



Clinical trial results:

A Randomized, Double-Blind, Parallel-Group, Active-Control Study to Compare the Efficacy and Safety of BAT1806 to RoActemra® in Rheumatoid Arthritis Patients With Inadequate Response to Methotrexate

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2018-002202-31 |
| Trial protocol | BG |
| Global end of trial date | 05 January 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 01 March 2022 |
| First version publication date | 01 March 2022 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | BAT-1806-002-CR |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03830203 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bio-Thera Solutions, Ltd. |
| Sponsor organisation address | Floor 5, Building A6, 11 Kai-Yuan Blvd, Huangpu District, Guangzhou, China, 510530 |
| Public contact | Clinical Development Department, Bio-Thera Solutions, Ltd., 86 2022233607, CT_Registration@bio-thera.com |
| Scientific contact | Clinical Development Department, Bio-Thera Solutions, Ltd., 86 2022233607, CT_Registration@bio-thera.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 | 05 January 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 January 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 January 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to demonstrate equivalent efficacy of BAT1806 and RoActemra in subjects with rheumatoid arthritis (RA) that is inadequately controlled by methotrexate (MTX).

Protection of trial subjects:

The clinical study protocol, protocol amendments, informed consent forms (ICFs), and any other appropriate study-related documents were reviewed and approved by independent ethics committees (IECs) and institutional review boards (IRBs) for each study center. Before entering the study, the investigator (or designee) explained to each subject (or their legally acceptable representatives, if applicable) the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. Subjects were given written information about the study, and, before any study procedures were performed, each subject voluntarily signed and dated the ICF. This was to be done during the Screening Period (Days -1 to -28). The master ICF and country-specific and site-specific versions are available upon request.

Background therapy:

All subjects continued taking their regular treatment of MTX (ranging between 10-25 mg/week) during the study, on a stable dose.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 24 December 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Georgia: 57 |
| Country: Number of subjects enrolled | China: 253 |
| Country: Number of subjects enrolled | Ukraine: 100 |
| Country: Number of subjects enrolled | Poland: 169 |
| Country: Number of subjects enrolled | Bulgaria: 42 |
| Worldwide total number of subjects | 621 |
| EEA total number of subjects | 211 |

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) | 553 |
| From 65 to 84 years | 68 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 621 subjects were randomized into this study from 55 sites during 19 Dec 2018 - 05 Jan 2020, 253 were from China, 169 were from Poland, 100 were from Ukraine, 57 were from Georgia, and 42 were from Bulgaria.

Pre-assignment

Screening details:

Subjects with RA inadequately controlled by MTX were screened in this study. A total of 935 subjects were screened and 621 subjects were randomized. Investigators completed the protocol defined screening procedures during ≤28-day screening period.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Treatment period 1 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Subject, Data analyst, Carer, Assessor |

Blinding implementation details:

The investigators, site staff assessing the safety and efficacy, other related study staff (including contract research organization and sponsor), all subjects, and central laboratories would remain blinded to the study treatment assignment throughout this study. The unblinded site staff who were not involved in any study treatment administration or assessment were responsible for preparing the infusion solution. The treatment assignment was not disclosed to any blinded personnel during study.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | BAT1806 |

Arm description:

Subjects randomized to the BAT1806 Arm at baseline received 12 doses of BAT1806 during the study (6 doses in treatment period 1 and 6 doses in treatment period 2).

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BAT1806 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection/infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Study treatment was administered at the study site every 4 weeks by 1-hour (±5 minutes) IV infusion at a dose of 8 mg/kg body weight by qualified study site staff. A maximum dose of 800 mg was allowed for each infusion. The dose of study treatment may have been reduced to 4 mg/kg body weight during the study due to laboratory abnormalities as described in the protocol.

| | |
|------------------|-----------|
| Arm title | RoActemra |
|------------------|-----------|

Arm description:

Subjects randomized to RoActemra at baseline received 6 doses in treatment period 1, followed by either 6 doses of RoActemra or 6 doses of BAT1806 in treatment period 2.

| | |
|--|--------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | RoActemra |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection/infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Study treatment was administered at the study site every 4 weeks by 1-hour(± 5 minutes) IV infusion at a dose of 8 mg/kg body weight by qualified study site staff. A maximum dose of 800 mg was allowed for each infusion. The dose of study treatment may have been reduced to 4 mg/kg body weight during the study due to laboratory abnormalities as described in the protocol

| Number of subjects in period 1 | BAT1806 | RoActemra |
|--|---------|-----------|
| Started | 312 | 309 |
| Completed | 299 | 288 |
| Not completed | 13 | 21 |
| Consent withdrawn by subject | 2 | 7 |
| Physician decision | - | 2 |
| Anaphylactic reaction or other serious hypersensit | 1 | 3 |
| Malignancy | 1 | - |
| Other | 4 | 3 |
| Death | 3 | 1 |
| Confirmed diverticulitis or any gastrointestinally | - | 1 |
| Pregnancy | - | 2 |
| Specific laboratory abnormalities | 2 | 2 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Treatment period 2 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

The investigators, site staff assessing the safety and efficacy, other related study staff (including contract research organization and sponsor), all subjects, and central laboratories would remain blinded to the study treatment assignment throughout this study. The unblinded site staff who were not involved in any study treatment administration or assessment were responsible for preparing the infusion solution. The treatment assignment was not disclosed to any blinded personnel during study.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|--|----------------------|
| Arm title | BAT1806 |
| Arm description: | |
| Subjects assigned to the BAT1806 at baseline received 12 doses of BAT1806 during the study (6 doses in Treatment Period 1 and 6 doses in Treatment Period 2). | |
| Arm type | Experimental |
| Investigational medicinal product name | BAT1806 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection/infusion |
| Routes of administration | Infusion |
| Dosage and administration details: | |
| Study treatment was administered at the study site every 4 weeks by 1-hour (\pm 5 minutes) IV infusion at a dose of 8 mg/kg body weight by qualified study site staff. A maximum dose of 800 mg was allowed for each infusion. The dose of study treatment may have been reduced to 4 mg/kg body weight during the study because of laboratory abnormalities. | |
| Arm title | RoActemra |
| Arm description: | |
| Subjects randomized to RoActemra at baseline received 6 doses in treatment period 1 followed by 6 doses of RoActemra in treatment period 2 | |
| Arm type | Active comparator |
| Investigational medicinal product name | RoActemra |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection/infusion |
| Routes of administration | Infusion |
| Dosage and administration details: | |
| Study treatment was administered at the study site every 4 weeks by 1-hour (\pm 5 minutes) IV infusion at a dose of 8 mg/kg body weight by qualified study site staff. A maximum dose of 800 mg was allowed for each infusion. The dose of study treatment may have been reduced to 4 mg/kg body weight during the study because of laboratory abnormalities. | |
| Arm title | RoActemra -> BAT1806 |
| Arm description: | |
| Subjects randomized to RoActemra at baseline received 6 doses in treatment period 1, followed by 6 doses of BAT1806 in treatment period 2. | |
| Arm type | Experimental |
| Investigational medicinal product name | RoActemra |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection/infusion |
| Routes of administration | Infusion |
| Dosage and administration details: | |
| Study treatment was administered at the study site every 4 weeks by 1-hour (\pm 5 minutes) IV infusion at a dose of 8 mg/kg body weight by qualified study site staff. A maximum dose of 800 mg was allowed for each infusion. The dose of study treatment may have been reduced to 4 mg/kg body weight during the study due to laboratory abnormalities as described in the protocol. Subjects received 6 doses of RoActemra in TP1 and 6 doses of BAT1806 in TP2. | |
| Investigational medicinal product name | BAT1806 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection/infusion |
| Routes of administration | Infusion |
| Dosage and administration details: | |
| Study treatment was administered at the study site every 4 weeks by 1-hour (\pm 5 minutes) IV infusion at a dose of 8 mg/kg body weight by qualified study site staff. A maximum dose of 800 mg was allowed for each infusion. The dose of study treatment may have been reduced to 4 mg/kg body weight during | |

the study due to laboratory abnormalities as described in the protocol. Subjects received 6 doses of RoActemra in TP1 and 6 doses of BAT1806 in TP2.

| Number of subjects in period 2^[1] | BAT1806 | RoActemra | RoActemra -> BAT1806 |
|---|---------|-----------|----------------------|
| Started | 290 | 145 | 142 |
| Completed | 280 | 141 | 134 |
| Not completed | 10 | 4 | 8 |
| Consent withdrawn by subject | 6 | 1 | 1 |
| Other | 2 | 2 | 5 |
| Sponsor request | - | - | 1 |
| Specific laboratory abnormalities | 2 | - | - |
| Subjects who are consistently noncompliant with th | - | - | 1 |
| Serious or opportunistic infection, including TB | - | 1 | - |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A subject is considered as completed the 24-week TP1 if the week 24 study visit is completed, and a subject is considered as completed the 24-week secondary TP2 if the Week 48 study visit is completed. In this study, there are some subjects – 10 subjects in total - who completed TP1 but did not enter in TP2 (subjects didn't receive dose at week 24 and early terminated at week 24), this is the reason why the number of subjects completing TP1 is not consistent with the number starting in TP2.

Baseline characteristics

Reporting groups

| | |
|---|-----------|
| Reporting group title | BAT1806 |
| Reporting group description: | |
| Subjects randomized to the BAT1806 Arm at baseline received 12 doses of BAT1806 during the study (6 doses in treatment period 1 and 6 doses in treatment period 2). | |
| Reporting group title | RoActemra |
| Reporting group description: | |
| Subjects randomized to RoActemra at baseline received 6 doses in treatment period 1, followed by either 6 doses of RoActemra or 6 doses of BAT1806 in treatment period 2. | |

| Reporting group values | BAT1806 | RoActemra | Total |
|---|---------|-----------|-------|
| Number of subjects | 312 | 309 | 621 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 279 | 274 | 553 |
| From 65-84 years | 33 | 35 | 68 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 50.9 | 50.7 | - |
| standard deviation | ± 11.93 | ± 12.37 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 269 | 265 | 534 |
| Male | 43 | 44 | 87 |
| RA Disease Characteristics at Baseline-Tender joint count (68 joints) | | | |
| Units: number | | | |
| arithmetic mean | 22.5 | 23.9 | - |
| standard deviation | ± 12.25 | ± 12.21 | - |
| RA Disease Characteristics-Swollen joint count (66 joints) | | | |
| Units: number | | | |
| arithmetic mean | 14.1 | 15.2 | - |
| standard deviation | ± 7.78 | ± 8.11 | - |
| RA Disease Characteristics-Subject's assessment of pain | | | |
| Units: mm | | | |
| arithmetic mean | 66.5 | 66.9 | - |
| standard deviation | ± 19.47 | ± 18.74 | - |
| RA Disease Characteristics-Subject's | | | |

| | | | |
|--|---------------------|---------------------|---|
| Global Assessment of Disease Activity Units: mm arithmetic mean standard deviation | 70.1 ± 17.45 | 70.5 ± 15.62 | - |
| RA Disease Characteristics -Physician's Global Assessment of Disease Activity Units: mm arithmetic mean standard deviation | 67.8 ± 14.76 | 70.3 ± 13.40 | - |
| RA Disease Characteristics-HAQ-DI Units: score arithmetic mean standard deviation | 1.56 ± 0.614 | 1.56 ± 0.545 | - |
| RA Disease Characteristics-CRP level Units: mg/L arithmetic mean standard deviation | 18.908 ± 22.9146 | 19.707 ± 25.9105 | - |
| RA Disease Characteristics-Tender joint count (28 joints) Units: number arithmetic mean standard deviation | 14.9 ± 6.3 | 15.4 ± 6.29 | - |
| RA Disease Characteristics-Swollen joint count (28 joints) Units: number arithmetic mean standard deviation | 10.9 ± 5.39 | 11.3 ± 5.13 | - |
| RA Disease Characteristics-ESR Units: mm/hour arithmetic mean standard deviation | 48.4 ± 22.49 | 50.7 ± 21.99 | - |
| RA Disease Characteristics-DAS28 (CRP) Units: score arithmetic mean standard deviation | 5.81 ± 0.938 | 5.89 ± 0.847 | - |
| RA Disease Characteristics -DAS28 (ESR) Units: score arithmetic mean standard deviation | 6.64 ± 0.877 | 6.71 ± 0.950 | - |

Subject analysis sets

| | |
|---|--|
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The FAS included all subjects that were randomized during the study. Subjects were analyzed according to randomized treatment. All efficacy endpoints were analyzed on the FAS as primary. | |
| Subject analysis set title | Safety Set in TP1 & TP2 (SAF in TP1 & TP2) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety Set (SAF) will include all randomized subjects that have received any treatment with study drug. Subjects will be analyzed according to treatment received at the start of TP1 and TP2. The SAF will be used for all analyses of safety, tolerability, and immunogenicity endpoints.

| | |
|----------------------------|---|
| Subject analysis set title | Pharmacokinetic Set in TP1 (PKS in TP1) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The PKS (TP1) included all randomized subjects that had received any treatment with study drug in TP1, and had at least 1 evaluable PK assessment postbaseline. Subjects were analyzed according to their treatment arm. The PKS was used for PK analyses.

| Reporting group values | Full Analysis Set (FAS) | Safety Set in TP1 & TP2 (SAF in TP1 & TP2) | Pharmacokinetic Set in TP1 (PKS in TP1) |
|--|-------------------------|--|---|
| Number of subjects | 621 | 621 | 619 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 553 | 553 | 551 |
| From 65-84 years | 68 | 68 | 68 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 50.5 | 50.5 | 50.5 |
| standard deviation | ± 11.98 | ± 11.98 | ± 11.98 |
| Gender categorical Units: Subjects | | | |
| Female | 534 | 534 | 532 |
| Male | 87 | 87 | 87 |
| RA Disease Characteristics at Baseline-Tender joint count (68 joints) Units: number | | | |
| arithmetic mean | 23.1 | 23.1 | 23.1 |
| standard deviation | ± 12.11 | ± 12.11 | ± 12.12 |
| RA Disease Characteristics-Swollen joint count (66 joints) Units: number | | | |
| arithmetic mean | 14.6 | 14.6 | 14.6 |
| standard deviation | ± 7.71 | ± 7.71 | ± 7.69 |
| RA Disease Characteristics-Subject's assessment of pain Units: mm | | | |
| arithmetic mean | 66.3 | 66.3 | 66.3 |
| standard deviation | ± 19.48 | ± 19.48 | ± 19.48 |
| RA Disease Characteristics-Subject's Global Assessment of Disease Activity Units: mm | | | |
| arithmetic mean | 70.2 | 70.2 | 70.2 |
| standard deviation | ± 17.31 | ± 17.31 | ± 17.29 |
| RA Disease Characteristics -Physician's Global Assessment of Disease Activity Units: mm | | | |

| | | | |
|---|---------------------|---------------------|-----------------|
| arithmetic mean standard deviation | 69.1 ± 14.87 | 69.1 ± 14.87 | 69.1 ± 14.87 |
| RA Disease Characteristics-HAQ-DI Units: score arithmetic mean standard deviation | 1.56 ± 0.603 | 1.56 ± 0.603 | 1.6 ± 0.6 |
| RA Disease Characteristics-CRP level Units: mg/L arithmetic mean standard deviation | 18.901 ± 23.8865 | 18.901 ± 23.8865 | 18.9 ± 23.9 |
| RA Disease Characteristics-Tender joint count (28 joints) Units: number arithmetic mean standard deviation | 15.2 ± 6.22 | 15.2 ± 6.22 | 15.2 ± 6.21 |
| RA Disease Characteristics-Swollen joint count (28 joints) Units: number arithmetic mean standard deviation | 11.2 ± 5.22 | 11.2 ± 5.22 | 11.2 ± 5.18 |
| RA Disease Characteristics-ESR Units: mm/hour arithmetic mean standard deviation | 49.1 ± 23.05 | 49.1 ± 23.05 | 49 ± 23.06 |
| RA Disease Characteristics-DAS28 (CRP) Units: score arithmetic mean standard deviation | 5.85 ± 0.892 | 5.85 ± 0.892 | 5.8 ± 0.89 |
| RA Disease Characteristics -DAS28 (ESR) Units: score arithmetic mean standard deviation | 6.68 ± 0.883 | 6.68 ± 0.883 | 6.7 ± 0.89 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | BAT1806 |
| Reporting group description: Subjects randomized to the BAT1806 Arm at baseline received 12 doses of BAT1806 during the study (6 doses in treatment period 1 and 6 doses in treatment period 2). | |
| Reporting group title | RoActemra |
| Reporting group description: Subjects randomized to RoActemra at baseline received 6 doses in treatment period 1, followed by either 6 doses of RoActemra or 6 doses of BAT1806 in treatment period 2. | |
| Reporting group title | BAT1806 |
| Reporting group description: Subjects assigned to the BAT1806 at baseline received 12 doses of BAT1806 during the study (6 doses in Treatment Period 1 and 6 doses in Treatment Period 2). | |
| Reporting group title | RoActemra |
| Reporting group description: Subjects randomized to RoActemra at baseline received 6 doses in treatment period 1 followed by 6 doses of RoActemra in treatment period 2 | |
| Reporting group title | RoActemra -> BAT1806 |
| Reporting group description: Subjects randomized to RoActemra at baseline received 6 doses in treatment period 1, followed by 6 doses of BAT1806 in treatment period 2. | |
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The FAS included all subjects that were randomized during the study. Subjects were analyzed according to randomized treatment. All efficacy endpoints were analyzed on the FAS as primary. | |
| Subject analysis set title | Safety Set in TP1 & TP2 (SAF in TP1 & TP2) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The Safety Set (SAF) will include all randomized subjects that have received any treatment with study drug. Subjects will be analyzed according to treatment received at the start of TP1 and TP2. The SAF will be used for all analyses of safety, tolerability, and immunogenicity endpoints. | |
| Subject analysis set title | Pharmacokinetic Set in TP1 (PKS in TP1) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The PKS (TP1) included all randomized subjects that had received any treatment with study drug in TP1, and had at least 1 evaluable PK assessment postbaseline. Subjects were analyzed according to their treatment arm. The PKS was used for PK analyses. | |

Primary: Proportion of Subjects Achieving ACR20 at Week 12

| | |
|---|---|
| End point title | Proportion of Subjects Achieving ACR20 at Week 12 |
| End point description: The primary endpoint for EMA is the proportion of subjects achieving ACR20 response at Week 12. | |
| End point type | Primary |
| End point timeframe: Baseline - Week 12 | |

| End point values | BAT1806 | RoActemra | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 309 | | |
| Units: Proportion of subjects | | | | |
| number (not applicable) | 68.97 | 64.82 | | |

Statistical analyses

| Statistical analysis title | ACR20 analysis for week 12 (Full Analysis Set) |
|---|--|
| Comparison groups | BAT1806 v RoActemra |
| Number of subjects included in analysis | 621 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 4.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.63 |
| upper limit | 11.93 |

Primary: Proportion of Subjects Achieving ACR20 at Week 24

| | |
|------------------------|--|
| End point title | Proportion of Subjects Achieving ACR20 at Week 24 |
| End point description: | The primary endpoint for FDA and NMPA is the proportion of subjects achieving ACR20 response at Week 24. |
| End point type | Primary |
| End point timeframe: | Baseline to Week 24 |

| End point values | BAT1806 | RoActemra | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 309 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 69.89 | 67.94 | | |

Statistical analyses

| Statistical analysis title | ACR20 analysis for Week 24 (Full Analysis Set) |
|----------------------------|--|
| Comparison groups | BAT1806 v RoActemra |

| | |
|---|----------------------|
| Number of subjects included in analysis | 621 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 1.94 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -4.04 |
| upper limit | 7.92 |

| | |
|---|--|
| Statistical analysis title | ACR20 analysis for Week 24 (Full Analysis Set) |
| Comparison groups | BAT1806 v RoActemra |
| Number of subjects included in analysis | 621 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 1.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.18 |
| upper limit | 9.07 |

Secondary: Proportion of Subjects Achieving ACR50 at Week 12

| | |
|---|---|
| End point title | Proportion of Subjects Achieving ACR50 at Week 12 |
| End point description: | |
| Proportion of subjects achieving ACR50 at Week 12 | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 12 | |

| | | | | |
|-------------------------------|-----------------|-----------------|--|--|
| End point values | BAT1806 | RoActemra | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 309 | | |
| Units: Proportion of subjects | | | | |
| number (not applicable) | 27.14 | 32.53 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | ACR50 analysis for week 12 (Full Analysis Set) |
| Comparison groups | RoActemra v BAT1806 |
| Number of subjects included in analysis | 621 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -5.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.93 |
| upper limit | 2.15 |

Secondary: Proportion of Subjects Achieving ACR50 at Week 24

| | |
|---|---|
| End point title | Proportion of Subjects Achieving ACR50 at Week 24 |
| End point description: | |
| Proportion of subjects achieving ACR50 at Week 24 | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 24 | |

| | | | | |
|-------------------------------|-----------------|-----------------|--|--|
| End point values | BAT1806 | RoActemra | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 309 | | |
| Units: Proportion of subjects | | | | |
| number (not applicable) | 42.33 | 42.70 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | ACR50 analysis at Week 24 (Full Analysis Set) |
| Comparison groups | BAT1806 v RoActemra |
| Number of subjects included in analysis | 621 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -0.36 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -6.72 |
| upper limit | 5.99 |

| | |
|---|---|
| Statistical analysis title | ACR50 analysis at Week 24 (Full Analysis Set) |
| Comparison groups | RoActemra v BAT1806 |
| Number of subjects included in analysis | 621 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.93 |
| upper limit | 7.2 |

Secondary: Proportion of Subjects Achieving ACR70 at Week 12

| | |
|---|---|
| End point title | Proportion of Subjects Achieving ACR70 at Week 12 |
| End point description: | |
| Proportion of subjects achieving ACR70 at Week 12 | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 12 | |

| | | | | |
|-------------------------------|-----------------|-----------------|--|--|
| End point values | BAT1806 | RoActemra | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 309 | | |
| Units: Proportion of subjects | | | | |
| number (not applicable) | 8.3 | 9.4 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | ACR70 analysis at week 12 (Full Analysis Set) |
| Comparison groups | BAT1806 v RoActemra |
| Number of subjects included in analysis | 621 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -1.09 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.3 |
| upper limit | 4.13 |

Secondary: Proportion of Subjects Achieving ACR70 at Week 24

| | |
|---|---|
| End point title | Proportion of Subjects Achieving ACR70 at Week 24 |
| End point description: | |
| Proportion of subjects achieving ACR70 at Week 24 | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 24 | |

| End point values | BAT1806 | RoActemra | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 309 | | |
| Units: Proportion of subjects | | | | |
| number (not applicable) | 20.53 | 22.31 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | ACR70 analysis at week 24 (Full Analysis Set) |
| Comparison groups | BAT1806 v RoActemra |
| Number of subjects included in analysis | 621 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -1.78 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -7.09 |
| upper limit | 3.53 |

| | |
|-----------------------------------|---|
| Statistical analysis title | ACR70 analysis at Week 24 (Full Analysis Set) |
| Comparison groups | BAT1806 v RoActemra |

| | |
|---|----------------------|
| Number of subjects included in analysis | 621 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -1.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.1 |
| upper limit | 4.55 |

Secondary: Change from Baseline in DAS28 (CRP) at Week 12

| | |
|---|--|
| End point title | Change from Baseline in DAS28 (CRP) at Week 12 |
| End point description: | |
| Based on observed values; no imputation of missing values | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 12 | |

| End point values | BAT1806 | RoActemra | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 290 | 280 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | -2.233 (± 1.0752) | -2.162 (± 1.0576) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in DAS28 (CRP) at Week 24

| | |
|---|--|
| End point title | Change from Baseline in DAS28 (CRP) at Week 24 |
| End point description: | |
| Based on observed values; no imputation of missing values | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 24 | |

| End point values | BAT1806 | RoActemra | | |
|--------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 278 | 270 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | -2.791 (\pm 1.1824) | -2.787 (\pm 1.1099) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in DAS28 (ESR) at Week 12

| | |
|---|--|
| End point title | Change from Baseline in DAS28 (ESR) at Week 12 |
| End point description: | |
| Based on observed values; no imputation of missing values | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 12 | |

| End point values | BAT1806 | RoActemra | | |
|--------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 290 | 280 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | -2.869 (\pm 1.5066) | -2.595 (\pm 1.3254) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in DAS28 (ESR) at Week 24

| | |
|---|--|
| End point title | Change from Baseline in DAS28 (ESR) at Week 24 |
| End point description: | |
| Based on observed values; no imputation of missing values | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 24 | |

| End point values | BAT1806 | RoActemra | | |
|--------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 279 | 271 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | -3.463 (\pm 1.4375) | -3.380 (\pm 1.4718) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pharmacokinetics Concentrations of Tocilizumab at week 12

| | |
|-----------------|---|
| End point title | Serum Pharmacokinetics Concentrations of Tocilizumab at week 12 |
|-----------------|---|

End point description:

Serum Pharmacokinetics Concentrations of Tocilizumab at week 12 (predose) was summarized for the PKS using descriptive statistics for each treatment arm separately.

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

End point timeframe:

Week 12

| End point values | BAT1806 | RoActemra | | |
|--------------------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 | 278 | | |
| Units: ug/mL | | | | |
| arithmetic mean (standard deviation) | 13.5377 (\pm 11.26505) | 13.9794 (\pm 20.0850) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pharmacokinetics Concentrations of Tocilizumab at week 24

| | |
|-----------------|---|
| End point title | Serum Pharmacokinetics Concentrations of Tocilizumab at week 24 |
|-----------------|---|

End point description:

Serum Pharmacokinetics Concentrations of Tocilizumab at week 24 (predose) was summarized for the PKS using descriptive statistics for each treatment arm separately.

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

End point timeframe:

Week 24

| End point values | BAT1806 | RoActemra | | |
|--------------------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 276 | 271 | | |
| Units: ug/mL | | | | |
| arithmetic mean (standard deviation) | 15.8013 (\pm 12.30081) | 15.3778 (\pm 17.0995) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ADA Incidence cumulative over TP1 (within week 24)

| | |
|---|--|
| End point title | ADA Incidence cumulative over TP1 (within week 24) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: baseline to week 24 | |

| End point values | BAT1806 | RoActemra | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 309 | | |
| Units: ADA positive: number of subjects | | | | |
| number (not applicable) | 64 | 42 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring during the study (from the time of receiving written informed consent to 8 weeks after the last dose of IMP) must be collected and documented on the relevant eCRF pages.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | BAT1806 arm |
|-----------------------|-------------|

| | |
|--------------------------------|--|
| Reporting group description: - | |
|--------------------------------|--|

| | |
|-----------------------|---------------|
| Reporting group title | RoActemra arm |
|-----------------------|---------------|

| | |
|--------------------------------|--|
| Reporting group description: - | |
|--------------------------------|--|

| | |
|-----------------------|-------------------------------|
| Reporting group title | TP1 RoActemra and TP2 BAT1806 |
|-----------------------|-------------------------------|

| | |
|--------------------------------|--|
| Reporting group description: - | |
|--------------------------------|--|

| Serious adverse events | BAT1806 arm | RoActemra arm | TP1 RoActemra and TP2 BAT1806 |
|---|------------------|------------------|-------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 19 / 312 (6.09%) | 12 / 167 (7.19%) | 10 / 142 (7.04%) |
| number of deaths (all causes) | 4 | 1 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Ovarian Cancer Stage III | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Renal Hamartoma | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Pregnancy, puerperium and perinatal conditions | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| Abortion Spontaneous | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 167 (1.20%) | 0 / 142 (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 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug Hypersensitivity | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (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 |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (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 |
| Uterine Haemorrhage | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine Polyp | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory Failure | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Contusion | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (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 Dislocation | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Joint Injury | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (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 |
| Patella Fracture | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (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 |
| Rib Fracture | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Spinal Cord Injury Cervical | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Coronary Artery Disease | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Myocardial Ischaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral Haemorrhage | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Lacunar Infarction | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Memory Impairment | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (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 |
| Ruptured Cerebral Aneurysm | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient Ischaemic Attack | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diverticular Perforation | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (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 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Cholangitis Acute | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 | | | |
| Lumbar Spinal Stenosis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Pathological Fracture | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (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 |
| Arthritis Infective | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Bronchitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Covid-19 | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Mediastinitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Pancreatic Abscess | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (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 |
| Salpingo-Oophoritis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 167 (0.00%) | 0 / 142 (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 |
| Septic Shock | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 167 (0.60%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Tooth Abscess | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 167 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 2 / 167 (1.20%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | BAT1806 arm | RoActemra arm | TP1 RoActemra and TP2 BAT1806 |
|---|--------------------|--------------------|-------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 213 / 312 (68.27%) | 119 / 167 (71.26%) | 98 / 142 (69.01%) |
| Investigations | | | |
| ALT increased | | | |
| subjects affected / exposed | 32 / 312 (10.26%) | 23 / 167 (13.77%) | 24 / 142 (16.90%) |
| occurrences (all) | 47 | 33 | 39 |
| AST increased | | | |
| subjects affected / exposed | 19 / 312 (6.09%) | 11 / 167 (6.59%) | 13 / 142 (9.15%) |
| occurrences (all) | 32 | 18 | 23 |
| LDL increased | | | |
| subjects affected / exposed | 10 / 312 (3.21%) | 13 / 167 (7.78%) | 7 / 142 (4.93%) |
| occurrences (all) | 23 | 23 | 12 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 17 / 312 (5.45%) | 6 / 167 (3.59%) | 5 / 142 (3.52%) |
| occurrences (all) | 31 | 9 | 6 |
| WBC count decreased | | | |
| subjects affected / exposed | 13 / 312 (4.17%) | 7 / 167 (4.19%) | 6 / 142 (4.23%) |
| occurrences (all) | 22 | 9 | 10 |
| Blood LDH increased | | | |

| | | | |
|--------------------------------------|------------------|-------------------|------------------|
| subjects affected / exposed | 12 / 312 (3.85%) | 7 / 167 (4.19%) | 5 / 142 (3.52%) |
| occurrences (all) | 21 | 11 | 11 |
| Transaminases increased | | | |
| subjects affected / exposed | 10 / 312 (3.21%) | 4 / 167 (2.40%) | 6 / 142 (4.23%) |
| occurrences (all) | 11 | 5 | 6 |
| GGT increased | | | |
| subjects affected / exposed | 10 / 312 (3.21%) | 2 / 167 (1.20%) | 4 / 142 (2.82%) |
| occurrences (all) | 13 | 4 | 5 |
| BP increased | | | |
| subjects affected / exposed | 5 / 312 (1.60%) | 6 / 167 (3.59%) | 4 / 142 (2.82%) |
| occurrences (all) | 7 | 6 | 4 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 6 / 312 (1.92%) | 3 / 167 (1.80%) | 4 / 142 (2.82%) |
| occurrences (all) | 11 | 5 | 8 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 5 / 312 (1.60%) | 6 / 167 (3.59%) | 2 / 142 (1.41%) |
| occurrences (all) | 7 | 8 | 3 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 7 / 312 (2.24%) | 3 / 167 (1.80%) | 7 / 142 (4.93%) |
| occurrences (all) | 8 | 3 | 10 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 20 / 312 (6.41%) | 24 / 167 (14.37%) | 13 / 142 (9.15%) |
| occurrences (all) | 39 | 46 | 24 |
| Neutropenia | | | |
| subjects affected / exposed | 26 / 312 (8.33%) | 15 / 167 (8.98%) | 13 / 142 (9.15%) |
| occurrences (all) | 36 | 25 | 28 |
| Anaemia | | | |
| subjects affected / exposed | 8 / 312 (2.56%) | 6 / 167 (3.59%) | 8 / 142 (5.63%) |
| occurrences (all) | 10 | 9 | 8 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 10 / 312 (3.21%) | 6 / 167 (3.59%) | 6 / 142 (4.23%) |
| occurrences (all) | 17 | 9 | 7 |
| Lymphopenia | | | |

| | | | |
|--|------------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 13 / 312 (4.17%) 16 | 2 / 167 (1.20%) 3 | 0 / 142 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 9 / 312 (2.88%) | 6 / 167 (3.59%) | 5 / 142 (3.52%) |
| occurrences (all) | 19 | 16 | 12 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 9 / 312 (2.88%) | 3 / 167 (1.80%) | 3 / 142 (2.11%) |
| occurrences (all) | 13 | 6 | 3 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 10 / 312 (3.21%) | 2 / 167 (1.20%) | 1 / 142 (0.70%) |
| occurrences (all) | 12 | 2 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 312 (2.88%) | 4 / 167 (2.40%) | 0 / 142 (0.00%) |
| occurrences (all) | 14 | 4 | 0 |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 22 / 312 (7.05%) | 13 / 167 (7.78%) | 14 / 142 (9.86%) |
| occurrences (all) | 34 | 21 | 25 |
| Liver injury | | | |
| subjects affected / exposed | 20 / 312 (6.41%) | 4 / 167 (2.40%) | 4 / 142 (2.82%) |
| occurrences (all) | 32 | 4 | 8 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Headache | | | |
| subjects affected / exposed | 7 / 312 (2.24%) | 5 / 167 (2.99%) | 4 / 142 (2.82%) |
| occurrences (all) | 7 | 5 | 4 |
| Dizziness | | | |
| subjects affected / exposed | 7 / 312 (2.24%) | 5 / 167 (2.99%) | 3 / 142 (2.11%) |
| occurrences (all) | 7 | 5 | 4 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 8 / 312 (2.56%) | 2 / 167 (1.20%) | 4 / 142 (2.82%) |
| occurrences (all) | 9 | 2 | 5 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 7 / 312 (2.24%) 7 | 5 / 167 (2.99%) 5 | 4 / 142 (2.82%) 4 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 44 / 312 (14.10%) | 34 / 167 (20.36%) | 14 / 142 (9.86%) |
| occurrences (all) | 57 | 49 | 20 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 17 / 312 (5.45%) | 5 / 167 (2.99%) | 8 / 142 (5.63%) |
| occurrences (all) | 21 | 7 | 9 |
| Urinary tract infection | | | |
| subjects affected / exposed | 13 / 312 (4.17%) | 9 / 167 (5.39%) | 7 / 142 (4.93%) |
| occurrences (all) | 13 | 11 | 7 |
| Bronchitis | | | |
| subjects affected / exposed | 7 / 312 (2.24%) | 4 / 167 (2.40%) | 5 / 142 (3.52%) |
| occurrences (all) | 9 | 4 | 5 |
| Metabolism and nutrition disorders | | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 31 / 312 (9.94%) | 12 / 167 (7.19%) | 11 / 142 (7.75%) |
| occurrences (all) | 50 | 17 | 17 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 14 / 312 (4.49%) | 12 / 167 (7.19%) | 5 / 142 (3.52%) |
| occurrences (all) | 21 | 22 | 7 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 18 / 312 (5.77%) | 7 / 167 (4.19%) | 4 / 142 (2.82%) |
| occurrences (all) | 30 | 15 | 5 |
| Hypokalaemia | | | |
| subjects affected / exposed | 12 / 312 (3.85%) | 4 / 167 (2.40%) | 7 / 142 (4.93%) |
| occurrences (all) | 18 | 7 | 7 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 6 / 312 (1.92%) | 7 / 167 (4.19%) | 4 / 142 (2.82%) |
| occurrences (all) | 10 | 9 | 5 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 25 June 2018 | duration of study corrected from 60 to 56 weeks with clarifications added for timing (at Week 52/8 weeks after the last dose of study drug) and duration (4 weeks) of the follow-up period; clarifications to Schedule of Assessments footnotes; and administrative changes. |
| 20 August 2018 | stable dose for MTX therapy allowed in the study changed from 7.5 to 25 mg/week to 10 to 25 mg/week with 7.5 mg/week allowed only in case of intolerance to a higher dose; addition of HBV serology screening criteria for European and Chinese sites; year of birth collected instead of date of birth; addition that vital signs were to be performed more frequently in TP2; addition that all clinical laboratory tests except CRP and IGRA were to be performed by local laboratories instead of central laboratory for Chinese sites; and administrative changes. |
| 17 September 2018 | inclusion criterion 6 was revised to remove the requirement of previous TNF inhibitor treatment for study entry; and total volume of blood sampling was updated. |
| 27 April 2020 | correction of Sponsor name; updated Medical Monitors and contact information; number of sites increased to approximately 55 sites; primary endpoint edited: was to be analyzed at 2 time points (Weeks 12 or 24) depending on the regulatory agency for submission and it was also estimated that 598 evaluable subjects completing Week 12 was needed; update of primary efficacy analysis based on change of primary endpoint; sample size re-estimation based on the recommendations of the 3 different agencies for the 2 different time points for the primary endpoint (meta analysis performed for re-estimation); addition of 5-minute window for IV infusion; updated rules for dose adjustment with regard to liver enzymes; allowed topical steroids or NSAIDs during the study; noted that any assessment required at Early Termination that had been performed at 4 weeks of the last study drug dosing did not need to be repeated at the Early Termination Visit in case of early withdrawal and that any scheduled assessment for Follow-Up Visit that had been performed at 8 weeks after the last study drug dosing need not be repeated at the Follow-Up Visit; AE monitoring was continued until 8 weeks after last dose of study drug and only an AE with increasing severity was to be recorded as a separate event; added that microscopy or other quantitative urine test was to be performed if there was any positive clinically significant result in urinalysis dipstick; removal of respiration rate assessment from vital signs and removal of cervical examination from physical examination; and addition of analysis that may be performed to evaluate the effects of COVID-19 per regulatory guidance. |
| 02 September 2020 | updated statistical analyses and sample size calculations per US FDA comments; clarified blinding details; and addition of separate (ie, outside of the protocol) population PK study. |

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.

In this study, randomization for both TP1 and TP2 occurred at baseline and the actual randomization was 2:1:1 to BAT1806 Arm, RoActemra Arm and RoActemraBAT1806 respectively.

Notes: