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 (± 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 (± 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 (±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 (±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	70.1	70.5	
standard deviation	± 17.45	± 15.62	-
RA Disease Characteristics -Physician's Global Assessment of Disease Activity			
Units: mm			
arithmetic mean	67.8	70.3	
standard deviation	± 14.76	± 13.40	-
RA Disease Characteristics-HAQ-DI			
Units: score			
arithmetic mean	1.56	1.56	
standard deviation	± 0.614	± 0.545	-
RA Disease Characteristics-CRP level			
Units: mg/L			
arithmetic mean	18.908	19.707	
standard deviation	± 22.9146	± 25.9105	-
RA Disease Characteristics-Tender joint count (28 joints)			
Units: number			
arithmetic mean	14.9	15.4	
standard deviation	± 6.3	± 6.29	-
RA Disease Characteristics-Swollen joint count (28 joints)			
Units: number			
arithmetic mean	10.9	11.3	
standard deviation	± 5.39	± 5.13	-
RA Disease Characteristics-ESR			
Units: mm/hour			
arithmetic mean	48.4	50.7	
standard deviation	± 22.49	± 21.99	-
RA Disease Characteristics-DAS28 (CRP)			
Units: score			
arithmetic mean	5.81	5.89	
standard deviation	± 0.938	± 0.847	-
RA Disease Characteristics -DAS28 (ESR)			
Units: score			
arithmetic mean	6.64	6.71	
standard deviation	± 0.877	± 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	69.1	69.1	69.1
standard deviation	± 14.87	± 14.87	± 14.87
RA Disease Characteristics-HAQ-DI			
Units: score			
arithmetic mean	1.56	1.56	1.6
standard deviation	± 0.603	± 0.603	± 0.6
RA Disease Characteristics-CRP level			
Units: mg/L			
arithmetic mean	18.901	18.901	18.9
standard deviation	± 23.8865	± 23.8865	± 23.9
RA Disease Characteristics-Tender joint count (28 joints)			
Units: number			
arithmetic mean	15.2	15.2	15.2
standard deviation	± 6.22	± 6.22	± 6.21
RA Disease Characteristics-Swollen joint count (28 joints)			
Units: number			
arithmetic mean	11.2	11.2	11.2
standard deviation	± 5.22	± 5.22	± 5.18
RA Disease Characteristics-ESR			
Units: mm/hour			
arithmetic mean	49.1	49.1	49
standard deviation	± 23.05	± 23.05	± 23.06
RA Disease Characteristics-DAS28 (CRP)			
Units: score			
arithmetic mean	5.85	5.85	5.8
standard deviation	± 0.892	± 0.892	± 0.89
RA Disease Characteristics -DAS28 (ESR)			
Units: score			
arithmetic mean	6.68	6.68	6.7
standard deviation	± 0.883	± 0.883	± 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 (± 1.1824)	-2.787 (± 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 (± 1.5066)	-2.595 (± 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 (± 1.4375)	-3.380 (± 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 (± 11.26505)	13.9794 (± 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 (± 12.30081)	15.3778 (± 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 occuring 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	13 / 312 (4.17%)	2 / 167 (1.20%)	0 / 142 (0.00%)
occurrences (all)	16	3	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	7 / 312 (2.24%)	5 / 167 (2.99%)	4 / 142 (2.82%)
occurrences (all)	7	5	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
Hypercholesterolae mia			
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: