16.

Arm type	Experimental

Investigational medicinal product name	BI 655066 90 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

90 mg BI 655066 administered by subcutaneous injection at Weeks 0, 4 and 16.

Investigational medicinal product name	Placebo matching BI 655066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2 placebo matching BI 655066 injections administered at Weeks 0 and 1 placebo matching BI 655066 injection at Weeks 4 and 16.

Arm title	BI 655066 180 mg

Arm description:

180 mg BI 655066 administered by subcutaneous injection as two injections plus a placebo matching BI 655066 injection at Week 0, followed by 180 mg BI 655066 administered as two injections at Weeks 4 and 16.

Arm type	Experimental
Investigational medicinal product name	BI 655066 180 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

180 mg BI 655066 administered by subcutaneous injection as two injections at Weeks 0, 4 and 16.

Investigational medicinal product name	Placebo matching BI 655066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matching BI 655066 injection administered at Week 0.

Arm title	Stelara®

Arm description:

Stelara® administered by subcutaneous injection plus two saline injections at Week 0, Stelara® injection plus one saline injection at Weeks 4 and 16. Stelara® dose was 45 mg for patients with body weight ≤100 kg at randomisation or 90 mg for patients with body weight >100 kg at randomisation.

Arm type	Active comparator
Investigational medicinal product name	Stelara®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Stelara® 45 mg or 90 mg was administered by subcutaneous injection at Weeks 0, 4 and 16.

Investigational medicinal product name	Saline injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Saline injection was done at Weeks 0, 4 and 16. 2 injections at Week 0 and 1 injection at Weeks 4 and 16.

Number of subjects in period 1[1]	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg
Started	43	41	42
Completed	39	39	40
Not completed	4	2	2
Adverse event, non-fatal	1	1	-
Lost to follow-up	1	-	-
Other reasoon	2	1	2

Number of subjects in period 1[1]	Stelara®
Started	40
Completed	39
Not completed	1
Adverse event, non-fatal	1
Lost to follow-up	-
Other reasoon	-

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 patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups

Reporting group title	BI 655066 18 mg

Reporting group description:

18 mg BI 655066 administered by subcutaneous injection plus two placebo matching BI 655066 injections at Week 0, followed by two placebo matching BI 655066 injections each at Weeks 4 and 16.

Reporting group title	BI 655066 90 mg

Reporting group description:

90 mg BI 655066 administered by subcutaneous injection plus two placebo matching BI 655066 injections at Week 0, followed by 90 mg BI 655066 plus one placebo matching BI 655066 injection at Weeks 4 and 16.

Reporting group title	BI 655066 180 mg

Reporting group description:

180 mg BI 655066 administered by subcutaneous injection as two injections plus a placebo matching BI 655066 injection at Week 0, followed by 180 mg BI 655066 administered as two injections at Weeks 4 and 16.

Reporting group title	Stelara®

Reporting group description:

Stelara® administered by subcutaneous injection plus two saline injections at Week 0, Stelara® injection plus one saline injection at Weeks 4 and 16. Stelara® dose was 45 mg for patients with body weight ≤100 kg at randomisation or 90 mg for patients with body weight >100 kg at randomisation.

Reporting group values	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg
Number of subjects	43	41	42
Age categorical			
Units: Subjects			

Age Continuous			
Safety Set (SAF) which Included all randomised patients who received at least 1 dose of trial medication and was based on the first treatment received.			
Units: Years			
arithmetic mean	44.1	49.3	44.9
standard deviation	± 14.2	± 13.3	± 14
Gender, Male/Female			
Units: Participants			
Female	20	11	13
Male	23	30	29

Reporting group values	Stelara®	Total	
Number of subjects	40	166	
Age categorical			
Units: Subjects			

Age Continuous			
Safety Set (SAF) which Included all randomised patients who received at least 1 dose of trial medication and was based on the first treatment received.			
Units: Years			
arithmetic mean	45.4		
standard deviation	± 12.1	-	

Gender, Male/Female Units: Participants			
Female	13	57	
Male	27	109	

End points

End points reporting groups

Reporting group title	BI 655066 18 mg

Reporting group description:

18 mg BI 655066 administered by subcutaneous injection plus two placebo matching BI 655066 injections at Week 0, followed by two placebo matching BI 655066 injections each at Weeks 4 and 16.

Reporting group title	BI 655066 90 mg

Reporting group description:

90 mg BI 655066 administered by subcutaneous injection plus two placebo matching BI 655066 injections at Week 0, followed by 90 mg BI 655066 plus one placebo matching BI 655066 injection at Weeks 4 and 16.

Reporting group title	BI 655066 180 mg

Reporting group description:

180 mg BI 655066 administered by subcutaneous injection as two injections plus a placebo matching BI 655066 injection at Week 0, followed by 180 mg BI 655066 administered as two injections at Weeks 4 and 16.

Reporting group title	Stelara®

Reporting group description:

Stelara® administered by subcutaneous injection plus two saline injections at Week 0, Stelara® injection plus one saline injection at Weeks 4 and 16. Stelara® dose was 45 mg for patients with body weight ≤100 kg at randomisation or 90 mg for patients with body weight >100 kg at randomisation.

Subject analysis set title	BI 655066 90+180 mg
Subject analysis set type	Full analysis

Subject analysis set description:

90 mg BI 655066 or 180 mg BI 655066 administered by subcutaneous injection at Weeks 0, 4 and 16, plus matching placebos.

Primary: Achievement of ≥90% reduction from baseline PASI score (PASI90) at Week 12

End point title	Achievement of ≥90% reduction from baseline PASI score (PASI90) at Week 12

End point description:

Percentage of participants who achieved ≥90% reduction from baseline in Psoriasis Area and Severity Index score (PASI90) at Week 12. PASI score ranges from 0 (best) to 72 (worst). Full Analysis Set (FAS): Which included all randomised patients who received at least 1 dose of trial medication and was based on the randomised treatment.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg	Stelara®
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43[1]	41[2]	42[3]	40[4]
Units: Percentage of participants				
number (confidence interval 95%)	32.6 (19.1 to 48.5)	73.2 (57.1 to 85.8)	81 (65.9 to 91.4)	40 (24.9 to 56.7)

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

[4] - FAS

End point values	BI 655066 90+180 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	83[5]			
Units: Percentage of participants				
number (confidence interval 95%)	77.1 (66.6 to 85.6)			

Notes:

[5] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The difference in proportion responding between BI 90+180 mg and Stelara® was estimated and tested using the Cochran-Mantel-Haenszel (CMH) risk difference estimate stratified by the randomisation factors of weight (≤100 kg vs. >100 kg) and prior exposure to 2 or more Tumour Necrosis Factor (TNF) antagonists with discontinuation due to lack of efficacy, with weights proposed by Greenland/Robins. Difference calculated as BI 90+180 mg minus Stelara®.

Comparison groups	Stelara® v BI 655066 90+180 mg
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	36.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	19
upper limit	53.8

Notes:

[6] - Pairwise comparisons of all doses and treatments were conducted using the same CMH methods; 95% confidence intervals (CI) as well as nominal p-values of the comparison of doses were provided. There were no adjustments for multiplicity.

Secondary: Achievement of ≥75% reduction from baseline in PASI score (PASI75) at Weeks 12 and 24

End point title	Achievement of ≥75% reduction from baseline in PASI score (PASI75) at Weeks 12 and 24

End point description:

Percentage of participants who achieved ≥75% reduction from baseline in Psoriasis Area and Severity Index score (PASI75) at Weeks 12 and 24. PASI score ranges from 0 (best) to 72 (worst).

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg	Stelara®
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43[7]	41[8]	42[9]	40
Units: Percentage of participants				
number (confidence interval 95%)				
Week 12	67.4 (51.5 to 80.9)	97.6 (87.1 to 99.9)	90.5 (77.4 to 97.3)	77.5 (61.5 to 89.2)
Week 24	55.8 (39.9 to 70.9)	92.7 (80.1 to 98.5)	92.9 (80.5 to 98.5)	70 (53.5 to 83.4)

Notes:

[7] - FAS

[8] - FAS

[9] - FAS

End point values	BI 655066 90+180 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	83[10]			
Units: Percentage of participants				
number (confidence interval 95%)				
Week 12	94 (86.5 to 98)			
Week 24	92.8 (84.9 to 97.3)			

Notes:

[10] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1 (Week 12)

Statistical analysis description:

The difference in proportion responding between BI 90+180 mg and Stelara® was estimated and tested using the Cochran-Mantel-Haenszel (CMH) risk difference estimate stratified by the randomisation factors of weight (≤100 kg vs. >100 kg) and prior exposure to 2 or more TNF antagonists with discontinuation due to lack of efficacy, with weights proposed by Greenland/Robins. Difference calculated as BI 90+180 mg minus Stelara®.

Comparison groups	Stelara® v BI 655066 90+180 mg
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0355 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	28.2

Notes:

[11] - Pairwise comparisons of all doses and treatments were conducted using the same CMH methods; 95% confidence intervals (CI) as well as nominal p-values of the comparison of doses were provided. There were no adjustments for multiplicity.

Statistical analysis title	Statistical analysis 2 (Week 24)

Statistical analysis description:

The difference in proportion responding between BI 90+180 mg and Stelara® was estimated and tested using the Cochran-Mantel-Haenszel (CMH) risk difference estimate stratified by the randomisation factors of weight (≤100 kg vs. >100 kg) and prior exposure to 2 or more TNF antagonists with discontinuation due to lack of efficacy, with weights proposed by Greenland/Robins. Difference calculated as BI 90+180 mg minus Stelara®.

Comparison groups	Stelara® v BI 655066 90+180 mg
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0062 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	21.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	36.2

Notes:

[12] - Pairwise comparisons of all doses and treatments were conducted using the same CMH methods; 95% confidence intervals (CI) as well as nominal p-values of the comparison of doses were provided. There were no adjustments for multiplicity.

Secondary: Achievement of 100% reduction from baseline in PASI score (PASI100) at Week 12

End point title	Achievement of 100% reduction from baseline in PASI score (PASI100) at Week 12

End point description:

Percentage of participants who achieved 100% reduction from baseline in Psoriasis Area and Severity Index score (PASI100) at Week 12.

PASI score ranges from 0 (best) to 72 (worst).

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg	Stelara®
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43[13]	41[14]	42[15]	40
Units: Percentage of participants				
number (confidence interval 95%)	14 (5.3 to 27.9)	41.5 (26.3 to 57.9)	50 (34.2 to 65.8)	17.5 (7.3 to 32.8)

Notes:

[13] - FAS

[14] - FAS

[15] - FAS

End point values	BI 655066 90+180 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	83[16]			

Units: Percentage of participants				
number (confidence interval 95%)	45.8 (34.8 to 57.1)			

Notes:

[16] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The difference in proportion responding between BI 90+180 mg and Stelara® was estimated and tested using the Cochran-Mantel-Haenszel (CMH) risk difference estimate stratified by the randomisation factors of weight (≤100 kg vs. >100 kg) and prior exposure to 2 or more TNF antagonists with discontinuation due to lack of efficacy, with weights proposed by Greenland/Robins. Difference calculated as BI 90+180 mg minus Stelara®.

Comparison groups	Stelara® v BI 655066 90+180 mg
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [17]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	27.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.3
upper limit	42.9

Notes:

[17] - Pairwise comparisons of all doses and treatments were conducted using the same CMH methods; 95% confidence intervals (CI) as well as nominal p-values of the comparison of doses were provided. There were no adjustments for multiplicity.

Secondary: Achievement of ≥50% reduction from baseline in PASI score (PASI50) at Week 12

End point title	Achievement of ≥50% reduction from baseline in PASI score (PASI50) at Week 12

End point description:

Percentage of participants who achieved ≥50% reduction from baseline in Psoriasis Area and Severity Index score (PASI50) at Week 12. PASI score ranges from 0 (best) to 72 (worst).

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg	Stelara®
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43[18]	41[19]	42[20]	40
Units: Percentage of participants				
number (confidence interval 95%)	93 (80.9 to 98.5)	100 (91.4 to 100)	95.2 (83.8 to 99.4)	87.5 (73.2 to 95.8)

Notes:

[18] - FAS

[19] - FAS

[20] - FAS

End point values	BI 655066 90+180 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	83[21]			
Units: Percentage of participants				
number (confidence interval 95%)	97.6 (91.6 to 99.7)			

Notes:

[21] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The difference in proportion responding between BI 90+180 mg and Stelara® was estimated and tested using the Cochran-Mantel-Haenszel (CMH) risk difference estimate stratified by the randomisation factors of weight (≤100 kg vs. >100 kg) and prior exposure to 2 or more TNF antagonists with discontinuation due to lack of efficacy, with weights proposed by Greenland/Robins. Difference calculated as BI 90+180 mg minus Stelara®.

Comparison groups	Stelara® v BI 655066 90+180 mg
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0706 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	21.1

Notes:

[22] - Pairwise comparisons of all doses and treatments were conducted using the same CMH methods; 95% confidence intervals (CI) as well as nominal p-values of the comparison of doses were provided. There were no adjustments for multiplicity.

Secondary: Achievement of PASI90 at Week 24

End point title	Achievement of PASI90 at Week 24

End point description:

Percentage of participants who achieved PASI90 at Week 24. PASI score ranges from 0 (best) to 72 (worst).

End point type	Secondary

End point timeframe:

Week 24

End point values	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg	Stelara®
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43[23]	41[24]	42[25]	40[26]
Units: Percentage of participants				
number (confidence interval 95%)	30.2 (17.2 to 46.1)	65.9 (49.4 to 79.9)	85.7 (71.5 to 94.6)	55 (38.5 to 70.7)

Notes:

[23] - FAS

[24] - FAS

[25] - FAS

[26] - FAS

End point values	BI 655066 90+180 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	83[27]			
Units: Percentage of participants				
number (confidence interval 95%)	75.9 (65.3 to 84.6)			

Notes:

[27] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The difference in proportion responding between BI 90+180 mg and Stelara® was estimated and tested using the Cochran-Mantel-Haenszel (CMH) risk difference estimate stratified by the randomisation factors of weight (≤100 kg vs. >100 kg) and prior exposure to 2 or more TNF antagonists with discontinuation due to lack of efficacy, with weights proposed by Greenland/Robins. Difference calculated as BI 90+180 mg minus Stelara®.

Comparison groups	Stelara® v BI 655066 90+180 mg
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	37.7

Notes:

[28] - Pairwise comparisons of all doses and treatments were conducted using the same CMH methods; 95% confidence intervals (CI) as well as nominal p-values of the comparison of doses were provided. There were no adjustments for multiplicity.

Secondary: Percentage change in PASI score from baseline at Week 12

End point title	Percentage change in PASI score from baseline at Week 12

End point description:

Percentage change in Psoriasis Area and Severity Index (PASI) from baseline at Week 12.

PASI score ranges from 0 (best) to 72 (worst).

End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg	Stelara®
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[29]	41[30]	41[31]	37[32]
Units: Percentage of PASI score				
arithmetic mean (standard deviation)	-79.7 (± 19.5)	-93.4 (± 7.7)	-90.7 (± 23.1)	-82.1 (± 19.5)

Notes:

[29] - FAS

[30] - FAS

[31] - FAS

[32] - FAS

End point values	BI 655066 90+180 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	82[33]			
Units: Percentage of PASI score				
arithmetic mean (standard deviation)	-92.1 (± 17.1)			

Notes:

[33] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Achievement of sPGA clear or almost clear at Week 12

End point title	Achievement of sPGA clear or almost clear at Week 12
End point description:	

Percentage of participants who achieved static Physician Global Assessment (sPGA) clear or almost clear at Week 12. sPGA is assessed on a six-point scale from 0 (clear) to 5 (severe).

End point type	Secondary
End point timeframe:	
Week 12	

End point values	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg	Stelara®
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43[34]	41[35]	42[36]	40
Units: Percentage of participants				
number (confidence interval 95%)	62.8 (46.7 to 77)	90.2 (76.9 to 97.3)	90.5 (77.4 to 97.3)	67.5 (50.9 to 81.4)

Notes:

[34] - FAS

[35] - FAS

[36] - FAS

End point values	BI 655066 90+180 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	83[37]			
Units: Percentage of participants				
number (confidence interval 95%)	90.4 (81.9 to 95.7)			

Notes:

[37] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The difference in proportion responding between BI 90+180 mg and Stelara® was estimated and tested using the Cochran-Mantel-Haenszel (CMH) risk difference estimate stratified by the randomisation factors of weight (≤100 kg vs. >100 kg) and prior exposure to 2 or more TNF antagonists with discontinuation due to lack of efficacy, with weights proposed by Greenland/Robins. Difference calculated as BI 90+180 mg minus Stelara®.

Comparison groups	Stelara® v BI 655066 90+180 mg
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0072 [38]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	21.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.7
upper limit	36.6

Notes:

[38] - Pairwise comparisons of all doses and treatments were conducted using the same CMH methods; 95% confidence intervals (CI) as well as nominal p-values of the comparison of doses were provided. There were no adjustments for multiplicity.

Secondary: Time to loss of PASI50 response

End point title	Time to loss of PASI50 response

End point description:

Time to loss of PASI50 response. 99999: Summary statistics were not calculable due to low number of patients with events.

End point type	Secondary

End point timeframe:

From first drug administration until end of follow-up period, up to 48 weeks.

End point values	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg	Stelara®
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43[39]	41[40]	42[41]	40[42]
Units: Days				
median (confidence interval 95%)	253 (212 to 285)	99999 (99999 to 99999)	99999 (99999 to 99999)	338 (253 to 99999)

Notes:

[39] - FAS

[40] - FAS

[41] - FAS

[42] - FAS

End point values	BI 655066 90+180 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	83[43]			
Units: Days				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[43] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
BI 655066 treatment groups BI 90 mg + 180 mg were tested vs. Stelara® using a stratified Kaplan-Meier estimate and the log-rank test.	
Comparison groups	Stelara® v BI 655066 90+180 mg
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [44]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.1844
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.4

Notes:

[44] - Pairwise comparisons of all doses and treatments were conducted using the same CMH methods; 95% confidence intervals (CI) as well as nominal p-values of the comparison of doses were provided. There were no adjustments for multiplicity.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 15 weeks after the last drug administration, up to 231 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	BI 655066 18 mg

Reporting group description:

18 mg BI 655066 administered by subcutaneous injection plus two placebo matching BI 655066 injections at Week 0, followed by two placebo matching BI 655066 injections each at Weeks 4 and 16.

Reporting group title	BI 655066 90 mg

Reporting group description:

90 mg BI 655066 administered by subcutaneous injection plus two placebo matching BI 655066 injections at Week 0, followed 90 mg BI 655066 plus one placebo matching BI 655066 injection at Weeks 4 and 16.

Reporting group title	BI 655066 180 mg

Reporting group description:

180 mg BI 655066 administered by subcutaneous injection as two injections plus a placebo matching BI 655066 injection at Week 0, followed 180 mg BI 655066 administered as two injections at Weeks 4 and 16.

Reporting group title	Stelara®

Reporting group description:

Stelara® administered by subcutaneous injection plus two saline injections at Week 0, Stelara® injection plus one saline injection at Weeks 4 and 16. Stelara® dose was 45 mg for patients with body weight ≤100 kg at randomisation or 90 mg for patients with body weight >100 kg at randomisation.

Serious adverse events	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 43 (11.63%)	6 / 41 (14.63%)	0 / 42 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 43 (2.33%)	1 / 41 (2.44%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland neoplasm			

subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications

Pelvic fracture

subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rib fracture

subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders

Acute myocardial infarction

subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Coronary artery occlusion

subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Surgical and medical procedures

Abortion induced

subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders

Cerebrovascular accident

subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Headache

subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perineal abscess			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Stelara®		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 40 (7.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Salivary gland neoplasm			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rib fracture			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery occlusion			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Immune system disorders

Allergy to arthropod bite

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Gastrointestinal disorders

Gastrointestinal haemorrhage

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Skin and subcutaneous tissue disorders

Erythema multiforme

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Infections and infestations

Bronchitis

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Diverticulitis

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Perineal abscess

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Urinary tract infection

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BI 655066 18 mg	BI 655066 90 mg	BI 655066 180 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 43 (76.74%)	32 / 41 (78.05%)	29 / 42 (69.05%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 43 (11.63%)	2 / 41 (4.88%)	3 / 42 (7.14%)
occurrences (all)	6	2	3
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 43 (2.33%)	1 / 41 (2.44%)	3 / 42 (7.14%)
occurrences (all)	1	1	3
Psoriasis			
subjects affected / exposed	3 / 43 (6.98%)	1 / 41 (2.44%)	0 / 42 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 43 (2.33%)	2 / 41 (4.88%)	3 / 42 (7.14%)
occurrences (all)	2	2	3
Back pain			
subjects affected / exposed	2 / 43 (4.65%)	4 / 41 (9.76%)	1 / 42 (2.38%)
occurrences (all)	2	4	1
Myalgia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	3 / 42 (7.14%)
occurrences (all)	0	1	3
Infections and infestations			
Folliculitis			
subjects affected / exposed	3 / 43 (6.98%)	1 / 41 (2.44%)	1 / 42 (2.38%)
occurrences (all)	3	1	1
Gastroenteritis			

subjects affected / exposed	1 / 43 (2.33%)	4 / 41 (9.76%)	0 / 42 (0.00%)
occurrences (all)	1	4	0
Nasopharyngitis			
subjects affected / exposed	15 / 43 (34.88%)	14 / 41 (34.15%)	11 / 42 (26.19%)
occurrences (all)	19	20	17
Rhinitis			
subjects affected / exposed	0 / 43 (0.00%)	3 / 41 (7.32%)	1 / 42 (2.38%)
occurrences (all)	0	4	1
Sinusitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 43 (0.00%)	3 / 41 (7.32%)	1 / 42 (2.38%)
occurrences (all)	0	3	1

Non-serious adverse events	Stelara®		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 40 (72.50%)		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Psoriasis			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Myalgia			

subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Infections and infestations			
Folliculitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Rhinitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2014	Global protocol amendment 1 introduced the following key changes: 1. The inclusion criterion 8 was modified to add having vasectomized sexual partner(s) as an acceptable option of contraception for female patients. 2. Rules for blinding/unblinding of the trial team, investigators, efficacy assessors, and patients were specified. Unblinding of the trial bioanalyst and bioanalytical laboratory to support PK/ADA sample bioanalysis was introduced and blinded data reviews of PK/ADA results by the trial team were specified. 3. A restriction on the use of moisturizers/emollients containing retinoids and the use of tanning beds was introduced. Their use was not allowed as it could ameliorate psoriasis disease activity. 4. It was specified that body temperature could be measured orally or tympanically. The same BP recording instrument was to be used if possible. 5. Procedures for re-screening of patients in exceptional cases were introduced. 6. Further details on the procedure of obtaining skin biopsies were added.
25 June 2014	Global protocol amendment 2 allowed for a pre-randomisation call to the IRT for logistical reasons.
03 July 2014	Global protocol amendment 3 introduced the following key changes: 1. Rules for roll-over to the open-label extension study 1311.13 were specified 2. Exclusion criterion 4 was specified with regards to latent and active tuberculosis. Patients with latent or active TB were to continue to be excluded from the trial, but in case of a positive QuantiFERON test and documentation of adequately treated infection with no signs and symptoms of currently ongoing active or latent TB infection, the patients could have been included. 3. Exclusion criterion 11, concerning prior participation in another trial, was modified to be consistent with the restricted medication rules.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported