



Clinical trial results:

A randomised, double-blind, placebo-controlled trial for establishing safety, tolerability, pharmacokinetics, pharmacodynamics and clinical efficacy of multiple subcutaneous doses of BI 655064 in healthy volunteers and in rheumatoid arthritis patients with prior inadequate response to methotrexate therapy.

Summary

EudraCT number	2012-004090-16
Trial protocol	DE ES CZ NL
Global end of trial date	27 April 2015

Results information

Result version number	v2 (current)
This version publication date	24 August 2016
First version publication date	08 May 2016
Version creation reason	<ul style="list-style-type: none">• New data added to full data set New data is not added, but a note is deleted from the Limitation and Caveats sections stating that "the PK outcome measures will be adapted as soon as the final report is available". The clinical trial report has been finalized now and no updates are required to the results which were posted earlier.

Trial information

Trial identification

Sponsor protocol code	1293.2
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01751776
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, +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 243 0127, 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	06 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 March 2015
Global end of trial reached?	Yes
Global end of trial date	27 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial objective was to evaluate safety and systemic and local tolerability of 4 weeks of repeated subcutaneous doses of 80, 120, 180 or 240 mg BI 655064 per week administered to healthy volunteers (HVs; Part 1, Phase Ib), and of 12 weeks of repeated doses of 120 mg BI 655064 per week in patients with rheumatoid arthritis (RA) who had prior inadequate response to methotrexate (MTX) therapy (Part 2, Phase IIa).

Protection of trial subjects:

Prior to the initiation of any trial-related procedure, all patients were informed about the trial verbally and in writing by the investigator. Each patient signed and dated an informed consent form according to Good Clinical Practice (GCP) and local regulatory and legal requirements. Separate informed consent was obtained for pharmacogenomic testing.

The trial had a multi-part design where the progression from one dose group to the higher one was contingent upon the favourable completion of the prior dose group. The accrued trial data were therefore evaluated by an independent Data Monitoring Committee (DMC), which in the absence of safety concerns, could recommend the initiation of the next higher dose group.

Healthy volunteers were exposed to the risks of the trial procedures and trial medication, and did not receive a direct benefit from participation in this trial. However, they were under close medical supervision throughout the trial. Doses of 80 and 120 milligram (mg) BI 655064 were expected to be well tolerated by healthy volunteers. Advancement to the 2 higher doses (180 and 240 mg) was only to be allowed after safety review of the lower doses by the DMC, including preliminary PK assessment and projection of the anticipated exposure to the higher doses.

All patients in Part 2 (Phase IIa) were to remain on background Methotrexate (MTX) for the 12 week period of BI 655064 treatment. Furthermore, therapy with systemic glucocorticoids (GCs) was permitted at up to a maximum dose of 10 mg prednisolone/day (or the equivalent) during the entire period of trial treatment. NSAIDs and analgesics were also permitted at the investigator's discretion. The theoretical risks of thromboembolic events and uncontrolled cytokine release were to be mitigated by close clinical and laboratory monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 January 2013
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	New Zealand: 52
--------------------------------------	-----------------

Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Poland: 46
Country: Number of subjects enrolled	Spain: 8
Worldwide total number of subjects	144
EEA total number of subjects	92

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)	126
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study included a part 1 (Phase Ib multiple rising dose) where 40 healthy volunteers were recruited, in 4 sequential groups of 10 subjects (8 of them received active drug, 2 placebo) each. Thereafter a part 2 (Phase 2a) was conducted. 67 patients with RA and who had prior inadequate response to MTX treatment were randomised into 2 arms.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they (the subjects) met all implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial drug if any 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, Subject, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

This study was a Randomised, placebo controlled and double blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1, Placebo BI 655064 80/120mg (HV)

Arm description:

Part 1, Healthy volunteers (HV): Placebo matching BI 655064 80 or 120 milligram (mg) injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.

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

Dosage and administration details:

Placebo matching BI 655064 80 or 120 milligram (mg) injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.

Arm title	Part 1, Placebo BI 655064 180/240mg (HV)
------------------	--

Arm description:

Part 1, Healthy volunteers (HV): Placebo matching BI 655064 180 or 240 mg injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks (180mg dosing group) or 8 weeks (240mg dosing group) follow-up period.

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

Dosage and administration details:

Placebo matching BI 655064 180 or 240 mg injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks (180mg dosing group) or 8 weeks (240mg dosing group) follow-up period.

Arm title	Part 1, BI 655064 80mg (HV)
Arm description: Part 1, Healthy volunteers (HV): 80 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Arm type	Experimental
Investigational medicinal product name	BI 655064
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: 80 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Arm title	Part 1, BI 655064 120mg (HV)
Arm description: Part 1, Healthy volunteers (HV): 120 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Arm type	Experimental
Investigational medicinal product name	BI 655064
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: 120 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Arm title	Part 1, BI 655064 180mg (HV)
Arm description: Part 1, Healthy volunteers (HV): 180 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Arm type	Experimental
Investigational medicinal product name	BI 655064
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: 180 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Arm title	Part 1, BI 655064 240mg (HV)
Arm description: Part 1, Healthy volunteers (HV): 240mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 8 weeks follow-up period.	
Arm type	Experimental
Investigational medicinal product name	BI 655064
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: 240 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 8 weeks follow-up period.	
Arm title	Part 2, Placebo BI 655064 120mg (RA)

Arm description:

Part 2, patients with Rheumatoid arthritis (RA) who had prior inadequate response to Methotrexat (MTX) therapy: Placebo matching BI 655064 120 milligram (mg) injected subcutaneous on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (once weekly for 12 weeks) followed by 8 weeks follow-up period.

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

Dosage and administration details:

Placebo matching BI 655064 120 milligram (mg) injected subcutaneous on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (once weekly for 12 weeks) followed by 8 weeks follow-up period.

Arm title	Part 2, BI 655064 120mg (RA)
------------------	------------------------------

Arm description:

Part 2, patients with Rheumatoid arthritis (RA) who had prior inadequate response to MTX therapy: 120 milligram (mg) of BI 655064 injected subcutaneous on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (once weekly for 12 weeks) followed by 8 weeks follow-up period.

Arm type	Experimental
Investigational medicinal product name	BI 655064
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Part 2, patients with Rheumatoid arthritis (RA): 120 milligram (mg) of BI 655064 injected subcutaneous on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (once weekly for 12 weeks) followed by 8 weeks follow-up period.

Number of subjects in period 1^[1]	Part 1, Placebo BI 655064 80/120mg (HV)	Part 1, Placebo BI 655064 180/240mg (HV)	Part 1, BI 655064 80mg (HV)
Started	4	4	8
Completed	4	4	8
Not completed	0	0	0
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Other reason not specified above	-	-	-

Number of subjects in period 1^[1]	Part 1, BI 655064 120mg (HV)	Part 1, BI 655064 180mg (HV)	Part 1, BI 655064 240mg (HV)
Started	8	8	8
Completed	8	8	8
Not completed	0	0	0
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-

Other reason not specified above	-	-	-
----------------------------------	---	---	---

Number of subjects in period 1 ^[1]	Part 2, Placebo BI 655064 120mg (RA)	Part 2, BI 655064 120mg (RA)
Started	23	44
Completed	19	40
Not completed	4	4
Adverse event, serious fatal	-	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	4	1
Other reason not specified above	-	1

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 of the trial medication.

Baseline characteristics

Reporting groups

Reporting group title	Part 1, Placebo BI 655064 80/120mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): Placebo matching BI 655064 80 or 120 milligram (mg) injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Reporting group title	Part 1, Placebo BI 655064 180/240mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): Placebo matching BI 655064 180 or 240 mg injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks (180mg dosing group) or 8 weeks (240mg dosing group) follow-up period.	
Reporting group title	Part 1, BI 655064 80mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): 80 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Reporting group title	Part 1, BI 655064 120mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): 120 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Reporting group title	Part 1, BI 655064 180mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): 180 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Reporting group title	Part 1, BI 655064 240mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): 240mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 8 weeks follow-up period.	
Reporting group title	Part 2, Placebo BI 655064 120mg (RA)
Reporting group description: Part 2, patients with Rheumatoid arthritis (RA) who had prior inadequate response to Methotrexat (MTX) therapy: Placebo matching BI 655064 120 milligram (mg) injected subcutaneous on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (once weekly for 12 weeks) followed by 8 weeks follow-up period.	
Reporting group title	Part 2, BI 655064 120mg (RA)
Reporting group description: Part 2, patients with Rheumatoid arthritis (RA) who had prior inadequate response to MTX therapy: 120 milligram (mg) of BI 655064 injected subcutaneous on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (once weekly for 12 weeks) followed by 8 weeks follow-up period.	

Reporting group values	Part 1, Placebo BI 655064 80/120mg (HV)	Part 1, Placebo BI 655064 180/240mg (HV)	Part 1, BI 655064 80mg (HV)
Number of subjects	4	4	8
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	21.5 ± 1.3	34 ± 15.4	25.9 ± 4.1

Gender, Male/Female			
Units: Participants			
Female	0	2	2
Male	4	2	6

Reporting group values	Part 1, BI 655064 120mg (HV)	Part 1, BI 655064 180mg (HV)	Part 1, BI 655064 240mg (HV)
Number of subjects	8	8	8
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	31.4	37.3	29.5
standard deviation	± 13.3	± 10.8	± 10.6
Gender, Male/Female			
Units: Participants			
Female	0	2	1
Male	8	6	7

Reporting group values	Part 2, Placebo BI 655064 120mg (RA)	Part 2, BI 655064 120mg (RA)	Total
Number of subjects	23	44	107
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	55.1	53.7	
standard deviation	± 8.3	± 13.3	-
Gender, Male/Female			
Units: Participants			
Female	18	37	62
Male	5	7	45

End points

End points reporting groups

Reporting group title	Part 1, Placebo BI 655064 80/120mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): Placebo matching BI 655064 80 or 120 milligram (mg) injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Reporting group title	Part 1, Placebo BI 655064 180/240mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): Placebo matching BI 655064 180 or 240 mg injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks (180mg dosing group) or 8 weeks (240mg dosing group) follow-up period.	
Reporting group title	Part 1, BI 655064 80mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): 80 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Reporting group title	Part 1, BI 655064 120mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): 120 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Reporting group title	Part 1, BI 655064 180mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): 180 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 6 weeks follow-up period.	
Reporting group title	Part 1, BI 655064 240mg (HV)
Reporting group description: Part 1, Healthy volunteers (HV): 240mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly, for 4 weeks) followed by 8 weeks follow-up period.	
Reporting group title	Part 2, Placebo BI 655064 120mg (RA)
Reporting group description: Part 2, patients with Rheumatoid arthritis (RA) who had prior inadequate response to Methotrexat (MTX) therapy: Placebo matching BI 655064 120 milligram (mg) injected subcutaneous on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (once weekly for 12 weeks) followed by 8 weeks follow-up period.	
Reporting group title	Part 2, BI 655064 120mg (RA)
Reporting group description: Part 2, patients with Rheumatoid arthritis (RA) who had prior inadequate response to MTX therapy: 120 milligram (mg) of BI 655064 injected subcutaneous on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (once weekly for 12 weeks) followed by 8 weeks follow-up period.	
Subject analysis set title	Part 1, Placebo BI 655064 (HV)
Subject analysis set type	Safety analysis
Subject analysis set description: Part 1, Healthy volunteers (HV): Placebo of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly) followed by a 6 weeks (120mg dosing group) or a 8 weeks (240mg dosing group) follow-up period. Within each dose group two subjects were to receive placebo.	

Primary: Part 1: Cmax after the first and last dose

End point title	Part 1: Cmax after the first and last dose ^[1]
End point description: Part 1: This outcome measure presents the maximum measured concentration of BI 655064 in plasma (Cmax) after the first and last (fourth) dose. More detailed time frame: Pharmacokinetic (PK) sample times: 0:30 hour (h) prior first administration of BI 655064 and 1 h, 8 h, 12 h, 24 h, 48 h, 72 h, 84 h, 96 h, 108 h, 120 h, 144 h, 167:30 h, 335:30 h, 503:30 h, 505 h, 516 h, 528 h, 552 h, 576 h, 600 h, 624 h, 648 h, 672 h, 696 h, 744 h, 816 h, 912 h, 1008 h, 1176 h, 1344 h, 1512 h, 1848 h thereafter; further administration times for BI 655064: 168 h, 336 h, and 504 h after first administration. All subjects were treated and provided data for at least 1 primary pharmacokinetic (PK) endpoint and	

therefore all subjects were also included in the PK set (PKS).

End point type	Primary
End point timeframe:	
after the first dose on day 1 and after the last dose on day 22	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Part 1, BI 655064 80mg (HV)	Part 1, BI 655064 120mg (HV)	Part 1, BI 655064 180mg (HV)	Part 1, BI 655064 240mg (HV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8 ^[2]	8 ^[3]	8 ^[4]	8 ^[5]
Units: microgram (µg)/ millilitre (mL)				
geometric mean (geometric coefficient of variation)				
after the first dose	1.59 (± 492)	7.7 (± 29.5)	9.87 (± 67.8)	18 (± 46.3)
after the last (fourth) dose	13.1 (± 59.1)	28.7 (± 35.6)	39.8 (± 37.4)	68.4 (± 21.9)

Notes:

[2] - PKS

[3] - PKS

[4] - PKS

[5] - PKS

Statistical analyses

Statistical analysis title	Cmax after the first dose of BI 655064, day 1
Statistical analysis description:	
Dose proportionality for Cmax was explored after the first administration of BI 65564 on Day 1.	
Comparison groups	Part 1, BI 655064 120mg (HV) v Part 1, BI 655064 80mg (HV) v Part 1, BI 655064 180mg (HV) v Part 1, BI 655064 240mg (HV)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other ^[6]
Parameter estimate	Slope
Point estimate	2.0506
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1843
upper limit	2.9168
Variability estimate	Standard error of the mean
Dispersion value	0.4242

Notes:

[6] - Measure type: Dose proportionality was explored using a regression model. Based on the estimate for the slope parameter, a two sided 95% confidence interval for the slope was computed. Perfect dose proportionality would correspond to a slope of 1. PK endpoints on the log-transformed scale.

Statistical analysis title	Cmax after the last dose of BI 655064, day 22
Statistical analysis description:	
Dose proportionality for Cmax was explored after the last administration of BI 65564 on Day 22.	
Comparison groups	Part 1, BI 655064 80mg (HV) v Part 1, BI 655064 120mg (HV)

	v Part 1, BI 655064 180mg (HV) v Part 1, BI 655064 240mg (HV)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other ^[7]
Parameter estimate	Slope
Point estimate	1.4227
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.0869
upper limit	1.7584
Variability estimate	Standard error of the mean
Dispersion value	0.1644

Notes:

[7] - Measure type: Dose proportionality was explored using a regression model. Based on the estimate for the slope parameter, a two sided 95% confidence interval for the slope was computed. Perfect dose proportionality would correspond to a slope of 1. PK endpoints on the log-transformed scale.

Primary: Part 1: AUC 0-infinity after the last dose

End point title	Part 1: AUC 0-infinity after the last dose ^[8]
End point description:	
Primary PK endpoint (Part 1): Area under the concentration-time curve of BI 655064 in plasma over the time interval from 0 extrapolated to infinite (AUC 0-infinity).	
End point type	Primary
End point timeframe:	
PK sample times: 1 h, 12 h, 24 h, 48 h, 72 h, 96 h, 120 h, 144 h, 168 h, 192 h, 240 h, 312 h, 408 h, 504 h, 672 h, 840 h, 1008 h, 1344 h after the last administration of BI 655064 on day 22	

Notes:

[8] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Part 1, BI 655064 80mg (HV)	Part 1, BI 655064 120mg (HV)	Part 1, BI 655064 180mg (HV)	Part 1, BI 655064 240mg (HV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8 ^[9]	8 ^[10]	8 ^[11]	8 ^[12]
Units: µg* hours (h)/mL				
geometric mean (geometric coefficient of variation)	3940 (± 53.9)	11000 (± 42.5)	19200 (± 41.1)	39300 (± 26.1)

Notes:

[9] - PKS

[10] - PKS

[11] - PKS

[12] - PKS

Statistical analyses

Statistical analysis title	AUC 0-infinity after the last dose
Statistical analysis description:	
Dose proportionality for AUC 0-infinity was explored after the last administration of BI 65564 on Day 22.	
Comparison groups	Part 1, BI 655064 80mg (HV) v Part 1, BI 655064 120mg (HV) v Part 1, BI 655064 180mg (HV) v Part 1, BI 655064 240mg (HV)

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other ^[13]
Parameter estimate	Slope
Point estimate	2.0091
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6607
upper limit	2.3575
Variability estimate	Standard error of the mean
Dispersion value	0.1706

Notes:

[13] - Dose proportionality was explored using a regression model. Based on the estimate for the slope parameter, a two sided 95% confidence interval for the slope was computed. Perfect dose proportionality would correspond to a slope of 1. PK endpoints on the log-transformed scale.

Primary: Part 1: AUCtau after the last dose

End point title	Part 1: AUCtau after the last dose ^[14]
End point description:	Area under the concentration-time curve of BI 655064 in plasma after the 4th dose over a uniform dosing interval t (AUC t,4) after the first and 4th dose. AUCtau is synonymus with AUC0-168.
End point type	Primary

End point timeframe:

PK sample times: 1, 12, 24, 48, 72, 96, 120, 144, 168, 192, 240, 312, 408, 504, 672, 840, 1008, 1344 h after the last administration of trial drug on day 22

Notes:

[14] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Part 1, BI 655064 80mg (HV)	Part 1, BI 655064 120mg (HV)	Part 1, BI 655064 180mg (HV)	Part 1, BI 655064 240mg (HV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: µg*h/mL				
geometric mean (geometric coefficient of variation)	1790 (± 56.4)	4140 (± 35.4)	5470 (± 37.4)	9460 (± 22.4)

Statistical analyses

Statistical analysis title	AUCtau after the last dose
Statistical analysis description:	Dose proportionality for AUCtau was explored after the last administration of BI 65564 on Day 22.
Comparison groups	Part 1, BI 655064 80mg (HV) v Part 1, BI 655064 120mg (HV) v Part 1, BI 655064 180mg (HV) v Part 1, BI 655064 240mg (HV)

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other ^[15]
Parameter estimate	Slope
Point estimate	1.4225
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.0876
upper limit	1.7574
Variability estimate	Standard error of the mean
Dispersion value	0.164

Notes:

[15] - Dose proportionality was explored using a regression model. Based on the estimate for the slope parameter, a two sided 95% confidence interval for the slope was computed. Perfect dose proportionality would correspond to a slope of 1. PK endpoints on the log-transformed scale.

Primary: Part 1: Percentage of subjects with drug related Adverse Events

End point title	Part 1: Percentage of subjects with drug related Adverse Events ^{[16][17]}
-----------------	---

End point description:

In Part 1 (Phase Ib): The primary safety endpoint was the percentage of subjects with AEs related to treatment with trial medication.

End point type	Primary
----------------	---------

End point timeframe:

from first administration of study medication (day 1) up to day 64 (dosing groups 80, 120, 180mg) or up to day 78 post-treatment (dosing group 240mg)

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

[17] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Part 1, BI 655064 80mg (HV)	Part 1, BI 655064 120mg (HV)	Part 1, BI 655064 180mg (HV)	Part 1, BI 655064 240mg (HV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8 ^[18]	8 ^[19]	8 ^[20]	8 ^[21]
Units: Percentage of participants				
number (not applicable)	25	12.5	50	0

Notes:

[18] - Of the 40 subjects, all were treated and included in the treated set (TS).

[19] - TS

[20] - TS

[21] - TS

End point values	Part 1, Placebo BI 655064 (HV)			
Subject group type	Subject analysis set			
Number of subjects analysed	8 ^[22]			
Units: Percentage of participants				

number (not applicable)	50			
-------------------------	----	--	--	--

Notes:

[22] - TS

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: American College of Rheumatology (ACR) 20 response rate at week 12

End point title	Part 2: American College of Rheumatology (ACR) 20 response rate at week 12 ^{[23][24]}
-----------------	--

End point description:

ACR20 (week 12) relative to the patient's status at baseline: that is, at least 20 percent (%) improvement (impr.) in swollen joint count, at least 20% impr. in tender joint count, and at least 20% impr. in ≥ 3 of the following 5 variables: 1) patient's assessment of pain on visual analogue scale (VAS), rated on a scale of 1 to 10; 2) patient's global assessment of disease on VAS, rated on a scale of 1 to 10; 3) investigator's global assessment of disease on VAS; 4) patient's assessment of disability on health assessment questionnaire (HAQ), rated on a scale of 1 to 3; and 5) concentrations of acute phase reactants. For all scales (1-4): smaller values better. ACR20 were evaluated descriptively. Data were analysed with a Bayesian approach using an informative prior for the placebo treatment group; predictive probability that treatment difference was larger than 0, 5, 10, 15, 20, 25, 30, 35, 40 or 45% was to be evaluated. "99999" entered instead of "not applicable" (system limitations)

End point type	Primary
----------------	---------

End point timeframe:

at week 12 (day 85) from the initiation of study treatment

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

[24] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Part 2, Placebo BI 655064 120mg (RA)	Part 2, BI 655064 120mg (RA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[25]	44 ^[26]		
Units: Percentage of participants				
number (not applicable)				
Subjects with ACR20 response	45.5	68.2		
Observed difference of ACR20 response (resp.)	99999	22.7		
Posterior mean difference (diff.) of ACR20 resp.	99999	33		
Probability that the diff. of ACR20 resp. is > 0%	99999	99.9		
Probability that the diff. of ACR20 resp. is > 5%	99999	99.7		
Probability that the diff. of ACR20 resp. is > 10%	99999	98.7		
Probability that the diff. of ACR20 resp. is > 15%	99999	96		

Probability that the diff. of ACR20 resp. is > 20%	99999	90		
Probability that the diff. of ACR20 resp. is > 25%	99999	79		
Probability that the diff. of ACR20 resp. is > 30%	99999	62.5		
Probability that the diff. of ACR20 resp. is > 35%	99999	42.9		

Notes:

[25] - Full analysis set (FAS): randomised and treated patients; Non-completers assumed to be failures (NCF)

[26] - FAS (NCF)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: ACR50 response rates at week 12

End point title	Part 2: ACR50 response rates at week 12 ^[27]
-----------------	---

End point description:

ACR 50 criteria at week 12 relative to the patient's status at baseline: that is, at least 50 % improvement in swollen joint count, at least 50% improvement in tender joint count, and at least 50% improvement in ≥ 3 of the following 5 variables: 1) patient's assessment of pain on the visual analogue scale (VAS), rated on a scale of 1 to 10; 2) patient's global assessment of disease on the VAS, rated on a scale of 1 to 10; 3) investigator's global assessment of disease on the VAS; 4) patient's assessment of disability on the health assessment questionnaire (HAQ), rated on a scale of 1 to 3; and 5) concentrations of acute phase reactants. For all scales (1-4): smaller values better. The percentage of subjects with ACR50 response is presented.

End point type	Secondary
----------------	-----------

End point timeframe:

at week 12 (day 85)

Notes:

[27] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Part 2, Placebo BI 655064 120mg (RA)	Part 2, BI 655064 120mg (RA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[28]	44 ^[29]		
Units: Percentage of participants				
number (confidence interval 95%)				
unadjusted	18.2 (5.2 to 40.3)	36.4 (22.4 to 52.2)		
adjusted	15.6 (5.5 to 36.9)	35.6 (22.3 to 51.5)		

Notes:

[28] - FAS (NCF)

[29] - FAS (NCF)

Statistical analyses

Statistical analysis title	Placebo vs. BI655064, unadjusted
----------------------------	----------------------------------

Statistical analysis description:

The exact 95% confidence interval was calculated by Clopper and Pearson.

Comparison groups	Part 2, BI 655064 120mg (RA) v Part 2, Placebo BI 655064 120mg (RA)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0754 ^[30]
Method	One-sided exact test (see description)
Parameter estimate	Risk difference, unadjusted
Point estimate	18.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	38.6

Notes:

[30] - one-sided exact test for superiority testing.

Statistical analysis title	Placebo vs. BI655064, adjusted
-----------------------------------	--------------------------------

Statistical analysis description:

The 95 % confidence interval was determined by root method to determine the cumulative distribution function.

Comparison groups	Part 2, Placebo BI 655064 120mg (RA) v Part 2, BI 655064 120mg (RA)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority ^[31]
Parameter estimate	Risk difference, adjusted
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	39

Notes:

[31] - Adjusted for treatment, region and anti-Tumour Necrosis Factor (TNF).

Secondary: Part 2: ACR70 response rates at 12 weeks

End point title	Part 2: ACR70 response rates at 12 weeks ^[32]
-----------------	--

End point description:

ACR70 criteria at week 12 relative to the patient's status at baseline: that is, at least 70 % improvement in swollen joint count, at least 70% improvement in tender joint count, and at least 70% improvement in ≥ 3 of the following 5 variables: 1) patient's assessment of pain on the visual analogue scale (VAS), rated on a scale of 1 to 10; 2) patient's global assessment of disease on the VAS, rated on a scale of 1 to 10; 3) investigator's global assessment of disease on the VAS; 4) patient's assessment of disability on the health assessment questionnaire (HAQ), rated on a scale of 1 to 3; and 5) concentrations of acute phase reactants. For all scales (1-4): smaller values better). The percentage of subjects with ACR50 response is presented.

End point type	Secondary
----------------	-----------

End point timeframe:

at week 12 (day 85)

Notes:

[32] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Part 2, Placebo BI 655064 120mg (RA)	Part 2, BI 655064 120mg (RA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[33]	44 ^[34]		
Units: Percentage of participants				
number (confidence interval 95%)				
unadjusted	13.6 (2.9 to 34.9)	18.2 (8.2 to 32.7)		
adjusted	13 (4 to 34.6)	17 (8.3 to 31.6)		

Notes:

[33] - FAS (NCF)

[34] - FAS (NCF)

Statistical analyses

Statistical analysis title	Placebo vs. BI 655064, unadjusted
Statistical analysis description: The exact 95% confidence interval was calculated by Clopper and Pearson.	
Comparison groups	Part 2, Placebo BI 655064 120mg (RA) v Part 2, BI 655064 120mg (RA)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3938 ^[35]
Method	one-sided exact test (see description)
Parameter estimate	risk difference, unadjusted
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.4
upper limit	22.3

Notes:

[35] - one-sided exact test for superiority testing.

Statistical analysis title	Placebo vs. BI 655064, adjusted
Statistical analysis description: The 95 % confidence interval was determined by root method to determine the cumulative distribution function.	
Comparison groups	Part 2, Placebo BI 655064 120mg (RA) v Part 2, BI 655064 120mg (RA)

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority ^[36]
Parameter estimate	risk difference, adjusted
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.9
upper limit	21.1

Notes:

[36] - Adjusted for treatment, region and anti-TNF history

Secondary: Part 2: EULAR DAS28-CRP at week 12

End point title	Part 2: EULAR DAS28-CRP at week 12 ^[37]
-----------------	--

End point description:

Response as assessed by European League Against Rheumatism (EULAR) categorization as good, moderate, or nonresponders based on improvement from baseline using the disease activity score in 28 joints and C-reactive protein (DAS28-CRP) at week 12. In this outcome measure the frequency of EULAR response rates (change from the day of first dose to the day of visit 14 in week 12) are presented. Improvement (impr.) is abbreviated in the category names.

End point type	Secondary
----------------	-----------

End point timeframe:

week 12 (day 85)

Notes:

[37] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Part 2, Placebo BI 655064 120mg (RA)	Part 2, BI 655064 120mg (RA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20 ^[38]	39 ^[39]		
Units: Percentage of participants				
number (not applicable)				
DAS28-CRP ≤3.2, improvement (>0.6 and ≤1.2)	5	2.6		
DAS28-CRP ≤3.2, improvement ≤0.6	0	0		
DAS28-CRP (>3.2 and ≤5.1), improvement >1.2	25	35.9		
DAS28-CRP (>3.2 and ≤5.1), impr. (>0.6 and ≤1.2)	5	7.7		
DAS28-CRP (>3.2 and ≤5.1), improvement ≤0.6	10	2.6		
DAS28-CRP >5.1, improvement >1.2	10	0		
DAS28-CRP >5.1, improvement (>0.6 and ≤1.2)	10	7.7		
DAS28-CRP >5.1, improvement ≤0.6	10	7.7		
DAS28-CRP ≤3.2, improvement >1.2	25	35.9		

Notes:

[38] - FAS (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: EULAR DAS28-ESR at week 12

End point title	Part 2: EULAR DAS28-ESR at week 12 ^[40]
-----------------	--

End point description:

Response as assessed by European League Against Rheumatism (EULAR) using Disease activity score in 28 joints and the erythrocyte sedimentation rate (DAS28-ESR) at week 12. In this outcome measure the frequency of EULAR response rates (change from the day of first dose to the day of visit 14 in week 12) are presented.

Improvement (impr.) is abbreviated in the category names.

End point type	Secondary
----------------	-----------

End point timeframe:

week 12 (day 85)

Notes:

[40] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Part 2, Placebo BI 655064 120mg (RA)	Part 2, BI 655064 120mg (RA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20 ^[41]	39 ^[42]		
Units: Percentage of participants				
number (not applicable)				
DAS28-ESR ≤3.2, improvement >1.2	10.5	20.5		
DAS28-ESR ≤3.2, improvement (>0.6 and ≤1.2)	0	0		
DAS28-ESR ≤3.2, improvement ≤0.6	0	0		
DAS28-ESR (>3.2 and ≤5.1), improvement >1.2	42.1	51.3		
DAS28-ESR (>3.2 and ≤5.1), impr. (>0.6 and ≤1.2)	5.3	5.1		
DAS28-ESR (>3.2 and ≤5.1), improvement ≤0.6	0	0		
DAS28-ESR >5.1, improvement >1.2	21.1	10.3		
DAS28-ESR >5.1, improvement (>0.6 and ≤1.2)	5.3	7.7		
DAS28-ESR >5.1, improvement ≤0.6	15.8	5.1		

Notes:

[41] - FAS (observed cases)

[42] - FAS (observed cases)

Statistical analyses

Secondary: Part 2: Percentage of patients with a decrease in DAS28-CRP of >1.2 at week 12

End point title	Part 2: Percentage of patients with a decrease in DAS28-CRP of >1.2 at week 12 ^[43]
-----------------	--

End point description:

Percentage of patients who had a decrease of >1.2 on the Disease activity score in 28 joints and C-reactive protein (DAS28-CRP) at week 12 (day 85) compared to baseline. The adjusted absolute risk difference was adjusted for treatment, region and anti-TNF history.

End point type	Secondary
----------------	-----------

End point timeframe:

baseline (day 1) and week 12 (day 85)

Notes:

[43] - 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Part 2, Placebo BI 655064 120mg (RA)	Part 2, BI 655064 120mg (RA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[44]	44 ^[45]		
Units: Percentage of participants				
number (confidence interval 95%)				
Unadjusted	59.1 (36.4 to 79.3)	65.9 (50.1 to 79.5)		
Adjusted	58.2 (36.7 to 77)	67.1 (51.6 to 79.6)		

Notes:

[44] - FAS (Last observation carried forward)

[45] - FAS (Last observation carried forward)

Statistical analyses

Statistical analysis title	Placebo vs. BI 655064, unadjusted
-----------------------------------	-----------------------------------

Statistical analysis description:

The exact 95% confidence interval was calculated by Clopper and Pearson.

Comparison groups	Part 2, BI 655064 120mg (RA) v Part 2, Placebo BI 655064 120mg (RA)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference, unadjusted
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	32.7

Statistical analysis title	Placebo vs. BI 655064, adjusted
Statistical analysis description: The 95 % confidence interval was determined by root method to determine the cumulative distribution function.	
Comparison groups	Part 2, BI 655064 120mg (RA) v Part 2, Placebo BI 655064 120mg (RA)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference, adjusted
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.9
upper limit	34.2

Secondary: Part 2: Change in DAS28-CRP score at week 12

End point title	Part 2: Change in DAS28-CRP score at week 12 ^[46]
End point description: Change at week 12 in the Disease activity score in 28 joints and C-reactive protein (DAS28-CRP) compared with the score at baseline. The mean was adjusted for region, anti-TNF history and baseline DAS28-CRP.	
End point type	Secondary
End point timeframe: baseline (day 1) and week 12 (day 85)	
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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.	

End point values	Part 2, Placebo BI 655064 120mg (RA)	Part 2, BI 655064 120mg (RA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[47]	44 ^[48]		
Units: units on a scale				
arithmetic mean (standard error)				
Mean	-1.45 (± 0.238)	-1.61 (± 0.14)		
Adjusted mean	-1.47 (± 0.215)	-1.6 (± 0.151)		

Notes:
[47] - FAS (last observation carried forward)
[48] - FAS (last observation carried forward)

Statistical analyses

Statistical analysis title	Placebo vs. BI 655064
Statistical analysis description: difference calculated as BI 655064 120mg minus placebo. The ANCOVA model was used. In this model	

the mean was adjusted for region, anti-TNF history and baseline DAS28-CRP.

Comparison groups	Part 2, BI 655064 120mg (RA) v Part 2, Placebo BI 655064 120mg (RA)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted mean
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.39
Variability estimate	Standard error of the mean
Dispersion value	0.266

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of study medication (day 1) up to day 64 (dosing groups 80, 120, 180mg) or up to day 78 post-treatment (dosing group 240mg) in part 1 and up to 141 days in part 2.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	18.0
--------------------	------

Reporting groups

Reporting group title	Part 1, Placebo (HV)
-----------------------	----------------------

Reporting group description:

Part 1, Healthy volunteers (HV): Placebo of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly) followed by a 6 weeks (120mg dosing group) or a 8 weeks (240mg dosing group) follow-up period. Within each dose group two subjects were to receive placebo.

Reporting group title	Part 1, BI 655064 80mg (HV)
-----------------------	-----------------------------

Reporting group description:

Part 1, Healthy volunteers (HV): 80 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly) followed by 6 weeks follow-up period.

Reporting group title	Part 1, BI 655064 120mg (HV)
-----------------------	------------------------------

Reporting group description:

Part 1, Healthy volunteers (HV): 120 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly) followed by 6 weeks follow-up period.

Reporting group title	Part 1, BI 655064 180mg (HV)
-----------------------	------------------------------

Reporting group description:

Part 1, Healthy volunteers (HV): 180 mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly) followed by 6 weeks follow-up period.

Reporting group title	Part 1, BI 655064 240mg (HV)
-----------------------	------------------------------

Reporting group description:

Part 1, Healthy volunteers (HV): 240mg of BI 655064 injected subcutaneous on days 1, 8, 15, and 22 (once weekly) followed by 8 weeks follow-up period.

Reporting group title	Part 2, Placebo (RA)
-----------------------	----------------------

Reporting group description:

Part 2, patients with Rheumatoid arthritis (RA): Placebo matching BI 655064 120mg injected subcutaneous on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (once weekly for 12 weeks) followed by 8 weeks follow-up period.

Reporting group title	Part 2, BI 655064 120mg (RA)
-----------------------	------------------------------

Reporting group description:

Part 2, patients with Rheumatoid arthritis (RA): 120 milligram (mg) of BI 655064 injected subcutaneous on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (once weekly for 12 weeks) followed by 8 weeks follow-up period.

Serious adverse events	Part 1, Placebo (HV)	Part 1, BI 655064 80mg (HV)	Part 1, BI 655064 120mg (HV)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Cardiopulmonary failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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	Part 1, BI 655064 180mg (HV)	Part 1, BI 655064 240mg (HV)	Part 2, Placebo (RA)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Cardiopulmonary failure			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2, BI 655064 120mg (RA)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 44 (4.55%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebral haemorrhage			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part 1, Placebo (HV)	Part 1, BI 655064 80mg (HV)	Part 1, BI 655064 120mg (HV)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	7 / 8 (87.50%)	6 / 8 (75.00%)
General disorders and administration site conditions			
Catheter site oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injection site bruising			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Injection site pain			

subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Injection site rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Vessel puncture site bruise			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Dyspareunia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Throat irritation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	3 / 8 (37.50%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	3	0	1
Head injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	3
Skin abrasion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Sunburn			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	1	0	3
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 8 (50.00%)	3 / 8 (37.50%)	2 / 8 (25.00%)
occurrences (all)	4	5	4
Lethargy			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Food poisoning			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Rash erythematous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Rash macular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Xeroderma			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Joint laxity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Chlamydial infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Fungal infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	1	0	2
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part 1, BI 655064 180mg (HV)	Part 1, BI 655064 240mg (HV)	Part 2, Placebo (RA)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	6 / 8 (75.00%)	17 / 23 (73.91%)
General disorders and administration site conditions			
Catheter site oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Injection site bruising			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	2 / 23 (8.70%)
occurrences (all)	2	1	2
Injection site pain			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 23 (0.00%) 0
Injection site rash subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 23 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 23 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 23 (0.00%) 0
Vessel puncture site bruise subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 23 (0.00%) 0
Reproductive system and breast disorders Dyspareunia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 23 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 23 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	1 / 8 (12.50%) 1	0 / 23 (0.00%) 0
Throat irritation subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 23 (0.00%) 0
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 23 (4.35%) 1
Injury, poisoning and procedural complications Contusion			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Head injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Laceration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 8 (37.50%)	1 / 8 (12.50%)	3 / 23 (13.04%)
occurrences (all)	3	1	3
Lethargy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Photophobia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Food poisoning			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Toothache			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	4
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rash pruritic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Xeroderma			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 23 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Joint laxity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Chlamydial infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	2	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	5 / 23 (21.74%)
occurrences (all)	0	0	5
Pharyngitis			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	1 / 23 (4.35%)
occurrences (all)	2	1	1
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1

Non-serious adverse events	Part 2, BI 655064 120mg (RA)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 44 (65.91%)		
General disorders and administration site conditions			
Catheter site oedema			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Injection site bruising			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Injection site pain			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Injection site rash			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	2		
Vessel puncture site bruise			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Dyspareunia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Throat irritation			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Head injury			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Laceration			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Skin abrasion			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Sunburn			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
Lethargy			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Photophobia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Food poisoning			

subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Dermatitis contact			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Rash erythematous			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Rash pruritic			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Rash macular			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Xeroderma			

subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Joint laxity			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Chlamydial infection			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Fungal infection			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	8		
Pharyngitis			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2013	<p>In Amendment 1, at the request of the Spanish health authority, more specific wording was included in inclusion criterion 7 with regard to contraception for patients with Rheumatoid arthritis (RA). The stopping criteria for the trial were clarified at the request of the Paul Ehrlich Institute (PEI). Additional information was provided with respect to Quantiferon TB Gold testing and the laboratory assay for CD40 receptor occupancy. It was also specified that the tender joint count (TJC), swollen joint count (SJC), and disease activity score in 28 joints (DAS 28) scores would be calculated automatically in the eCRF in order to minimize the risk of investigator error. In addition, several typographical errors and inconsistencies in the CTP were corrected.</p> <p>In the original CTP, it was planned to treat an additional cohort of patients with RA at a dose of 180 mg BI 655064.</p>
10 June 2013	<p>In Amendment 2, this planned cohort was canceled due to concerns from the regulatory authority (PEI) and the trial team about projected too-high exposure to BI, and the total number of patients to be enrolled in the trial was adjusted as a result. The amendment also specified that the trial bioanalysts could have indirect unblinded access to PK, PD, and biomarker data. In addition, there were some changes in the collection of biomarker samples to facilitate evaluation of the effectiveness of BI 655064, clarification of PK and safety endpoints, and correction of additional typographical and language errors. The primary PK endpoints for Part 1 were also clarified in Amendment 2 (that is, that the primary endpoints were C_{max} and AUC_t after the first and last dose, and AUC_{0-∞} after the last dose).</p>
09 December 2013	<p>In Amendment 3, the inclusion and exclusion criteria for Part 2 of the trial were changed in order to allow a larger patient population to be tested, without interfering with the scientific validity of the trial. These alterations included allowing patients with RA who had previously had no response to anti-TNF medications to participate in the trial and adjustment of the trial analysis to include anti-TNF history in the model; the cut-off CRP value for inclusion was lowered from 1.0 to 0.8 mg/dL and the option to be included based on ESR values was also added; patients with a history of RA of longer than 5 years were also to be allowed to participate; and exclusion with regard to malignancies was updated to align with BI standards. The CTP was also amended to allow testing of the 240 mg dose of BI 655064 in healthy subjects. Some clarifications were also made in the trial flowchart and the assessment of AEs was updated to include drug-induced liver injury. The change in DAS28-CRP at Week 12 compared with baseline was also added as a secondary endpoint.</p>
07 May 2014	<p>In Amendment 4, the TCM responsibilities were reassigned. In addition, in order to increase the pool of potential participants, the dosing requirements for patients with MTX intolerance were adapted and it was specified that patients who had anti-rheumatoid factor positivity could be enrolled in the trial. DAS28-ESR EULAR response was added as a secondary endpoint. AE reporting was updated, an interim PK analysis was added in Part 2, and the randomization process was clarified.</p>
23 July 2014	<p>In Amendment 5, it was clarified that the trial was a Phase Ib (healthy subjects)/Phase IIa (patients with RA) study, and that the statistical testing would be applied to both parts of the trial. The joint assessment form was also updated.</p>

16 October 2014	In Amendment 6, an additional interim analysis was added to evaluate data for the primary endpoint from the first 36 patients who completed the Phase IIa part of the trial. DAS28-CRP AUC0-12week was added to the 'other efficacy endpoints'. IgG and IgM analyses were added to the safety laboratory tests. In addition, the statistical analyses were updated: a Bayesian efficacy analysis was added as the primary analysis of the primary endpoint and an exploratory analysis of steady state at Week 12 were added. It was specified that the informative prior for the Bayesian analysis was an expected response rate of 25% in the placebo group. The sample size computation was also adapted.
-----------------	--

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported