



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 | v2 (current) |
| This version publication date | 13 December 2021 |
| First version publication date | 10 November 2017 |
| Version creation reason | |

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, clintrriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintrriage.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 | Spain: 9 |
| 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 | 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 | 72 |

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 | Investigator, Subject, 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 randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | BI 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: $\text{DAS28 (ESR)} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.70 \cdot \ln(\text{ESR}) + 0.014 \cdot (\text{GH})$, where, TJC28 = 28 joint count for tenderness, SJC28 = 28 joint count for swelling, $\ln(\text{ESR})$ = 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 | BI 695500 v Rituxan® |
| 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 (t_{1/2}) 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: $\text{Ln}(\text{AUC0-tz}) = \text{overall mean} + \text{treatment effect} + \text{random error}$.

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: $\text{Ln}(\text{AUC0-tz}) = \text{overall mean} + \text{treatment effect} + \text{random error}$.

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: $\text{Ln}(\text{AUC0-tz}) = \text{overall mean} + \text{treatment effect} + \text{random error}$.

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: $\ln(\text{AUC}_{0-\text{inf}} \text{ pred}) = \text{overall mean} + \text{treatment effect} + \text{random error}$.

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 $\text{AUC}_{0-\text{inf}} \text{ pred}$ 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: $\ln(\text{AUC}_{0-\text{inf}} \text{ pred}) = \text{overall mean} + \text{treatment effect} + \text{random error}$.

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: $\ln(\text{AUC}_{0-\text{inf pred}}) = \text{overall mean} + \text{treatment effect} + \text{random error}$.

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: $\text{Ln}(\text{AUC}_{0-336}) = \text{overall mean} + \text{treatment effect} + \text{random error}$. | |
| 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: $\text{Ln}(\text{AUC}_{0-336}) = \text{overall mean} + \text{treatment effect} + \text{random error}$. | |
| 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: $\ln(\text{AUC}_{0-336}) = \text{overall mean} + \text{treatment effect} + \text{random error}$. 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: $\text{Ln}(\text{Cmax}) = \text{overall mean} + \text{treatment effect} + \text{random error}$. | |
| 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: $\text{Ln}(\text{Cmax}) = \text{overall mean} + \text{treatment effect} + \text{random error}$. | |
| 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: $\text{Ln}(\text{Cmax}) = \text{overall mean} + \text{treatment effect} + \text{random error}$. | |
| 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: $\text{Ln}(\text{AUC0-inf, ppk}) = \text{overall mean} + \text{treatment effect} + \text{random error}$.

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: $\ln(\text{AUC}_{0-\text{inf}}, \text{ppk}) = \text{overall mean} + \text{treatment effect} + \text{random error}$.

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: $\ln(\text{AUC}_{0-\text{inf}}, \text{ppk}) = \text{overall mean} + \text{treatment effect} + \text{random error}$.

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 | 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.

| | |
|-----------------------|---------|
| 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.

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

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

| | | | |
|---|-----------------|----------------|-----------------|
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 65 (1.54%) | 0 / 110 (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 |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 65 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 / 65 (0.00%) | 0 / 110 (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 | | | |
| Anaphylactoid reaction | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 65 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 65 (0.00%) | 2 / 110 (1.82%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 65 (0.00%) | 0 / 110 (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%) | 0 / 65 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 / 65 (0.00%) | 0 / 110 (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%) | 0 / 65 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 65 (0.00%) | 0 / 110 (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 / 65 (0.00%) | 0 / 110 (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%) | 1 / 65 (1.54%) | 0 / 110 (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 |
| Infections and infestations | | | |
| Abscess neck | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 65 (0.00%) | 0 / 110 (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 / 65 (0.00%) | 0 / 110 (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 / 65 (0.00%) | 0 / 110 (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 |

| | | | |
|---|-----------------|----------------|-----------------|
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 65 (1.54%) | 0 / 110 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 65 (1.54%) | 0 / 110 (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 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 65 (1.54%) | 0 / 110 (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 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 65 (0.00%) | 1 / 110 (0.91%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 65 (0.00%) | 0 / 110 (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 / 65 (0.00%) | 0 / 110 (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 | MabThera | Rituxan |
|---|-------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 116 (14.66%) | 24 / 65 (36.92%) | 14 / 110 (12.73%) |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 4 / 65 (6.15%) | 1 / 110 (0.91%) |
| occurrences (all) | 1 | 4 | 1 |
| Headache | | | |

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

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: