Clinical trial results:
Efficacy, pharmacokinetics, and safety of BI 695500 versus rituximab in patients with moderately to severely active rheumatoid arthritis: a randomized, double-blind, parallel arm, multiple dose, active comparator trial

Summary

EudraCT number	2011-002894-48
Trial protocol	GB EE PT NL BE DE HU NO GR ES BG
Global end of trial date	28 October 2016

Results information

Result version number	v1
This version publication date	10 November 2017
First version publication date	10 November 2017

Trial information

Trial identification

Sponsor protocol code	1301.1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01682512
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	13 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2014
Global end of trial reached?	Yes
Global end of trial date	28 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this trial are:
To show pharmacokinetic (PK) similarity of BI 695500 to MabThera® and Rituxan® and of Rituxan® to MabThera® (three-way PK similarity).
To establish statistical equivalence of efficacy of BI 695500 and Rituxan® in patients with moderately to severely active rheumatoid arthritis (RA), based on the change in Disease Activity Score 28 (DAS28) measured at 24 weeks compared to Baseline.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were 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. Other medication considered necessary for the patient's safety, including rescue medication for the treatment of infusion-related reactions, was permitted at the Investigator's discretion.

Background therapy:

Patients continued to receive an appropriate standard of care by continuing to take their regular methotrexate (MTX) therapy (15-25 milligram (mg)/week) and a stable weekly dose of adequate folic acid (at least 5 mg per week or as per local practice), from their usual source. Patients may also continue to receive treatment with oral corticosteroids at a dose of ≤ 10 mg/day prednisolone or equivalent

Evidence for comparator:

Rituxan® and MabThera®

Actual start date of recruitment	27 September 2012
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	Argentina: 65
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Ireland: 3

Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Ukraine: 19
Country: Number of subjects enrolled	United States: 331
Worldwide total number of subjects	509
EEA total number of subjects	73

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)	395
From 65 to 84 years	114
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled into this multi-center, randomized, double-blind, parallel arm, multiple dose, active comparator 2 part trial from 27 September 2017. Trial was terminated on 3 September 2015 and last subject completed 28 October 2016.

Pre-assignment

Screening details:

509 subjects were screened for eligibility to participate in the trial. 293 subjects met all inclusion and exclusion criteria and were randomised to receive treatment. 6 subjects were included in an open-label safety run-in prior to randomisation in Part I.

Period 1

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

Blinding implementation details:

Subjects, investigators and trial personnel remained blinded with regard to the randomized treatment assignments until after database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 695500

Arm description:

Patients administered 1000 milligram per 100 milliliter (1000 mg per 100 mL) of BI 695500 concentrate for solution for intravenous (IV) infusion each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.

Arm type	Experimental
Investigational medicinal product name	BI 695500
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients administered 1000 milligram per 100 milliliter (1000 mg per 100 mL) of BI 695500 concentrate for solution for intravenous (IV) infusion each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.

Arm title	Rituxan®

Arm description:

Patients administered 1000 mg per 100 mL of Rituxan® injection for intravenous (IV) use each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26. One subject was randomized in part-II but not treated. Consequently, number of subjects that randomized were 111 but only 110 reported to ensure consistent reporting with baseline characteristics that include only treated patients.

Arm type	Active comparator
Investigational medicinal product name	Rituxan®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients administered 1000 mg per 100 mL of Rituxan® injection for intravenous (IV) use each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.

Arm title	MabThera®

Arm description:

Patients administered 1000 mg per 100 mL of MabThera® concentrate for solution for intravenous (IV) infusion each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.
One subject was randomized in part-I but not treated. Consequently, number of subjects that randomized were 66 but only 65 reported to ensure consistent reporting with baseline characteristics that include only treated patients.

Arm type	Active comparator
Investigational medicinal product name	MabThera®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients administered 1000 mg per 100 mL of MabThera® concentrate for solution for intravenous (IV) infusion each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.

Number of subjects in period 1[1]	BI 695500	Rituxan®	MabThera®
Started	116	110	65
Completed	44	40	48
Not completed	72	70	17
Consent withdrawn by subject	2	6	2
Physician decision	-	2	-
Adverse event, non-fatal	6	5	2
Primary lack of efficacy	10	7	7
Secondary lack of efficacy	1	1	-
Study terminated by sponsor	46	42	-
Lost to follow-up	3	-	2
Protocol deviation	2	3	2
Other than stated above	2	4	2

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 randomized after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	BI 695500
Reporting group description:	
Patients administered 1000 milligram per 100 milliliter (1000 mg per 100 mL) of BI 695500 concentrate for solution for intravenous (IV) infusion each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.	
Reporting group title	Rituxan®
Reporting group description:	
Patients administered 1000 mg per 100 mL of Rituxan® injection for intravenous (IV) use each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26. One subject was randomized in part-II but not treated. Consequently, number of subjects that randomized were 111 but only 110 reported to ensure consistent reporting with baseline characteristics that include only treated patients.	
Reporting group title	MabThera®
Reporting group description:	
Patients administered 1000 mg per 100 mL of MabThera® concentrate for solution for intravenous (IV) infusion each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26. One subject was randomized in part-I but not treated. Consequently, number of subjects that randomized were 66 but only 65 reported to ensure consistent reporting with baseline characteristics that include only treated patients.	

Reporting group values	BI 695500	Rituxan®	MabThera®
Number of subjects	116	110	65
Age categorical			
The safety randomized analysis set (SAFR) contained all randomized subjects who received at least one dose of trial medication and subjects were classified according to treatment received.			
Units: Subjects			

Age Continuous			
The safety randomized analysis set (SAFR) contained all randomized subjects who received at least one dose of trial medication and subjects were classified according to treatment received.			
Units: years			
arithmetic mean	54.7	54.0	54.8
standard deviation	± 10.46	± 11.10	± 12.22
Gender, Male/Female			
The safety randomized analysis set (SAFR) contained all randomized subjects who received at least one dose of trial medication and subjects were classified according to treatment received.			
Units: Subjects			
Female	94	96	52
Male	22	14	13

Reporting group values	Total		
Number of subjects	291		
Age categorical			
The safety randomized analysis set (SAFR) contained all randomized subjects who received at least one dose of trial medication and subjects were classified according to treatment received.			
Units: Subjects			

Age Continuous			
The safety randomized analysis set (SAFR) contained all randomized subjects who received at least one dose of trial medication and subjects were classified according to treatment received.			
Units: years arithmetic mean standard deviation	- 		
Gender, Male/Female			
The safety randomized analysis set (SAFR) contained all randomized subjects who received at least one dose of trial medication and subjects were classified according to treatment received.			
Units: Subjects			
Female	242		
Male	49		

End points

End points reporting groups

Reporting group title	BI 695500

Reporting group description:

Patients administered 1000 milligram per 100 milliliter (1000 mg per 100 mL) of BI 695500 concentrate for solution for intravenous (IV) infusion each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.

Reporting group title	Rituxan®

Reporting group description:

Patients administered 1000 mg per 100 mL of Rituxan® injection for intravenous (IV) use each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.
One subject was randomized in part-II but not treated. Consequently, number of subjects that randomized were 111 but only 110 reported to ensure consistent reporting with baseline characteristics that include only treated patients.

Reporting group title	MabThera®

Reporting group description:

Patients administered 1000 mg per 100 mL of MabThera® concentrate for solution for intravenous (IV) infusion each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.
One subject was randomized in part-I but not treated. Consequently, number of subjects that randomized were 66 but only 65 reported to ensure consistent reporting with baseline characteristics that include only treated patients.

Primary: Change of Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28 [ESR]) from Baseline to Week 24 - Part I

End point title	Change of Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28 [ESR]) from Baseline to Week 24 - Part I[1]

End point description:

The DAS28 score was derived using the formula: DAS28 (ESR) = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*ln(ESR) + 0.014*(GH), where, TJC28 = 28 joint count for tenderness, SJC28 = 28 joint count for swelling, Ln(ESR) = natural logarithm of ESR, GH = the General Health component of the DAS [Patients mark on a visual analogue scale (VAS) their overall assessment of how their rheumatoid arthritis (RA) affects them, rating how they are managing from 0 (very well) to 100 (very poor). This is equivalent to the General Health component of the DAS (GH)]. DAS28 values range from 2.0 to 10.0 while higher values mean a higher disease activity. A clinically important change in DAS28 score is defined as an improvement in DAS28 score of at least 1.2.
The full analysis set (FAS) contained all randomized subjects who received at least one dose of trial medication, had at least one assessment of primary efficacy endpoint at Baseline and at post-baseline visit prior or at Week 24 visit.

End point type	Primary

End point timeframe:

Baseline and Week 24

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	BI 695500	Rituxan®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[2]	61[3]		
Units: Unit on scale				
least squares mean (confidence interval 90%)	-1.8 (-2.08 to -1.50)	-1.4 (-1.64 to -1.09)		

Notes:

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted mean difference was calculated as: BI 695500 – Rituxan®. A restricted maximum likelihood (REML)-based Mixed-Effect Model Repeated Measure (MMRM) approach was used.

Comparison groups	Rituxan® v BI 695500
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	equivalence[4]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.83
upper limit	-0.03

Notes:

[4] - Equivalence for the change in DAS28 (ESR) was evaluated based on the two-sided 90% Confidence Interval (CI) for the treatment difference with respect to the mean change in the DAS28(ESR) score compared to baseline. Null hypothesis of non-equivalence was to be rejected if the 90% CI is fully contained within the interval of [-0.5, 0.5].

Primary: PK (Part I only): AUC0-tz (area under the plasma concentration versus time curve from time zero to the last measurable concentration, determined over both dosages)

End point title	PK (Part I only): AUC0-tz (area under the plasma concentration versus time curve from time zero to the last measurable concentration, determined over both dosages)

End point description:

Pharmacokinetic (PK) (Part I only): AUC0-tz (area under the plasma concentration versus time curve from time zero to the last measurable concentration, determined over both dosages). Time zero was the time the first dose started. Only subjects randomized in part I of this study are included. As per protocol all the following criteria had to be fulfilled for a patient to be defined as PK evaluable for the Pharmacokinetic analysis set (PKS): Full first and second dose given. Pre-dose concentration available prior to the second dose. Ability to estimate AUC during the infusion phases. Ability to estimate the AUC for the distribution phase after the second dose. Ability to estimate the terminal half-life (t1/2) after the second dose. Pharmacokinetic analysis set (PKS) consisted of all randomized subjects who were PK evaluable based on protocol defined criteria.

End point type	Primary

End point timeframe:

Blood PK samples were collected at -00:05 (hours: min) prior to first infusion and 03:55, 24:00, 335:55, 338:00, 339:55, 342:00, 344:00, 360:00, 432:00, 504:00, 672:00, 1176:00, 1512:00, 2352:00 and 2688:00 after first infusion.

End point values	BI 695500	Rituxan®	MabThera®	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56[5]	56[6]	55[7]	
Units: Hour(h)*Microgram(ug)/Milliliter (mL)				
geometric mean (geometric coefficient of variation)	171000 (± 41.1)	167000 (± 40.5)	193000 (± 37.9)	

Notes:

[5] - PKS

[6] - PKS

[7] - PKS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-tz)=overall mean+treatment effect+random error.
Adjusted ratio of Geometric Means (gMeans): BI 695500 versus Rituxan®; standard error is geometric standard error.

Comparison groups	BI 695500 v Rituxan®
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[8]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	102.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.5
upper limit	115.76
Variability estimate	Standard error of the mean
Dispersion value	107.7

Notes:

[8] - The similarity of AUC(o- tz) was compared between treatment groups BI 695500 and Rituxan.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-tz)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: BI 695500 versus MabThera®; standard error is geometric standard error.

Comparison groups	BI 695500 v MabThera®
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[9]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	88.21

Confidence interval	
level	90 %
sides	2-sided
lower limit	78.24
upper limit	99.46
Variability estimate	Standard error of the mean
Dispersion value	107.5

Notes:

[9] - The similarity of AUC(o- tz) was compared between treatment groups BI 695500 and MabThera.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-tz)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: Rituxan® versus MabThera®; standard error is geometric standard error.

Comparison groups	Rituxan® v MabThera®
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[10]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	86.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	76.5
upper limit	97.09
Variability estimate	Standard error of the mean
Dispersion value	107.449

Notes:

[10] - The similarity of AUC(o- tz) was compared between treatment groups Rituxan and MabThera.

Primary: PK (Part I only): AUC0-inf pred (area under the plasma concentration versus time curve from time zero to infinity, determined over both dosages)

End point title	PK (Part I only): AUC0-inf pred (area under the plasma concentration versus time curve from time zero to infinity, determined over both dosages)

End point description:

PK (Part I only): AUC0-inf pred (area under the plasma concentration versus time curve from time zero to infinity, determined over both dosages, and extrapolated to infinity using predicted last observed quantifiable concentration). Time zero was the time the first dose started. Only subjects randomized in part I of this study are included. PKS

End point type	Primary

End point timeframe:

Blood PK samples were collected at -00:05 (hours: min) prior to first infusion and 03:55, 24:00, 335:55, 338:00, 339:55, 342:00, 344:00, 360:00, 432:00, 504:00, 672:00, 1176:00, 1512:00, 2352:00 and 2688:00 after first infusion.

End point values	BI 695500	Rituxan®	MabThera®	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56[11]	56[12]	54[13]	
Units: h*ug/mL				
geometric mean (geometric coefficient of variation)	174000 (± 42.2)	169000 (± 42.0)	202000 (± 35.3)	

Notes:

[11] - PKS

[12] - PKS

[13] - PKS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-inf pred)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: BI 695500 versus Rituxan®; standard error is geometric standard error.

Comparison groups	BI 695500 v Rituxan®
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[14]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	102.46
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.26
upper limit	116.3
Variability estimate	Standard error of the mean
Dispersion value	107.939

Notes:

[14] - The similarity of AUC(o-inf pred) was compared between treatment groups BI 695500 and Rituxan.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-inf pred)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: BI 695500 versus MabThera®; standard error is geometric standard error.

Comparison groups	BI 695500 v MabThera®
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other[15]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	86
Confidence interval	
level	90 %
sides	2-sided
lower limit	76.38
upper limit	96.82

Variability estimate	Standard error of the mean
Dispersion value	107.404

Notes:

[15] - The similarity of AUC(o-inf pred) was compared between treatment groups BI 695500 and MabThera.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-inf pred)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: Rituxan® versus MabThera®; standard error is geometric standard error.

Comparison groups	Rituxan® v MabThera®
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other[16]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	83.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	74.57
upper limit	94.47
Variability estimate	Standard error of the mean
Dispersion value	107.386

Notes:

[16] - The similarity of AUC(o-inf pred) was compared between treatment groups Rituxan and MabThera.

Primary: PK (Part I only): AUC0-336 (area under the plasma concentration versus time curve from time zero to 336 hours)

End point title	PK (Part I only): AUC0-336 (area under the plasma concentration versus time curve from time zero to 336 hours)

End point description:

PK (Part I only): AUC0-336 (area under the plasma concentration versus time curve from time zero to 336 hours after the first dose). Time zero was the time the first dose started. Only subjects randomized in part I of this study are included. AUC0-336 was calculated as a partial area i.e., as the AUC from time zero to time point 336 hours, following the algorithm defined for AUCs (linear up-log down trapezoidal rule). If the end time did not coincide exactly with 336 hours, then a linear or logarithmic interpolation was done to estimate the concentration at 336 hours, according to the AUC calculation method. PKS

End point type	Primary

End point timeframe:

Blood PK samples were collected at -00:05 (hours: min) prior to first infusion and 03:55, 24:00, 335:55, 338:00, 339:55, 342:00, 344:00, 360:00, 432:00, 504:00, 672:00, 1176:00, 1512:00, 2352:00 and 2688:00 after first infusion.

End point values	BI 695500	Rituxan®	MabThera®	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56[17]	56[18]	55[19]	
Units: h*ug/mL				
geometric mean (geometric coefficient of variation)	49800 (± 40.1)	51900 (± 28.9)	55600 (± 30.7)	

Notes:
[17] - PKS
[18] - PKS
[19] - PKS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-336)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: BI 695500 versus Rituxan®; standard error is geometric standard error.

Comparison groups	BI 695500 v Rituxan®
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[20]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	95.87
Confidence interval	
level	90 %
sides	2-sided
lower limit	86.21
upper limit	106.62
Variability estimate	Standard error of the mean
Dispersion value	106.608

Notes:
[20] - The similarity of AUC(0-336) was compared between treatment groups BI 695500 and Rituxan.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-336)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: BI 695500 versus MabThera®; standard error is geometric standard error.

Comparison groups	BI 695500 v MabThera®
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[21]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	89.46
Confidence interval	
level	90 %
sides	2-sided
lower limit	80.23
upper limit	99.74
Variability estimate	Standard error of the mean
Dispersion value	106.775

Notes:

[21] - The similarity of AUC(0-336) was compared between treatment groups BI 695500 and MabThera.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-336)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: Rituxan® versus MabThera®; standard error is geometric standard error.

Comparison groups	Rituxan® v MabThera®
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[22]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	93.31
Confidence interval	
level	90 %
sides	2-sided
lower limit	85.11
upper limit	102.29
Variability estimate	Standard error of the mean
Dispersion value	105.7

Notes:

[22] - The similarity of AUC(0-336) was compared between treatment groups Rituxan and MabThera.

Primary: PK (Part I only): observed Cmax (maximum plasma concentration, determined after the second dose)

End point title	PK (Part I only): observed Cmax (maximum plasma concentration, determined after the second dose)

End point description:

PK (Part I only): observed Cmax (observed maximum plasma concentration, determined after the second dose). Only subjects
randomized in part I of this study are included. PKS.

End point type	Primary

End point timeframe:

Blood PK samples were collected at -00:05 (hours: min) prior to first infusion and 03:55, 24:00, 335:55, 338:00, 339:55, 342:00, 344:00, 360:00, 432:00, 504:00, 672:00, 1176:00, 1512:00, 2352:00 and 2688:00 after first infusion.

End point values	BI 695500	Rituxan®	MabThera®	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56[23]	56[24]	55[25]	
Units: microgram per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)	434 (± 31.1)	462 (± 32.0)	486 (± 28.1)	

Notes:

[23] - PKS

[24] - PKS

[25] - PKS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(Cmax)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: BI 695500 versus Rituxan®; standard error is geometric standard error.

Comparison groups	BI 695500 v Rituxan®
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[26]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	93.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	85.32
upper limit	103.5
Variability estimate	Standard error of the mean
Dispersion value	105.995

Notes:

[26] - The similarity of observed Cmax was compared between treatment groups BI 695500 and Rituxan.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(Cmax)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: BI 695500 versus MabThera®; standard error is geometric standard error.

Comparison groups	BI 695500 v MabThera®
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[27]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	89.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	81.51
upper limit	97.83
Variability estimate	Standard error of the mean
Dispersion value	105.657

Notes:

[27] - The similarity of observed Cmax was compared between treatment groups BI 695500 and MabThera.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(Cmax)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: Rituxan® versus MabThera®; standard error is geometric standard error.

Comparison groups	Rituxan® v MabThera®

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[28]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	95.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	86.62
upper limit	104.25
Variability estimate	Standard error of the mean
Dispersion value	105.744

Notes:

[28] - The similarity of observed Cmax was compared between treatment groups Rituxan and MabThera.

Secondary: Percentage of patients meeting the ACR20 (American College of Rheumatology 20% response criteria) at week 24

End point title	Percentage of patients meeting the ACR20 (American College of Rheumatology 20% response criteria) at week 24

End point description:

A subject has an ACR20 response if all of the following occur: - a > 20% improvement in the swollen joint count (66 joints) - a > 20% improvement in the tender joint count (68 joints) - a > 20% improvement in at least 3 of the following assessments: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function, as measured by the Health Assessment Questionnaire - Disability Index, or Acute phase reactant (C-reactive protein). The percentage of subjects meeting the ACR20 response criteria at Week 24 is presented for subjects randomised to receive BI 695500, Rituxan and MabThera. FAS. Missing data have been imputed according to LOCF (last observation carried forward) and/or NRI (Non Responder Imputation).

End point type	Secondary

End point timeframe:

Week 24

End point values	BI 695500	Rituxan®	MabThera®	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94[29]	90[30]	64[31]	
Units: Percentage of participants				
number (not applicable)	26.6	23.3	56.3	

Notes:

[29] - FAS

[30] - FAS

[31] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: PK (Part I only): AUC0-inf, ppk (area under the plasma concentration versus time curve from time zero to infinity, based on individual predicted concentrations for missing data derived from a population PK model, determined

over both dosages)	
End point title	PK (Part I only): AUC0-inf, ppk (area under the plasma concentration versus time curve from time zero to infinity, based on individual predicted concentrations for missing data derived from a population PK model, determined over both dosages)

End point description:

Time zero was the time the first dose started. Only subjects randomized in part I are included. Modeling approach was used to impute missing values as well as impute missing concentrations after the first dose with a sampling schedule identical to the first 2 weeks after the second dose. A unit dose 1000 mg was used in calculating the imputed values. The resulting dataset thus consisted of PK evaluable and PK non-evaluable patients with both measured as well as imputed concentration values. The prediction of these concentrations was based on a mixed effect modeling approach and included significant covariates identified during the PK model development (including age, body surface area, body mass index, weight, gender, race, and formulation). Pharmacokinetic full analysis set (PKFS) included all randomized subjects with at least one valid PK concentration measurement. A valid PK concentration measurement is a value greater than lower limit of quantification provided by Charles River

End point type	Secondary

End point timeframe:

Blood PK samples were collected at -00:05 (hours: min) prior to first infusion and 03:55, 24:00, 335:55, 338:00, 339:55, 342:00, 344:00, 360:00, 432:00, 504:00, 672:00, 1176:00, 1512:00, 2352:00 and 2688:00 after first infusion.

End point values	BI 695500	Rituxan®	MabThera®	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66[32]	65[33]	65[34]	
Units: h*ug/mL				
geometric mean (geometric coefficient of variation)	165000 (± 42.9)	158000 (± 50.0)	180000 (± 40.6)	

Notes:

[32] - PKFS

[33] - PKFS

[34] - PKFS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-inf, ppk)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: BI 695500 versus Rituxan®; standard error is geometric standard error.

Comparison groups	BI 695500 v Rituxan®
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other[35]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	104.49
Confidence interval	
level	90 %
sides	2-sided
lower limit	91.92
upper limit	118.78

Variability estimate	Standard error of the mean
Dispersion value	108.044

Notes:

[35] - The similarity of AUC(0-inf, ppk) was compared between treatment groups BI 695500 and Rituxan.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-inf, ppk)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: BI 695500 versus MabThera®; standard error is geometric standard error.

Comparison groups	BI 695500 v MabThera®
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other[36]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	91.39
Confidence interval	
level	90 %
sides	2-sided
lower limit	81.38
upper limit	102.64
Variability estimate	Standard error of the mean
Dispersion value	107.253

Notes:

[36] - The similarity of AUC(0-inf, ppk) was compared between treatment groups BI 695500 and MabThera.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis of variance (ANOVA) model on logarithmic scale: Ln(AUC0-inf, ppk)=overall mean+treatment effect+random error.
Adjusted ratio of gMeans: Rituxan® versus MabThera®; standard error is geometric standard error.

Comparison groups	Rituxan® v MabThera®
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other[37]
Method	ANOVA
Parameter estimate	Adjusted ratio of gMeans (%)
Point estimate	87.47
Confidence interval	
level	90 %
sides	2-sided
lower limit	77.12
upper limit	99.21
Variability estimate	Standard error of the mean
Dispersion value	107.896

Notes:

[37] - The similarity of AUC(0-inf, ppk) was compared between treatment groups Rituxan and MabThera.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study medication and prior to the last date of study medication plus 6 months (180 days); up to 48 weeks

Adverse event reporting additional description:

The safety randomized analysis set (SAFR) contained all randomized subjects who received at least one dose of trial medication and subjects were classified according to treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	BI 695500

Reporting group description:

Patients administered 1000 milligram per 100 milliliter (1000 mg per 100 mL) of BI 695500 concentrate for solution for intravenous (IV) infusion each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.

Reporting group title	Rituxan®

Reporting group description:

Patients administered 1000 mg per 100 mL of Rituxan® injection for intravenous (IV) use each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.

Reporting group title	MabThera®

Reporting group description:

Patients administered 1000 mg per 100 mL of MabThera® concentrate for solution for intravenous (IV) infusion each at Day 1 and 15. Patients with response to treatment were administered additional infusions at Week 24 and 26.

Serious adverse events	BI 695500	Rituxan®	MabThera®
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 116 (7.76%)	9 / 110 (8.18%)	5 / 65 (7.69%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 116 (0.00%)	1 / 110 (0.91%)	0 / 65 (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
Femoral neck fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 110 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fibula fracture			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (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
Hip fracture			
subjects affected / exposed	0 / 116 (0.00%)	1 / 110 (0.91%)	0 / 65 (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
Joint injury			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (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
Multiple fractures			
subjects affected / exposed	0 / 116 (0.00%)	1 / 110 (0.91%)	0 / 65 (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
Road traffic accident			
subjects affected / exposed	0 / 116 (0.00%)	1 / 110 (0.91%)	0 / 65 (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
Tibia fracture			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 116 (0.00%)	2 / 110 (1.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 116 (0.00%)	0 / 110 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pericardial effusion			
subjects affected / exposed	0 / 116 (0.00%)	0 / 110 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 116 (0.00%)	1 / 110 (0.91%)	0 / 65 (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
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 116 (0.86%)	2 / 110 (1.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactoid reaction			
subjects affected / exposed	0 / 116 (0.00%)	1 / 110 (0.91%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 116 (0.00%)	1 / 110 (0.91%)	0 / 65 (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
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc degeneration			
subjects affected / exposed	0 / 116 (0.00%)	1 / 110 (0.91%)	0 / 65 (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
Musculoskeletal chest pain			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (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
Musculoskeletal pain			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (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
Osteoarthritis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 110 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (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
Gastroenteritis viral			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (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

Pneumonia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 110 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 110 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 116 (0.00%)	0 / 110 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 116 (0.86%)	1 / 110 (0.91%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 110 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	BI 695500	Rituxan®	MabThera®
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 116 (14.66%)	14 / 110 (12.73%)	24 / 65 (36.92%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 116 (0.86%)	1 / 110 (0.91%)	4 / 65 (6.15%)
occurrences (all)	1	1	4
Headache			

subjects affected / exposed	5 / 116 (4.31%)	7 / 110 (6.36%)	4 / 65 (6.15%)
occurrences (all)	5	7	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 116 (0.00%)	1 / 110 (0.91%)	5 / 65 (7.69%)
occurrences (all)	0	1	5
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 116 (2.59%)	3 / 110 (2.73%)	4 / 65 (6.15%)
occurrences (all)	4	3	6
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 116 (0.86%)	1 / 110 (0.91%)	4 / 65 (6.15%)
occurrences (all)	1	1	4
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	8 / 116 (6.90%)	2 / 110 (1.82%)	6 / 65 (9.23%)
occurrences (all)	8	2	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2012	Logistical & administrative changes including clarifying schedule of assessments for open-label run-in, adding cut-off for platelet count to exclusion criteria, clarifying endpoints, adding AUC(0-336).
22 May 2012	Logistical & administrative changes including change to product descriptions for MabThera and Rituxan, allowing unblinded treatment, removing reference to human anti-chimeric antibodies sampling
20 December 2012	Logistical & administrative changes including addition of ESR measurements, updating primary PK endpoint in synopsis, change minimum improvement in DAS28-CRP, addition of blood sampling to Week 32.
04 February 2013	Administrative changes to reflect removal of text relating to unblinding subjects discontinuing trial and additional blood sampling at Week 32 in Part I.
05 April 2013	Logistical & administrative changes including additional blood sampling for first 8 subjects of each dose group for stability testing, moving text for listedness evaluation.
02 July 2014	Logistical & administrative changes including change of Trial Clinical Monitor, interim analysis to include PK similarity primary analysis, all subjects to enter safety follow up, expand PK endpoints.
09 September 2014	Logistical & administrative changes including all PK data to be reviewed by independent data monitoring committee, clarifications regarding re-randomisation, clarify serious AE reporting for cancers.
23 December 2014	Logistical & administrative changes including change in Part II comparison product, revise subject numbers based on change in margin, change ACR20 response rate at Week 24 to secondary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study program was terminated and this study was discontinued on 3 September 2015. As a result no patients receiving study treatment in Part II of the study reached Week 24, and no conclusions regarding the efficacy of BI 695500 can be made.

Notes: