BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	761354
Received Date	September 29, 2022
BsUFA Goal Date	September 29, 2023
Division/Office	DRTM/OII/OND
Review Completion Date	See DARRTS stamped date
Product Code Name	BIIB800, BAT1806
Proposed Nonproprietary Name[1]	Tocilizumab-bavi
Proposed Proprietary Name[1]	Tofidence
Pharmacologic Class	Interleukin-6 (IL-6) receptor antagonist
Applicant	Biogen
Applicant Proposed Indication(s)	Rheumatoid Arthritis (RA), Polyarticular juvenile idiopathic arthritis (PJIA ≥ 2 years), Systemic juvenile idiopathic arthritis (SJIA ≥ 2 years)
Recommendation on Regulatory Action	Approval

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ACR20	≥20% from baseline in tender and swollen joint counts and ≥20% improvement from baseline in 3 of the 5 other ACR-core set measures
ACR50	≥50% from baseline in tender and swollen joint counts and ≥50% improvement from baseline in 3 of the 5 other ACR-core set measures
ACR70	≥70% from baseline in tender and swollen joint counts and ≥70% improvement from baseline in 3 of the 5 other ACR-core set measures
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DAS	Disease Activity Score
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMARD	Disease Modifying Anti-Rheumatic Drug
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
EU-RoActemra	European Union-approved RoActemra
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice

GMR	Geometric Mean Ratio
HAQ-DI	Health Assessment Questionnaire-Disability Index
HDL	High Density Lipoprotein
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
US-Actemra	U.S.-licensed ACTEMRA

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1. Executive Summary

1.1. Product Introduction

Biogen MA Inc. (also referred to as the "Applicant" in this review) has submitted a biologic license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for BIIB800 (also referred to as "BAT1806" in this review) as a proposed biosimilar to US-licensed Actemra (tocilizumab).

BAT1806 is a recombinant humanized monoclonal immunoglobulin (Ig)G1 anti-interleukin-6 receptor (IL-6R) antibody. It is proposed as a biosimilar to US-licensed Actemra. BAT1806 binds to soluble IL-6R and membrane bound IL-6R thereby inhibiting IL-6 signaling through these receptors. BAT1806 is manufactured using recombinant Chinese hamster ovary (CHO) cell line.

The Applicant is seeking licensure of BAT1806 for the following indications for which Actemra has been previously approved[2]:

1) Rheumatoid arthritis (RA): Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
2) Polyarticular Juvenile Arthritis (PJIA): Treatment of patients 2 years of age and older with active systemic juvenile idiopathic arthritis.
3) Systemic Juvenile Idiopathic Arthritis (SJIA): Treatment of patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

Tocilizumab is a recombinant humanized monoclonal antibody that binds to both soluble- and membrane-bound interleukin-6 receptors (sIL-6R and mIL-6R) and has been shown to inhibit downstream IL-6-mediated signaling through these receptors. Interleukin-6 (IL-6) is a pleiotropic proinflammatory cytokine produced by various cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts and has effects on many physiological processes such as inflammation, immune response, hematopoiesis, and acute-phase reactions. IL-6 is also produced by synovial and

[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125472s046lbl.pdf

endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as RA.

BAT1806 has the same mechanism of action as that of U.S.-licensed Actemra.

BAT1806 is proposed as below:

For intravenous infusion:

- Injection: in 80 mg/4mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) single-dose vials for further dilution prior to intravenous (IV) infusion.

Each strength of BAT1806 in single dose vial is the same as that of US-Actemra. BAT1806 also has the same dosage form and route of administration as that of US-Actemra.

Additionally, the condition(s) of use for which the applicant is seeking licensure have been previously approved for US-Actemra.

1.4. Inspection of Manufacturing Facilities

An on-site pre-license inspection for the drug substance and drug product manufacturing facility, (b) (4) was conducted in (b) (4) and found satisfactory. Based on the final inspection conclusions, the OPMA team has recommended an approval action for BLA 761354 from the facilities assessment standpoint.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Biogen provided adequate data to establish the scientific bridge to justify the relevance of data generated from the comparative clinical study, Study BAT-1806-002-CR, which used EU-RoActemra as the comparator, to the assessment of biosimilarity:

- The Office of Pharmaceutical Products, OPQ, CDER has determined, and I agree, that based on the data provided by the Applicant, the analytical component of the scientific bridge between BAT1806, US-Actemra, and EU-RoActemra was established.
- The Office of Clinical Pharmacology (OCP) has determined, and I agree, that based on the data provided by the Applicant, the PK data establish the PK component of the scientific bridge.

1.6. Biosimilarity Assessment

Table 1. Summary and Assessment of Biosimilarity

Comparative Analytical Studies[3]	
Summary of Evidence	• BIIB800 is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components. • BIIB800 has the same strength and dosage forms for the IV route of administration as US-Actemra. • The analytical portion of the scientific bridge between BIIB800, US-Actemra, and EU-RoActemra was established to support the relevance of the data generated from studies EU-RoActemra as the comparator for the assessment of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	• The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the pharmacology/toxicology assessment.
Clinical Studies	
Clinical Pharmacology Studies	

[3]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

Summary of Evidence	• PK similarity has been demonstrated between BAT1806 and US-Actemra (Study BAT-1806-001-CR), and supports a demonstration of no clinically meaningful differences between BAT1806 and US-Actemra for the IV administration route. • PK similarity between BAT1806, US-Actemra, and EU-RoActemra (Study BAT-1806-001-CR) provides the PK component of the scientific bridge to support the relevance of the comparative data generated using EU-RoActemra to the assessment of biosimilarity • Similar incidence of ADA and NAb formation in BAT1806 compared to US-Actemra and to EU-RoActemra in healthy subjects (Study BAT-1806-001-CR) and compared to EU-RoActemra in patients with RA (Study BAT-1806-002-CR) including following the single transition from EU-RoActemra to BAT1806. • Given the scientific bridge was established (based on the analytical and PK comparisons) between BAT1806, US-Actemra, and EU-RoActemra to justify the relevance of data generated with EU-RoActemra as the comparator, these collective immunogenicity results support a demonstration of no clinically meaningful differences between BAT1806 and US-licensed Actemra.
Assessment of Residual Uncertainties	• There are no clinical pharmacology residual uncertainties regarding the PK assessments.
Additional Clinical Studies	

Summary of Evidence	• In the comparative clinical study BAT1806-002- CR, there were no meaningful differences in terms of efficacy between BAT1806 and EU-RoActemra. • In the comparative clinical study BAT1806-002-CR and the PK similarity study BAT1806-001-CR the frequency of treatment emergent adverse events, serious adverse events and events leading to discontinuation of the study drug had no meaningful differences between the treatment arms. • Given the scientific bridge was established (based on the analytical and PK comparisons) between BAT1806, US-Actemra, and EU-RoActemra to justify the relevance of the data generated with EU-RoActemra as the comparator, the evidence from the comparative clinical study BAT1806-002-CR supports a demonstration of no clinically meaningful difference between BAT1806 and US-Actemra in the studied population (RA).
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or statistical perspective regarding the demonstration of no clinically meaningful differences between BAT1806 and US-Actemra.
Extrapolation	

Summary of Evidence	• DRTM has determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (RA), to support licensure of BAT1806 as a biosimilar, under section 351(k) of the PHS Act, for the following indications for which US-licensed Actemra has been previously approved: - Treatment of polyarticular juvenile idiopathic arthritis in patients 2 year and older. - Treatment of systemic juvenile idiopathic arthritis in patients 2 years and older. • DRTM has also determined that the Applicant has provided adequate scientific justification for extrapolating data and information submitted in the application to support licensure for BAT1806/BIIB800 as a biosimilar for indications for which licensure is not being sought at this time and for which US-Actemra has been previously approved and for which BAT1806/BIIB800 has not been directly studied: - Cytokine Release Syndrome (CRS) - Coronavirus Disease 2019 (COVID-19)
Assessment of Residual Uncertainties	• There were no residual uncertainties regarding the extrapolation of data and information to support licensure of BAT1806 as a biosimilar to US-Actemra for the above indications.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that BAT1806 is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between BAT1806 and US-Actemra in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that BAT1806 is biosimilar to US-Actemra for each of the following indications for which US-Actemra has been previously approved and for which the Applicant is seeking licensure of BAT1806: Moderately to severely active Rheumatoid Arthritis (RA) in adult patients who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs

(DMARDs), Polyarticular juvenile idiopathic arthritis (PJIA ≥ 2 years), and Systemic juvenile idiopathic arthritis (SJIA ≥ 2 years).[4]

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Clinical Team Leader/CDTL

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

The Division had several interactions with the Applicant during the development of BAT1806. The Applicant sought scientific advice from both the US FDA and European Medicines Agency (EMA) Committee for Human Medicinal Products (CHMP).

Under IND 142381, Bio-Thera Solutions Ltd. had a pre-IND Biosimilar Biological Product Development (BPD) Type 2 meeting on August 4, 2020. Details regarding the chemistry manufacturing and controls (CMC), analytical similarity data, quality, nonclinical and clinical development programs were discussed. The Applicant sought advice regarding the proposed clinical study design, study population, and evaluation of immunogenicity. Key points of the meeting included that the design of the PK similarity study BAT-1806-001-CR was acceptable, however the justification of the 4 mg/kg dose used in the study would need to be provided as well as additional post-hoc analyses for PK parameters. The study design and endpoints for the comparative clinical study BAT-1806-002 -CR were considered acceptable. The statistical approach and similarity margins for the comparative clinical study were discussed and agreement was reached regarding the proposed similarity margin for the ACR20 endpoint (an equivalence margin of [-12.0%, +15.0%]) at Week 24. The Division stated that the Applicant may apply the multiple imputation approach as a supportive analysis. The initial meeting was conducted with the Sponsor Bio-Thera. In 2022, the IND was transferred to Biogen.

On April 13, 2022, the Applicant (Biogen) submitted the initial pediatric study plan (iPSP). On September 15, 2022, the Applicant submitted the Agreed iPSP.

A BPD Type 4 meeting with written responses was provided on June 26, 2022. The key discussion included comments regarding the content and format of the BLA. Submission of additional post-hoc exploratory analyses regarding the impact of COVID-19 on study BAT-1806-002-CR were also discussed.

[4]The proposed BAT1806 labeling states: Biosimilarity of TOFIDENCE has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

Table 2. Table Listing in vivo pharmacology, pharmacokinetic, and US GLP-compliant toxicology studies that were reviewed.

Study Title	Study Number	Species	Number Per Treatment Arm	Study Duration	Route of administration/ Dose
Animal Studies					
Collagen Induced Arthritis in Non-human Primate and Its Application in Evaluation of a Biosimilar Compound BAT1806	BAT1806-201501	cynomolgus monkeys	9	74 days	IV
Pharmacokinetic Study of BAT1806 Injection After Single Intravenous Infusion to Cynomolgus Monkeys	P17-S136-PK	cynomolgus monkeys	8	28 days	IV
Local Tolerance Test for Recombinant Humanized Anti-Human Interleukin-6 Receptor Monoclonal Antibody Injection following Repeat Intravenous Injection to Rabbits	Q17-S136-IR	New Zealand White rabbit	6	29 days	IV

Note: Pharmacokinetic studies that did not include US-licensed Actemra were not reviewed. Only toxicology studies that were US FDA GLP compliant were reviewed.

The clinical studies submitted to support the biosimilarity of BAT1806 to US-Actemra include a 3-way single-dose comparative PK study between IV administered BAT1806, US-Actemra, and EU-RoActemra, and a comparative clinical study of BAT1806 and EU-RoActemra in patients with RA. A summary of the objectives, designs, study populations, and treatment groups are presented in Table 3.

Table 3. BAT1806 Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
BAT-1806-001-CR	NCT03606876	Comparative pharmacokinetics and safety of BAT1806, US-Actemra and EU-RoActemra	Double-blind, randomized, parallel-group, active-controlled, three-way pairwise	Healthy male subjects	BAT1806: 46 US-Actemra: 48 EU-RoActemra: 44
Comparative Clinical Study					
BAT-1806-002-CR	NCT038302303	Comparative clinical study to demonstrate equivalent efficacy of BAT1806 and EU-RoActemra in patients with RA inadequately controlled by MTX	Double-blind, randomized, parallel group, active-controlled	Patients with Rheumatoid Arthritis and inadequate response to MTX	BAT1806: 312 EU-RoActemra →BAT1806: 142 RoActemra: 167

Study BAT-1806-001-CR was conducted in China. Study BAT-1806-002-CR was conducted in 5 countries (China, Poland, Ukraine, Georgia, and Bulgaria).

Authors:
Stefanie Freeman, M.D.
Clinical Reviewer

Raj Nair, M.D.
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3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality (OPQ), CDER, recommended approval of BIIB800, 20 mg/mL BIIB800 in 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL vials for IV administration only. Refer to the Comparative Analytical Assessment chapter, OPQ Executive Summary, and related primary reviews for detailed information.
The OPQ team determined that the data submitted in this application were adequate to support the following conclusions:

- The manufacture of BIIB800 in 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL

vials for IV administration only is well-controlled and leads to a product that is pure, potent, and safe.
- BIIB800 is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components.
- BIIB800 has the same strengths and dosage forms (80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL in vials) for the IV route of administration as US-Actemra.
- Based on the comparative protein concentration data and manufacturing data, the 20 mg/mL BIIB800 in 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL vials have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as the corresponding strengths of US-Actemra.
- The applicant used a comprehensive array of analytical methods that were suitable to evaluate the critical quality attributes of BIIB800, US-Actemra, and EU-RoActemra to support a demonstration that BIIB800 is highly similar to US-Actemra and to establish the analytical component of the scientific bridge.

The OPQ review team recommends that this product be approved for human use under conditions specified in the package insert. The CMC post-marketing commitments (PMC) listed below should be included in the action letter.

4510-1 To implement [redacted] (b) (4) of the sterile filter during sterile filtration

Final report submission date: 03/31/2024

4510-2 To implement revised procedure with target flushing volume of ≥ [redacted] (b) (4) L for post-use filter integrity test

Final report submission date: 03/31/2024

The CDTL and Division Signatory agree with the above assessments and recommendations.

3.2. Devices

3.2.1. Center for Devices and Radiological Health (CDRH)

Not applicable.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

Not applicable.

3.3. Office of Study Integrity and Surveillance (OSIS)

The biopharmaceutical inspection was requested for the clinical site and bioanalytical site of Study BAT-1806-001-CR. OSIS declined to conduct a biopharmaceutical inspection and recommended accepting data for Agency review based on the recent inspectional history of the sites. For more detailed information, refer to the review memo by Dr. Perez dated December 12, 2022.

3.4. Office of Scientific Investigations (OSI)

The following clinical study sites were selected from the comparative clinical study BAT-1806-002-CR for inspection by the CDER Office of Scientific Investigations (OSI).

- Site #POL010 (Dr. Agnieszka Zielinska)
- Site # POL006 (Dr. Slawomir Jeka)

These two clinical sites were selected for inspections based on risks, enrollment, and prior inspections. Based on the inspection results, the study appears to have been conducted adequately, and the data generated by these clinical investigator (CI) sites appear acceptable in support of this BLA. For further details, please see Dr. Suyoung Tina Chang's OSI Clinical Inspection Summary Review dated August 23, 2023.

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4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

The Sponsor is developing BAT1806, a recombinant humanized anti-human interleukin-6 receptor monoclonal antibody, as a biosimilar to US-licensed Actemra (tocilizumab). Reviewed studies in their nonclinical program included: comparisons of BAT1806 to US-licensed Actemra and/or EU-approved RoActemra in binding studies with IL-6R, a collagen induced arthritis (CIA) model using female cynomolgus monkeys, a pharmacokinetic (PK) study in male and female monkeys with a single intravenous (IV) dose, and a GLP IV local tolerance study in rabbits. Pharmacokinetic studies that did not include US-licensed Actemra were not reviewed. Only toxicology studies that were US FDA GLP compliant were reviewed.

The binding specificity of recombinant humanized anti-human interleukin-6 receptor

monoclonal antibody, BAT1806 or US-licensed Actemra (US-Actemra), to human IL-6R (hIL-6R), monkey IL-6R (cIL-6R), mouse IL-6R (mIL-6R , human TNFα hTNFα) and human IL-6 (hIL-6) was measured using ELISA methods. The affinity of BAT1806 and US-Actemra to its targets (i.e., hIL-6R and cIL-6R) were similar. In contrast, BAT1806 or US-Actemra had no specific binding affinity to mIL-6R, hTNFα and hIL-6.

The efficacy of BAT1806 for the treatment of rheumatoid arthritis was tested in a bovine type II CIA model using female cynomolgus monkeys. Monkeys (3 groups, 9 animals/group) received IV infusions of 30 mg/kg BAT1806, 30 mg/kg US-Actemra, or negative control (i.e., sodium chloride solution). Markers of inflammation (i.e., erythrocyte sedimentation rate and C-reactive protein) were reduced in animals treated with BAT1806 and US-Actemra, compared to the negative control.

PK exposures to BAT1806, US-Actemra, and EU-RoActemra in monkeys were evaluated. Monkeys (n=4/sex/group) were given a single IV infusion dose at 10 mg/kg of either: 1) BAT1806 (b) (4)L (batch N20171101), 2) BAT1806 (b) (4)L (batch A0520180402), 3) US-Actemra (batch B3014B04), or 4) EU-RoActemra (batch B2057B28). All PK parameters were shown to be similar across the different drug products tested and there were no statistically significant differences, including between sexes. Between two batches of BAT1806, no scale-up production effects on PK parameters were detected. PK parameters, C_{max} and $AUC_{(0-240h)}$, of BAT1806, US-Actemra, and EU-RoActemra ratios were within 80-125% and that exposure of BAT1806 (b) (4)L was similar to BAT1806 (b) (4)L, US-Actemra and EU-RoActemra. The results indicated similar C_{max} and $AUC_{(0-240h)}$ for all four products in a monkey PK study after a single IV dose.

An FDA GLP compliant study was conducted to evaluate and compare the IV local irritation of BAT1806 and EU-RoActemra in male New Zealand White rabbits (n=6/group, 3 groups in total). Animals were intravenously administered in the right ear vein with drugs on Days 1 and 15. At the same dosing times, all animals were treated with negative control (sodium chloride injection) in the left ear vein. Animals were necropsied on either Day 18 (n=3/group) or maintained for a 14 day recovery period (Day 29; n=3/group). There were no macroscopic or microscopic findings at the injection sites of animals euthanized as scheduled. Similar to the EU-RoActemra, BAT1806 was not shown to be a local irritant in rabbits.

A GLP study was conducted to evaluate the hemolytic and aggregation effect of BAT1806 using human red blood cells (RBCs). No hemolysis or aggregation was observed in human RBCs with BAT1806 produced at (b) (4)L or (b) (4)L scale, or EU-Actemra.

Details of the nonclinical program are provided in Section 14.3 (Nonclinical Appendices).

Nonclinical Recommendation: Given an adequate scientific bridge was established to support the relevance of data generated with EU-RoActemra to the assessment of biosimilarity, the information in the pharmacology/toxicology assessment support the

determination of biosimilarity.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The BAT1806 drug product is a concentrate for solution for infusion and is intended for intravenous infusion. The quantitative composition, function, and quality standard of each component in the finished drug product are provided in the table below. All excipients are compendial grade (see the table below). No novel excipients are used for the manufacture of the drug product and proposed levels are less than or equal to FDA-approved IV products.

The BAT1806 product, presented at three strengths (80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL), is supplied in a (b) (4) glass vial closed with a stopper and seal with a flipoff cap. All packaging components are suitable for pharmaceutical use, and the materials of construction of the container components are compliant with compendial regulations (see the table below).

Table 4. Quantitative Composition of Drug Product

Component	Function	Quality Standard	Amount per mL	Nominal Concentration	Nominal Amount (mg) per Vial [a]		
					80 mg	200 mg	400 mg
Tocilizumab	Active Ingredient	See 3.2.S.4.1; *Specifications*	20mg	20 mg/mL	80	200	400
L-Histidine	(b) (4)	Compendial	0.81mg	5.2 mM	3.24	8.10	16.20
L-Histidine hydrochloride monohydrate		Compendial	1.01 mg	4.8 mM	4.04	10.10	20.20
Arginine hydrochloride		Compendial	10.53 mg	50 mM	42.12	105.30	210.60
Sucrose		Compendial	20 mg	20 mg/mL	80.0	200.0	400.0
Polysorbate 80		Compendial	0.5 mg	0.5 mg/mL	2.0	5.0	10.0
Water for injection		Compendial	QS to final volume	QS to final volume	QS to (b) (4)	QS to	QS to

[a] Nominal quantity excludes overfill, see Module 3, 3.2.P.2.3 *Manufacturing Development Studies*.
QS = Quantum sufficit

Source: Excerpted from Sponsor submission

Table 5. Compendial Excipient Specifications

Excipient	Grade[a]
L-Histidine	Ph.Eur., USP-NF, JP
L-Histidine hydrochloride monohydrate	Ph.Eur., BP, JP
Arginine hydrochloride	Ph.Eur., BP, JP, USP-NF
Sucrose	USP-NF, Ph.Eur., JP
Polysorbate 80	Ph.Eur.
Water for injections	Ph.Eur., USP-NF

JP = Japan Pharmacopoeia; Ph.Eur. = European Pharmacopoeia; USP-NF = United States Pharmacopoeia-National Formulary; BP = British Pharmacopoeia
[a]Current edition of the relevant compendia

Source: Excerpted from Sponsor submission

Table 6. Description of the Primary Container Closure

Item	Description
Vial	Nominal size: 6 mL, 15 mL, 25 mL Material: (b) (4) clear glass compliant with USP/Ph.Eur./JP
Stopper	Nominal Size: 20 mm Material: (b) (4) rubber compliant with USP/Ph.Eur.
Seal	Material: Aluminum crimp seal with (b) (4) flip off button

Source: Excerpted from Sponsor submission

Comments on Excipients

Excipients are within the ranges that are found in the FDA inactive ingredient database.

Comments on Impurities of Concern

Extractable and leachables studies were conducted with the primary container closure system, ((b) (4) glass vial and (b) (4) rubber stopper). The evaluation of extractables and leachables was done in a separate review. Overall, there were no significant toxicological concerns from extractables and leachables studies conducted with the container closure system or materials used in the manufacturing line/equipment.

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5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 7. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• A PK similarity study (BAT-1806-001-CR) evaluated PK similarity between BAT1806, EU-RoActemra, and US-Actemra in healthy subjects following IV administration. • PK similarity has been demonstrated between BAT1806 and US-Actemra, and supports a demonstration of no clinically meaningful differences between BAT1806 and US-Actemra for the IV route of administration. • PK similarity between BAT1806, EU-RoActemra, and US-Actemra provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-RoActemra to the assessment of biosimilarity.
Pharmacodynamics	• Not Applicable
Immunogenicity	• Similar incidence of ADA and NAb formation was observed between BAT1806, EU-RoActemra and US-Actemra in healthy subjects (Study BAT-1806-001-CR) and between BAT1806 and EU-RoActemra in subjects with RA (Study BAT-1806-002-CR), including following the single transition from EU-RoActemra to BAT1806. Given the scientific bridge was established (based on the analytical and PK comparisons) between BAT1806, US-Actemra, and EU-RoActemra to justify the relevance of data generated with EU-RoActemra as the comparator, these collective immunogenicity results support the assessment of no clinically meaningful differences between BAT1806 and US-Actemra.

The clinical development for BAT1806 included 2 clinical studies (see Table 3 in Section 2.2 for details):

1) BAT-1806-001-CR: "A Randomized, Double-blinded, Single-dose, 3-arm Parallel, Comparative Study to Evaluate the Pharmacokinetics and Safety of BAT1806 Injection vs Actemra® in Healthy Chinese Male Subjects"
2) BAT-1806-002-CR: "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"

In this application, the Applicant seeks the approval of intravenous (IV) route of administration for BAT1806.

PK similarity was established in the PK similarity study (Study BAT-1806-001-CR) between BAT1806, EU-RoActemra, and US-Actemra. Study BAT-1806-001-CR established the PK component of the scientific bridge to support the relevance of comparative clinical data generated using EU-RoActemra from Study BAT-1806-002-CR to the assessment of biosimilarity.

The summaries of the PK similarity findings are given in Table 8. Considering the nonlinear PK characteristics of tocilizumab, the primary PK endpoint is area under the serum drug concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{last}) for IV administration.

In the PK similarity study BAT-1806-001-CR, the 90% confidence interval (CI) for the least square (LS) geometric means ratios (LS GMRs) for AUC from time 0 to infinity ($AUC_{0\text{-}inf}$), AUC_{last}, and C_{max} were contained within the prespecified criteria of 80% to 125%.

Table 8. Summary of statistical analyses for assessment of PK similarity (Study BAT-1806-001-CR)

Parameter	Geometric Mean (%GeoCV)			Geometric Mean Ratio* (90% CI)		
	BAT1806 (N=45)	US-Actemra (N=42)	EU-RoActemra (N=42)	BAT1806 vs US-Actemra	BAT1806 vs EU-RoActemra	EU-RoActemra vs US-Actemra
Primary						
AUC_{last} (ug.h/mL)	10260 (17.8)	10390 (16.4)	10580 (21.5)	98.18 (92.89, 103.78)	97.39 (91.01, 104.20)	100.09 (94.76,107.27)
Secondary						
C_{max} (ug/mL)	88.28 (14.5)	91.29 (16.4)	96.28 (17.6)	96.25 (91.70, 101.03)	91.71 (86.90, 96.79)	104.95 (99.19,111.06)

$AUC_{0\text{-}inf}$ (ug.h/mL)	10840 (16.6)	10690 (15.4)	11080 (19.5)	100.82 (95.76, 106.15)	98.06 (92.10, 104.41)	102.82 (96.99, 108.99

*Presented as percent.
Source: Table 11-2 and Table 11-3 in Clinical Study Report BAT-1806-001-CR

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

PK similarity was shown through the three pair-wise comparisons between BAT1806, US-Actemra, and EU-RoActemra following IV administration (Study BAT-1806-001-CR).

The clinical studies adequately showed PK similarity between BAT1806 and US-Actemra and showed no increase in immunogenicity risk for BAT1806 when compared to US-Actemra. There are no residual uncertainties from the clinical pharmacology assessment.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

In the PK similarity study in healthy subjects, BAT-1806-001-CR, following IV administration of BAT1806, EU-RoActemra, or US-Actemra, the 90% CIs for the GMRs of BAT1806 to EU-RoActemra, BAT1806 to US-Actemra, and EU-RoActemra to US-Actemra for the tested PK parameters (i.e., AUC_{last}, C_{max}, $AUC_{0\text{-}inf}$) were all within the PK similarity acceptance interval of 80% to 125%. These pairwise comparisons met the pre-specified criteria for PK similarity between BAT1806, EU-RoActemra, and US-Actemra; thus, the PK portion of the scientific bridge was established to support the relevance of the data generated using EU-RoActemra.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

5.3.1. Study BAT1806-001-CR

Clinical Pharmacology Study Design Features

Study BAT-1806-001-CR was a randomized, double-blinded, single-dose, 3-arm parallel clinical study to establish pairwise PK similarity between BAT1806 vs EU-approved Actemra, BAT1806 vs US-licensed Actemra, US-licensed Actemra vs EU-approved Actemra in healthy Chinese male subjects and to evaluate the clinical safety, tolerability, and immunogenicity. The single dose administered was at 4 mg/kg intravenously.

Pharmacokinetic blood samples were collected from subjects to determine the serum concentration of tocilizumab, thus, to evaluate the change and similarity of the PK of the 3 Investigational Products (IPs). The time points for sampling were as follows: prior to infusion of IP, 30 minutes after the start of IP infusion, at the end of infusion (immediately after 60-minute infusion), at 2, 3, 4, 5, 9, and 13 hours after the start of

infusion, at 24 hours (Day 2), 48 hours (Day 3), 72 hours (Day 4), 96 hours (Day 5), 168 hours (Day 8), 240 hours (Day 11), 336 hours (Day 15), 504 hours (Day 22), 672 hours (Day 29), 1008 hours (Day 43), and 1344 hours (Day 57) after the start of infusion.

The time points for sampling of immunogenicity were as follows: prior to infusion of IP (Day 1), 336 hours (Day 15), 1008 hours (Day 43), 1344 hours (Day 57) after the start of infusion.

Clinical Pharmacology Study Endpoints

The primary PK parameters for BAT1806, US-Actemra, and EU-RoActemra comparisons was AUC_{last}. PK similarity was then assessed for each of the 3 pairwise comparisons with no adjustment for multiplicity since all 3 comparisons needed to demonstrate PK similarity. If the 90% CIs for the geometric LS mean ratio were entirely within the 80.00% to 125.00% equivalence margin for each primary PK parameter, then PK similarity could be demonstrated.

Bioanalytical PK Method and Performance

The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated.

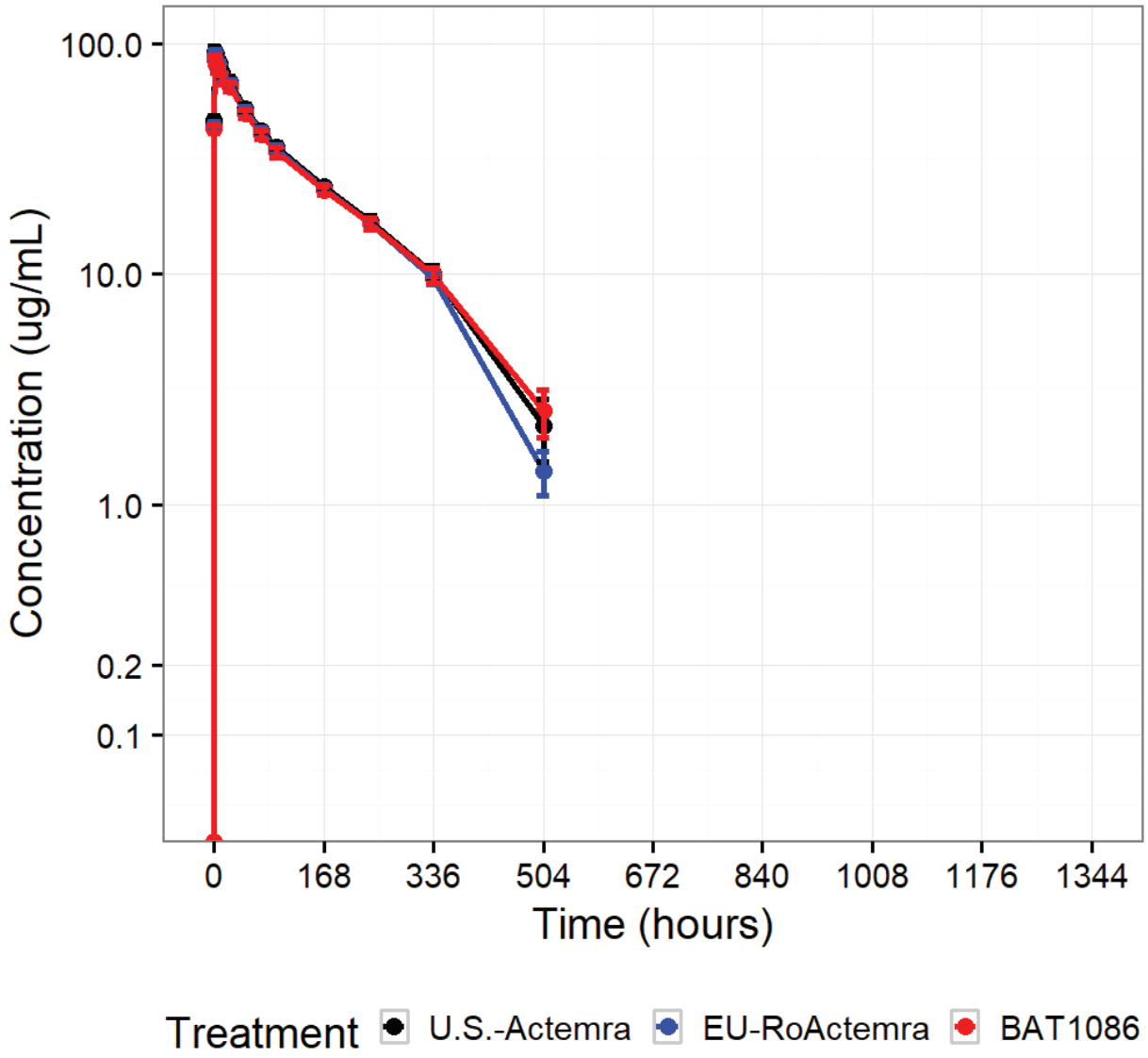
The serum concentrations of BAT1806 were appropriately quantified using a validated electrochemiluminescence assay (ECL) in Study BAT1806-001-CR (Method ICSH 18-023, Validation Report 8380-507). During the method validation, BAT1806 was used to establish the standard curves, and the accuracy and precision (± 20.0%, ± 25.0% for LLOQ and ULOQ) was evaluated using BAT1806 as QC samples. See detailed information about the assay validation in Appendix 13.4.1.

PK Similarity Assessment

In total,138 subjects were randomized (46 subjects to BAT1806 group, 44 subjects to EU-RoActemra group, and 48 subjects to Actemra-US group), and 129 subjects received a single dose of IP. 9 subjects discontinued prior to treatment, and 129 subjects (93.5%) completed the study.

Mean study drug concentrations over time for all 3 treatment arms are depicted in Figure 1.

Figure 1. Arithmetic Mean (95% confidence interval) Study Drug Serum Concentration-Time Profiles for All Treatments on Linear Scale



BQL rule: Below lower limit of quantification (LLOQ) data was excluded (LLOQ = 0.2 ug/mL) except for the predose PK samples.
Source: Reviewer's analysis

The PK similarity results are presented in Table 8 above. The GMRs and 90% CIs of AUC_{last} fell in the pre-specified similarity range of 80% to 125%. The PK data generated in Study BAT-1806-001 at a single IV dose of 4 mg/kg along with the PK data generated in Study BAT-1806-002 at multiple IV doses of 8 mg/kg every 4 weeks (see section 5.4.2 below) support the conclusion of PK similarity among BAT1806, US-Actemra, and EU-RoActemra following IV administration.

5.4. Clinical Immunogenicity Studies

5.4.1. Study BAT-1806-001-CR

Serum immunogenicity samples were collected at baseline, Day 15, Day 43, Day 57 (final visit or early termination), following a single dose IV administration of BAT1806, US-Actemra, and EU-RoActemra. The ADA-positive results on Day 57 (Final Visit) were reported by 19 (42.2%), 10 (23.8%), and 12 (28.6%) subjects in BAT1806, EU-RoActemra, and US-Actemra groups, respectively.

The NAb-positive results on Day 57 (Final Visit) were reported by 14 (31.1%), 9 (21.4%), and 12 (28.6%) subjects in BAT1806, EU-RoActemra, and US-Actemra groups, respectively.

Overall, the incidence of ADA and NAb incidences were numerically higher in the BAT1806 group as compared to the EU-RoActemra and US-Actemra groups, however, these slight differences in ADA did not obviously alter the average PK profiles in healthy subjects and therefore, were not considered to be clinically meaningful.

5.4.2. Study BAT-1806-002-CR

Immunogenicity upon repeated IV dosing was evaluated in Study BAT-1806-002-CR.

Design features of the clinical immunogenicity assessment

Study BAT1-806-002-CR was a multicenter, multinational, randomized, double-blind, parallel-group, active-control study to compare efficacy, safety, immunogenicity, and PK of BAT1806 compared with EU-RoActemra in subjects with RA that was inadequately controlled by methotrexate (MTX).

Bioanalytical PK Method and Performance

The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated.

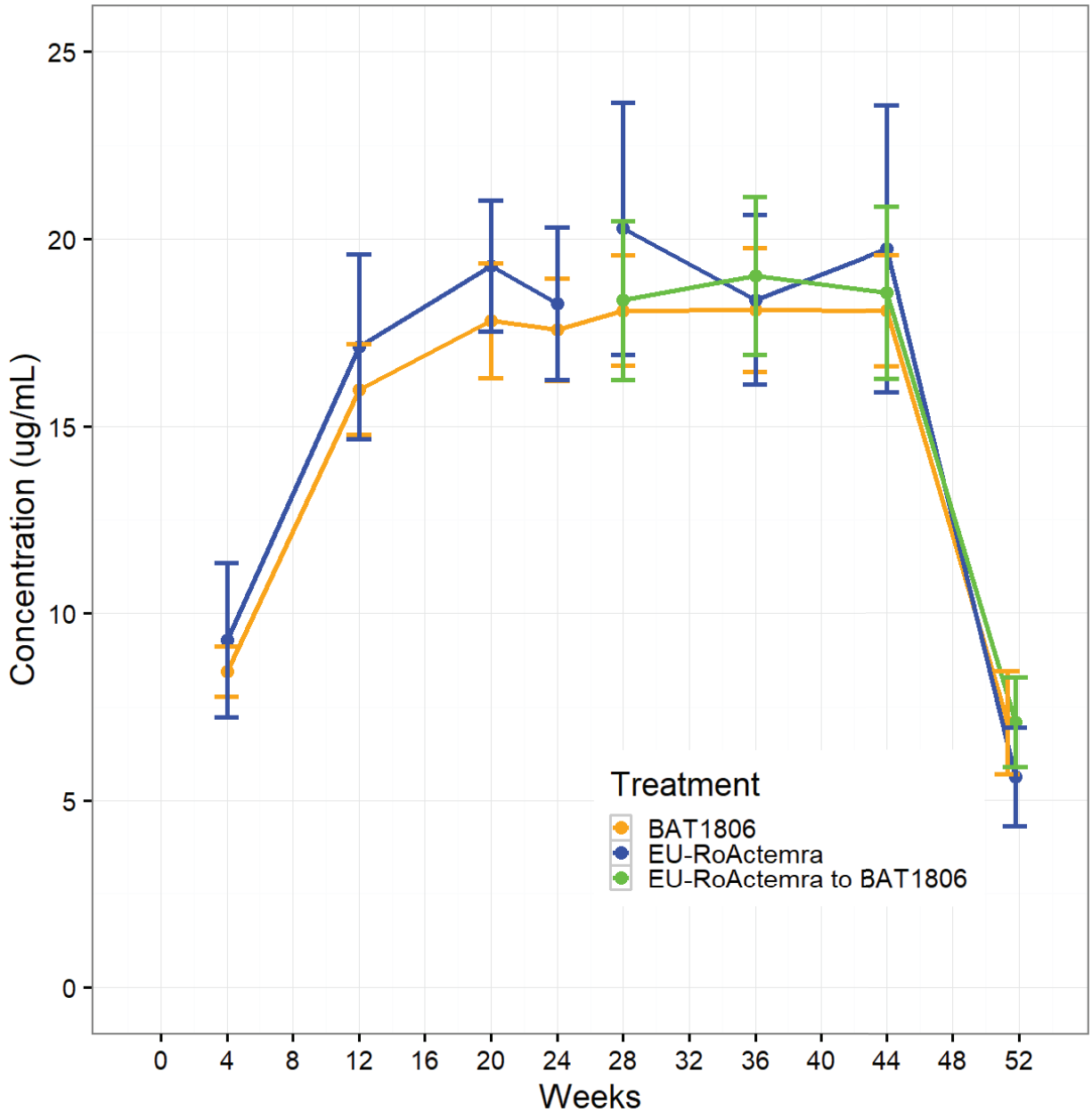
The serum concentrations of BAT1806 and EU-RoActemra were appropriately quantified using a validated ELISA assay in Study BAT-1806-002-CR (validation reports 8380-507). During the method validation, BAT1806 and EU-RoActemra was used to establish the standard curves, and the accuracy and precision (± 20.0%, ± 25.0% for LLOQ and ULOQ) was evaluated using BAT1806 and EU-RoActemra as QC samples. See detailed information about the assay validation in Appendix 13.4.1.

Pharmacokinetics Assessment

In the comparative clinical study BAT1806-002-CR, trough PK samples were collected. The average of observed trough concentrations at each sampling time point are

depicted in Figure 2 below. No meaningful differences were observed.

Figure 2. Arithmetic Mean (± 95% confidence interval) - Trough Concentration over Time (Linear Scale)



Source: Reviewer's analysis

Immunogenicity endpoints

Anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were selected as the immunogenicity endpoints. Descriptive statistics were summarized for the incidence of

ADA and NAb and the ADA titers.

Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product, U.S.-licensed reference product, and non-U.S.-licensed comparator product (as applicable) in the study samples

The ADA response to study drug were detected using a validated electrochemiluminescence (ECL) assay in Study BAT-1806-002-CR (Method ICSH 18-031, validation reports 8380-508). Positive control greater than or equal to16.0 ng/ mL can tolerate 200 µg/mL drug.

The NAb against study drug were detected using a validated ECL assay in Study BAT-1806-002-CR (Method ICSH 18-032, validation reports 8380-503).

Refer to the Office of Biotechnology Products Immunogenicity review for the assessment of ADA and NAb assay methods.

Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/Nab formation

Blood samples for ADA and Nab assay were collected in Study BAT-1806-002-CR from Week 0, Week 4, Week 12, Week 24, Week 28, Week 36, Week 48, and Week 52. ADA and Nab samples were collected with serum PK samples at each timepoint. The last dose, either BAT1806 or EU-RoActemra, was administered at Week 44. The last ADA and Nab samples were collected at Week 52, 8 weeks after the last dose.

Incidence of ADA and Nab (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

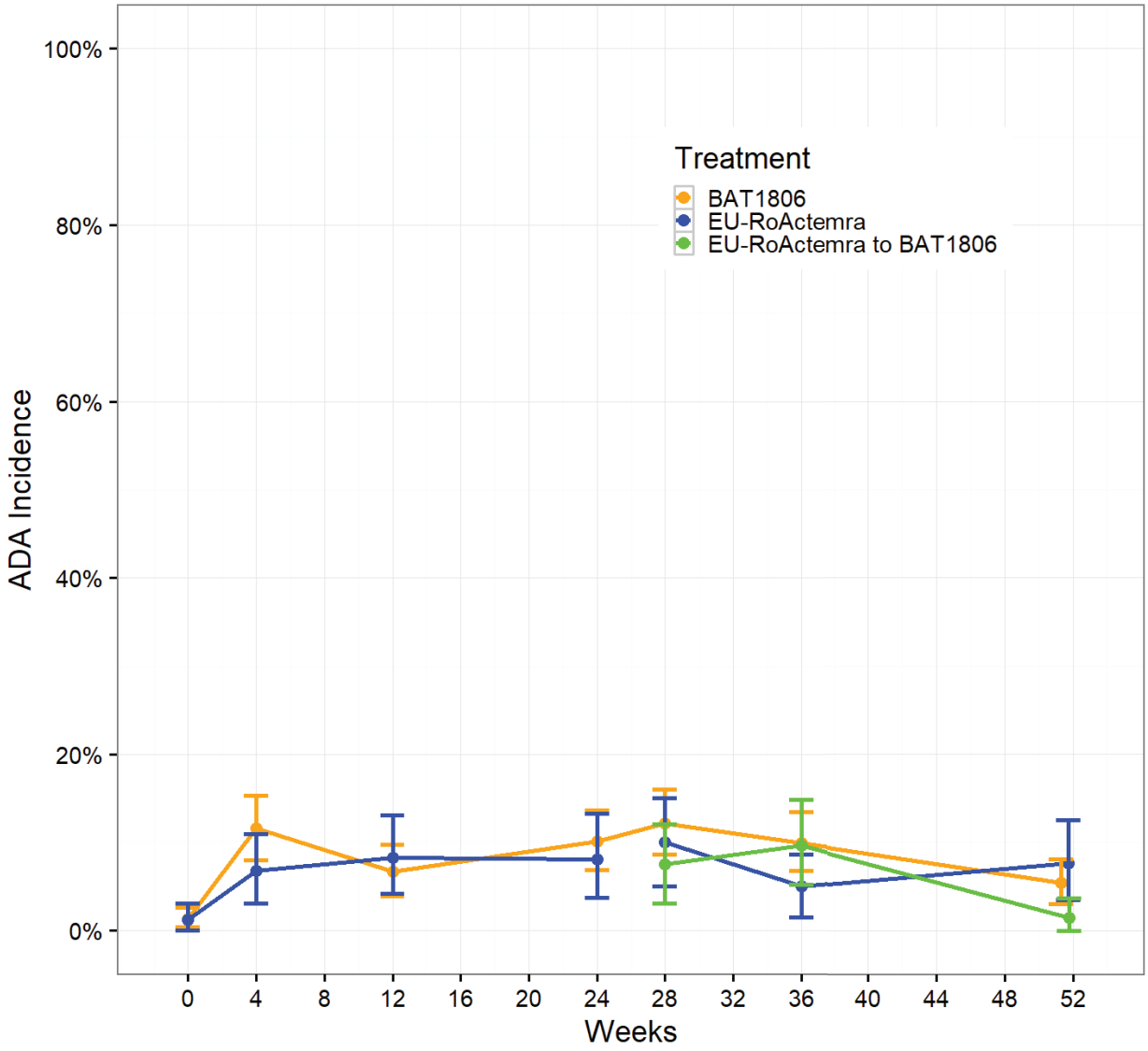
The number and percent of ADA and NAb positive subjects are listed in Table 9, and the time course of ADA development is depicted in Figure 3. The treatment-induced ADA incidence and NAb incidence were numerically higher in subjects received BAT1806 compared to EU-RoActemra up to Week 24 before the single transition. NAb incidences were 100% and 98.4% out of ADA positive subjects in EU-RoActemra and BAT1806 groups, respectively. These slight differences were not considered to be clinically meaningful. The impact of ADA and NAb on PK and efficacy is discussed below.

Table 9. Immunogenicity results for binding ADA and NAb in Treatment Period 1 of Study BAT-1806-002-CR.

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced*	
BAT1806	312	4/312 (1.3%)	63/312 (20.2%)	63/312 (20.2%)
EU-RoActemra	309	5/309 (1.6%)	41/309 (13.3%)	42/309 (13.6%)

*Reviewer's analysis
Source: Table 42 in Clinical Study Report BAT-1806-002-CR

Figure 3. Antidrug Antibody Incidence (mean with 95% confidence interval), Overall Period, Safety Analysis Set

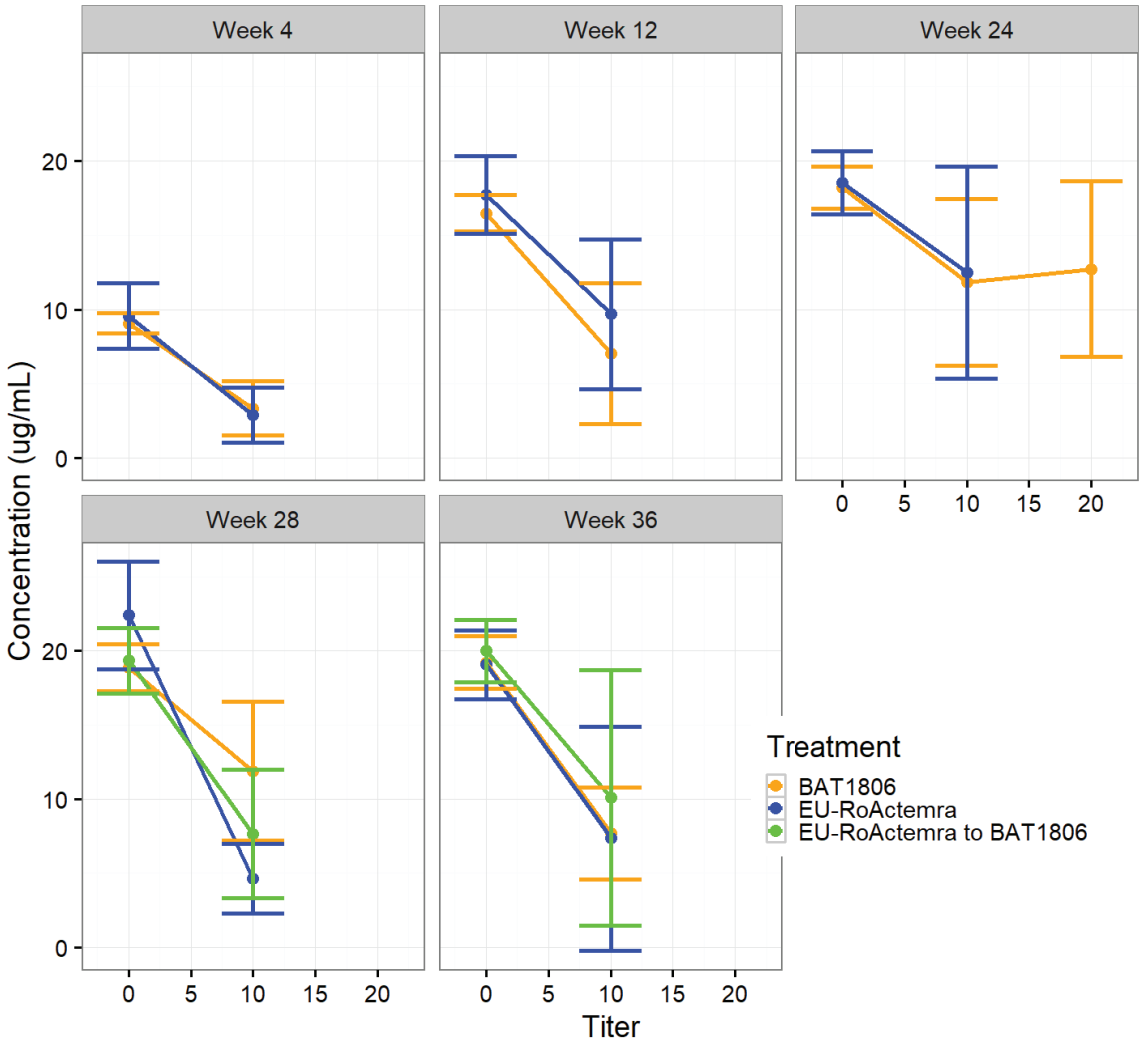


Source: Reviewer's analysis

Impact of ADA and NAb on the PK, and clinical outcomes of the proposed product

The impact of ADA development on study drug PK is depicted in Figure 4 for each post-treatment visit. The development of ADA (ADA positive with a titer of 10 or 20) decreased study drug concentration compared to subjects with negative ADA (i.e., titer = 0). The development of ADA decreased drug PK for BAT1806 and EU-RoActemra in a comparable magnitude in core period (Week 0 to Week 24), and following a single transition from EU-RoActemra to BAT1806 (see Figure 4 Panels for Week 28 and Week 36), the ADA effect on drug PK for BAT1806 remained comparable to EU-RoActemra or BAT1806.

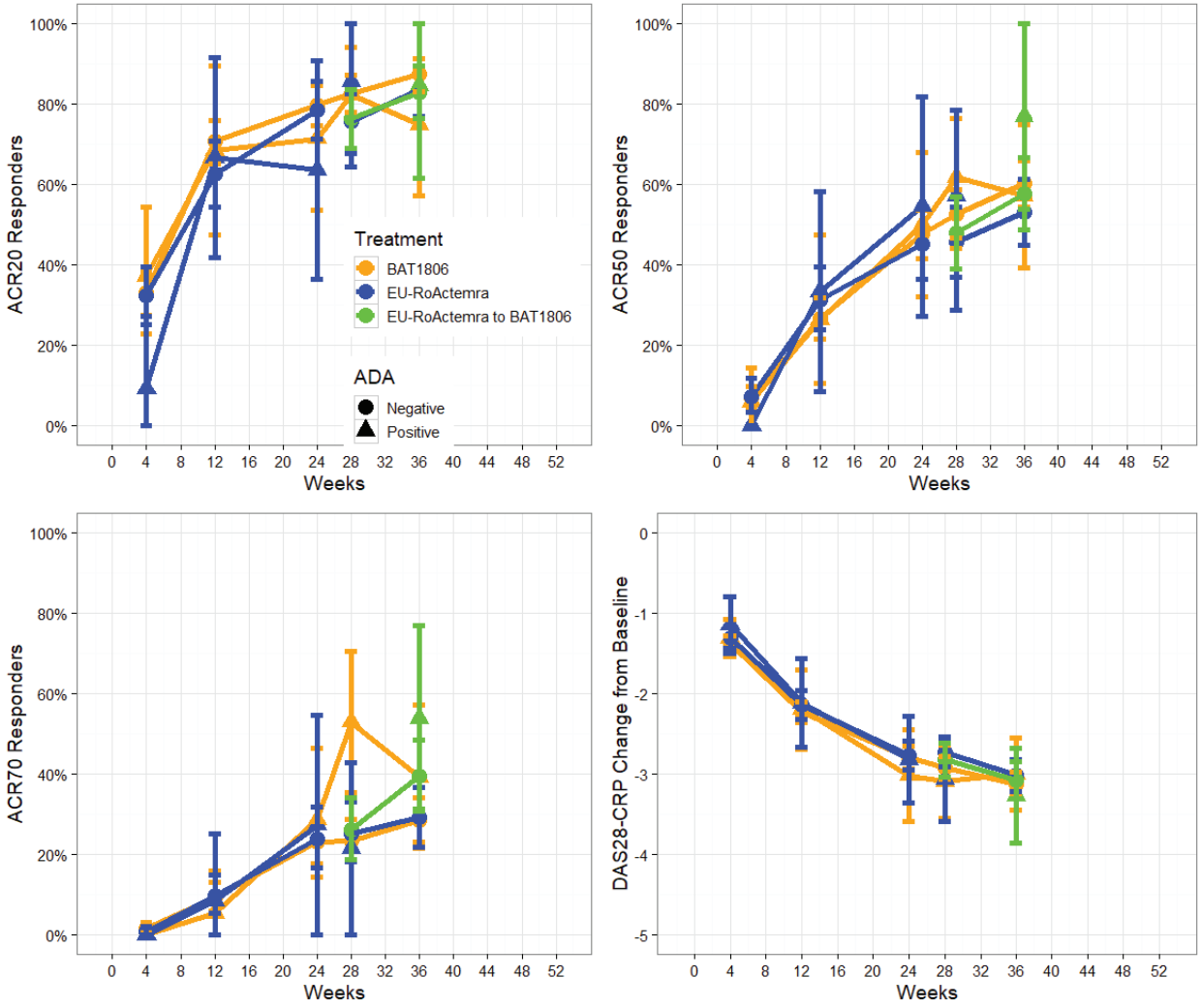
Figure 4. Anti-drug Antibody Effect on Pharmacokinetics at Each Visit (mean with 95% confidence interval)



Source: Reviewer's analysis

The development of ADA has no impact on clinical efficacy endpoints ACR20, ACR50, ACR70 responder rate and DAS28-CRP through Week 36 in both EU-RoActemra and BAT1806 arms (Figure 5).

Figure 5. Summary of ACR20, ACR50, and ACR70 and DAS28-CRP by ADA Status in Study BAT1806-002-CR



Source: Reviewer's analysis.

The Applicant also evaluated the association between ADA development and treatment related adverse events (AEs) (Table 10). Further analysis of overall TEAE by ADA status was also conducted. The association between ADA status and treatment related AEs as well as overall TEAE was comparable between EU-RoActemra and BAT1806 arms. See also Section 6.4.

Table 10. Related AEs by ADA Status in TP1 and TP2 Combined in Study BAT1806-002-CR SAF

	RoActemra -RoActemra		RoActemra -BAT1806		BAT1806	
	ADA positive (N=41) n (%)	ADA negative (N=125) n (%)	ADA positive (N=31) n (%)	ADA negative (N=111) n (%)	ADA positive (N=91) n (%)	ADA negative (N=219) n (%)
Number of subjects with at least 1 related TEAE	18 (43.9)	78 (62.4)	16 (51.6)	65 (58.6)	46 (50.5)	126 (57.5)
Blood and lymphatic system disorders	7 (17.1)	25 (20.0)	6 (9.4)	17 (15.3)	10 (11.0)	32 (14.6)
Cardiac disorders	1 (2.4)	2 (1.6)	0	2 (1.8)	2 (2.2)	1 (0.5)
Ear and labyrinth disorders	0	0	1 (3.2)	0	0	0
Eye disorders	0	2 (1.6)	0	0	0	0
Gastrointestinal disorders	2 (4.9)	8 (6.4)	2 (6.5)	6 (5.4)	2 (2.2)	14 (6.4)
General disorders and administration site conditions	0	3 (2.4)	0	4 (3.6)	3 (3.3)	8 (3.7)
Hepatobiliary disorders	2 (4.9)	16 (2.8)	4 (12.9)	17 (15.3)	12 (13.2)	29 (13.2)
Immune system disorders	2 (4.9)	1 (0.8)	0	0	0	2 (0.9)
Infections and infestations	7 (17.1)	40 (32.0)	4 (12.9)	23 (20.7)	18 (19.8)	42 (19.2)
Injury, poisoning and procedural complications	0	0	0	2 (1.8)	0	0
Investigations	12 (29.3)	42 (33.6)	11 (35.5)	39 (35.1)	26 (28.6)	65 (29.7)
Metabolism and nutrition disorders	5 (12.2)	19 (15.2)	1 (3.2)	16 (14.4)	13 (14.3)	37 (16.9)
Musculoskeletal and connective tissue disorders	0	2 (1.6)	0	4 (3.6)	0	14 (6.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (1.1)	0
Nervous system disorders	0	5 (4.0)	1 (3.2)	0	2 (2.2)	2 (0.9)
Psychiatric disorders	0	0	0	0	0	2 (0.9)
Renal and urinary disorders	1 (2.4)	1 (0.8)	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	1 (1.1)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	2 (4.9)	6 (4.8)	0	4 (3.6)	2 (2.2)	8 (3.7)
Skin and subcutaneous tissue disorders	1 (2.4)	5 (4.0)	0	5 (4.5)	1 (1.1)	8 (3.7)
Vascular disorders	0	1 (0.8)	0	4 (3.6)	4 (4.4)	2 (0.9)

ADA = anti-drug antibody, AE, adverse event, N=number of subjects in the Safety Analysis Set, n=number of subjects, TEAE=treatment-emergent adverse event, TP=Treatment Period. ADA status refers to combined TP1 + TP2.
System organ class is from the MedDRA dictionary, version 23.1.
A subject experiencing multiple occurrences of an adverse event was counted at most once per system organ class.

Source: Table 33 in Module 5, Section 5.3.5.3 BAT-1806 (tocilizumab biosimilar) Integrated Summary of Immunogenicity

In conclusion, the ADA effect on study drug PK was similar between BAT1806 and EU-RoActemra. No ADA or NAb effect on clinical efficacy and safety was observed in either the BAT1806 or EU-RoActemra arms.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

Comparative Efficacy:

Study BAT-1806-002-CR was a randomized, multi-center, multi-national, double-blind, parallel-group, and active-control study to compare the efficacy and safety of BIIB800 (originally, BAT1806) to EU-RoActemra in rheumatoid arthritis patients with an inadequate response to methotrexate. Of 935 subjects screened, 621 were randomized (309 to EU-RoActemra and 312 to BAT1806) across 55 study sites. Randomization was stratified by region (Central Europe or Asia Pacific) and previous biologic or targeted synthetic disease-modifying antirheumatic drug (tsDMARD) use (Yes or No). The study duration was approximately 56 weeks, including an overall treatment period of 48 weeks.

The primary endpoint was the percentage of subjects achieving an American College of Rheumatology 20% (ACR20) response at Week 24. The primary estimand to evaluate similarity of efficacy of BAT1806 and EU-RoActemra used composite variable and treatment policy strategies for death and all other intercurrent events, respectively. Under the primary estimand, death was handled as ACR20 non-response and missing Week 24 ACR data was imputed as non-response.

At Week 24, 210 (68.0%) and 218 (69.9%) of subjects in the EU-RoActemra and BAT1806 groups, respectively, achieved ACR20 responses. The estimated treatment difference (90% confidence interval) was 1.94% (-4.04%, 7.92%). The 90% CI is within the prespecified interval of [-12.0%, +15.0%]. Sensitivity and supplementary analyses support the primary analysis results. Therefore, similarity in efficacy between EU-RoActemra and BAT1806 can be concluded.

Comparative Safety and Immunogenicity:

Safety data for BAT1806 was available from 2 clinical studies. This included Study BAT-1806-001-CR and BAT-1806-002-CR. The comparative safety of BAT1806 to EU-RoActemra was evaluated in Study BAT-1806-002-CR conducted in RA patients. In Study BAT-1806-001-CR the Applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated with EU-RoActemra as the comparator.

The safety database for BAT1806 includes a total of 499 subjects who received at least one dose of BAT1806 (45 healthy subjects, and 454 RA patients) and is adequate to provide a reliable descriptive comparison between the products.

The observed safety for BAT1806 in the two clinical trials is consistent with the known adverse event profile of US-Actemra. Although numerical differences were identified,

there were no clinically significant differences between BAT1806 and EU-RoActemra in treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, adverse event leading to discontinuations, or anti-drug antibodies (ADA) between the treatment groups in Study BAT1806-002-CR. In addition, a single transition of patients treated with EU-RoActemra to BAT1806 did not result in an increase in immunogenicity or clinically significant adverse reactions.

Overall, the data provided from the comparative clinical study BAT1806-002-CR and from Study BAT1806-001-CR are adequate to support the demonstration of no clinically meaningful differences between BAT1806 and US-Actemra. The Applicant provided adequate data to establish the scientific bridge between BAT1806, EU-RoActemra, and US-Actemra to justify the relevance of the data generated with EU-RoActemra as the comparator to the assessment of biosimilarity.

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6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical and statistical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. BAT1806-002-CR

Data and Analysis Quality

There are no concerns regarding data quality and integrity.

Study Design and Endpoints

The primary objective of Study BAT1806-002-CR was to demonstrate similar efficacy of BAT1806 and EU-RoActemra in subjects with RA that is inadequately controlled by MTX.

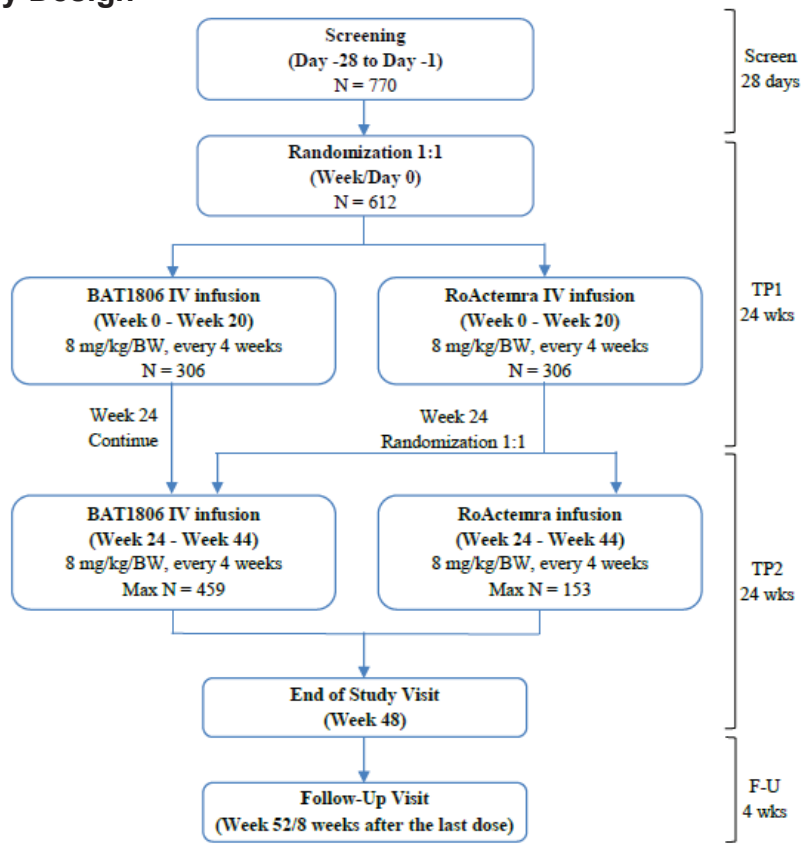
Study BAT-1806-002-CR was a randomized, multi-center, multi-national, double-blind, parallel-group, and active-control study to compare the efficacy and safety of BAT1806

to EU-RoActemra in rheumatoid arthritis patients with an inadequate response to methotrexate.

There were 55 study sites (29 in China, 7 in Ukraine, 10 in Poland, 4 in Georgia, and 5 in Bulgaria).

The study design consisted of screening, two treatment periods, and follow-up (Figure 6).

Figure 6. Study Design



Abbreviations: BW = body weight; F-U = follow-up; IV = intravenous; Max = maximum; N = number of subjects; TP = treatment period; wk(s) = week(s).

Source: Figure 1, page 30 of 381 of protocol (version 6.0, dated 02 Sep 2020)

During the double-blind treatment period 1 (TP1), after completion of screening procedures, at the Baseline Visit, eligible subjects were randomized (using a computerized Interactive Voice and Web Response System: IWRS) in a 1:1 ratio to receive either BAT1806 or EU-RoActemra by intravenous (IV) infusion every four (4) weeks until Week 20. Per the study protocol, in the double-blind treatment period 2 (TP2), from Week 24, subjects continued study treatment with IV infusions every 4 weeks until Week 44. Subjects who were randomized to BAT1806 continued treatment with BAT1806 while subjects who were randomized to EU-RoActemra were randomized

in a 1:1 ratio to either BAT1806 (transition or switch treatment) or EU-RoActemra (continued on TP1 treatment).

Randomization was stratified by region (Central Europe/Asia Pacific) and previous biologic or targeted synthetic disease modifying antirheumatic drugs (DMARD) use (Yes/No). Randomization for both TP1 and TP2 occurred at the beginning of TP1.

In TP1 and TP2, 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. 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. In each of TP1 and TP2, subjects received a total of 6 doses of either BAT1806 or EU-RoActemra.

During the study, all subjects continued taking their regular MTX therapy at a stable dose. There was an End-of-Study (EOS) Visit at Week 48 and a safety Follow-Up at Week 52 (eight weeks after the last dose of study drug).

The study duration was approximately 56 weeks. This included a screening period of up to 4 weeks, an overall treatment period of 48 weeks (with last dose of study treatment administered at Week 44 and EOS Visit performed at Week 48), and a 4-week follow-up period (8 weeks after last dose of study treatment at Week 44).

The identities of the investigational products were as follows (Table 11):

Table 11. Identities of Investigational Products

Study Drug	Formulation and Strength
BAT1806 (Test drug)	20 mg/mL
RoActemra (Reference product)	20 mg/mL

Source: Adapted from Table 3, page 42 of 149 of protocol (version 6.0, dated 02 Sep 2020)

Study Population

<u>The key enrollment criteria for study BAT-1806-002-CR</u>

Inclusion Criteria

1. Male or female subjects 18 years of age or older who fulfil the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010

revised classification criteria for RA diagnosis for at least 6 months before screening, based on the medical history record.

2. Present with active RA, as defined by:
    a. ≥ 6 out of 68 tender joints at screening and randomization) AND
    b. ≥ 6 out of 66 swollen joints at screening and randomization) AND
    c. Serum C-reactive protein (CRP) > upper limit of normal (ULN) value or erythrocyte sedimentation rate ESR ≥ 28 mm/hour at screening.
3. Have received not more than 2 biological agents other than interleukin-6 inhibitors or targeted synthetic DMARDs (e.g., tofacitinib) in total for RA treatment.
4. Receiving MTX therapy according to the following:
   a. MTX treatment by any route of administration for ≥ 12 weeks prior to randomization, with at least the last 4 consecutive weeks prior to randomization on a stable dose ranging between 10 to 25 mg/week. b. Subjects continued on their stable MTX dose and route of administration throughout the study
5. If using oral corticosteroids, must have been on a stable ≤ 10 mg dose of prednisone/day or equivalent for at least 4 consecutive weeks prior to randomization and was willing to continue at this level throughout the study.
6. If taking nonsteroidal anti-inflammatory drugs (NSAIDs), must have been on a stable dose for at least 2 consecutive weeks before randomization and was willing to continue at this level throughout the study

Exclusion Criteria:

1. Has RA of ACR functional class IV or is wheelchair/bed bound.
2. Known hypersensitivity to tocilizumab or to study treatment excipients.
3. Previous exposure to any authorized or investigational IL-6 inhibitor (e.g., tocilizumab including biosimilar products, sarilumab, sirukumab, etc).
4. Received other biological agents (see exclusion criterion #3) or any tsDMARDs ≤ 10 weeks prior to randomization.
5. Received any cell-depleting therapy e.g., rituximab) ≤ 12 months prior to randomization.
6. Been treated with an investigational drug other than those prohibited or device ≤ 8 weeks or 5 half-lives of the drug (whichever was longer) before randomization.
7. Received any conventional DMARDs other than MTX ≤ 4 weeks prior to randomization. For leflunomide, the washout period before randomization must have been a minimum of 12 weeks or a minimum of 4 weeks was accepted after documented completion of standard cholestyramine or activated charcoal washout procedure.
8. Exposure to alkylating agents such as cyclophosphamide or chlorambucil.
9. Treatment with intra-articular or parenteral corticosteroids ≤ 4 weeks before randomization (inhaled corticosteroids for stable medical conditions were allowed)
10. Undergone joint surgery ≤ 12 weeks prior to randomization on any joint to be assessed during the study) or has any surgery planned during the study.

11. Evidence of malignancy, lung infection, or abnormalities suggestive of active tuberculosis (TB) on chest radiography performed within 12 weeks prior to the Screening Visit or during the screening period.
12. Any recurrent bacterial, fungal, or viral infection that based on the investigator´s clinical assessment makes the patient unsuitable for the study, including recurrent/disseminated herpes zoster. History of invasive infection.
13. Met any of the following criteria relative to latent or active TB infection: a. History of active TB ≤ 3 years prior to Screening. If > 3 years, documentation of completion of adequate therapy must have been available. b. Presence of signs or symptoms suggestive of active TB upon medical history and/or physical examination during Screening. c. Recent close contact with a person with active TB. d. Positive interferon-gamma release assay (IGRA) result at Screening
14. Current or history of diverticulitis, complications of diverticulitis, history of diverticulosis requiring antibiotic treatment, current or history of chronic ulcerative lower gastrointestinal tract diseases or any other lower gastrointestinal condition that may predispose to perforation.
15. Any history of malignancy or lymphoproliferative disease at any time, except curative treatment for nonmelanoma skin cancer or resected carcinoma in situ of the cervix.
16. Have a transplanted organ/tissue or stem cell transplantation.
17. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious, or gastrointestinal condition, which in the opinion of the investigator places the patient at unacceptable risk.
18. History of demyelinating diseases (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
19. Received any live or attenuated vaccine ≤ 4 weeks prior to randomization or plans to receive it during the study including the safety follow up period.
20. Pregnant or nursing (lactating) women.

Allowed Concomitant Medications
The following requirements for the prior/concomitant therapy were followed in this study:

- Subject received MTX therapy according to the following:
    - MTX treatment by any route of administration for ≥ 12 weeks before randomization, with at least the last 4 consecutive weeks before randomization on a stable dose ranging between 10 to 25 mg/week.
    - Subjects continued their stable MTX dose and route of administration throughout the study. The MTX dose may have been reduced or temporarily discontinued only for safety reasons (i.e., unacceptable side effects). The dose change and reason were to be clearly documented in the subject's medical record and in the clinical database.
- Subjects on folic acid supplementation at enrollment were recommended to continue taking it as per local standard for the duration of the study. It was recommended initiating folic acid supplementation at a dose ≥ 5 mg/week or as per local standard at the time of enrollment and continuing throughout the study for subjects who were not receiving it.

- If using oral corticosteroids, subject was to be on a stable ≤ 10 mg dose of prednisone/day or equivalent for at least 4 consecutive weeks before randomization and willing to continue at this level throughout the study. The dose of oral corticosteroids may have been decreased at the discretion of the investigator if the subject developed unacceptable side effects.
- If taking NSAIDs (including cyclooxygenase [COX] inhibitors), subject must have been on a stable dose for at least 2 consecutive weeks before randomization and willing to continue at this level throughout the study. The NSAIDs dose could have been increased (not above the maximum approved dose) for up to 2 weeks during the study to treat an RA flare. Reduction in the dose may have been done at the discretion of the investigator if the subject developed unacceptable side effects. Any change in dose was to be documented on the concomitant medication page in the clinical database.
- Subjects who were not on stable NSAIDs may have been treated with a NSAIDs course of maximum 2-week duration to treat a flare. The NSAIDs were not to be administered within 24 hours before study assessments.
- Short courses of analgesics other than NSAIDs or COX inhibitors (e.g., paracetamol, low potency opioids, combination drugs) of ≤ 7-day duration were permitted in the course of the study to treat a flare. The NSAIDs or other analgesics were not to be administered within 24 hours before study assessments.
- Subjects taking concomitant medications that are metabolized through the CYP450 enzymes pathway were to be monitored as doses of such medications might have needed to be increased to maintain therapeutic effect. These medications include atorvastatin, calcium channel blockers, benzodiazepines, theophylline, and warfarin.
- Topical steroids or topical NSAIDs were allowed.

Prohibited Medication/Therapy
The following concomitant medications/therapies were not permitted during the treatment:

- Any biological agents for treatment of RA or any tsDMARDs
- Other investigational drug or device
- Any conventional DMARDs other than MTX (e.g., hydroxychloroquine, sulfasalazine, iguratimod)
- High potency opioids including, but not limited to, hydrocodone, oxycodone, hydromorphone, oxymorphone, morphine, fentanyl, and meperidine
- Alkylating agents such as cyclophosphamide or chlorambucil
- IV immunoglobulins or plasmapheresis
- Intra-articular or parenteral corticosteroids (inhaled corticosteroids for stable medical conditions were allowed)
- Any herbal remedies, traditional medicines, or other not approved medications for RA
- Joint surgery on any joint to be assessed during the study
- Any live or attenuated vaccine

Rescue Medication
An increase in dose of NSAIDs if a subject was on stable NSAIDs therapy or initiation of NSAIDs without exceeding the maximum approved dose was allowed to treat a flare for no more than 2 consecutive weeks.
Analgesics other than NSAIDs (see Section 9.4.7.1) up to the maximum recommended doses may have been used to treat a flare for no more than 7 consecutive days.
The NSAIDs or other analgesics administered to treat a flare were not to be taken within 24 hours before study assessments.

Discontinuations
Removal of Subjects from Therapy or Assessment
Study drug administration may have been stopped for any of the following reasons:

- Use of nonpermitted concurrent therapy
- Noncompliance with the study drug or study schedule
- Lost to follow-up
- Occurrence of AEs not compatible with the continuation of subject participation in the
- study, in the investigator's opinion, or unacceptable to the subject to continue
- Intercurrent illness

Subjects were permanently withdrawn from the study drug treatment for any of the following
reasons:

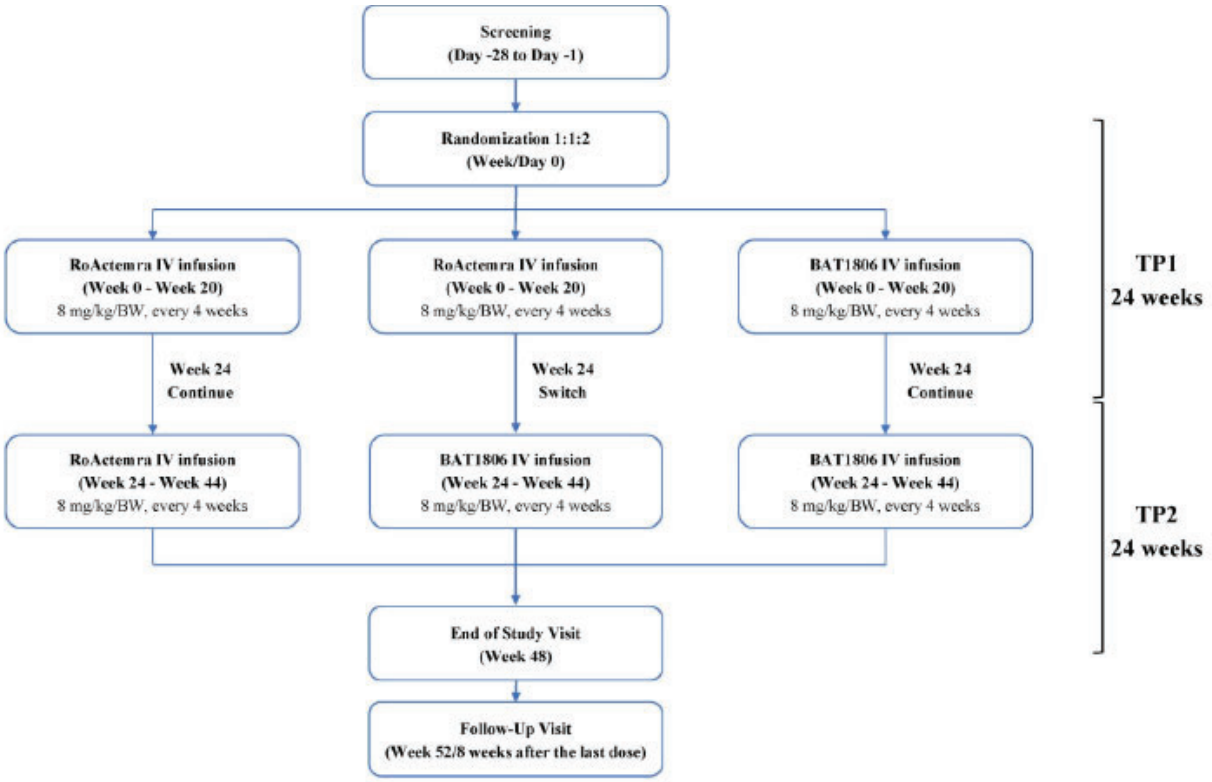
- Pregnancy
- Malignancy
- Demyelinating disorder
- Specific laboratory abnormalities
- Serious or opportunistic infection, including TB
- Confirmed diverticulitis or any gastrointestinally active ulcerative condition
- Anaphylactic reaction or other serious hypersensitivity or infusion-related reaction
- Subjects who were consistently noncompliant with the study treatment
- Subject request
- Investigator request
- Sponsor request

Subjects who stopped the study drug for any reason were not replaced. Subjects were free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal were documented in the clinical database.

Subjects prematurely withdrawn from the study were invited to attend an Early Termination Visit at 4 weeks after the last dose of study drug and a Follow-Up Visit at 8

weeks after the last dose of study drug. In case of early withdrawal, any assessment required at the Early Termination Visit that had been performed at 4 weeks of the last study drug dosing did not need to be repeated at the Early Termination Visit; any scheduled assessment for Follow-Up Visit that had been performed at 8 weeks after the last study drug dosing did not need to be repeated at the Follow-Up Visit.
The Bio-Thera CSR presented the following diagram of the actual study design implementation:

Figure 7. Study Flow as Implemented



Abbreviations: BW = body weight; IV = intravenous; TP = treatment period

Source: Figure 2, page 24 of 3002 of the Bio-Thera CSR (version 1.1)

In the actual implementation of the study, at Day 0, eligible subjects were randomized (1:1:2) to receive EU-RoActemra up to Week 48, EU-RoActemra up to Week 24 followed by BAT1806 up to Week 48, or BAT1806 up to Week 48, once every 4 weeks.

The original planned (per the protocol) versus the actual randomization schemes are different because the latter does not consider subjects who would discontinue the study after Week 24. However, the two randomization procedures are equivalent up to Week

24. Thus, there are no randomization scheme issues that would affect the assessment of the primary efficacy endpoint.

The protocol was amended five times with the most recent version of the Clinical Study Protocol Version 6.0, dated September 2, 2020. Protocol Amendments 1-4 occurred prior to the start of subject enrollment. The protocol amendments from versions 4-6 were mostly based on regulatory recommendations or advice.

The primary endpoint was the percentage of subjects achieving an American College of Rheumatology 20% (ACR20) response at Week 24. The ACR response criteria involved 20% improvement from baseline in tender joint count (68 joints) and swollen joint count (66 joints), plus 20% improvement from baseline in at least 3 of the following 5 components:

- Subject's assessment of pain Visual Analog Scale (VAS) (0 to 100 mm, higher scale indicates worsen)
- Subject's Global Assessment of Disease Activity VAS (0 to 100 mm, higher scale indicates worsen)
- Physician's Global Assessment of Disease Activity VAS (0 to 100 mm, higher scale indicates worsen)
- Health Assessment Questionnaire – Disability Index (HAQ-DI)
- Acute phase reactant (CRP) level

A subject is considered a responder under the ACR20 criteria if they achieve the criteria above with respect to the 20% improvement. If a subject's baseline value for a component was zero, the subject was considered as not achieving 20% improvement from baseline for that component because there is no room for improvement.

A number of planned site visits were replaced by remote visits because of the COVID-19 pandemic. Section 6.3 of the SAP (page 27 of 72) states that where a subject cannot physically attend a scheduled assessment due to the COVID-19 pandemic or related reasons, the data presented in Table 12 will be attempted to be assessed from remote assessment (telephone call or virtual assessment).

Table 12. Remote Assessments

Able to be Assessed During Remote Assessment	Unable to be Assessed During Remote Assessment

Efficacy:
• HAQ-DI (ADHAQ, ADHAQSUM)
 	
• VAS (ADVAS):
  • Subject's assessment of pain
  • Subject's Global Assessment of Disease Activity
  • Physician's Global Assessment of Disease Activity
 	
Safety:
• Adverse Events (ADAE)
• Concomitant Medications (ADCM)
	Efficacy:
	• Joint Counts (ADJNT, ADJNTSUM)
	
	Safety:
	• 12-Lead ECG (ADEG)
	• Study Drug Administration (ADEX)
	• Laboratory Assessments (ADLB)
	• Serology Assessment (ADMB)
	• Physical Examination (ADPE)
	• Procedures, including Chest X-Ray (ADPR)
	• Vital Signs (ADVS)
	
	Other:
	• Immunogenicity Sample (ADIS)
	• PK Sample (ADPC)

HAQ-DI = Health Assessment Questionnaire – Disability Index; VAS = Visual Analog Scale
Source: Table in Section 6.3 of SAP, page 27 of 72

Tender/Swollen joint count assessment was performed by examining and counting the number of individual joints exhibiting signs of swelling (66 joints) or tenderness (68 joints). Joint counts were normally performed at scheduled visits by the investigator or a designee experienced in performing such procedures.

Table 13 presents the Applicant's illustration of the calculation rules for "as observed" (prior to imputation) ACR component data that are missing.

Table 13. Sample ACR20 Calculation Rules Scenarios

Scenario	Both Joint Counts Available?	Joint Count A	Joint Count B	>= 3 Other Components Available?	Comp A	Comp B	Comp C	ACR20
A	Yes	Resp	Resp	Yes	Resp	Resp	Resp	Resp
B	Yes	Resp	Non-Resp	Yes	Resp	Resp	Resp	Non-Resp
C	Yes	Non-Resp	Non-Resp	Yes	Resp	Resp	Resp	Non-Resp
D	No	Missing	Non-Resp	Yes	Resp	Resp	Resp	Non-Resp
E	Yes	Resp	Resp	Yes	Non-Resp	Non-Resp	Non-Resp	Non-Resp
F	Yes	Resp	Non-Resp	Yes	Non-Resp	Non-Resp	Non-Resp	Non-Resp
G	Yes	Non-Resp	Non-Resp	Yes	Non-Resp	Non-Resp	Non-Resp	Non-Resp
H	No	Missing	Non-Resp	Yes	Non-Resp	Non-Resp	Non-Resp	Non-Resp
I	No	Missing	Resp	Yes	Non-Resp	Non-Resp	Non-Resp	Non-Resp
J	No	Missing	Missing	Yes	Non-Resp	Non-Resp	Non-Resp	Non-Resp
K	Yes	Non-Resp	Non-Resp	No	Missing	Missing	Missing	Non-Resp
L	No	Missing	Non-Resp	No	Missing	Missing	Missing	Non-Resp
M	Yes	Resp	Non-Resp	No	Missing	Missing	Missing	Non-Resp
N	No	Missing	Resp	Yes	Resp	Resp	Resp	Missing
O	No	Missing	Missing	Yes	Resp	Resp	Resp	Missing
P	No	Missing	Resp	Yes	Resp	Resp	Non-Resp	Missing
Q	No	Missing	Missing	Yes	Resp	Resp	Non-Resp	Missing
R	No	Missing	Resp	Yes	Resp	Non-Resp	Non-Resp	Missing
S	No	Missing	Missing	Yes	Resp	Non-Resp	Non-Resp	Missing
T	Yes	Resp	Resp	No	Missing	Missing	Missing	Missing
U	No	Missing	Resp	No	Missing	Missing	Missing	Missing
V	No	Missing	Missing	No	Missing	Missing	Missing	Missing

Source: Table in section 9.2.1 of the SAP, page 41 of 72 (65 of 96).

The following were the secondary endpoints for efficacy and safety:

Efficacy

- Change from baseline in Disease Activity Score on 28 Joints (DAS28; C-reactive protein [CRP]) and DAS28 (erythrocyte sedimentation rate [ESR]) over the course of the study
- Percentage of subjects achieving ACR20, ACR50, and ACR70 response over the course of the study
- Change from baseline in ACR and DAS28 individual components over the course of the study, including Swollen Joint Count in 66 joints (SJC66), Tender Joint Count in 68 joints (TJC68), pain VAS, total Health Assessment Questionnaire – Disability Index (HAQ-DI), Subject's Global Assessment of Disease Activity visual analogue scale (VAS), Physician's Global Assessment of Disease Activity VAS, CRP, and ESR

Safety

- Adverse events (AEs), including treatment-emergent AEs (TEAEs), SAEs, related AEs, and related SAEs

- Laboratory parameters, including hematology, chemistry with lipids panel, and urinalysis
- Vital signs
- Physical examination
- 12-lead ECG

The Applicant did not provide ordering of the secondary efficacy endpoints or control of Type I error. Thus, the secondary endpoints analyses results for this BLA are considered descriptive.

Statistical Methodologies

Analysis Sets

The following analysis sets of subjects were defined in the SAP:

- **Full Analysis Set (FAS)**: All randomized subjects in the study. All efficacy endpoints were analyzed on the FAS as primary and analyzed as randomized.

- **Per-protocol Set**: A subset of the FAS, excluding subjects with major protocol deviations affecting the efficacy at Week 24. A supportive per-protocol analysis was performed on PPS to confirm the FAS analysis for the primary endpoint.

  Major protocol deviations included, but were not limited to:

  - Randomization criteria violations
  - Inclusion/Exclusion criteria violations
  - Inadequate compliance with study drug
  - Prohibited medications taken
  - Significant deviations from the study drug administration schedule
  - No valid evaluation of the primary efficacy endpoint
  - Other protocol deviations that could affect subjects' efficacy outcomes

Safety Set: All randomized subjects that received any treatment with study drug and analyzed as treated.

Intercurrent Events

Intercurrent events (ICEs) are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. The following ICEs were anticipated by the Applicant during the study:

- Death
- Discontinuation of study treatment related to the COVID-19 pandemic
- Discontinuation of study treatment not related to the COVID-19 pandemic
- Missed study treatment infusion related to the COVID-19 pandemic
- Missed study treatment infusion not related to the COVID-19 pandemic
- Administration of rescue medication within 1 day prior to an ACR assessment.

ICEs related to the COVID-19 pandemic refers to subjects being unable to attend the study site due to traffic control or site closure. The expectation was that either no data has been collected or remote assessments have been performed where applicable.

Treatment dosing affected the ACR20 assessment at the following visit. When discontinuation of study treatment or a missed dose occurs at a visit, the affected ACR20 components are at the following visit, scheduled 4 weeks after dosing. Thus, if a study treatment infusion at Week 20 is missed, the ACR20 components at Week 24 will be affected, and will require ICE handling.

Efficacy Estimands and Data Handling

It is necessary to address ICEs when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated. The SAP defined two estimands for analyses (Table 14). The primary estimand was used in the analysis of the primary endpoint (primary analysis).

Table 14. Study Estimands

	Primary Estimand	Secondary Estimand
Treatment conditions of interest	BAT1806 + MTX vs EU-RoActemra + MTX	BAT1806 + MTX vs RU-RoActemra + MTX
Population	RA patients with inadequate response to MTX	RA patients with inadequate response to MTX
Endpoint	ACR20 at Week 24	ACR20 at Week 24
Population level summary	Difference between treatments in proportion of subjects achieving ACR20 response at Week 24	Difference between treatments in proportion of subjects achieving ACR20 response at Week 24

ICEs and strategies to handle ICEs	• Death prior to assessment of ACR at Week 24 *Composite variable strategy* • Discontinuation of study treatment (up to Week 20 dosing) related to the COVID-19 pandemic *Treatment policy strategy* • Discontinuation of study treatment (up to Week 20 dosing) not related to the COVID-19 pandemic *Treatment policy strategy* • Missed study treatment infusion (any dosing up to Week 20) related to the COVID-19 pandemic *Treatment policy strategy* • Missed study treatment infusion (any dosing up to Week 20) not related to the COVID-19 pandemic *Treatment policy strategy* • Administration of rescue medication within 1 day prior to an ACR assessment up to Week 24 *Treatment policy strategy*	• Death prior to assessment of ACR at Week 24 *Composite variable strategy* • Discontinuation of study treatment (up to Week 20 dosing) related to the COVID-19 pandemic *Hypothetical strategy* • Discontinuation of study treatment (up to Week 20 dosing) not related to the COVID-19 pandemic *Treatment policy strategy* • Missed study treatment infusion (any dosing up to Week 20) related to the COVID-19 pandemic *Hypothetical strategy* • Missed study treatment infusion (any dosing up to Week 20) not related to the COVID-19 pandemic *Treatment policy strategy* • Administration of rescue medication within 1 day prior to an assessment of ACR up to Week 24 *Treatment policy strategy*
	ICE(s) with a composite variable strategy take priority over ICEs with other strategies. Secondary Estimand: ICE(s) related to discontinuation of study treatment infusion or missed study treatment infusion takes priority over ICE(s) related to rescue medication intake.	

Source: Table from SAP, section 7.2.1, page 30 of 72 (54 of 96)

A summary of ICEs and handling strategies for each estimand is presented in Table 15. Using the composite variable strategy, death (ICE1) prior to Week 24 ACR assessment will be handled as ACR20 non-response. This ICE1 handling applies to both primary and secondary estimands.

Using the treatment policy strategy for the primary estimand (ICE2-6), available data occurring on or after the ICE will be analyzed as observed. Missing data will be (single) imputed as ACR20 non-response.

For the secondary estimand:

- Using the treatment policy strategy (ICE3, 5, and 6), available data on or after the ICE will be analyzed as observed. Missing Week 24 ACR components will be multiple imputed by a missing at random (MAR) application of SAS Proc MI
- Using the hypothetical strategy (ICE2 and 4), available data occurring on or after the ICE will be set to missing, and multiple imputed by a missing not at random (MNAR) application of SAS Proc MI

Table 15. ICEs and Handling Strategies

ICE		ICE Handling Strategies			
		Primary Estimand		Secondary Estimand	
		Strategy	Imputation	Strategy	Imputation
Death	ICE1	Composite variable	NR	Composite variable	NR
Discontinuation of Treatment	ICE2	Treatment policy	NR	Hypothetical	MNAR
	ICE3	Treatment policy	NR	Treatment policy	MAR
Missed Treatment Infusion	ICE4	Treatment policy	NR	Hypothetical	MNAR
	ICE5	Treatment policy	NR	Treatment policy	MAR
Rescue Medication	ICE6	Treatment policy	NR	Treatment policy	MAR

ICE1: Death prior to assessment
ICE2: Discontinuation of study treatment (up to Week 20 dosing) related to the COVID-19 pandemic
ICE3: Discontinuation of study treatment (up to Week 20 dosing) not related to the COVID-19 pandemic
ICE4: Missed study treatment infusion (at Week 20) related to the COVID-19 pandemic
ICE5: Missed study treatment infusion (at Week 20) not related to the COVID-19 pandemic
ICE6: Administration of rescue medication within 1 day prior to an ACR assessment
NR = non-response

Source: Reviewer's Table

Note that the (1) ICE handling using the treatment policy approach to missing data are different for each estimand and (2) hypothetical strategy corresponds only to the ICEs related to the COVID-19 pandemic (i.e., ICE2 and 4).

The Applicant used the secondary estimand in the analysis of the primary endpoint. However, per Section 2.1, the multiple imputation approach may be used as supportive analysis. Thus, the reviewer considers the Applicant's analysis of the primary endpoint using the secondary estimand as a supplementary analysis.

Analysis

The primary analysis of the primary estimand is based on the proportion of subjects achieving ACR20 response at Week 24. ICEs and missing data imputation are handled as previously described. The statistical model is a logistic regression with treatment arm and strata (geographical region and previous biologic or targeted synthetic DMARD use) as factors, applied on the FAS. Estimates for the response rate in each treatment arm, as well as the difference in rates and the corresponding 2-sided 90% CIs, were calculated using the procedure by Ge et al. (2011). Similarity between the two treatment arms would be concluded if the 2-sided 90% CI TOST at α=0.05) is contained within the pre-specified interval, [-12.0%, +15.0%].

Similarity Margins and Sample Size

The Applicant conducted a meta-analysis of five studies on "tocilizumab" to derive an estimate for the expected proportion of subjects achieving ACR20 at Week 24 for the reference product, EU-RoActemra (Table 16). The Biogen CSR stated that the 5 studies were similar on the following characteristics:

- "Tocilizumab" administered as IV 8 mg/kg dose, Q4W

- DMARDs used as background therapy (data from MTX only treated patients could be obtained for the TOWARD study)
- Primary endpoint of ACR20 at Week 24 or Week 16 (CHARISMA)

Table 16. Meta-Analysis of Studies

	RoActemra 8 mg/kg + DMARDs		Placebo + DMARDs		
Study	**Non-Responder**	**Responder**	**Non-Responder**	**Responder**	**Weight (Fixed)**
CHARISMA	13/50 (26.0%)	37/50 (74.0%)	29/49 (59.2%)	20/49 (40.8%)	3.6%
LITHE	174/398 (43.7%)	224/398 (56.3%)	287/393 (73.0%)	106/393 (27.0%)	29.1%
OPTION	85/205 (41.5%)	120/205 (58.5%)	150/204 (73.5%)	54/204 (26.5%)	15.1%
RADIATE	85/170 (50.0%)	85/170 (50.0%)	142/158 (89.9%)	16/158 (10.1%)	12.1%
TOWARD	187/456 (41.0%)	269/456 (59.0%)	168/224 (75.0%)	56/224 (25.0%)	40.1%
Total	673/1626 (41.4%)	953/1626 (58.6%)	920/1217 (75.6%)	297/1217 (24.4%)	100%

Source: Table 1, page 22 of 72 of SAP

Based on a fixed effects model, the point estimate of the risk difference (95% CI) was 33.9% (30.5%, 37.3%). The reported study heterogeneity p-value was 0.31. Retaining 60% of the treatment effect for the lower bound and 50% of the treatment effect for the asymmetric upper bound, a similarity margin of [-12.0%, +15.0%] was chosen for assessing similarity at Week 24.

Assumptions for sample size calculation:

- 2-sided 90% CI α 0.05)
- Reference proportion of 58.6%
- True hypothesized difference of zero
- Equivalence margin of [-12.0%, +15.0%]

Using the above assumptions, a total of 598 evaluable subjects in the study (299 per arm) would provide 89% power to show equivalence of BAT1806 with EU-RoActemra for the difference in proportion of ACR20 responders at Week 24.

A pooled Z-test and binomial enumeration power calculation method in nQuery, yielded 301 subjects per group with 89.65% power. Thus, the Applicant's sample size calculation appears to be correct.

Subject Disposition

Table 17 presents a summary of subject disposition. From a total of 935 screened subjects, 621 were randomized. Based on the actual study design implementation, the 621 subjects were randomized at baseline in a 1:1:2 fashion to the following respective groups: EU-RoActemra up to Week 48, EU-RoActemra up to Week 24 and BAT1806 thereafter, and BAT1806 up to Week 48, once every 4 weeks, at a starting dose of 8 mg/kg.

Table 17. Subject Disposition

	EU-RoActemra (EU-RoA)				
	EU-RoA to EU-RoA	EU-RoA to BAT1806	Total	BAT1806	Total (%)
FAS	167	142	309	312	621 (100.0)
SAF Throughout the Study	167	142	309	312	621 (100.0)
PPS at Week 24	151	151	302	299	601 (96.8)
Completed TP1	146	142	288	299	587 (94.5)
Completed TP1 not entering TP2	1	0	1	9	10 (1.6)
Entering TP2	145	142	287	290	577 (92.9)
Entering and completed TP2	139	135	274	282	556 (89.5)
Completed the study	141	134	275	280	555 (89.4)
Withdrawn from the study	26	8	34	32	66 (10.6)

FAS=Full Analysis Set; PPS=Per-Protocol Set; SAF=Safety Set; TP1=Treatment Period 1; TP2=Treatment Period 2

Source: Condensed version of Table 7 of Biogen CSR, page 74 (Verified by Reviewer)

A total of 587 (94.5%) subjects completed TP1 and 555 (89.4%) subjects completed the study. There were 66 (10.6%) subjects who did not complete the study. The most common reasons for discontinuation were withdrawal of consent (3.5%), other (3.4%), and specific laboratory abnormalities (1.3%) (data not presented).

Twelve (12) subjects that were randomized to EU-RoActemra to BAT1806 (RoA to BAT) were actually randomized to RoA to RoA. The Reviewer determined this when comparing the "ACTARM" and "TRTSEQA" variables to "TRTSEQP" in the adsl.xpt (subject-level) dataset. Thus, the correct FAS counts should be 167 and 142 subjects randomized to RoA to RoA and RoA to BAT, respectively. For the FAS, Table 7 of the Biogen CSR reported 155 and 154 subjects in the RoA to RoA and RoA to BAT groups, respectively. However, this does not affect the efficacy assessment at Week 24 because the two groups are combined into one EU-RoActemra group and then compared to BAT1806.

The overall discontinuation rate (10.6%) is approximately what was initially expected at the start of the study.

There does not appear to be major imbalances in subject disposition between the EU-RoActemra and Bat1806 treatment groups.

Demographics and Baseline Characteristics

Table 18 and Table 19 present the demographic and baseline disease characteristics, respectively, for the FAS. The summaries for "Region" and "Previous biologic or tsDMARD use", as well as the ACR components, are based on the actual (IWRS) stratification.

Table 18. Subject Demographic and Other Baseline Characteristics (FAS)

	EU-RoActemra (N=309)	BAT1806 (N=312)	Total (N=621)
Age (years)			
Mean (SD)	50.1 (12.02)	50.9 (11.93)	50.5 (11.98)
Sex, n (%)			
Male	44 (14.2%)	43 (13.8%)	87 (14.0%)
Female	265 (85.8%)	269 (86.2%)	534 (86.0%)
Race, n (%)			
White	182 (58.9%)	186 (59.6%)	368 (59.3%)
Black	0	0	0
Asian	127 (41.1%)	126 (40.4%)	253 (40.7%)
Native Hawaiian or Pacific Islander	0	0	0
Other	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	7 (2.3%)	4 (1.3%)	11 (1.8%)
Not Hispanic or Latino	302 (97.7%)	308 (98.7%)	610 (98.2%)
Weight (Kg)			
Mean (SD)	66.62 (14.9)	66.2 (13.6)	66.4 (14.3)
BMI (kg/m^2)			
Mean (SD)	24.8 (4.8)	24.8 (4.4)	24.81 (4.5)
Region, n (%)			
Central Europe	182 (58.9%)	186 (59.6%)	368 (59.3%)
Asia Pacific	127 (41.1%)	126 (40.4%)	253 (40.7%)

FAS=Full Analysis Set, N=number of subjects, SD=standard deviation, tsDMARD=targeted synthetic disease-modifying antirheumatic drug

Source: Table 10, page 79, of Biogen CSR (Verified by Reviewer)

The subject demographic and other baseline characteristics do not appear to be unbalanced between the EU-RoActemra and BAT1806 groups. The majority of subjects were female (86%), with a mean age of 50.5 years. Approximately 59% were White and 41% were Asian, reflective of the population in the regions in which the study was conducted (Europe and China).

Table 19. Rheumatoid Arthritis Disease Characteristics at Baseline (FAS) [Mean (SD)]

	EU-RoActemra (N=309)	BAT1806 (N=312)	Total (N=621)
TJC (68 joints)	23.8 (11.95)	22.5 (12.25)	23.1 (12.11)
SJC (66 joints)	15.2 (7.62)	14.1 (7.78)	14.6 (7.71)
Subject's assessment of pain (VAS; 0 to 100 mm)	66.2 (19.52)	66.5 (19.47)	66.3 (19.48)
Subject's assessment of disease activity (VAS; 0 to 100 mm)	70.2 (17.19)	70.1 (17.45)	70.2 (17.31)
Physician's assessment of disease activity (VAS; 0 to 100 mm)*	70.5 (14.87)	67.8 (14.76)	69.1 (14.87)
HAQ-DI	1.56 (0.59)	1.56 (0.61)	1.56 (0.60)
CRP level (mg/L)	18.89 (24.87)	18.91 (22.91)	18.90 (23.89)
DAS28-CRP	5.89 (0.84)	5.81 (0.94)	5.85 (0.89)
DAS28-ESR	6.72 (0.89)	6.64 (0.88)	6.68 (0.88)
Previous biologic or tsDMARD use, n (%)			
Yes	110 (35.6)	99 (31.7)	209 (33.7)
	199 (64.4)	213 (68.3)	412 (66.3%)
At least one concomitant medication taken	309 (100)	312 (100%)	621 (100%)

*306, 311, and 617 subjects in the EU-RoActemra, BAT1806, and Total columns, respectively
FAS=Fulla Analysis Set, SD=standard deviation, TJC=tender joint count, SJC=swollen joint count, VAS=visual analog scale, HAQ-DI=Health Assessment Questionnaire – Disability Index, CRP=C-reactive protein, DAS28=Disease Activity Score on 28 Joints, ESR=erythrocyte sedimentation rate

Source: Table 11, page 11, of Biogen CSR (Verified by Reviewer)

In general, RA disease characteristics at baseline are representative of a RA patient population with moderately to severely active disease and were similar between the EU-RoActemra and BAT1806 groups.

Stratification Factors

Information about stratification factors is presented in the Appendix.

Analysis of Primary Clinical Endpoint(s)

Primary Efficacy Results

A summary of the Applicant's primary efficacy analysis is presented in Table 20. Of the 621 subjects in the FAS, approximately 90% were evaluable for ACR20. The adjusted ACR20 response rates were approximately 68% and 70% in the EU-RoActemra and

BAT1806 groups, respectively. The estimated treatment difference (90% CI) was 1.94% (-4.04%, 7.92%). The 90% CI was within the pre-specified similarity margins of [-12.0%, 15.0%]. Therefore, BAT1806 and EU-RoActemra are similar with respect to the primary efficacy endpoint.

Table 20. Proportion of Subjects Achieving ACR20 Response at Week 24 (Full Analysis Set)

Statistic	EU-RoActemra	BAT1806	Total
Number of Subjects in FAS	309	312	621
Number of subjects evaluable for ACR20 response	274 (88.7%)	283 (90.7%)	557 (89.7%)
Subjects achieving ACR20 response (observed data)	210 (68.0%)	218 (69.9%)	428 (68.9%)
Primary Estimand			
Adjusted ACR20 response rate	67.94%	69.89%	
% Estimated treatment difference (SE)	1.94 (3.64)		
90% CI	(-4.04, 7.92)		
Pre-specified equivalence margins	[-12.0%, +15.0%]		

Source: Copied from a portion of Table 21, page 101 of 3002, Bio-Thera CSR (Verified by Reviewer)

Sensitivity Analyses of Primary Efficacy Endpoint

This section presents three sensitivity analyses of the primary efficacy endpoint: actual stratification, tipping point analysis (TPA), and generalized linear modeling. The actual stratification analysis was not pre-specified and post hoc because it was added after database lock. The Applicant stated that the reason for this analysis was that there were 75 subjects who had different electronic data capture (EDC) strata than to which they were randomized.

1. Actual Stratification (EDC)

Table 21 presents the results of the re-analysis of the primary estimand using the actual stratification factors. The point estimate, and lower and upper bounds of the 90% CI in the actual stratification analysis are all lower than those corresponding to the randomized stratification presented in the primary efficacy results. However, the 90% CI is still within the pre-specified margins.

Table 21. Randomized versus Actual Stratification Factors

	% Estimated treatment difference (90% CI)
Randomized Strata	1.94 (-4.04, 7.92)
Actual Strata (EDC)	1.54 (-4.44, 7.53)

Source: Applicant's Table 22 (page 107, Biogen CSR) (Verified by Reviewer)

2. Tipping Point Analysis (TPA)

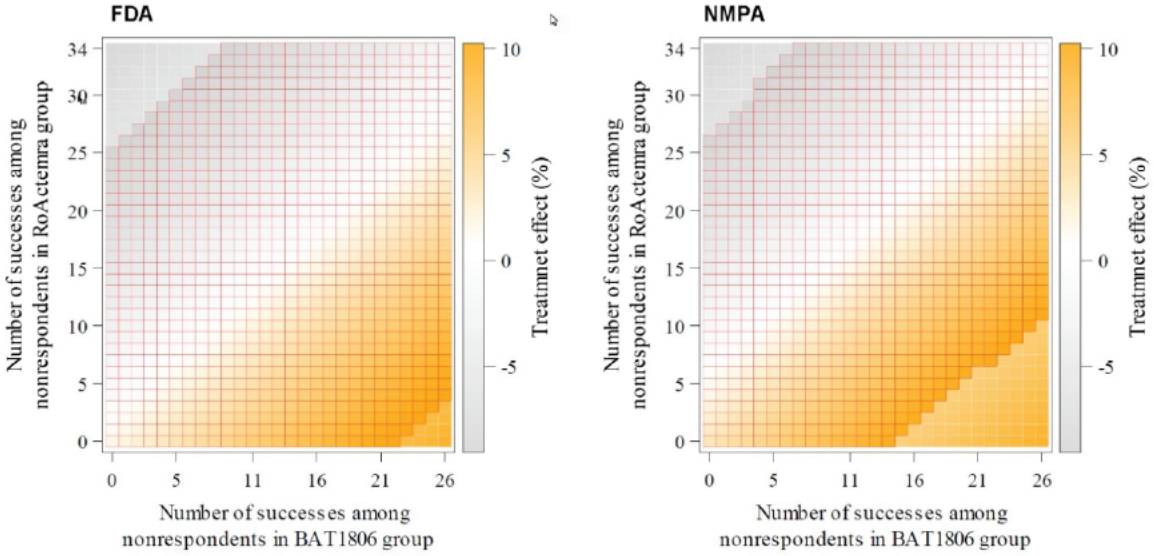
The Applicant performed a two-dimensional TPA based on the binary response of ACR20. Among 621 subjects in the FAS used in the primary analysis, 64 subjects had missing data (see Reviewer's additional analyses) and were imputed as non-responders per the composite approach (for death) and treatment policy approach (for all other ICEs). The composite approach was applied to 4 subjects that died and the treatment policy approach was applied to the remaining 60 subjects. To perform TPA, all 60 subjects (26 in BAT1806 and 34 in EU-RoActemra) were initially imputed as non-response then gradually switching the ACR20 non-responders to responder in each group until the total number of subjects with missing data was reached.

Figure 8 (graph on the left) presents the Applicant's TPA results. The graph on the right is intended for the Chinese Agency submission and is not relevant in this review. It is difficult to decipher the TPA results from the graph itself, but the Biogen CSR stated that:

a. A minimum of 23 subjects (out of 26 subjects) in the BAT1806 group are required to be imputed as responder over and above the EU-RoActemra group to no longer achieve equivalence (i.e., the upper bound of the 2-sided 90% CI is greater than 15.0%)
b. A minimum of 26 subjects (out of 34 subjects) in the EU-RoActemra group are required to be imputed as responder over and above the BAT1806 group to no longer achieve equivalence (i.e., the lower bound of the 2-sided 90% CI is lower than -12.0%)

The CSR stated that the TPA results confirm that the outcomes for the primary estimand of the analysis are robust. The TPA analysis will be further evaluated in a later section by the Reviewer.

Figure 8. Tipping Point Analysis on Primary Estimand



Note 1: The treatment policy approach is applied for all intercurrent events other than death (composite variable strategy). Any available data (including data available under occurrence of an intercurrent event) is analyzed as observed, and any missing data are imputed by gradually increasing the number of imputed responders in each treatment group until the earlier of nonequivalence is reached or no further missing data are available for imputation.
Note 2: Logistic regression model is applied with treatment group (BAT1806 versus RoActemra, reference RoActemra), and randomized strata (region and previous biologic or tsDMARD use) as terms in the model.
Note: The red grid highlights combinations that resulted in equivalence.

Source: Figure 10, page 108 of Biogen CSR

3. Generalized Linear Model (GLM)

The Applicant performed a GLM (using a GEE marginal model) on the primary estimand applying a treatment policy approach for all ICEs other than death and not imputing missing data. Whereas the primary analysis considers only Week 24 data, the GLM analysis accounts for the data in preceding weeks as well. The estimated treatment difference (90% CI) was -0.10% (-5.96%, 5.76%). The 90% CI was within the pre-specified margins of [-12.0%, +15.0%]. The Reviewer was able to verify the Applicant's results.

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Supplementary Analyses of Primary Efficacy Endpoint

1. Secondary Estimand

Recall that the differences between the primary and secondary estimands were in the handling of missing data under the treatment policy strategy and the use of hypothetical strategy for ICEs in the secondary estimand that were COVID-19 pandemic related.

Under the treatment policy strategy for ICEs not related to the COVID-19 pandemic, missing data was imputed as non-response in the primary estimand and imputed via multiple imputation (MAR approach) on each ACR20 component in the secondary estimand.

Under the treatment policy strategy in the primary estimand for COVID-19 pandemic related ICEs, missing Week 24 data was (single) imputed as non-response. Under the hypothetical strategy in the secondary estimand for COVID-19 pandemic related ICEs, available data occurring on or after the ICE was set to missing and imputed via multiple imputation (MNAR approach).

For the secondary estimand, the ACR20 response probabilities were 73.01% and 73.79% for RoActemra and BAT1806, respectively. They are larger than estimates under the primary estimand in Table 20. The estimated treatment difference (standard error) was 0.79% (3.66%) and the 90% CI was (-5.23%, 6.80%) which was within the pre-specified margins of [-12.0%, +15.0%].

Using the Applicant's imputed dataset (admi.xpt), the Reviewer obtained an estimated treatment difference (SE) of 0.81% (3.68%) and the 90% CI of (-5.25%, 6.87%). The results were slightly different from the Applicant's results, but the 90% CI was still within [-12.0%, +15.0%]. The slight difference in results can possibly be attributed to a difference in the computing environment.

2. Per Protocol Population

Using the PPS for analysis instead of the FAS, the estimated treatment difference (SE) was 2.32% (3.66%) and the 90% CI was (-3.70%, 8.35%) which was within the pre-specified margins of [-12.0%, +15.0%].

Potential Effects of Missing Data

Analyses of the potential effects of missing data did not appear to affect the overall conclusion for the primary endpoint, proportion of patient achieving ACR20 at Week 24. See previous sections on intercurrent events and their analyses.

Analysis of Secondary Clinical Endpoint(s)

This section presents the Applicant's analyses results on two selected secondary endpoints.

1. Percentage of Subjects Achieving ACR20, ACR50, and ACR70 Responses

The percentage of subjects achieving ACR20, ACR50, and ACR70 responses are presented in Table 22. The results for ACR50 and ACR70 are identical to those presented in the Applicant's Table 25 (Biogen CSR, p. 114). The results for the three endpoints were generally similar across the two study groups across visits.

Table 22. Percentage of Subjects Achieving ACR20, ACR50, and ACR70 Response (FAS)

		ACR20		ACR50		ACR70	
Visit Week	Statistic	EU-RoActemra N=309	BAT1806 N=312	EU-RoActemra N=309	BAT1806 N=312	EU-RoActemra N=309	BAT1806 N=312
4	No. Evaluable	307 (98.4)	303 (98.1)	308 (99.7)	304 (97.4)	308 (99.7)	304 (97.4)
	No. Responders	97 (31.1)	101 (32.7)	20 (6.5)	20 (6.4)	2 (0.6)	4 (1.3)
8	No. Evaluable	286 (91.7)	289 (93.5)	290 (93.9)	296 (94.9)	297 (96.1)	300 (96.2)
	No. Responders	154 (49.4)	161 (52.1)	60 (19.4)	54 (17.3)	16 (5.2)	20 (6.4)
12	No. Evaluable	285 (91.3)	292 (94.5)	291 (94.2)	298 (95.5)	292 (94.5)	298 (95.5)
	No. Responders	182 (58.3)	205 (66.3)	91 (29.4)	78 (25.0)	29 (9.4)	26 (8.3)
16	No. Evaluable	278 (89.1)	283 (91.6)	289 (93.5)	290 (92.9)	290 (93.9)	295 (94.6)
	No. Responders	200 (64.1)	198 (64.1)	105 (34.0)	97 (31.1)	43 (13.9)	37 (11.9)
20	No. Evaluable	275 (88.1)	282 (91.3)	281 (90.9)	287 (92.0)	286 (92.6)	289 (92.6)
	No. Responders	216 (69.2)	215 (69.6)	112 (36.2)	116 (37.2)	57 (18.4)	50 (16.0)
24	No. Evaluable	274 (87.8)	283 (91.6)	283 (91.6)	286 (91.7)	284 (91.9)	291 (93.3)
	No. Responders	210 (67.3)	218 (70.6)	132 (42.7)	132 (42.3)	69 (22.3)	64 (20.5)

Source: Reviewer's Table

2. Change From Baseline in DAS28-CRP and DAS28-ESR

Table 23 presents the change from baseline in DAS28-CRP and DAS-ESR through Week 24 using the observed values of the FAS. The results for the two endpoints were generally similar across the two study groups across visits.

Table 23. Change From Baseline in DAS28-CRP and DAS28-ESR Through Week 24 Using Observed Values (FAS)

		DAS28-CRP		DAS28-ESR	
Visit	Statistic	RoActemra N=309	BAT1806 N=312	RoActemra N=309	BAT1806 N=312
Baseline	n	309	312	309	312
	Mean (SD)	5.89 (0.842)	5.81 (0.938)	6.72 (0.889)	6.64 (0.877)
Week 4	n	307	303	306	303
	Mean (SD)	-1.311 (0.7731)	-1.375 (0.8182)	-1.610 (1.1159)	-1.685 (1.1274)
Week 8	n	284	279	284	283
	Mean (SD)	-1.910 (1.0395)	-1.964 (1.0128)	-2.410 (1.5200)	-2.496 (1.2796)
Week 12	n	280	290	280	290
	Mean (SD)	-2.162 (1.0576)	-2.233 (1.0752)	-2.595 (1.3254)	-2.869 (1.5066)
Week 16	n	271	276	272	277
	Mean (SD)	-2.385 (1.0988)	-2.393 (1.2377)	-2.953 (1.4198)	-3.015 (1.5010)
Week 20	n	272	279	272	280
	Mean (SD)	-2.599 (1.1004)	-2.612 (1.1665)	-3.132 (1.3775)	-3.274 (1.4967)
Week 24	n	270	278	271	279
	Mean (SD)	-2.787 (1.1099)	-2.791 (1.1824)	-3.380 (1.4718)	-3.463 (1.4375)

Abbreviations: CRP = C-reactive protein; DAS28 = Disease Activity Score on 28 joints; ESR = erythrocyte sedimentation rate; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation.

Source: Table 27 of Biogen CSR, page 119 (Verified by Reviewer)

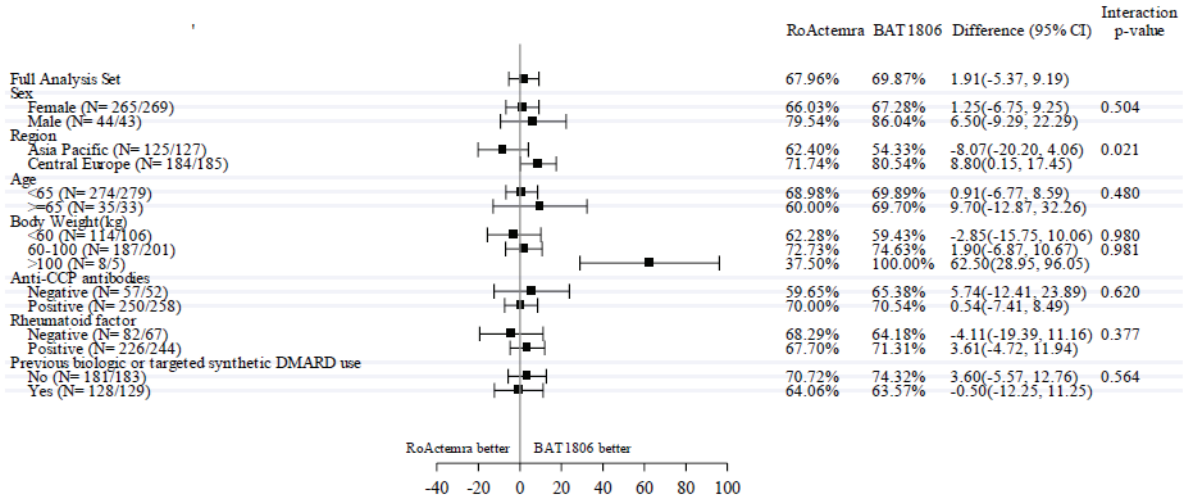
Other Clinical Endpoints

The Applicant presented analyses of the possible impact of the pandemic on the study subject participation during follow-up. See the Appendix for details.

Subgroup Analysis

The Applicant performed exploratory subgroup analyses to evaluate the consistency in the primary endpoint (Figure 9). It was noted that there was an impact of region favoring BAT1806 in Central Europe and EU-RoActemra in Asia Pacific.

Figure 9. Subgroup Analysis - Proportion of Subjects Achieving ACR20 Response at Week 24 (Primary Estimand) (FAS)



Source: Figure 14.2.1.1.15 of Bio-Thera CSR

The Reviewer performed subgroup analyses by repeating the primary analysis on each subgroup category. Subgroup analysis for ethnicity was not performed because there were too few subjects for a second category (<2% for "Hispanic or Latino"). Subgroup analysis for race is the same as region ("White" for Central Europe and "Asian" for Asia Pacific). The results are as follows:

Table 24. Reviewer's Subgroup Analysis

Subgroup	n (RoA/BAT)	PE (90% CI)*
Sex		
Female	265/269	0.76 (-5.79, 7.31)
Male	44/43	8.14 (-5.25, 21.53)
Region		
Asia Pacific	125/127	-8.17 (-18.26, 1.93)
Central Europe	184/185	8.81 (1.55, 16.07)
Age		
< 65 years	274/279	0.45 (-5.85, 6.74)
>= 65 years	35/33	13.86 (-4.82, 32.55)
Previous biologic or tsDMARD Use		
No	181/183	3.69 (-3.93, 11.31)
Yes	128/129	-0.58 (-10.16, 9.00)
n=number of subjects; RoA = US RoActemra; BAT = BAT1806; PE = point estimate; CI = confidence interval; * in percent (%)		

Source: Reviewer's Table

The results are not the same but consistent with the Applicant's results. The reason for this is that the Applicant's results appeared to have been calculated using a treatment-by-subgroup interaction model whereas the Reviewer's results were based on the analysis of the actual subgroup category.

There were no notable efficacy trends favoring either treatment in these subgroup analyses except Region and Body Weight. The result for the Central Europe group presented a higher trend than Asia Pacific. For Body Weight, the result for the ">100" group presented a higher trend than the "<60" and "60-100" groups. These results are exploratory and should be treated as such.

Additional Analyses

The following five (5) analyses were performed by the Reviewer: (1) Verification of subject responses from component datasets, (2) Reviewer's ACR20 response data findings versus the Applicants, (3) Verification of ICE status, (4) Secondary estimand ICE handling, and (5) Tipping point analysis. These analyses verified the Applicant's results. See the Appendix for details.

Conclusions and Recommendations

The conclusions from the statistical reviewer's analyses agreed with those of the Applicant. For the primary analysis the statistical reviewer obtained a 90% confidence interval for the difference in treatment effects between BAT1806 and EU-RoActemra groups of (-0.0404, 0.0792) which is contained in the prespecified similarity interval of [-0.12, +0.15]. The supportive and sensitivity analyses of the primary endpoint as well as selected secondary endpoints at Week 24, as discussed in this review, further support the conclusion of similar efficacy for BAT1806 and EU-RoActemra. The efficacy based on the primary endpoint, and the selected secondary endpoints, support a demonstration of no clinically meaningful efficacy differences between BAT1806 and US-Actemra, as the Applicant provided adequate data to establish the scientific bridge between BAT1806, US-Actemra, and EU-RoActemra to justify the relevance of data generated with EU-RoActemra to the assessment of biosimilarity.

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6.3. Review of Safety Data

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

The Applicant provided safety data from 2 clinical studies presented in Table 3.

The safety database for the current submission includes data from a total of 750 subjects from the two clinical studies including 129 healthy volunteers in Study BAT-1806-001-CR and 621 patients with RA in Study BAT-1806-002. Of these, 499 subjects received BAT1806 (45 healthy volunteers in Study BAT-1806-001-CR and 454 patients in Study BAT-1806-002-CR). The size of the safety database is adequate to provide a reliable descriptive comparison between the products.

The primary study to characterize safety was the comparative clinical study, BAT-1806-002-CR conducted in patients with RA. It provided a comparison between BAT1806 and EU-RoActemra over a treatment period of 48 weeks. This study provided a comparison of efficacy, safety and immunogenicity between BAT1806 and RoActemra. RA patients were initially randomized to BAT1806 or EU-RoActemra during treatment period 1(TP1). After Week 24, patients who received EU-RoActemra in TP1 either remained on EU-RoActemra or transitioned to BAT1806 for treatment period 2 (TP2). Patients initially randomized to BAT1806 during TP1 remained on BAT1806 through TP2. TP1 of the study provided a comparison of safety and immunogenicity between BAT1806 and EU-RoActemra through Week 24. TP2 of this study provided additional safety information for patients who transitioned from EU-RoActemra to BAT1806. Patients were to receive 6 doses of treatment (BAT1806 or EU-RoActemra) during each of the two treatment periods.

While Study BAT-1806-002-CR provides the main safety information relevant to the review, additional safety information was also provided from the bridging PK study conducted in healthy male volunteers, BAT-1806-001-CR.

Adverse events across both clinical studies were evaluated. Analysis of adverse events were conducted based on the known safety profile of US-Actemra (also referred to as Actemra). Comparison of safety between BAT1806 and the safety profile for US-Actemra will be discussed in the following review sections.

US-Actemra is an immunosuppressant drug with a well-characterized safety profile. Approved labeling for US-Actemra[5] includes a boxed warning for serious and fatal infections. Additional warnings and precautions are for gastrointestinal perforations, hepatotoxicity, laboratory changes requiring monitoring (LFTs, neutrophils, platelets,

[5] US Actemra PI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125276s138lbl.pdf

and lipids), hypersensitivity reactions including anaphylaxis and death, and to avoid use of live vaccines while receiving Actemra. As an immunosuppressant there is an increased risk for development of malignancies. Demyelinating disorders have also been reported in RA clinical studies and patients are to be monitored for signs and symptoms of demyelinating disorders. The most common adverse reactions include upper respiratory tract infections, nasophyngitis, headache, hypertension, and increased ALT.

Clinical Studies to Evaluate Safety

Study BAT-1806-001-CR

Study BAT-1806-001-CR was a randomized, double-blinded, single-dose, 3-arm parallel, comparative study to evaluate the pharmacokinetics, safety and immunogenicity of BAT1806 compared to US-licensed Actemra and EU-RoActemra. A total of 138 subjects were planned to be enrolled and randomized at a ratio of 1:1:1 to receive single intravenous infusion of 4 mg/kg BAT1806, EU-RoActemra or US-Actemra administrated over a 60-minute intravenous (IV) infusion.

The study included a screening period of up to 7 days. Subjects were admitted to the clinical pharmacology unit one day prior to dosing. Dosing was administered on Day 1 and follow-up was required to Day 57 post-dose.

Safety evaluations were conducted for vital signs, physical examinations, injection site reaction, ECG, clinical laboratory tests and adverse events throughout the study. Immunogenicity (ADA, NAb and associated titers) were also evaluated.

The key inclusion criteria for the study included male subjects between 18-55 years. The inclusion criteria required a BMI between 18-28 kg/m^2, body weight between 55-85 kg and a normal physical examination. Subjects were excluded for the following:

- Daily smoking amount of >5 cigarettes within 3 months prior to the study;
- Any current or history of severe allergic reaction to foods or drugs, history of allergy to tocilizumab or severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies;
- Prior use of prescription medication, over-the-counter drugs, any vitamin products or herbs within 28 days before screening;
- Having any diseases that increase the risk of bleeding, acute gastritis or gastric and duodenal ulcers;
- Having clinically significant laboratory abnormalities or other clinically significant diseases (including but not limited to gastrointestinal, renal, liver, neurological, hematological, endocrine, tumor, lung, immune, mental or cardiovascular diseases).

The study was conducted at a single study site in China and 138 healthy male subjects were enrolled. Nine subjects were prematurely withdrawn from the study prior to dosing.

The safety analysis set (SAS) included all healthy subjects who received study drug and were analyzed according to treatment received (N = 129, overall). The safety analysis population was used for all analyses of safety, dosing, demographic, and immunogenicity summaries. Overall, 45 subjects received BAT1806, 42 subjects received EU-RoActemra, and 42 subjects received US-Actemra.

Study BAT-1806-002-CR

Study BAT-1806-002-CR was a multicenter, randomized, double-blind, parallel-group, active-controlled study to compare efficacy, safety, immunogenicity, and PK of BAT1806 compared with EU-RoActemra in patients with moderately to severely active RA inadequately controlled by MTX.

The study was composed of a ≤ 28-day screening period, a 24-week initial treatment period (TP1), a 24-week secondary treatment period (TP2), and a 4-week follow-up period. Patients received either BAT1806 or EU-approved RoActemra 8 mg/kg by 60 min intravenous infusion every 4 weeks.

Patients were randomized 1:1:2 to receive EU-RoActemra for up to Week 48, receive EU-RoActemra to Week 24 followed by BAT1806 until Week 48, or to receive BAT1806 for up to Week 48.

The main eligibility criteria for the study are included in section 6.2.

A total of 621 patients were randomized. This included 155 patients randomized to the EU-RoActemra→ EU-RoActemra arm, 154 patients to the EU-RoActemra→BAT1806 arm, and 312 patients to the BAT1806→BAT1806 arm. All 621 randomized patients in TP1 received at least 1 dose of study treatment.

Of the 621 randomized patients, 587 (94.5%) completed TP1 (288/309 patients who were randomized to EU-RoActemra and 299/312 patients who were randomized to BAT1806).

A total of 577 (92.9%) patients entered TP2 (287 patients who were randomized to EU-RoActemra in TP1 and 290 patients who were randomized to BAT1806 in TP1). Of the 287 patients who were randomized to EU-RoActemra in TP1 and who entered TP2, 145 patients continued to receive EU-RoActemra (EU-RoActemra→EU-RoActemra) in TP2 and 142 patients were administered BAT1806 in TP2 (EU-RoActemra→BAT1806). A total of 556 (89.5%) patients completed TP2 and 555 (89.4%) patients completed the study (See Table 17).

Patients must have been receiving MTX therapy (treatment by any administration route) for ≥12 weeks before randomization, on a stable dose ranging between 10 to 25

mg/week for at least the 4 consecutive weeks prior to randomization. Patients were also to continue on their stable MTX dose and route of administration throughout the study.

Safety evaluations in the study included evaluations of AEs, laboratory parameters including hematology, chemistry with lipid panel, urinalysis, vital signs, physical examination and ECGs.

Exposure
In the two clinical studies that support this submission a total of 750 subjects were enrolled (129 healthy male volunteers in Study BAT-1806-001-CR and 621 patients with RA in Study BAT-1806-002-CR). Of these, a total of 499 subjects received at least one dose of BAT1806. This included 45 subjects in Study BAT-1806-001 CR who received a single 4 mg/kg dose and 454 RA patients in Study BAT-1806-002-CR who received 8mg/kg doses (142 patients who transitioned to BAT1806 in TP2 in the EU-RoActemra →BAT1806 group, and 312 in the BAT1806 →BAT1806 group).

In TP1 for Study BAT-1806-002-CR a similar mean number of doses were administered in the EU-RoActemra (5.4 doses) and BAT1806 (5.5 doses) arms. In TP2 the mean number of doses administered were also similar between the treatment arms. The mean number of doses was 5.7, 5.6 and 5.8 in the continued EU-RoActemra arm, RoActemra→BAT1806, and BAT1806→BAT1806 arm, respectively.

Compliance

Doses of study drug (BAT1806 or EU-RoActemra) were to be administered to patients at the study site by study site staff. Patients who were consistently noncompliant with the study treatment missed ≥ 2 consecutive doses) were to be discontinued from study treatment and withdrawn from the study based on the agreement between the Sponsor and the investigator.

Treatment compliance was evaluated by comparing the number of doses administered with the number of doses planned, and comparing the amount of the total dose administered with the amount of total dose planned. Percent compliance was then calculated. Treatment compliance was similar across all groups in the Study BAT-1806-002-CR. In TP1, mean compliance was 93.5% in the EU-RoActemra group and 93.9% in the BAT1806 group. In TP2, mean compliance was 95.4% in the EU-RoActemra→ EU-RoActemra group, 94.8% in the EU-RoActemra→BAT1806 group, and 96.6% in the BAT1806→BAT1806 group.

Safety Analyses
Safety and tolerability assessments included the incidence of treatment emergent adverse events (TEAEs), SAEs, clinically abnormal laboratory parameters, vital signs, physical examinations, 12-lead ECGs and immunogenic response.

Categorization of Adverse Events

Adverse events (AEs) were coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) versions 21.1 for Study BAT-1806-001-CR and 23.1 for Study BAT-1806-002-CR. Treatment emergent adverse events (TEAE) were defined as AEs that commenced or worsened on or after the first dose of study drug. Severity of AEs in Study BAT-1806-001-CR was assessed as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), and grade 5 (fatal) based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Any adverse events which could not be graded using the CTCAE were categorized by the investigator as mild, moderate, severe, life-threatening or fatal. Causal relationship to the study drug was categorized in to 6 categories (definitely related, probably related, possibly related, unlikely related, definitely unrelated, and unable to determine). Events with relationship to study drug classified as definitely related, probably related, possibly related, and unable to determine were considered as related events for the study analysis. TEAEs for Study BAT-1806-002-CR were defined as an AE on or after the first dose of study treatment, or worsens in severity during treatment relative to the pretreatment state, up to and including 8 weeks (56 days) after the last date of dosing with study drug. For Study BAT-1806-002-CR adverse event severity was assessed by the investigator as mild for an AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities; moderate for an AE that is sufficiently discomforting to interfere with normal everyday activities; intervention maybe needed; and severe events were AE that prevents normal everyday activities; treatment or other intervention usually needed. Assessment of causality to the study drug included 5 categories (unrelated, unlikely, possible, probably and certain). TEAEs categorized as possible, probably, and certain causality were considered related to study treatment. To further analyze events of interest the Applicant used Standard MedDRA queries.

The Applicant's definition of AEs and SAEs and the approach to collecting and coding of AEs was acceptable.

Safety Analyses

The safety analyses submitted by the Applicant were from the individual studies and were not pooled. This was due to the difference in the study populations and study designs including dosing and duration of the studies. During the BPD Type 4 meeting, the Applicant and the Agency agreed the study safety analyses would be provided for each study individually.

All subjects randomized and treated with at least 1 dose of study drug, defined the safety population, and were included in the safety analyses.

Safety and tolerability analyses included the incidence of treatment emergent adverse events (TEAEs), SAEs, clinically abnormal laboratory parameters, vital signs, physical examinations, 12-lead ECGs and immunogenic response.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Population Demographics
Study BAT-1806-001-CR was conducted at a single site in China. All patients were Asian males and were between the ages of 18 to 51 years. Demographics were generally similar between the 3 treatment groups.

The demographics were generally balanced between study arms for Study BAT-1806-002-CR (Table 17 and Table 18). The enrolled study population is consistent with the population of patients with RA eligible for treatment with tocilizumab. Study BAT-1806-002-CR enrolled approximately 40% of patients from study sites in China (29 sites) and approximately 60% of patients from sites in Central Europe which included Bulgaria (5 sites), Georgia (4 sites), Poland (10 sites), and Ukraine (7 sites).

Other Product-Specific Safety Concerns

None.

Overall AE Profile

A summary of the AEs observed in the clinical studies BAT-1806-001 and BAT-1806-002-CR are presented below with the primary focus on the comparative clinical study BAT-1806-002-CR. No new safety signals were identified in the BAT1806 treatment arm compared with the known adverse event profile of US-Actemra. The overall TEAEs were similar between treatment arms in both studies. While some numerical differences in adverse events were observed, the overall differences were generally small and likely due to chance. The observed differences do not appear to indicate a meaningful difference between the treatment arms. An imbalance in deaths was observed in the BAT1806 arm in Study BAT-1806-002-CR with four deaths reported in the BAT1806 arm compared to one in the EU-RoActemra comparator arm. Review of the adverse events leading to death did not show any clear pattern regarding timing or type of events. All deaths occurred during TP1 and patients had received between 1 to 3 doses of BAT1806. There were no major differences in SAE, TEAEs, AEs leading to discontinuation, and adverse events of special interest (AESI) based on the known safety profile of US-Actemra between the treatment groups. In addition, the safety observed in the single-dose PK study in healthy male subjects further supports the comparable safety profile between BAT1806 and US-Actemra. No increase in adverse events were observed following the single transition from EU-RoActemra to BAT1806 during TP2 in Study BAT-1806-002-CR.

Deaths

No deaths were reported in Study BAT-1806-001.

There were 5 deaths that occurred in Study BAT-1806-002. One death was reported in the EU-RoActemra arm and 4 in the BAT1806 arm. One death in the BAT1806 was considered by the Applicant to be non-treatment emergent. All of the adverse events leading to death occurred during TP1. In the EU-RoActemra arm one patient experienced a fatal infection. In the BAT1806 arm no pattern of fatal events were observed in regard to the type or timing of events.

The 5 fatal events occurring in patients in Study BAT-1806-002 are described below.

EU-RoActemra Study Arm:

- Patient (b) (6), a 55-year-old female was randomized to the EU-RoActemra→ BAT1806 arm. She had a medical history of pneumonia and bronchiectasis and was receiving concomitant methotrexate, folic acid, and etoricoxib. She had serious TEAEs of localized infection (deep neck space infection) and mediastinitis on Study Day 79, followed by development of septic shock on Study Day 98 and cerebral hemorrhage on Study Day 111. She died on Study Day 121. The patient received a total of 3 doses of EU-RoActemra prior to the event during TP1.

BAT1806 Study Arm:

- Patient (b) (6), a 53-year-old female was randomized to the BAT1806 arm. The patient had a serious TEAE of ruptured cerebral aneurysm on Study Day 8 and died on Study Day 22. She had a medical history including hyperlipidemia, anemia and leukopenia and was receiving concomitant methotrexate, folic acid, and celecoxib. The patient reported an AE of pharyngitis on Study Day 4 and was treated with amoxicillin. The symptoms resolved on Day 5 however the patient visited the hospital on Study Day 6 due to gingival swelling and pain (toothache) treated with cephalosporin injection. On Day 8 she reported a headache and was hospitalized for a ruptured cerebral aneurysm. She had received 1 dose of BAT1806 prior to the fatal event. An autopsy was not performed.
- Patient (b) (6), a 49-year-old female, was randomized to the BAT1806 arm. She had a medical history of proteinuria, hypertension and hypertriglyceridemia. Her concomitant medications included MTX, folic acid, and etoricoxib. She had received treatment with immunosuppressive agents prior to her enrollment in the clinical study. The patient was diagnosed with ovarian cancer stage III on Study Day 67 and died on Study Day 356. She received a total of 3 doses of BAT1806. At the time of diagnosis, an abdominal CT scan showed multiple peritoneal and intra-abdominal metastases.

- Patient (b) (6), a 47-year-old female, was randomized to the BAT1806 arm. She received a total of 2 doses of BAT1806. She died on Study Day 81 (cause of death unknown). She had a medical history of hypertension, hyperlipidemia and obesity. Her concomitant medications included ramipril, metoprolol, pantoprazole, MTX, methylprednisolone, rosuvastatin and ketoprofen. The investigator considered the event was unrelated to study drug.
- Patient (b) (6), a 64-year-old female was randomized to the BAT1806 arm. She had a medical history of arteriosclerosis, hypertension, cholelithiasis, type 2 diabetes mellitus, and hypercholesterolemia. Her concomitant medications included bisoprolol, ramipril, metformin, MTX, folic acid, prednisone, timonacic, drotaverine, and pantoprazole. The patient had a nonserious event of cholelithiasis on Study Day 27 and a serious adverse event of pancreatic abscess on Study Day 37. The pancreatic abscess required surgical drainage and following the procedure the patient experienced a myocardial infarction, atrial fibrillation, and pneumonia. She died of cardiopulmonary failure on Study Day 82. She received one dose of BAT1806. The Sponsor considered the event of cardiopulmonary failure to be non-treatment emergent as the last dose of BAT1806 was administered approximately 2.5 months before the onset of the fatal event. The investigator considered the event was unrelated to study drug and likely resulting from cholelithiasis and pancreatic abscess.

Overall, there is an imbalance of fatal events with more events occurring in the BAT1806 arm in Study BAT-1806-002-CR. There were four fatal events in the BAT1806 arm compared to one in the EU-RoActemra arm. All of the fatal events during the study occurred during TP1. Patients who died in the BAT1806 arm received between 1-3 total doses. The time to onset of the initially reported fatal adverse events ranged from 8-67 days following the first dose of BAT1806. One patient in the BAT1806 arm who died of an unknown cause, died on Study Day 81. No pattern related to timing or type of fatal events was observed in the BAT1806 treatment arm. One patient in the BAT1806 arm had a fatal event related to an ovarian carcinoma diagnosed on Study Day 67. She had received 3 doses of BAT1806 and had received prior immunosuppressants to treat RA before enrolling in the clinical trial. Given the long latency for cancer development the relationship to BAT1806 based on the limited exposure (3 doses) is less likely. In one case the cause of death is unknown. In this case the patient had received 2 doses of BAT1806. One patient receiving BAT1806 died following a ruptured cerebral aneurysm after receiving a single dose. There is limited clinical information in the case to know if this patient had a pre-existing aneurysm. In the EU-RoActemra arm a patient died following the development of an infection. One patient in the BAT1806 arm developed a pancreatic abscess leading to complications post-surgical drainage and ultimately cardiopulmonary failure after a protracted course. She had received one dose of BAT1806 prior to the initial event. It is considered that her cholelithiasis likely contributed to the initial event and development of pancreatic abscess. As tocilizumab is an immunosuppressant, it is possible that BAT1806 may have increased the risk for infection. Given the immunosuppressive effects of tocilizumab,

serious infections including fatal events are known risks and included in approved labeling. In the fatal events that occurred in Study BAT-1806-002-CR, the relationship to BAT1806 is not clear. No increase in fatal infections were observed in the BAT1806 arm compared to EU-RoActemra. Overall, while there is a numerical imbalance in fatal events between the two arms, review of the individual cases did not demonstrate a clear pattern of events and supports that the observed differences in arms are more likely the result of chance and were determined not to be meaningful differences.

Treatment Emergent Adverse Events

Study BAT-1806-001-CR

The incidence of TEAEs was similar between the 3 treatment groups in the healthy volunteer population. Overall, 100 (77.5%) subjects experienced at least one TEAE; 31 (68.9%) subjects in the BAT1806 group, 36 (85.7%) in the EU-RoActemra group and 33 (78.6%) in the US-Actemra group. There were no serious adverse events (SAEs) or fatal AEs reported during the study. No TEAEs led to study discontinuation.

Adverse events were most commonly reported to the MedDRA System Organ Classes (SOCs) of Investigations (82 subjects), Metabolism and Nutrition Disorders (39 subjects), Blood and Lymphatic System Disorders (6 subjects) and Infections and Infestations (6 subjects). Adverse events reported in the investigations SOC were generally related to laboratory abnormalities. The most frequent preferred terms (PT) in the SOC were decreased neutrophil count, decreased white blood cell count, and an increase in ALT and AST. Fewer AEs of decreases in neutrophils and white blood cells were noted in the BAT1806 group compared to the US-Actemra and EU-RoActemra arms. Other reported adverse events were generally similar between the BAT1806 arm, US-Actemra and EU-RoActemra arms. The most common TEAEs by MedDRA System Organ Class (SOC) and Preferred Terms (PT) are shown below in Table 25.

Table 25. Study BAT1806-001-CR most frequently (≥3% in any treatment arm) reported TEAEs by SOC and PT in Healthy Subjects

	BAT1806 (N = 45) n (%)	EU-RoActemra (N = 42) n (%)	US-Actemra (N = 42) n (%)
TEAEs	31 (68.9)	36 (85.7)	33 (78.6)
Investigations	**24 (53.3)**	**29 (69.0)**	**29 (69.0)**
Neutrophil count decreased	12 (26.7)	20 (47.6)	25 (59.5)
White blood cell count decreased	7 (15.6)	12 (28.6)	16 (38.1)
Alanine aminotransferase increased	9 (20.0)	11 (26.2)	8 (19.0)
Aspartate aminotransferase increased	9 (20.0)	10 (23.8)	5 (11.9)
Blood bilirubin increased	0 (0.0)	5 (11.9)	5 (11.9)
Blood creatine phosphokinase increased	1 (2.2)	4 (9.5)	3 (7.1)
Neutrophil count increased	2 (4.4)	3 (7.1)	0 (0.0)

Lymphocyte count decreased	2 (4.4)	2 (4.8)	0
Metabolism and nutrition disorders	**12 (26.7)**	**18 (42.9)**	**9 (21.4)**
Hypertriglyceridemia	10 (22.2)	12 (28.6)	6 (14.3)
Hyperuricemia	4 (8.9)	7 (16.7)	5 (11.9)
Hyperkalemia	0 (0.0)	2 (4.8)	0 (0.0)
Blood and lymphatic system disorders	**2 (4.4)**	**4 (9.5)**	**0 (0.0)**
Leukocytosis	2 (4.4)	3 (7.1)	0 (0.0)
Infections and Infestations	**2 (4.4)**	**3 (7.1)**	**1 (2.4)**
Urinary Tract Infection	2 (4.4)	1 (2.4)	1 (2.4)
Cardiac Disorders	0 (0.0)	4 (9.5)	1 (2.4)
Arrhythmia Supraventricular	0 (0.0)	2 (4.8)	1 (2.4)
Renal and Urinary Disorders	1 (2.2)	1 (2.4)	2 (4.8)
Respiratory, Thoracic and Mediastinal	0 (0.0)	1 (2.4)	2 (4.8)

Abbreviations: SOC= MedDRA system organ class, PT= MedDRA preferred term, TEAE= Treatment Emergent Adverse Events, N= number of patients, n= number of patients in each category. SOC noted in bold text and gray shading.
Source: Adapted from Applicant's Study BAT-1806-001-CR, CSR Tables 14.3.1.2.

In Study BAT-1806-001-CR clinically relevant findings in ECGs and vital signs were to be reported as adverse events. No clinically significant post-baseline ECG abnormalities were reported in the BAT1806 arm. During the study, infusion site reactions were to be monitored and no infusion site reactions were observed.

Study BAT-1806-002-CR

In Study BAT1806-002-CR, 621 patients with RA were randomized to EU-RoActemra or BAT1806. During the study 467 patients (75.2%) had a total of 2424 TEAEs.

The proportion of patients with TEAE and SAEs were generally similar between treatment arms in both TP1 and TP2. Events leading to action taken with study drug and discontinuation of study drug were also similar between treatment arms. As noted previously, more deaths were observed in the BAT1806 arm during TP1 compared to the EU-RoActemra arm (Table 26). No deaths occurred during TP2.

Table 26. Study BAT-1806-002-CR Summary of Safety

	Treatment Period 1		Treatment Period 2		
	EU-RoActemra N=309 n (%)	BAT1806 N=312 n (%)	EU-RoActemra → EU-RoActemra N=145 n (%)	EU-RoActemra →BAT1806 N=142 n (%)	BAT1806 N=290 n (%)
Any TEAE	196 (63.4)	201 (64.4)	90 (62.1)	92 (64.8)	162 (55.9)
Any serious TEAE	13 (4.2)	11 (3.5)	4 (2.8)	5 (3.5)	8 (2.8)
Any severe TEAE	8 (2.6)	11 (3.5)	2 (1.4)	1 (0.7)	2 (0.7)

Any TEAE leading to action taken with study drug	81 (26.2)	58 (18.6)	27 (18.6)	26 (18.3)	45 (15.5)
Any TEAE leading to study drug stopped	16 (5.2)	11 (3.5)	1 (0.7)	1 (0.7)	5 (1.7)
Any TEAE leading to death	1 (0.3)	3 (1.0)	0	0	0
Any AE leading to death	1 (0.3)	4 (1.3)	0	0	0

Abbreviations: AE= Adverse event, TEAE=Treatment emergent adverse event, N= number of patients, n= number of patients in each category.
Source: Adapted from Applicant's Summary of Clinical Safety Table 6; Study BAT-1806-002-CR CSR Table 14.3.1.1, Table 14.3.1.5.

The most commonly reported AEs by SOC and PT are shown below in (Table 27). Overall, the type and frequency of adverse events were similar between treatment arms in both TP1 and TP2. The common adverse events were also consistent with the known safety profile for US-Actemra.

The most frequently reported TEAEs were reported to the SOCs of Investigations, Infections and Infestations, and Metabolism and Nutrition Disorders. The most frequent TEAEs by PT were upper respiratory tract infection, ALT increased, and leukopenia.

Table 27. Study BAT-1806-002-CR Most Common TEAEs Occurring in ≥2% of Patients by System Organ Class (SOC) and Preferred Term (PT)

	Treatment Period 1		Treatment Period 2		
	EU-RoActemra N=309 n (%)	BAT1806 N=312 n (%)	EU-RoActemra → EU-RoActemra N=145 n (%)	EU-RoActemra →BAT1806 N=142 n (%)	BAT1806 N=290 n (%)
Any TEAE	196 (63.4)	201 (64.4)	90 (62.1)	92 (64.8)	162 (55.9)
Investigations	**89 (28.8)**	**79 (25.3)**	**34 (23.4)**	**45 (31.7)**	**67 (23.1)**
ALT increased	36 (11.7)	26 (8.3)	7 (4.8)	15 (10.6)	13 (4.5)
AST increased	19 (6.1)	14 (4.5)	5 (3.4)	6 (4.2)	9 (3.1)
LDL increased	15 (4.9)	8 (2.6)	7 (4.8)	5 (3.5)	7 (2.4)
Blood bilirubin increased	3 (1.0)	9 (2.9)	4 (2.8)	5 (3.5)	13 (4.5)
WBC count decreased	7 (2.3)	4 (1.3)	4 (2.8)	6 (4.2)	12 (4.1)
Blood LDH increased	8 (2.6)	9 (2.9)	6 (4.1)	4 (2.8)	8 (2.8)
Transaminases increased	5 (1.6)	5 (1.6)	3 (2.1)	3 (2.1)	6 (2.1)
GGT increased	2 (0.6)	6 (1.9)	1 (0.7)	3 (2.1)	6 (2.1)
BP increased	7 (2.3)	4 (1.3)	2 (1.4)	1 (0.7)	2 (0.7)
Blood cholesterol increased	4 (1.3)	4 (1.3)	2 (1.4)	4 (2.8)	4 (1.4)
Neutrophil count decreased	6 (1.9)	2 (0.6)	3 (2.1)	0	5 (1.7)
Infections and infestations	**69 (22.3)**	**66 (21.2)**	**41 (28.3)**	**32 (22.5)**	**59 (20.3)**
Upper respiratory tract infection	32 (10.4)	29 (9.3)	15 (10.3)	6 (4.2)	20 (6.9)
Nasopharyngitis	6 (1.9)	10 (3.2)	2 (1.4)	7 (4.9)	7 (2.4)

Urinary tract infection	4 (1.3)	6 (1.9)	7 (4.8)	6 (4.2)	7 (2.4)
Bronchitis	4 (1.3)	4 (1.3)	3 (2.1)	2 (1.4)	4 (1.4)
Metabolism and nutrition disorders	**47 (15.2)**	**53 (17.0)**	**19 (13.1)**	**21 (14.8)**	**44 (15.2)**
Hyperlipidemia	18 (5.8)	22 (7.1)	6 (4.1)	7 (4.9)	21 (7.2)
Hypercholesterolemia	16 (5.2)	10 (3.2)	5 (3.4)	1 (0.7)	8 (2.8)
Hypertriglyceridemia	7 (2.3)	11 (3.5)	6 (4.1)	3 (2.1)	12 (4.1)
Hypokalemia	5 (1.6)	9 (2.9)	3 (2.1)	5 (3.5)	6 (2.1)
Hyperuricemia	5 (1.6)	2 (0.6)	6 (4.1)	2 (1.4)	5 (1.7)
Blood and lymphatic system disorders	**43 (13.9)**	**33 (10.6)**	**25 (17.2)**	**22 (15.5)**	**35 (12.1)**
Leukopenia	28 (9.1)	12 (3.8)	15 (10.3)	10 (7.0)	15 (5.2)
Neutropenia	23 (7.4)	16 (5.1)	7 (4.8)	9 (6.3)	12 (4.1)
Anaemia	2 (0.6)	3 (1.0)	4 (2.8)	8 (5.6)	5 (1.7)
Thrombocytopenia	6 (1.9)	6 (1.9)	3 (2.1)	5 (3.5)	7 (2.4)
Lymphopenia	0	5 (1.6)	2 (1.4)	0	9 (3.1)
Gastrointestinal disorders	**28 (9.1)**	**35 (11.2)**	**15 (10.3)**	**10 (7.0)**	**25 (8.6)**
Mouth ulceration	8 (2.6)	4 (1.3)	3 (2.1)	3 (2.1)	6 (2.1)
Abdominal pain upper	3 (1.0)	8 (2.6)	3 (2.1)	1 (0.7)	1 (0.3)
Abdominal discomfort	1 (0.3)	5 (1.6)	1 (0.7)	1 (0.7)	6 (2.1)
Diarrhoea	1 (0.3)	6 (1.9)	3 (2.1)	0	5 (1.7)
Hepatobiliary disorders	**29 (9.4)**	**34 (10.9)**	**16 (11.0)**	**13 (9.2)**	**26 (9.0)**
Hepatic function abnormal	17 (5.5)	14 (4.5)	9 (6.2)	10 (7.0)	10 (3.4)
Liver injury	5 (1.6)	13 (4.2)	3 (2.1)	2 (1.4)	14 (4.8)
Musculoskeletal and connective tissue disorders	**13 (4.2)**	**23 (7.4)**	**2 (1.4)**	**4 (2.8)**	**15 (5.2)**
Arthralgia	9 (2.9)	6 (1.9)	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	**16 (5.2)**	**19 (6.1)**	**6 (4.1)**	**5 (3.5)**	**10 (3.4)**
Nervous system disorders	**11 (3.6)**	**14 (4.5)**	**5 (3.4)**	**7 (4.9)**	**13 (4.5)**
Headache	3 (1.0)	2 (0.6)	2 (1.4)	4 (2.8)	5 (1.7)
Dizziness	3 (1.0)	4 (1.3)	3 (2.1)	2 (1.4)	3 (1.0)
Skin and subcutaneous disorders	**12 (3.9)**	**12 (3.8)**	**2 (1.4)**	**9 (6.3)**	**11 (3.8)**
Rash	2 (0.6)	2 (0.6)	0	4 (2.8)	6 (2.1)
General disorders and administration site conditions	**8 (2.6)**	**21 (6.7)**	**3 (2.1)**	**2 (1.4)**	**6 (2.1)**
Injury, poisoning and Procedural complications	**5 (1.6)**	**9 (2.9)**	**7 (4.8)**	**4 (2.8)**	**6 (2.1)**
Cardiac disorders	**5 (1.6)**	**10 (3.2)**	**4 (2.8)**	**3 (2.1)**	**6 (2.1)**
Vascular disorders	**13 (4.2)**	**8 (2.6)**	**1 (0.7)**	**6 (4.2)**	**4 (1.4)**
Hypertension	8 (2.6)	4 (1.3)	0	5 (3.5)	3 (1.0)

Abbreviations: TEAE=treatment emergent adverse, SOC= MedDRA System Organ Class (gray), PT= MedDRA Preferred Term, n= number of subjects with event, N= total number of subjects, E= number of events

Source: Adapted from Applicant's Summary of Clinical Safety Table 7; Clinical Study Report BAT-1806-002-CR Table 14.3.1.2.

The type and frequency of adverse events were generally similar between treatment arms although some numerical differences were observed. The proportion of patients with events in the General Disorder and Administration SOC were higher in the BAT1806 arm. More events of pyrexia were observed in patients in the BAT1806 arm

during TP1 with 6 patients (1.9%) having a reported event of pyrexia in TP1 and none in the EU-RoActemra arm. No other patterns of AEs were observed in the General Disorders and Administration SOC.

Some numerical differences were identified between treatment arms within the SOCs of Investigations, Metabolism and nutritional disorders, and Blood and lymphatic disorders related to reported PTs for laboratory investigations. Review of the clinical laboratories demonstrated similar change in mean and median parameters. Review of clinical hematology laboratories showed similar decreases in mean and median leukocytes and other hematologic parameters between treatment arms throughout the study. Based on laboratory shifts in TP1, 24.6% of patients in the EU-RoActemra arm had a shift to low leukocytes compared to 18.4% in the BAT1806 arm. Through TP2 a similar number of patients had shifts to low leukocyte values with 25.5%, 22.7%, and 24.8% having a shift to low levels in TP2 for EU-RoActemra, EU-RoActemra→BAT1806 and BAT1806 arms respectively. Shifts from normal to low neutrophils during TP1 occurred in 30.4% of patients in the EU-RoActemra arm compared to 23.5% in the BAT1806 arm. Shifts in LFTs were similar between treatment arms. Laboratory review of mean and median serum potassium was also similar between treatment arms during the study. Mean and median cholesterol and triglyceride levels were also similar between dose arms.

The overall severity of treatment emergent adverse events (TEAEs) was similar between treatment arms in both study periods. The majority of reported adverse events were mild. During TP1, 77 patients (24.9%) in the EU-RoActemra arm had a moderate TEAE and 8 patients (2.5%) had a severe TEAE. In the BAT1806 arm 67 patients (21.5%) had a moderate TEAE and 11 patients (3.5%) had a severe TEAE. During TP2 moderate adverse events were reported in 23.4%, 21.8% and 16.9% of patients in the EU-RoActemra→ EU-RoActemra arm, EU-RoActemra→BAT1806 and BAT1806 arms respectively. The frequencies of severe adverse events in TP2 were also similar between arms and reported in 1.4%, 0.7%, and 0.7% of patients in the EU-RoActemra→ EU-RoActemra arm, EU-RoActemra→BAT1806 and BAT1806 arms respectively. Throughout the full duration of the study 4.2% of patients in the EU-RoActemra→ EU-RoActemra and BAT1806 arms had a severe TEAE and 2.8% of patients who transitioned from EU-RoActemra→BAT1806 had a severe TEAE.

Severe AEs reported in the BAT1806 arm included events of ruptured cerebral aneurysm, ovarian cancer, osteoporosis, joint swelling (3 severe events), hyperlipidemia, pneumonia, hypertension, acute myocardial infarction, death (unknown cause), ALT elevation and events of cardiopulmonary failure, pneumonia, and atrial fibrillation and myocardial infarction which occurred in one patient.

Severe AEs reported in patients in the EU-RoActemra arm during the duration of the study were hypertension, hyperlipidemia, and ALT, and AST increases in one patient, and conjunctivitis and blepharitis in one patient. Other severe AEs reported in during TP1 included diverticular perforation and peritonitis (one patient), localized infection in

neck, mediastinitis, septic shock, and cerebral hemorrhage (in one patient), joint swelling, memory impairment, neutropenia, and tooth abscess.

In patients who transitioned to BAT1806 (EU-RoActemra → BAT1806 arm) during TP2, a severe event of lumbar spinal stenosis was reported.

Serious Adverse Events

BAT-1806-001-CR

No SAEs were reported in Study BAT-1806-001-CR.

BAT-1806-002-CR

In Study BAT-1806-002-CR a similar proportion of patients in each study arm had SAEs. A total of 41 patients (6.6%) had 51 treatment emergent SAEs. Throughout the course of the study 12 patients (7.2%) in the EU-RoActemra→ EU-RoActemra arm, 10 patients (7.0%) from the EU-RoActemra→BAT1806 arm and 19 patients (6.1%) from the BAT1806 arm had SAEs. SAEs were most commonly reported in the Infections and Infestations SOC, and were generally balanced by treatment arm (Table 28and Table 29).

SAEs (by PT) that were reported in more than one patient included events of pneumonia (2 [0.3%] patients in TP1, 2 [0.3%] patients in TP2, total of 4 [0.6%] patients throughout the study), lumbar spinal stenosis (2 [0.3%] patients in TP2) and spontaneous abortion (2 [0.3%] patients in TP1, 0 patients in TP2). No other preferred terms were reported in more than one patient.

During TP1 a similar number of patients had SAEs in the EU-RoActemra arm (13 patients [4.2%]) and BAT1806 arm (11 patients [3.5%]). During TP2 a similar number of SAEs were also observed between treatment arms (for TP 1 and Table 29 for TP2). The most common SAEs in both treatment periods were related to Infection and Infestations. During TP1 five (5) patients in the EU-RoActemra arm (1.6%) and 3 patients (1%) in the BAT1806 arm had SAE of infections. Throughout the entire study 5 patients (3%) in the EU-RoActemra→ EU-RoActemra arm, 4 patients (2.8%) in the EU-RoActemra→BAT1806 arm, and 5 patients (1.6%) in the BAT1806 arm had an SAE in the SOC of Infections and Infestations.

The most common infection was pneumonia which occurred in 4 patients. Other serious infections were reported only in single patients. In the BAT1806 arm during TP1, serious infections also included an event of infective arthritis and a pancreatic abscess. In the EU-RoActemra arm during TP1, eight (8) serious infections were reported in 5 patients. Other than pneumonia the serious infections in the EU-RoActemra arm included bronchitis, localized infection and mediastinitis, peritonitis, septic shock, and tooth abscess. The serious events of localized infection, mediastinitis, septic shock, and

cerebral hemorrhage occurred in one patient. During TP2, two patients in each treatment arm had serious events of infections. Serious events of infection in the EU-RoActemra arm included events of pneumonia and appendicitis, in the EU-RoActemra →BAT1806 arm there were events of COVID-19 and laryngitis, and in the BAT1806 arm there were events of pneumonia and salpingo-oophoritis (Table 28 and Table 29).

Table 28. Study BAT-1806-002-CR, Serious Adverse Events by System Organ Class (SOC) and Preferred Term (PT) for Treatment Period 1

	Treatment Period 1	
	EU-RoActemra N=309 n (%) E	BAT1806 N=312 n (%) E
Any Serious TEAE	13 (4.2) 19	11 (3.5) 13
Infections and Infestation	5 (1.6) 8	3 (1.0) 3
Pneumonia	1 (0.3) 1	1 (0.3) 1
Arthritis infective	0	1 (0.3) 1
Bronchitis	1 (0.3) 1	0
Localized infection	1 (0.3) 1	0
Mediastinitis	1 (0.3) 1	0
Pancreatic Abscess	0	1 (0.3) 1
Peritonitis	1 (0.3) 1	0
Septic Shock	1 (0.3) 2	0
Tooth abscess	1 (0.3) 1	0
Injury, Poisoning and procedural complications	1 (0.3) 1	1 (0.3) 1
Joint dislocation	0	1 (0.3) 1
Spinal cord injury cervical	1 (0.3) 1	0
Nervous System Disorders	2 (0.6) 2	2 (0.6) 2
Cerebral hemorrhage	1 (0.3) 1	0
Lacunar infarction	0	1 (0.3) 1
Memory impairment	1 (0.3) 1	0
Ruptured cerebral aneurysm	0	1 (0.3) 1
Musculoskeletal and connective tissue disorders	0	1 (0.3) 1
Osteoporosis	0	1 (0.3) 1
Cardiac Disorders	0	1 (0.3) 1
Coronary artery disease	0	1 (0.3) 1
Reproductive system	3 (1.0) 3	0
Adenomyosis	1 (0.3) 1	0
Uterine hemorrhage	1 (0.3) 1	0
Uterine polyp	1 (0.3) 1	0
Neoplasm benign, malignant and unspecified	0	1 (0.3) 1
Ovarian cancer	0	1 (0.3) 1
Pregnancy, puerperium and perinatal conditions	2 (0.6) 2	0
Abortion spontaneous	2 (0.6) 2	0
Gastrointestinal Disorders	1 (0.3) 1	0
Diverticular perforation	2 (0.6) 2	0
General disorders and administration site conditions	0	1 (0.3) 1
Death	0	1 (0.3) 1
Hepatobiliary Disorders	0	1 (0.3) 2

Cholangitis acute	0	1 (0.3) 1
Cholecystitis acute	0	1 (0.3) 1
Immune system disorders	1 (0.3) 1	0
Drug hypersensitivity	1 (0.3) 1	0
Respiratory, thoracic and mediastinal disorders	1 (0.3) 1	0
Respiratory failure	1 (0.3) 1	0
Vascular disorders	0	1 (0.3)
Thrombophlebitis	0	1 (0.3) 1

Abbreviations: TEAE= Treatment-emergent adverse events, n= number of subjects with event, N= total number of subjects, E= number of events, SOC= MedDRA System Organ Class, PT= Preferred Term.
Source: Adapted from Applicant's Clinical study report BAT-1806-002-CR Table 14.3.1.3.

Table 29. BAT-1806-002-CR, Serious Adverse Events by System Organ Class (SOC) and Preferred Term (PT) for Treatment Period 2

	Treatment Period 2		
	EU-RoActemra → EU-RoActemra N=145 n (%) E	EU-RoActemra →BAT1806 N=142 n (%) E	BAT1806 N=290 n (%) E
Any Serious TEAE	4 (2.8) 5	5 (3.5) 5	8 (2.8) 9
Infections and Infestation	2 (1.4) 2	2 (1.4) 2	2 (0.7) 2
pneumonia	1 (0.7) 1	0	1 (0.3) 1
Appendicitis	1 (0.7) 1	0	0
COVID-19	0	1 (0.7) 1	0
Laryngitis	0	1 (0.7) 1	0
Salpingo-oophoritis	0	0	1 (0.3) 1
Injury, Poisoning and procedural complications	3 (2.1) 3	0	1 (0.3) 1
Contusion	1 (0.7) 1	0	0
Joint injury	1 (0.7) 1	0	0
Patella fracture	1 (0.7) 1	0	0
Rib fracture	0	0	1 (0.3) 1
Nervous System Disorders	0	1 (0.7) 1	1 (0.3) 1
Syncope	0	1 (0.7) 1	0
Transient ischemic attack	0	0	1 (0.3) 1
Musculoskeletal and connective tissue disorders	0	1 (0.7) 1	2 (0.7) 3
Lumbar spinal stenosis	0	1 (0.7) 1	1 (0.3) 1
Pathological fracture	0	0	1 (0.3) 1
Spondylolisthesis	0	0	1 (0.3) 1
Cardiac Disorders	0	0	2 (0.7) 2
Acute Myocardial infarction	0	0	1 (0.3) 1
Myocardial ischemia	0	0	1 (0.3) 1
Neoplasm benign, malignant and unspecified	0	1 (0.7) 1	0
Renal hamartoma	0	1 (0.7) 1	0

Abbreviations: SOC= MedDRA System Organ Class, PT= Preferred Term, n= number subjects with events, N= total number of subjects, for treatment Period 2 includes only patients who received study drug in TP2, E= number of events, TEAE= Treatment-emergent adverse events.

Source: Adapted from Applicant's Clinical study report BAT-1806-002-CR Table 14.3.1.3.

More serious cardiac disorders were observed in the BAT1806 arm during TP1 and TP2. Serious cardiac events were uncommon but included events in 3 patients in the BAT1806 arm and none in the EU-RoActemra arm. The 3 events in the BAT1806 arm were coronary artery disease, acute myocardial infarction, and myocardial ischemia.

In the BAT1806 arm one event of ovarian carcinoma was seen in TP1 and in the EU-RoActemra →BAT1806 arm a serious event of renal hamartoma was reported in TP2. In the hepatobiliary SOC a serious adverse event of acute cholecystitis and cholangitis occurred in one patient in BAT1806 during TP1. A serious event of thrombophlebitis was also reported in the vascular disorder SOC during TP1 in the BAT1806 arm. Serious events in the Musculoskeletal and connective tissue disorders SOC included an event of lumbar spinal stenosis in the EU-RoActemra→BAT1806 arm during TP2. In the BAT1806 arm an event of osteoporosis was reported during TP1 and serious events of pathological fracture and lumbar spinal stenosis and spondylolisthesis (both in the same patient) was reported during TP2.

Although small numerical differences were observed between the serious events between study arms, no distinct pattern of events was identified. No increase in serious adverse events were observed following the single transition from EU-RoActemra to BAT1806 in TP2. The frequency and types of serious adverse events were generally similar and consistent with the serious adverse events for US-Actemra and described in the USPI.

Dropouts and/or Discontinuations

BAT-1806-001-CR

In Study BAT-1806-001-CR no subjects discontinued from study treatment due to an AE.

BAT-1806-002-CR

In Study BAT-1806-002-CR the protocol defined rules for dosage adjustment or discontinuation related to laboratory abnormalities. The dosage could be reduced to 4 mg/kg body weight, interrupted or permanently discontinued for the following laboratory findings:

- Liver enzyme (ALT or AST) increased above baseline and > 1 to 3 × ULN:
  - Liver enzymes were to be assessed before the next scheduled administration of study treatment. In case of confirmed persistent elevation of liver enzymes above baseline and > 1 × ULN, the dose was to be reduced to 4 mg/kg or the next dose of study treatment was to be withheld until ALT or AST had normalized or recovered to baseline values. Study

treatment was to be restarted at 4 mg/kg or 8 mg/kg dose as clinically appropriate.

- Liver enzyme ALT or AST) increased above baseline to > 3 × ULN to ≤ 5 × ULN:
  - Liver enzymes were to be assessed before the next scheduled administration of study treatment. In case of confirmed persistent elevation of liver enzymes > 3 × ULN before the next dose, the next dose of study treatment was to be withheld until liver enzymes ≤ 3 × ULN and the recommendations above for liver enzymes ≤ 3 × ULN were to be followed. For 2 consecutive scheduled visits with dose interruption because of ALT and/or AST > 3 × ULN, study treatment was to be permanently discontinued.
- Liver enzyme (ALT or AST) increased > 5 × ULN:
  - Study treatment was to be permanently discontinued
- Low ANC:
  - If ANC decreased to 500/μL to 1000/μL, study treatment was to be interrupted until ANC recovered to > 1000/μL, and then treatment was to be restarted at 4 mg/kg dose and increased to 8 mg/kg as clinically appropriate.
  - If ANC < 500/μL, study treatment was to be permanently discontinued
- Low platelet count:
  - If platelets count decreased to 50,000 to 100,000/μL, study treatment was to be interrupted until platelets count recovered to > 100,000/μL, and then treatment was to be restarted at 4 mg/kg dose and increased to 8 mg/kg as clinically appropriate.
  - If platelets count < 50,000/μL, study treatment was to be permanently discontinued.

In Study BAT-1806-002, 34 patients (5.5%) had adverse events (46 total events) leading to discontinuation of the study drug. The proportion of patients with TEAEs leading to discontinuation of study drug was similar between treatment arms. In TP1, 16 (5.2%) patients in the EU-RoActemra arm and 11 patients (3.5%) in the BAT1806 arm had TEAEs leading to study drug discontinuation. Adverse events leading to study drug discontinuation during TP1 and TP2 are shown below in Table 30. Some patients had more than one AE leading to treatment discontinuation. The majority of the TEAE leading to study drug discontinuation occurred during TP1.

During TP2 one patient (0.7%) in the EU-RoActemra→ EU-RoActemra arm had an event of pneumonia, and one patient (0.7%) in the EU-RoActemra→BAT1806 arm had a TEAE of lumbar spinal stenosis leading to study drug discontinuation. In the BAT1806 arm during TP2, 5 patients (1.7%) had TEAEs (spondylolisthesis and lumbar spinal stenosis [both events in one patient], thrombocytopenia, neutrophil count decreased, ALT increase, and acute myocardial infarction) leading to study drug discontinuation.

Adverse events that most commonly led to discontinuation of treatment were within the SOCs of Infections and Infestations (arthritis infective, localized infection, mediastinitis,

pancreatic abscess, peritonitis, pneumonia, septic shock and streptococcal infection), Investigations (ALT, AST, hepatic function abnormal, hepatic enzymes increased, neutrophil and platelet counts decreased) and Musculoskeletal and Connective Tissue Disorders (rheumatoid arthritis, spondylolisthesis, and osteoporosis).

Table 30. Treatment Emergent Adverse Events Leading to Study Drug Discontinuation During TP1 and TP2

	Actual Sequence of Treatments		
Adverse Event Preferred Term	**BAT1806**	**EU-RoActemra**	**EU-RoActemra -> BAT1806**
Abortion spontaneous	0	2	0
Acute myocardial infarction	1	0	0
Alanine aminotransferase increased	1	1	0
Arthritis infective	1	0	0
Aspartate aminotransferase increased	0	1	0
Bone neoplasm	0	0	1
Cerebral haemorrhage	0	1	0
Diverticular perforation	0	1	0
Drug hypersensitivity	0	1	0
Face oedema	0	1	0
Hepatic enzyme increased	2	0	0
Hepatic function abnormal	1	1	0
Hepatic mass	1	0	0
Hypersensitivity	0	1	0
Hypertension	0	1	0
Liver injury	1	1	0
Localised infection	0	1	0
Lumbar spinal stenosis	1	0	1
Lymphadenopathy	0	0	1
Mediastinitis	0	1	0
Memory impairment	0	2	0
Mouth ulceration	1	0	0
Neutrophil count decreased	1	0	0
Osteoporosis	2	0	0
Ovarian cancer stage III	1	0	0
Pancreatic abscess	1	0	0
Peritonitis	0	1	0
Platelet count decreased	1	0	0
Pneumonia	0	2	0
Rash	0	1	0
Rheumatoid arthritis	1	1	0
Septic shock	0	2	0
Spondylolisthesis	1	0	0
Streptococcal infection	0	1	0
Thrombocytopenia	1	0	0

Abbreviations: TP1= treatment period 1, TP2= treatment period 2
Source: Reviewer's Table, JMP analysis

One hundred ninety-six (196) patients (31.6%) had TEAEs (363 events) leading to any action taken with study drug. The proportion of RA patients who had a TEAE leading to action taken with study drug was higher in EU-RoActemra arm in TP1 (26.2%) compared to the BAT1806 arm (18.6%). Action taken with study drug due to TEAE were similar between treatment arms during TP2 (TP2: EU-RoActemra→EU-RoActemra 18.6%, EU-RoActemra→BAT1806 18.3%, BAT1806 15.5%). The most frequent action taken was dose reduction, followed by temporary interruptions. The most common adverse events leading to dose reduction were similar between both the EU-RoActemra and BAT1806 arms and were most frequently within the SOCs of Investigations followed by events in the Hepatobiliary SOC. The most common events leading to temporary interruption were within the SOC of Infections (PTs: upper respiratory tract infection, bronchitis, pneumonia), Investigations (PTs: ALT increased, AST increased) and Blood and lymphatic disorders (PTs: neutropenia, thrombocytopenia) and were generally similar between to the study arms.

The events leading to study drug discontinuation, or other action taken with study drug were similar between treatment arms during TP1 and remained similar following the transition of patients from EU-RoActemra to BAT1806 during TP2.

Adverse Events of Special Interest (AESI)

Although no adverse events of special interest (AESIs) were specified in the study protocols, AEs associated with the known profile for US-Actemra were reviewed and are described in further detail below.

Infections
US-Actemra is an immunosuppressant with a boxed warning for increased risk of serious infections including fatal infections. The most common serious infections for US-Actemra include pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial arthritis[6]. Opportunistic infections have also been reported. US-Actemra is not to be administered in patient with active infections.

Study exclusions for BAT1806-002-CR included evidence of lung infection, or abnormalities suggestive of active tuberculosis (TB) on chest radiography performed within 12 weeks prior to the screening visit or during the screening period. Patients were excluded if they had a history of active TB within 3 years of screening. The study also had exclusions for any recurrent bacterial, fungal, or viral infection that based on the investigator´s clinical assessment would make the patient unsuitable for the study, including recurrent/disseminated herpes zoster. Patients with a history of invasive infection or active infection at the time of screening were excluded.

[6] Actemra USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125276s134lbl.pdf

In both the BAT-1806-001-CR and BAT-1806-002-CR clinical studies adverse events of infections, serious, and opportunistic infections were evaluated. The infections occurred in a similar proportion of patients and with similar severity across the study arms.

One case of TB was reported in a patient in the EU-RoActemra→ EU-RoActemra arm in Study BAT-1806-002-CR. No cases of TB infection were reported in patients receiving BAT1806 during the clinical studies.

Infections observed with BAT1806 in the clinical studies were consistent with the current labeling for US-Actemra.

Viral Reactivation
Viral reactivation has also been reported with immunosuppressive biologic therapies. Patients with positive HIV, hepatitis B, or hepatitis C serological results were excluded from Study BAT-1806-002-CR.

In Study BAT-1806-002-CR a total of 5 patients (0.8%) had events of herpes zoster. A similar frequency of the event was observed between the treatment arms. Throughout the study two patients (1.2%) in the EU-RoActemra arm, one patient (0.7%) in the EU-RoActemra →BAT1806 arm, and two patients (0.6%) in the BAT1806 arm had events of herpes zoster infection. No serious events of herpes zoster were reported.

Hypersensitivity and Infusion Related Reactions
Hypersensitivity reactions including anaphylaxis have been reported in association with US-Actemra and have been observed in clinical studies and in the postmarketing setting. Hypersensitivity reactions leading to treatment discontinuations described in Actemra USPI also include events of generalized erythema, rash, and urticaria. Hypersensitivity events were evaluated in the clinical studies for BAT1806.

In Study BAT-1806-002, RA patients who experienced an anaphylactic or other serious hypersensitivity or infusion related reaction were to be withdrawn from the study. Following completion of the infusion, patients were to remain at the study site for at least one hour for monitoring of any potential hypersensitivity or infusion-related reactions.

One patient in the EU-RoActemra→ EU-RoActemra arm had a serious hypersensitivity reaction that led to study withdrawal. No patients had hypersensitivity or infusion related reactions leading to withdrawal in the BAT1806 arm. Within the SOC of Immune System Disorders, six (6) patients had AEs related to hypersensitivity events. This included three (3) patients in BAT1806 arm, two (2) patients in EU-RoActemra→BAT1806 arm, who both had events in TP1 while receiving EU-RoActemra, and one (1) patient in the EU-RoActemra→ EU-RoActemra arm. In the BAT1806 arm the reported events were allergy in two patients of mild severity and one patient with a report of anaphylaxis of moderate severity. The event of anaphylaxis was not considered serious. In the three (3) patients with events who were receiving EU-RoActemra, one event was drug

hypersensitivity which was considered serious and of moderate severity leading to study withdrawal, described earlier. The two other patients had reports of allergic reaction (1 mild, 1 moderate). A review of the Standardized MedDRA Queries (SMQ) (narrow) for hypersensitivity, identified these six patients described. A review of the Hypersensitivity SMQ (broad) terms showed a similar number of events in patients treated with EU-RoActemra or BAT1806 with 24 patients (7.8%) receiving EU-RoActemra with an event in the broad search query and 22 patients (7.1%) in the BAT1806 arm. The most common events reported in the SMQ were related to rashes. Events of urticaria were reported in 2 patients treated with EU-RoActemra and 1 patient receiving BAT1806.

Gastrointestinal Perforations
The USPI for Actemra includes a risk for gastrointestinal perforations that have been reported primarily as a complication of diverticulitis in patients treated with Actemra. In Study BAT-1806-002 patients with a history of or current diverticulitis, or chronic ulcerative lower GI tract disease that may predispose to perforation were excluded.

One patient in the EU-RoActemra arm during TP1 had a serious event of diverticular perforation and peritonitis. No events of gastrointestinal perforation were reported in the BAT1806 arm.

Malignancy
Immunosuppression may result in an increased risk for malignancies. Patients with a history of malignancy were excluded from Study BAT-1806-002-CR.

One event of malignancy (ovarian carcinoma) was reported in the BAT1806 arm. The patient had received 3 doses of BAT1806 prior to her diagnosis. No events of malignancy were reported in the EU-RoActemra arm. Given the relatively short duration of the clinical trials and long-latency for events of malignancy there is limited information available regarding malignancies from the clinical program for BAT1806.

Demyelinating Disorders
Patients with a history of demyelinating diseases or neurologic symptoms of demyelinating disease were excluded from Study BAT-1806-002-CR. There were no reports of new onset of demyelinating disorders in the clinical studies.

Laboratory Parameters
Abnormalities in laboratory parameters observed with US-Actemra include events of neutropenia, thrombocytopenia, elevated liver enzymes (transaminase elevations) and lipid abnormalities (including elevation in total cholesterol, triglycerides, LDL cholesterol and/or HDL cholesterol).

In both clinical studies patients with abnormalities in renal or hepatic parameters were excluded.

Clinical laboratory evaluations included hematology, clinical chemistry and urinalysis.

The most frequently reported laboratory abnormalities were similar between treatment arms in the BAT-1806-001-CR and BAT-1806-002-CR clinical studies (Table 25, Table 27). Review of clinical laboratory parameters (mean, median, shifts) demonstrated similar findings in study arms between EU-RoActemra and BAT1806 in Study BAT-1806-002-CR during the course of the study. The laboratory changes were consistent with the known laboratory changes described in the Actemra USPI.

Vital Signs and ECGs
No notable differences were observed between treatment arms in vital sign changes including systolic and diastolic blood pressure, heart rate, or body temperature. Clinically significant ECG abnormalities were to be reported as adverse events. Clinically significant abnormal ECGs were reported infrequently and occurred at a similar frequency across treatment arms during the study.

6.3.3. Additional Safety Evaluations

Not Applicable.

6.4. Clinical Conclusions on Immunogenicity

Immunogenicity for BAT1806 was evaluated in both Study BAT-1806-001-CR conducted in a healthy volunteer population and Study BAT-1806-002-CR conducted in RA patient population.

Study BAT1806-001-CR
In this study there were 45 subjects from the BAT1806 arm, 42 subjects from the EU-RoActemra arm and 42 subjects from the US-Actemra arm with evaluable ADA following the single intravenous (IV) infusion of 4 mg/kg body weight. In this study two subjects in the BAT1806 treatment group had positive ADA results prior to dosing. One also had positive NAb.

Immunogenicity results for Study BAT1806-001-CR are described in Section 5.4.1. The majority of ADA positive subjects were also NAb positive.

A higher incidence of ADA was found in the healthy volunteer population compared to the RA population (BAT-1806-002-CR) which likely reflects the study population which included healthy volunteers who were not receiving concomitant MTX.

Evaluation of safety based on ADA subgroups was conducted and no increases in overall treatment emergent adverse events were observed in the ADA positive patients compared to ADA negative patients. One NAb positive patient in the BAT1806 arm had an event within the hypersensitivity SMQ (rash). No other patients had events within the hypersensitivity SMQ. No significant differences in immunogenicity between treatment groups was observed in this study.

Study BAT1806-002-CR
In this study RA patients received a starting dose of 8 mg/kg dosed every 4 weeks for up to 48 weeks. This study included a single transition at Week 24 for a subgroup of patients originally randomized to EU-RoActemra. In the clinical trial patients were receiving MTX for ≥12 weeks prior to randomization, and on a stable dose ranging between 10 to 25 mg/week. Patients were required to continue their stable MTX dose and route of administration throughout the study. ADA data was available from 312 patients on BAT1806 and 167 patients on EU-RoActemra in both treatment periods (48 weeks) and from 142 patients treated with EU-RoActemra for 24 weeks followed by BAT1806 for 24 weeks. Immunogenicity and PK sampling was conducted at baseline, Weeks 4,12, 24, 28, 36,48, and 52. Immunogenicity and PK results from Study BAT1806-002-CR are described in Section 5.4.2.

ADA incidence in Study BAT1806-002-CR was numerically higher in the BAT1806 arm compared with EU-RoActemra arm through TP1. The majority of ADA positive subjects were also positive in the NAb assay. A single transition occurred for EU-RoActemra to BAT1806 at Week 24. Results for patients who transitioned showed a similar incidence of ADA and NAb to patients who remained on EU-RoActemra from Weeks 24-Week 52.

Review of efficacy data for patients who were ADA positive compared to ADA negative demonstrated similar treatment responses for both subgroups for the ACR20, ACR50 and ACR70 responses. Similar treatment responses were also observed for the subgroups on DAS28-ESR.

Review of safety by ADA subgroups did not demonstrate an increase in TEAEs in the ADA positive subgroup compared to the ADA negative subgroup. Evaluation by events within the SMQs of Hypersensitivity did not demonstrate an increase in events associated with ADAs in any of the study arms. The Applicant identified patients with at least one TEAE in the SMQ for hypersensitivity during the treatment periods. The majority of the events in the Hypersensitivity SMQ occurred in ADA negative patients. One event of anaphylactic reaction was reported in a patient in the BAT1806 arm. This patient was negative for ADA. One AE of infusion related reaction was also reported in an ADA negative patient in the EU-RoActemra→BAT1806 arm. In the BAT1806 arm, two patients who were ADA positive (2/91, 2.2%) and 17 patients who were ADA negative (17/219, 7.8%) had events within the Hypersensitivity SMQ. Hypersensitivity events in ADA positive patients in the BAT1806 arm included an event of urticaria in one patient and a rash in one patient. In the EU-RoActemra→BAT1806 arm no ADA positive patients (n=31) had events within the Hypersensitivity SMQ. No meaningful differences in immunogenicity between treatment groups was identified.

The immunogenicity evaluation included assessment of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) in healthy subjects (from single dose PK study) and in patients with RA (multiple doses up to Week 48). Assessment of the impact of ADA on PK, efficacy and safety were conducted. A higher proportion of subjects in the BAT1806

arms developed ADAs compared to those receiving EU-RoActemra or US-Actemra. PK parameters and efficacy were generally comparable across the treatment arms regardless of the ADA status (see discussion in clinical pharmacology sections 5.4.1 and 5.4.2). Safety was also comparable across the treatment arms and regardless of the ADA subgroup. Although some numerical differences in development of ADA were identified with most ADA positive subjects also developing NAb, no impact was observed on PK, efficacy or safety of BAT1806 compared to EU-RoActemra/US-Actemra arms. The numeric differences in ADA observed do not preclude an assessment of biosimilarity between BAT1806 and US-Actemra. See Clinical pharmacology section 5.4.1 and 5.4.2 for further discussion.

Authors:

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6.5. Extrapolation

The Applicant submitted data and information in support of a demonstration that BAT1806 is highly similar to US-Actemra notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between BAT1806 and US-Actemra in terms of safety, purity and potency.

Given the scientific bridge was established (based on the three-way analytical and PK comparisons between BAT1806/BIIB800, US-Actemra, and EU-RoActemra) to justify the relevance of data generated with EU-RoActemra as the comparator, the collective evidence from the comparative clinical study supports a demonstration of no clinically meaningful differences between BAT1806/BIIB800 and US-Actemra in the studied indication (RA). In addition to the RA indication, the Applicant is also seeking licensure of BAT1806/BIIB800 for the following indication(s) for which US-Actemra has been previously approved and for which BAT1806/BIIB800 has not been directly studied:

1. Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis
2. Patients 2 years of age and older with active systemic juvenile idiopathic arthritis

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of BAT1806/BIIB800 as a biosimilar for each indication for which licensure is sought and for which US-Actemra has been previously approved.

The Applicant has also provided justification for extrapolating data and information submitted in the application to support licensure for BAT1806/BIIB800 as a biosimilar for indications for which licensure is not being sought at this time and for which US-

Actemra has been previously approved and for which BAT1806/BIIB800 has not been directly studied:

- Cytokine Release Syndrome (CRS)
- Coronavirus Disease 2019 (COVID-19)

In addition, the Applicant is not seeking licensure for BAT1806 for Giant Cell Arteritis (GCA).

This Applicant's scientific justifications were evaluated and considered adequate, as summarized below.

Therefore, the totality of the evidence provided by the Applicant supports licensure of BAT1806/BIIB800 for each of the following indications for which Biogen is seeking licensure of BAT1806/BIIB800: rheumatoid arthritis, patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis, and patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

Mechanism of Action

The Applicant provided data to support that BAT1806 has the same known and potential mechanisms of action as US-Actemra, which supports extrapolation to indications not directly studied in the BAT1806 clinical program. Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and has been shown to competitively inhibit IL-6-mediated signaling through these receptors. This MOA is common in all approved indications of US-Actemra. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. Elevated serum IL-6 levels are present in a number of inflammatory diseases including PJIA, and SJIA. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis, PJIA, and SJIA. IL-6 elevations have been observed in patients with CRS and have been described in patients with respiratory failure due to COVID-19 infections. The biological activities of BAT1806 and US-Actemra were evaluated by a comprehensive set of comparative functional and binding assays. The data provided by the Applicant showed that Fab and Fc binding and bioactivity properties and the inhibition of IL-6-dependent signaling through Janus-activated kinase-signal transducer and activator of transcription (JAK-STAT) pathways are similar to US-Actemra. The product quality reviewers concluded that the comparative analytical assessment was acceptable.

The Applicant provided adequate information to support that BAT1806 has the same known and potential mechanisms of action as US-Actemra for RA, PJIA, SJIA, CRS, and COVID-19.

Pharmacokinetics (PK)

PK similarity was demonstrated in Study BAT-1806-001-CR, conducted in healthy volunteers. The clinical pharmacology review team concluded that the data from Study BAT-1806-001-CR supports a demonstration of PK similarity of BAT1806 to US-Actemra. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between BAT1806 and US-Actemra in the indications sought for licensure. Therefore, a similar PK profile would be expected between BAT1806 and US-Actemra in patients with PJIA, and SJIA. In addition, a similar PK profile would be expected between BAT1806 and US-Actemra in patients with CRS and COVID-19, indications not currently being sought for licensure.

The Applicant provided adequate justification that a similar PK profile is expected between BAT1806 and US-Actemra for PJIA, SJIA, CRS, and COVID-19.

Immunogenicity

In the BAT1806 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (RA and healthy subjects). Although the incidence of immunogenicity was slightly higher when comparing BAT1806 and US-Actemra/EU-RoActemra arms in Study BAT1806-001-CR in healthy subjects, and in the comparative clinical study (BAT1806-002-CR) in RA patients, no clinically relevant impact was identified in PK, efficacy, or safety. Similar immunogenicity would be expected between BAT1806 and US-Actemra in patients across all the indications being sought for licensure.

The Applicant provided adequate justification that similar immunogenicity is expected for PJIA, SJIA, CRS and COVID-19.

Toxicity

The Applicant demonstrated that are no clinically meaningful differences in safety between BAT1806 and EU-RoActemra in subjects with RA and between BAT1806, US-Actemra, and EU-RoActemra following single doses in healthy subjects. Together with the demonstration of analytical and PK similarity between BAT1806, US-Actemra, and EU-RoActemra, a similar safety profile would be expected in across all indications being sought for licensure.

The Applicant provided adequate justification that a similar safety profile would be expected between BAT1806 and US-Actemra for PJIA, SJIA, CRS, and COVID-19.

Additional factors considered (if applicable)

None

Conclusions

DRTM concludes that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity and toxicity profile) for extrapolation of the data and information submitted in the application to support licensure of BAT1806/BIIB800 for each of the following indications for which the Applicant is seeking licensure of BAT1806: patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis, and patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

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7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, tocilizumab-bavi, was found to be conditionally accepted by the Agency. See DMEPA review dated June 16, 2023 for full details.

7.2. Proprietary Name

The proposed proprietary name for BAT1806/BIIB800 is conditionally approved as Tofidence. This name has been reviewed by the Division of Medication Error and Prevention (DMEPA), who concluded the name was acceptable. See DMEPA review dated December 21, 2022 for full details.

7.3. Other Labeling Recommendations

BAT1806 is proposed as a biosimilar to US-Actemra. The Applicant is seeking licensure for only the IV route of administration and for the following indications, for which US-Actemra has been previously approved: rheumatoid arthritis, polyarticular juvenile idiopathic arthritis in patients 2 years of age and older, and systemic juvenile idiopathic arthritis in patients 2 years of age and older. The Applicant is not seeking approval for any other indications for which US-Actemra has been previously approved.

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The proposed prescribing information has incorporated relevant data and information from the US-Actemra prescribing information with appropriate modifications relevant to the indications and route of administration.

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8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the Applicant.

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9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

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10. Pediatrics

The Applicant's iPSP was discussed at the PeRC meeting on August 23, 2022. PeRC agreed with the Applicant's plans to provide an assessment via extrapolation for pediatric patients 2 to less than 17 years of age with PJIA and SJIA. The pediatric study plan was agreed upon on September 15, 2022.

The Applicant has provided the pediatric assessment for PJIA ages 2 years and older, and SJIA ages 2 years and older, based on a demonstration of biosimilarity and providing an adequate scientific justification to support the extrapolation of data and information to support licensure. As the approved labeling for US-Actemra includes pediatric information for SJIA under 2 years of age, Pediatric Research Equity Act (PREA) is addressed based on the inclusion of the relevant pediatric information in the labeling for BAT1806. The labeling for US-Actemra does not include adequate pediatric information and PREA requirements were waived for PJIA under 2 years for US-Actemra. Additionally, the currently proposed presentations are adequate for pediatric dosing for the age ranges proposed.

This application was discussed at the PeRC meeting on August 1, 2023, and PeRC agreed that all pediatric populations for the proposed indications were adequately assessed as required under PREA and no pediatric studies will be required.

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11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

The CMC post-marketing commitments (PMC) are listed below:

4510-1 To implement [redacted] (b) (4) of the sterile filter during sterile filtration

Final report submission date: 03/31/2024

4510-2 To implement revised procedure with target flushing volume of ≥ [redacted] (b) (4) L for post-use filter integrity test

Final report submission date: 03/31/2024

Authors:

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12. Division Director or Designated Signatory Comments

I concur with the review and conclusions by the review team. The regulatory action is Approval.

Author:

Rachel Glaser, M.D.
Associate Director for Therapeutic Review

13. Appendices

13.1. References

US-Actemra United States Prescribing Information (USPI), last revised December, 2022. Available online at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125276s138lbl.pdf

13.2. Financial Disclosure

The Applicant has adequately disclosed potential financial interests/arrangements with clinical investigators as recommended in the FDA Guidance for Industry Financial

Disclosure by Clinical Investigators.[7] The provided financial certification and disclosure forms attest that no clinical investigators reported disclosable financial interests or arrangements that would result in a conflict of interest. Review of the documents does not raise concerns regarding the integrity of the submitted data to the current application and do not affect the review or recommendation for action.

Covered Clinical Study: (BAT-1806-002-CR and BAT-1806-001)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 257 (55 primary investigators and 200 sub-investigators in Study BAT-1806-002-CR and 2 in BAT-1806-001-CR)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

The BAT-1806-002 study included 55 primary investigators and 200 sub-investigators. The Applicant indicated that financial disclosure forms were available for 254 of the 255

[7] For further information, see Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators

investigators (55 primary investigators and 199 sub-investigators). There is 1 investigator whose financial disclosures are not available. The Applicant provided an additional FDA Form 3454 to certify that efforts were made to obtain these financial disclosures.

13.3. Nonclinical Appendices

13.3.1. Nonclinical Pharmacology

In Vitro Pharmacology

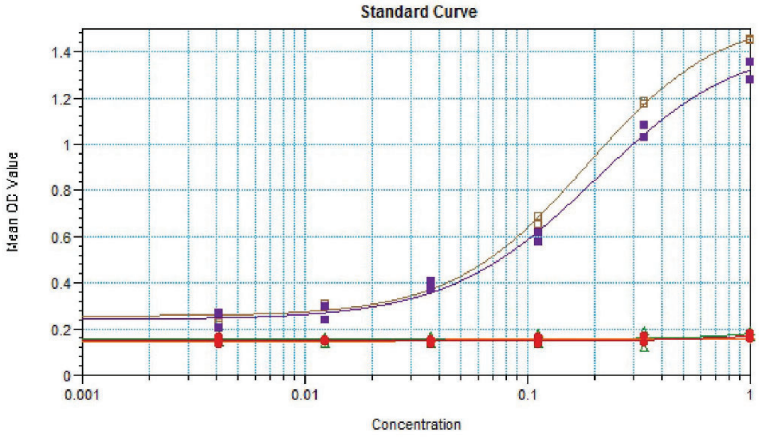
Experimental Project: Binding Specificity of Recombinant Humanized Anti-human Interleukin-6 Receptor Monoclonal Antibody Injection BAT1806 to Antigen (Study BAT1806-20160301)

Methods:
The binding specificity of recombinant humanized anti-human interleukin-6 receptor monoclonal antibody, BAT1806 or US-licensed Actemra (US-Actemra), to human IL-6R (hIL-6R), monkey IL-6R (cIL-6R), mouse IL-6R (mIL-6R , human TNFα hTNFα) and human IL-6 (hIL-6) was measured using an ELISA method. Anti-human interleukin-6 receptor monoclonal antibody used were Actemra (Roche, batch no.: B1014B02, B1015B02, B1016B01, B2029B02, B2023B01), and BAT1806 (Bio-Thera, batch no.: N20150611U, N20150701, N20150706U, N20150711U, N20150801, N20150802, N20150803U, N2015901).

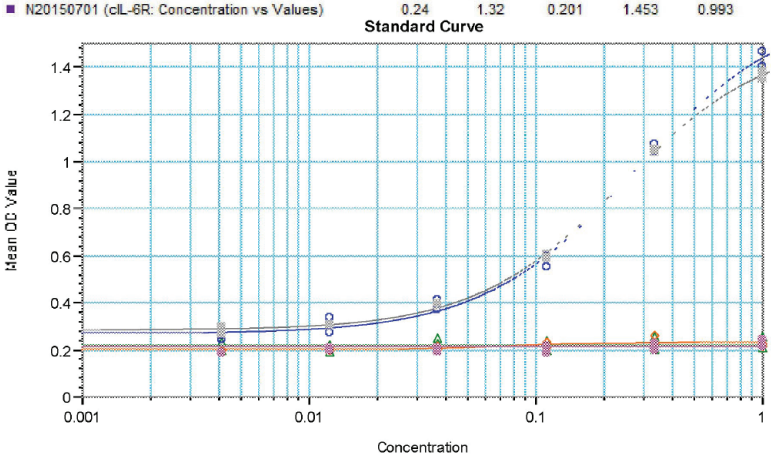
Results:
The results showed concentration-dependent binding of recombinant humanized anti-interleukin-6 receptor monoclonal antibodies, BAT1806 or US-Actemra, to hIL-6R and cIL-6R. The affinity of BAT1806 and US-Actemra to its targets were comparable. In contrast, BAT1806 or US-Actemra had no specific binding affinity to mIL-6R, hTNFα and hIL-6.

Shown below as examples were standard curves of binding data of BAT1806 (batch number: N20150701, top panel) and US-Actemra (batch no.: B1014B02, bottom panel).

Figure 10. Binding curves of BAT1806 (batch number: N20150701, top panel) and US-Actemra (batch no.: B1014B02, bottom panel) to various ligands



y = ((A - D)/(1 + (x/C)^B)) + D:	A	B	C	D	R^2
N20150701 (hIL-6R: Concentration vs Values)	0.255	1.444	0.183	1.56	0.998
N20150701 (mIL-6R: Concentration vs Values)	0.156	1.831	21.13	6.599	0.164
N20150701 (hIL-6: Concentration vs Values)	0.144	3.625	0.036	0.16	0.695
N20150701 (TNFα: Concentration vs Values)	0.148	1.782	1.187	0.198	0.275
N20150701 (cIL-6R: Concentration vs Values)	0.24	1.32	0.201	1.453	0.993



y = ((A - D)/(1 + (x/C)^B)) + D:	A	B	C	D	R^2
B1014B02 (mIL-6R: Concentration vs Values)	0.217	77.894	0.023	0.226	0.148
B1014B02 (hIL-6R: Concentration vs Values)	0.268	1.291	0.276	1.66	0.995
B1014B02 (hIL-6: Concentration vs Values)	0.201	2.327	0.074	0.233	0.561
B1014B02 (TNFα: Concentration vs Values)	0.212	243.206	0.707	0.219	0.047
B1014B02 (cIL-6R: Concentration vs Values)	0.284	1.336	0.241	1.527	0.999

Source: Excerpted from Applicant submission

In Vivo Pharmacology

Collagen Induced Arthritis in Non-human Primate and Its Application in Evaluation of a Biosimilar Compound BAT1806 (Study BAT1806-201501)

Method:
The purpose was to establish a bovine type II collagen induced arthritis (CIA) model using female cynomolgus monkeys, as well as to test the efficacy of BAT1806 in this animal model. Twenty-seven (27) cynomolgus monkeys (age: 5-6 years; body weight: 3-6 kg) were divided into 3 groups (9 animals/group): proposed drug group (BAT1806

group), positive control group (US-licensed Actemra group; also referred to as MRA group), and negative control group (NS group). The study duration was 74 days and consisted of: 1) Day 1-14: baseline collection period; 2) Day 0-Day 32: modelling period of CIA; 3) Day 33-Day 74: drug efficacy assessment period. On Day 33, the groups were IV infused with 30 mg/kg BAT1806, 30 mg/kg US-Actemra or 0.9% sodium chloride infusion solution, respectively.

Figure 11. Timeline of experimental procedures

Clinical evaluation score: weekly
ESR: week-2, week4, week1'
Biochemical tests: week-2, week2, week4, week1', week2', week3', week4'
X ray: week-2, week2, week4, week1', week4'

Baseline were collected on day -14
1st immunization of collagen was on day 0 and 2nd booster shot on day 21
BAT-1806, MRA and saline were administrated on day 33

Source: Excerpted from Applicant submission

Results:
Animal weights were decreased in all groups after the first inoculation of collagen. However, weights in BAT1806 group and MRA group stopped decreasing after the compound administration, while that of the NS group continued decreasing.

Erythrocyte sedimentation rate (ESR; a faster-than-normal rate may indicate inflammation) was shown to increase in all groups after collagen administration with Day 28 values significantly higher than baseline ($P<0.01$) indicating an inflammatory response. Day 40 values (1 week after compound administration) of all groups were significantly lower than those on Day 28. However, Day 40 values of the BAT1806 and MRA groups were similar and were lower than that of the NS group.

C-reactive protein (CRP; an indicator of the presence of inflammation) values on Day 28 increased for all groups following the first collagen administration compared to baseline, indicating an inflammatory response. Day 40 values of all groups were significantly lower than those on Day 28. However, Day 40 values of the BAT1806 and MRA groups were similar and were lower than that of the NS group. Some of the CRP levels fluctuated 2 weeks after compound administration, which were correlated with the anti-drug antibody concentrations. Similar observations were described in the paper by Y. Uchiyama, et al., 2008.

IL-6 levels of the BAT1806 and MRA groups on Day 40 were significantly higher than

levels on Day 28 and were higher than the value of the NS group on Day 40. However, IL-6 levels were lower at later time points. IL-6R levels of the BAT1806 and MRA groups on Day 40 were significantly higher than on Day 28 and were higher than that of NS group on Day 40. It was assumed that IL-6R was bound in the circulation by BAT1806 or MRA.

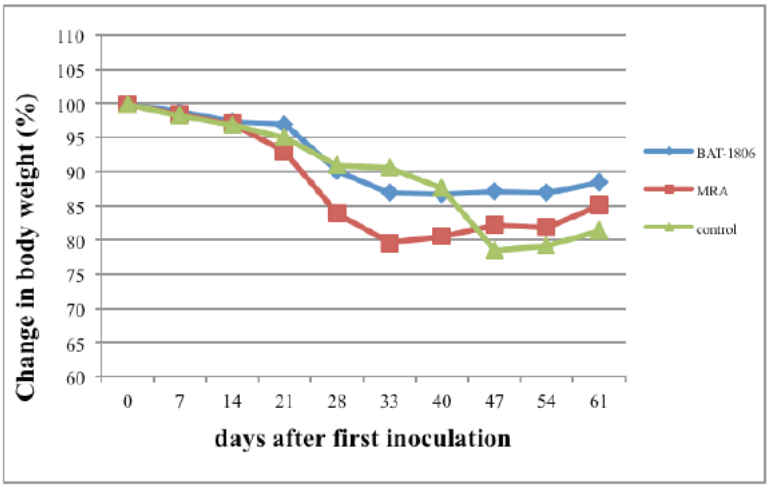
Anti-Type II collagen IgG values of BAT1806, MRA and NS groups increased after first inoculation, and kept increasing along with the experimental progress during the entire study. The results of Anti-type II collagen antibody showed no significant differences between all groups at all time points.

Serum concentrations of drug for the BAT1806 group and MRA group on Day 47 were significantly lower than on Day 40, as the concentration kept decreasing during the 4 weeks period of PD and efficacy monitoring and was cleared by Day 61.

Serum titers of anti-drug antibody of the BAT1806 group on day 47 exhibited an increase in 3 out of 9 animals while the MRA group exhibited an increase in 3 out of 7 animals. The serum titers of anti-BAT1806/MRA antibody correlated with the sudden decreases of serum drug concentrations during the 4 weeks period of PD and efficacy monitoring. There were no differences between groups.

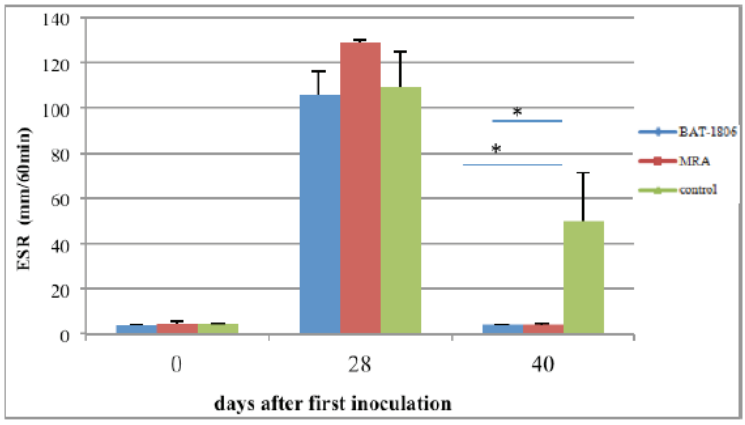
In summary, with BAT1806/MRA treatments, the effects seen included cessation of body weight loss, reductions of ESR, CRP levels, and swelling (middle finger width), and increased levels of serum IL-6 and IL- 6R. Increased levels of anti-drug antibody were observed in 3 animals of both BAT1806 and US-Actemra groups. This correlated with reduction of serum drug levels. Increased levels of anti-type II collagen IgG antibodies were detected in both BAT1806 and US-Actemra-treated animals throughout the study duration.

Figure 12. Percentage of weight loss in different groups



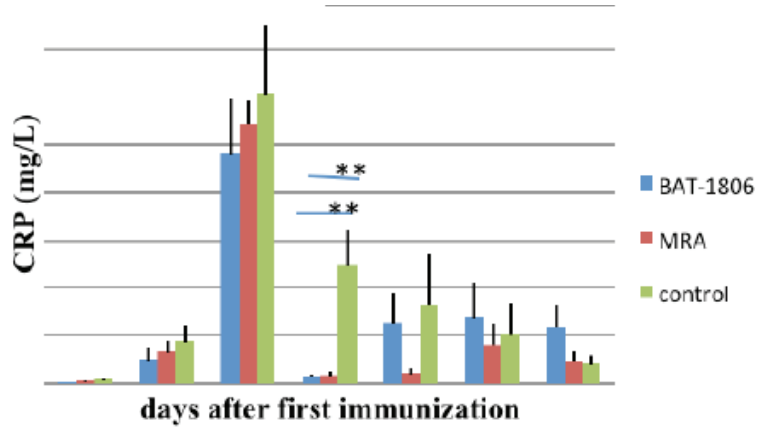
Source: Excerpted from Applicant submission

Figure 13. Comparative analysis of ESR in different groups



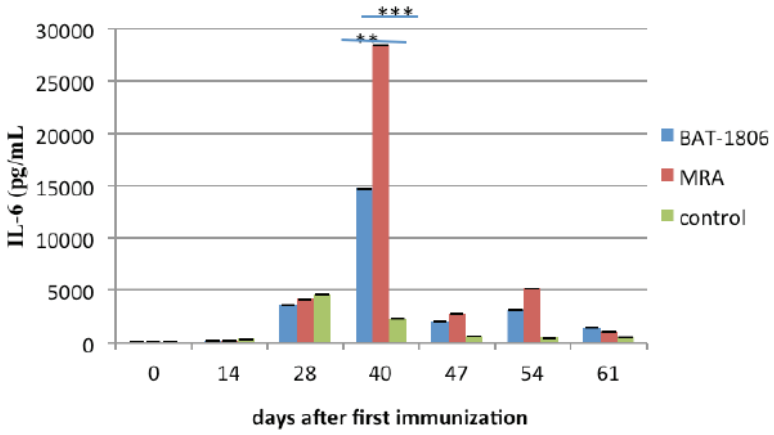
Source: Excerpted from Applicant submission

Figure 14. Comparative analysis of CRP in different groups on Days 0, 14, 28, 40, 47, 54, and 61



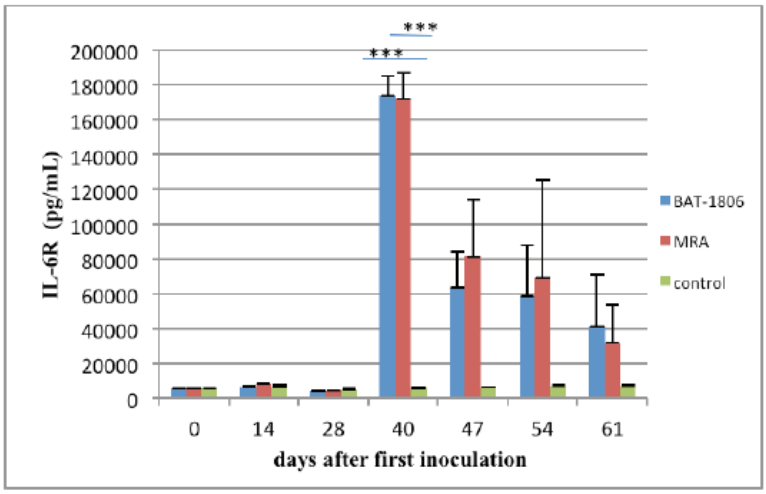
Source: Excerpted from Applicant submission

Figure 15. Comparative analysis of IL-6 between different groups



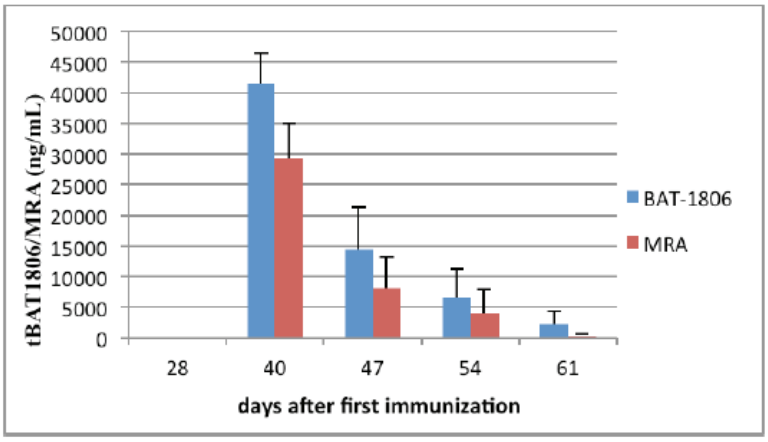
Source: Excerpted from Applicant submission

Figure 16. Comparative analysis of IL-6R in different groups



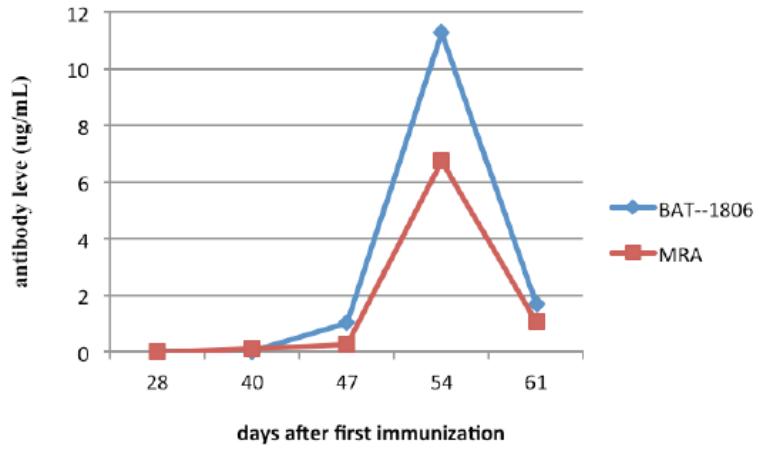
Source: Excerpted from Applicant submission

Figure 17. Analytical results of serum drug concentrations in different groups



Source: Excerpted from Applicant submission

Figure 18. Trends of serum concentration of anti-drug antibody in different groups



Source: Excerpted from Applicant submission

13.3.2. Nonclinical Pharmacokinetics

Pharmacokinetic Study of BAT1806 Injection After Single Intravenous Infusion to Cynomolgus Monkeys (Non-GLP) (Study P17-S136-PK)

Method:
This study was to evaluate pharmacokinetic parameters of BAT1806 to US-licensed Actemra (US-Actemra) and EU-approved RoActemra (EU-RoActemra). Different batches of BAT1806 were compared, as a change in formulation and batch scale up (from (b) (4)L to (b) (4)L) to support the use of the (b) (4)L batch in the PK study and the comparative clinical study. For BAT1806 produced at (b) (4)L, each vial of the drug product contained 80 mg BAT1806 drug substance, (b) (4) sucrose, and 2 mg polysorbate 80. Following scale-up production to (b) (4)L, the drug product formulation was changed to 80 mg BAT1806 drug substance, 3.24 mg L-histidine, 4.04 mg L-histidine hydrochloride monohydrate, 42.12 mg arginine hydrochloride, 80 mg sucrose, and 2 mg polysorbate 80.

Cynomolgus monkeys (n=4/sex/group) were given a single IV infusion dose (3 mL/min) at 10 mg/kg of either: 1) BAT1806 (b) (4)L (batch N20171101), 2) BAT1806 (b) (4)L (batch A0520180402), 3) US-Actemra (batch B3014B04), or 4) the EU-RoActemra (batch B2057B28). Blood samples were collected pre-dose, and 5 minutes (min), 30 min, 1 hour (h), 2 h, 5 h,10 h, 24 h, 48 h, 4 days, 7 days, 10 days, 14 days, 19 days, 24 days, and 28 days after dosing. The serum drug concentrations were determined using a validated ELISA method with lower and upper limits of quantitation of 25-1600 ng/mL.

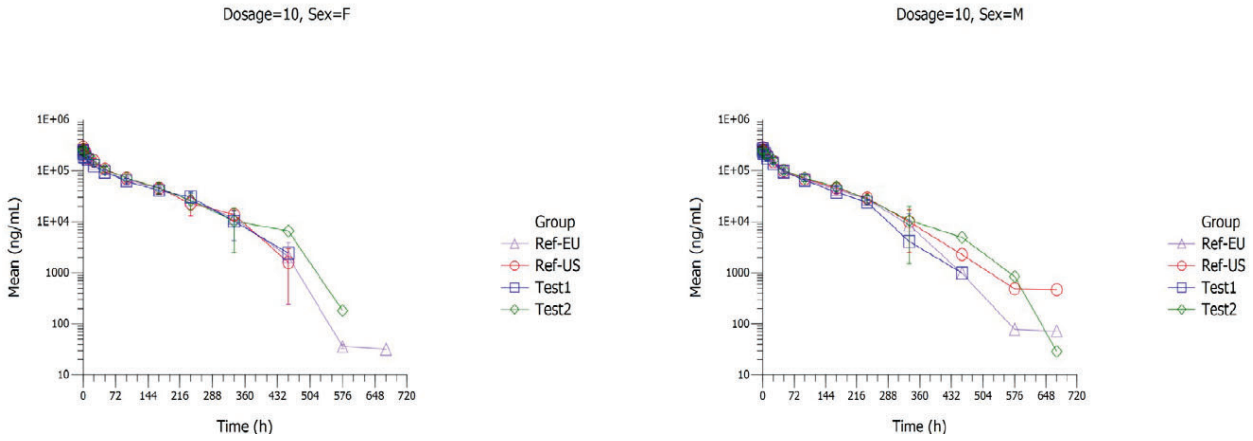
Results:
Linear clearance was noted between 72 and 336 hours postdose. However, from approximately 336 hours onwards, an accelerated clearance was noted in all dosed groups. Increased clearance appeared slightly more apparent in animals dosed with BAT1806 (b) (4)L as compared to US-Actemra, EU-RoActemra and to BAT1806 (b) (4)L. Linear clearance was noted up to 336 hours but was consistent up to 240 hours for all animals and groups, and as such, this timepoint was selected for the AUC time interval for exposure comparisons. Both Cmax and AUC$_{(0\text{-}240h)}$ data was used to compare the four drug products. Similarity of PK parameters (C_{max}, AUC $_{(0\text{-}240)}$, AUC $_{(0\text{-}t)}$, AUC_{last}, AUC_{inf}, Vd, Cl, MRT, $t_{1/2}$,) was evaluated by calculating the ratios of BAT1806/reference product (EU-RoActemra and US-Actemra) for the mean C_{max} and AUC values. The C_{max} or AUC$_{(0\text{-}240h)}$ test/test or test/reference mean ratio percentage was considered similar if within the 80-125% range and the corresponding 90 percent confidence intervals.

All PK parameters were shown to be similar across the different drug products tested and there were no statistically significant differences, including between sexes. Between two batches of BAT1806, no scale-up production effects on PK parameters were detected.

Calculations showed that the C_{max} and AUC$_{(0\text{-}240h)}$ of BAT1806, US-Actemra, and EU-RoActemra ratios were within the range of 80-125% and that exposure of BAT1806 (b) (4)L was similar to BAT1806 (b) (4)L, US-Licensed Actemra and EU-RoActemra. AUC$_{(0\text{-}inf)}$ was not demonstrated as a result of the nonlinear clearance. However, nonlinear clearance was noted for all products, (BAT1806, US-Actemra, and EU-RoActemra) and was considered more of a function of the clearance mechanism on tocilizumab.

The results indicated similar exposures for all four tocilizumab products in a monkey PK study after a single IV dose.

Figure 19. Mean Concentration–Time Curve of Male and Female Cynomolgus Monkeys Administered a Single Intravenous Dose of 10 mg/kg BAT1806, US-Actemra, and EU-RoActemra (Report P17-S136-PK)



F = Female; M = Male; Ref-EU = EU-RoActemra or EU Recombinant Humanized Anti-Human Interleukin-6 Receptor Monoclonal Antibody Injection; Ref-US = US-Actemra or US Recombinant Humanized Anti-Human Interleukin-6 Receptor Monoclonal Antibody Injection; Test1 – BAT1806 produced at (b)(4)L also referred to as Test Article 1; Test2 - BAT1806 produced at (b)(4)L also referred to as Test Article 2; h = Hour.
Source: Report P17-S136-PK.

Source: Excerpted from Applicant submission

Figure 20. Mean PK Measurements Following a Single Intravenous Infusion of BAT1806, US-Actemra, and EU-RoActemra to Male and Female Monkeys (Report P17-S136-PK)

Group (mg/kg)		$t_{1/2}$ (h)	C_{max} (mg/mL)	AUC_{last} (h*mg/mL)	AUC_{inf} (h*mg/mL)	$AUC_{(0-240h)}$ (h*mg/mL)	V (mL/kg)	Cl (mL/h/kg)	MRT (h)
Test Article 1 (10)	M	56.95 ± 11.92	0.26 ± 0.02	18.53 ± 0.73	18.71 ± 0.75	17.01 ± 1.16	44.07 ± 9.77	0.54 ± 0.02	91.85 ± 10.65
	F	74.76 ± 18.08	0.24 ± 0.03	19.05 ± 2.64	19.58 ± 2.57	16.61 ± 1.77	55.63 ± 14.56	0.52 ± 0.07	106.40 ± 12.68
	T	65.86 ± 17.08	0.25 ± 0.03	18.79 ± 1.81	19.15 ± 1.81	16.81 ± 1.40	49.85 ± 13.04	0.53 ± 0.05	99.13 ± 13.34
Test Article 2 (10)	M	52.46 ± 18.41	0.26 ± 0.02	21.76± 4.36	21.92 ± 4.20	19.05 ± 2.63	36.61 ± 16.32	0.47 ± 0.09	104.56 ± 20.03
	F	67.68 ± 5.28	0.26± 0.04	20.71 ± 4.17	21.32 ± 3.78	18.75 ± 2.82	46.81 ± 8.47	0.48 ± 0.10	95.85 ± 27.78
	T	60.07 ± 14.95	0.26 ± 0.03	21.23 ± 3.99	21.62 ± 3.71	18.90 ± 2.53	41.71 ± 13.22	0.48 ± 0.09	100.21 ± 21.37
US-Actemra (10)	M	64.85 ± 10.83	0.28 ± 0.01	21.34 ± 3.03	21.57 ± 3.11	18.77 ± 1.92	43.28 ± 1.76	0.47 ± 0.08	102.96 ± 17.11
	F	64.25 ± 10.12	0.28 ± 0.02	21.00 ± 4.43	21.31 ± 4.21	18.81 ± 3.00	44.30 ± 7.50	0.48 ± 0.11	96.71 ± 19.53
	T	64.55± 9.71	0.28 ± 0.02	21.17 ± 3.52	21.44 ± 3.43	18.79 ± 2.33	43.79 ± 5.07	0.48 ± 0.09	99.84 ± 17.32
EU-RoActemra (10)	M	57.03 ± 5.49	0.27 ± 0.02	20.32 ± 0.89	20.40 ± 1.01	17.99 ± 0.57	40.29 ± 2.66	0.49 ± 0.02	101.26 ± 9.50
	F	61.33 ± 16.40	0.24 ± 0.01	20.11 ± 2.42	20.42 ± 2.02	17.54 ± 1.91	44.17 ± 15.22	0.49 ± 0.05	107.40 ± 10.87
	T	59.18 ± 11.55	0.25 ± 0.02	20.21 ± 1.69	20.41 ± 1.48	17.77 ± 0.33	42.23 ± 10.33	0.49 ± 0.03	104.33 ± 10.00

Values expressed as Mean ± SD
AUC_{last} = Area under the serum concentration-time curve from the time of dosing to last observation; AUC_{inf} = Area under the serum concentration-time curve (0-∞); $AUC_{(0-240h)}$ = Area under the serum concentration-time curve (0-240h). ; C_{max} = Maximum concentration observed; Cl = Clearance; F = Female; M = Male; MRT = Mean residence time; Mean = Mean Value; SD = Standard Deviation; T = Total; $t_{1/2}$ = Terminal half-life; V = Apparent volume of distribution.
Test Article 1; Recombinant Humanized Anti-Human Interleukin-6 Receptor Monoclonal Antibody Injection (produced at (b)(4)L)
Test Article 2; Recombinant Humanized Anti-Human IL-6 Receptor Monoclonal Antibody Injection (produced at (b)(4)L)
US-Actemra = US reference product (tocilizumab marketed in the US)
EU-RoActemra = EU reference product (tocilizumab marketed in the EU)
Source: Report P17-S136-PK.

Source: Excerpted from Applicant submission

Figure 21. Exposure Comparison Analysis of BAT1806, US-Actemra, and EU-RoActemra in Male and Female Cynomolgus Monkeys (Report P17-S136-PK)

Group Comparison	Mean Parameters	Unit	Ratio %	90% CI	
				Lower	Upper
BAT1806 (b) (4)L, BAT1806 (b) (4)L	(C_{max}) 0.26/0.25	µg/mL	103.99	95.31	113.45
	($AUC_{(0-240h)}$) 18.90/16.81	h*mg/mL	111.89	101.81	122.97
BAT1806 (b) (4)L, EU-RoActemra	(C_{max}) 0.25/0.25	µg/mL	101.95	93.45	111.23
	($AUC_{(0-240h)}$) 18.90/17.77	h*mg/mL	105.77	96.24	116.24
BAT1806 (b) (4)L, US-Actemra	(C_{max}) 0.25/0.28	µg/mL	91.99	84.31	100.36
	($AUC_{(0-240h)}$) 18.90/18.70	h*mg/mL	100.47	91.42	110.42

$AUC_{(0-240h)}$ = Area under the serum concentration-time curve (0-240h); C_{max} = Maximum concentration observed; CI = Confidence interval;; TA = test article.
BAT1806 (b) = BAT1806 produced at (b) Recombinant Humanized Anti-Human Interleukin-6 Receptor Monoclonal Antibody Injection
BAT1806 (4)L = BAT1806 produced a (4)L, Recombinant Humanized Anti-Human IL-6 Receptor Monoclonal Antibody Injection
US-Actemra = US reference product (tocilizumab marketed in US)
EU-RoActemra = EU reference product (tocilizumab marketed in EU)
C_{max} and AUC values presented to 2 decimal places
Source: Report P17-S136-PK.

Source: Excerpted from Applicant submission

13.3.3. General Toxicology

Local Tolerance Test for Recombinant Humanized Anti-Human Interleukin-6 Receptor Monoclonal Antibody Injection following Repeat Intravenous Injection to Rabbits (Study Q17-S136-IR)

Method:
An FDA GLP compliant study was conducted to evaluate and compare the intravenous local irritation of BAT1806 and EU-RoActemra in male New Zealand White rabbits (n=6/group, 3 groups in total). Animals were intravenously administered in the right ear vein with drugs (4.6 mL/animal, 8 mg/mL): Group 1) BAT1806 produced at (b) (4)L (Batch No. N20171101), Group 2) BAT1806 produced at (b) (4)L (Batch No. A0520180402), or Group 3) EU-RoActemra, respectively, on Day 1 and Day 15. At the same dosing times, all animals were treated with negative control (sodium chloride injection, 4.6 mL/animal) via intravenous injection in the left ear vein. The injection sites of animals were examined before and 1 hour after each dose and at 4, 24, 48, 72 hours post dose and once daily thereafter and were evaluated for changes, including erythema, hyperemia, edema, ulceration and induration. Animals were necropsied on either Day 18 (n=3/group) or maintained for a 14 day recovery period (Day 29; n=3/group) to assess

reversibility of any local tolerance effects. At necropsy, histopathology samples were taken of the ear tissue (5 samples per injection site).

Results:
Results of concentration and homogeneity of test articles were within acceptable ranges.

A single Group 1 animal showed clinical signs of gastrointestinal effects (leftover food, reduced drinking, oliguria, anuria, reduced defecation, lack of defecation, soft stool, loose stool, jelly like substances in the stool, dirty anal area from Day 7) and flaccid skin, thin, lethargy, morbus asthenicus from Day 13. The effects were not resolved after veterinary treatment and the animal was euthanized on Day 16. Gastrointestinal effects are common spontaneous findings in New Zealand White rabbits and were considered not treatment-related.

During the study, no abnormal clinical sign related to administration was noted in other animals.

There were no macroscopic or microscopic findings at the injection sites of animals euthanized as scheduled on Days 18 and 29, or on the one animal euthanized on Day 16. Similar to the EU-RoActemra reference product, BAT1806 batches produced at (b) (4)L or (b) (4)L was not shown to be a local irritant in rabbits.

<u>In Vitro Hemolysis Test of Recombinant Humanized Anti-Human Interleukin-6 Receptor Monoclonal Antibody Injection with Human Red Blood Cells</u> (Study O17-S136-HE)

Method:
A GLP study was conducted to evaluate the hemolytic and aggregation effect of BAT1806 using human red blood cells (RBCs). This study used the maximum concentration for clinical use (8 mg/mL) for: 1) BAT1806 produced at (b) (4)L (batch N20171101), 2) BAT1806 produced at (b) (4)L (batch A0520180402), and 3) EU-RoActemra (Lot No. B2057B28). Samples of RBCs suspension 2% (v/v) were mixed with one of the three test drugs, negative control only (sodium chloride injection), or positive control only (sterile water for injection). The mixed samples were incubated at 37 °C for 3 hours. Samples were assessed visually for hemolytic or aggregation.

Results:
Results of concentration and homogeneity of test articles were within acceptable ranges.

Complete hemolysis occurred with the positive control solution while neither hemolysis nor aggregation was observed with the negative control solution. No hemolysis or aggregation was observed in human RBCs with BAT1806 produced at (b) (4)L or (b) (4)L, or EU-RoActemra.

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13.4. Clinical Pharmacology Appendices

13.4.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity study BAT-1806-001-CR, serum BAT1806, US-Actemra, and EU-RoActemra concentrations measured using a validated ELISA (METHOD ICSH 18-023) were suitable for assessment of PK similarity. Both the method validation entitled "ICSH 18-023" and sample analysis for the study were performed at (b) (4) In this method, Recombinant Human IL-6R-His (Recombinant Human IL-6R-His, (b) (4)) coated in 96-well plate was used to capture serum BAT1806, US-Actemra, and EU-RoActemra and Human Ani-Tocilizumab HRP-conjugated (b) (4)) was used to detect the bound analytes. Table 31 shows the summary of ELISA method performance in quantification of BAT1806, US-Actemra and EU-RoActemra during the method validation.

Table 31. Summary of the bioanalytical method validation and in-study performance for measurement of BAT1806, US-Actemra, and EU-RoActemra

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of an immunoassay method for the quantification of BAT1806 and tocilizumab in human serum by enzyme-linked immunosorbent assay (ELISA) ICSH 18-023, Module 5.3.1.4 ICSH 18-023 Addendum 01, Module 5.3.1.4 ICSH 18-023 Addendum 02, Module 5.3.1.4		
Method description	Sandwich ELISA (see Section 1.5.1 for method description).		
Materials used for standard calibration curve and concentration	BAT1806, 19.0 mg/mL		
Validated assay range	0.200 to 10.0 µg/mL (Anchor point 0.100, 20.0 µg/mL)		
Material used for quality controls (QCs) and concentration	BAT1806, 19.0 mg/mL RoActemra, 20.3 mg/mL Actemra, 21.7 mg/mL Pooled normal healthy serum (NHS)		
Minimum required dilutions (MRDs)	1:150		
Source and lot of reagents	BAT1806 lot no.: N20170301 Source: Bio-Thera Solution, Ltd Expiration date 28 Feb 2019 RoActemra lot no.: B2057B28 Source: Bio-Thera Solution, Ltd Expiration date: 31 Mar 2019 Actemra lot no.: B3011B02 Source: Bio-Thera Solution, Ltd Expiration date: 30 Nov 2018 Human-anti Tocilizumab HRP-conjugated lot no.: HCA257P Source: (b) (4) Expiration/Re-test date: 28 Nov 2018 Recombinant IL-6R-His lot no.: T20180121-250MZ-3 Source: Bio-Thera Solution, Ltd Expiration/Re-test date: 31 Jan 2020 Blank matrix Human serum AU005-MAR-2018-001997 Expiration date: 31 Mar 2019		
Regression model and weighting	4-parameter logistical fit, weighted $1/Y^2$		
Validation parameters	**Method validation summary**		**Source location (8380-507, unless otherwise indicated)**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9	Table 2
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.5 to 5.5%	Table 2
	Cumulative precision (%CV) from LLOQ to ULOQ	2.5 to 6.9%	Table 2

Performance of QCs during accuracy and precision runs[1]	Cumulative accuracy (%bias) in 5 QCs BAT1806	-3.5 to 4%	Table 4-3
	Cumulative accuracy (%bias) in 5 QCs RoActemra	-3.5 to 4.5%	Table 4-4
	Cumulative accuracy (%bias) in 5 QCs Actemra	-10.5 to -0.1%	Table 4-5
	Inter-batch %CV BAT1806	≤ 13.9%	Table 4-3
	Inter-batch %CV RoActemra	≤ 13.5%	Table 4-4
	Inter-batch %CV Actemra	≤ 14.0%	Table 4-5
	Total error (%TE) BAT1806	≤ 19.5%	Table 4-3
	Total error (%TE) RoActemra	≤ 16.5%	Table 4-4
	Total error (%TE) Actemra	≤ 20.3%	Table 4-5
Selectivity & matrix effect	10/10 (100%) met criteria for BAT1806, RoActemra and Actemra. No matrix effect was observed in normal human serum.		Table 6 Table 7 Table 8
Interference & specificity	Interference IL-6 receptor was assessed at 100 and 10.0 ng/mL levels. Interference samples met criteria.		Table 15
Hemolysis effect	5/5 (100%) met criteria for BAT1806, RoActemra and Actemra.No matrix effect was observed in 10% hemolysis human serum		Table 9 Table 10 Table 11
Lipemic effect	5/5 (100%) met criteria for BAT1806, RoActemra and Actemra. No matrix effect was observed in lipemic human serum		Table 9 Table 10 Table 11
Dilution linearity & hook effect	Up to dilution factor: 1:3000 (excluded MRD) No hook effect was observed up to the concentration of 900 µg/mL		Table 12 Table 13 Table 14
Bench-top/process stability	At least 91 hours 02 mins at room temperature (BAT1806)		Table 22 Table 23 Table 24
Freeze-Thaw stability	At least six F/T when storage at -10 ºC to -30 ºC At least six F/T when storage at -60 ºC to -80 ºC		Tables 16 & 17 Tables 18 & 19 Tables 20 & 21
Long-term storage[2]	At least 786 days at -60 ºC to -80 ºC (BAT1806 and Actemra/RoActemra) At least 292 days at -10 ºC to -30 ºC (BAT1806 and Actemra)		8380-507 Addendum 01 Table 6-1 Table 6-2 Table 6-3
Parallelism[3]	4/4 samples met acceptance criteria. Cumulative CV%: 2.0, 2.3, 3.8, 5.0%		8380-505 Table 15
	3/3 samples met acceptance criteria. %CV: 6.1, 3.1, 0.3%		8395-767 Table 18
Carry over	NR		-

Method performance in Study BAT-1806-CR-001 (Module 5.3.1.4)		
Assay passing rate	89/89 runs (100%) were accepted	8380-505 Table 1
Standard curve performance	%Bias range 0.200 to 10.0 µg/mL: -7.0 to 4.8% %CV range 0.200 to 10.0 µg/mL: ≤ 5.4%	8380-505 Table 3
QC performance	All QC data met the acceptance criteria. • LQC (0.600 µg/mL) ○ %Bias: 40.1%[4] ○ %CV: 183.6%[4] • MQC (2.00 µg/mL) ○ %Bias: -1.4% ○ %CV: 7.8% • HQC (8.00 µg/mL) ○ %Bias: 5.4% ○ %CV: 9.2%	8380-505 Table 5
Method reproducibility	Incurred sample re-analysis was performed on 136/2581 of study samples, and 95.7% of the samples met the pre-specified criteria.	8380-505 Table 11
Study sample analysis/stability	All PK samples were analyzed during the F/T period and RT period, and during the long-term stability period of validation.	8380-505 Section 10.3
Standard calibration curve performance during accuracy and precision runs	NA	
Method performance in Study BAT1-806-CR-002 (Module 5.3.1.4)		
Assay passing rate	240/253 batches (95%) met the acceptance criteria	8395-767 Table 1
Standard curve performance	%Bias range 0.200 to 10.0 µg/mL: -1.5 to 5.1% %CV range 0.200 to 10.0 µg/mL: ≤6.0%	8395-767 Table 2
QC performance	All QC data met the acceptance criteria. Cumulative bias range: -0.5to 4.8% Cumulative precision: ≤12.2%	8395-767 Table 12
Method reproducibility	Incurred sample reproducibility was performed on 372/5721 samples. Of these, three samples didn't have valid values, and four samples were mistakenly selected as ISR samples, 29 samples exhibited poor reproducibility and were classed as failures. Therefore, of the 336 samples, 92.1% met the required criteria indicating that the method generated reproducible results and was fit for purpose.	8395-767 Table 16
Study sample analysis/stability	The longest possible storage duration of the study samples (from first sample collection on 04 Jan 2019 to the last sample analysis on 23 Feb 2021) was 781 days. All samples were analyzed within the above established storage stability duration, as well as established benchtop and freezer thaw stability.	8395-767 Section 12.3.1
Standard calibration curve performance during accuracy and precision runs	NA	

Source: Table 6 in 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

13.5. Statistical Appendices

13.5.1. Stratification Factors

The stratification factors are presented in Table 32. Per the Biogen CSR, 75 subjects had a different electronic data capture (EDC) stratum than to which they were randomized (IWRS):

- 3 subjects were randomized under a different region
  - 1 subject in BAT1806 group was ascribed to Asia Pacific when the EDC stratum was Central Europe
  - 2 subjects in the EU-RoActemra group were ascribed to Central Europe when the EDC stratum was Asia Pacific
- 72 subjects were randomized under a different DMARD stratum than that in the EDC
  - 38 subjects were randomized to BAT1806 of which 25 subjects were in Central Europe
  - 34 subjects were randomized to EU-RoActemra of which 24 subjects were in Central Europe

The Biogen CSR stated that corrective actions were taken after these issues were identified, including additional training of Clinical Research Associates and study site personnel.

Table 32. Stratification Factors (FAS)

	EU-RoActemra (N=309)	BAT1806 (N=312)	Total (621)
Randomized Stratification Factors (as captured in IWRS), n (%)			
Central Europe, with previous biological or tsDMARD use	68 (22.0%)	69 (22.1%)	137 (22.1%)
Central Europe, w/o previous biological or tsDMARD use	116 (37.5%)	116 (37.2%)	232 (37.4%)
APAC, with previous biological or tsDMARD use	60 (19.4%)	60 (19.2%)	120 (19.3%)
APAC, w/o previous biological or tsDMARD use	65 (21.0%)	67 (21.5%)	132 (21.3%)
Actual Stratification Factors (as captured in the EDC), n (%)			
Central Europe, with previous biological or tsDMARD use	49 (15.9%)	47 (15.1%)	96 (15.5%)
Central Europe, w/o previous biological or tsDMARD use	133 (43.0%)	139 (44.6%)	272 (43.8%)
APAC, with previous biological or tsDMARD use	61 (19.7%)	52 (16.7%)	113 (18.2%)
APAC, w/o previous biological or tsDMARD use	66 (21.4%)	74 (23.7%)	140 (22.5%)

APAC=Asia Pacific, EDC=electronic data capture, IWRS=interactive web response system, N=no. of subjects, tsDMARD=targeted synthetic disease-modifying antirheumatic drug

Source: Table 12, page 82 of Biogen CSR (Verified by Reviewer)

It is difficult to compare subject numbers for the randomized versus actual stratification factors in Table 32. Table 33 presents a similar comparison but ignoring the treatment group assignment. The diagonal values in green are the numbers of subjects whose

randomized and actual strata matched while those in the off-diagonals are mismatches. A total of 75 subjects had incorrect strata:

- There were 3 subjects that had incorrect geographical strata: 2 in Central Europe who were supposed to be in Asia Pacific and 1 in Asia Pacific who was supposed to be in Central Europe.
- There were 72 subjects who had incorrect DMARD strata: 23 in Asia Pacific and 49 in Central Europe.

These numbers are consistent with the Applicant's results above. The primary analysis using the correct strata is further investigated by the Reviewer in a later section.

Table 33. Randomized versus Actual Strata

		Actual (EDC)					
		Asia Pacific		Central Europe			
Randomized (IWRS)		No DMARD	DMARD	No DMARD	DMARD	Total	Total
Asia Pacific	No DMARD	124	8	0	0	132	252 (41%)
	DMARD	15	104	0	1	120	
Central Europe	No DMARD	1	0	227	4	232	369 (59%)
	DMARD	0	1	45	91	137	
	Total	140	113	272	96	621	621
		253 (41%)		368 (59%)		621	

EDC: electronic data capture, IWRS: interactive web response system; DMARD: disease-modifying antirheumatic drug

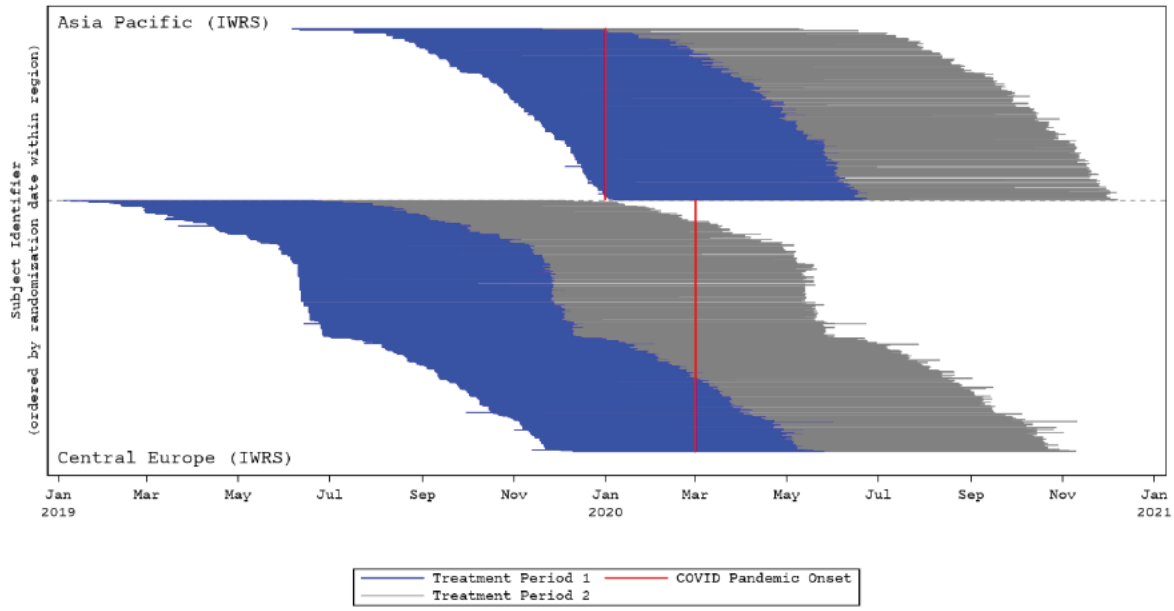
Source: Reviewer's Table

13.5.2. Other Clinical Endpoints

The Biogen CSR presented the possible impact of the COVID-19 pandemic on the study subject participation during the study follow-up in Figure 22 (by region) and Figure 23 (by region and treatment). An explanation of the graphs is provided below Figure 22.

The CSR stated that the onset of the pandemic occurred before Week 24 for 240 (95.2%) and 102 (27.6%) of subjects in Asia Pacific and Central Europe, respectively.

Figure 22. COVID-19 Pandemic Impact On Subject Participation by Region for All Treatments FAS



Note 1: On the x-axis, time is plotted, from the beginning of the study (from randomization) to the end of the study (or to the end of the subject's participation in the study for any reason). These correspond to the first and last study visits per TP (TP1 weeks 0-24, TP2 weeks 24-48) for each subject respectively. On the y-axis, each subject, and their corresponding study participation relative to the entire study duration, is described by a horizontal line. The blue segment of the line indicates the subject's participation in TP1, the gray segment of the line indicates the subject's participation in TP2. A dotted line delineates the 2 regions, with Asia Pacific in the upper panel, and Central Europe in the lower panel. The vertical red line on 01 January 2020 and 01 March 2020 indicates the COVID-19 pandemic declaration dates in countries in Asia Pacific and in Central Europe, respectively.
Note 2: One subject from Poland was randomized with stratification factor 'Asia Pacific', 2 subjects from China were randomized with stratification factor 'Central Europe' in IWRS.
Source: Figure 3 of Biogen CSR, page 85

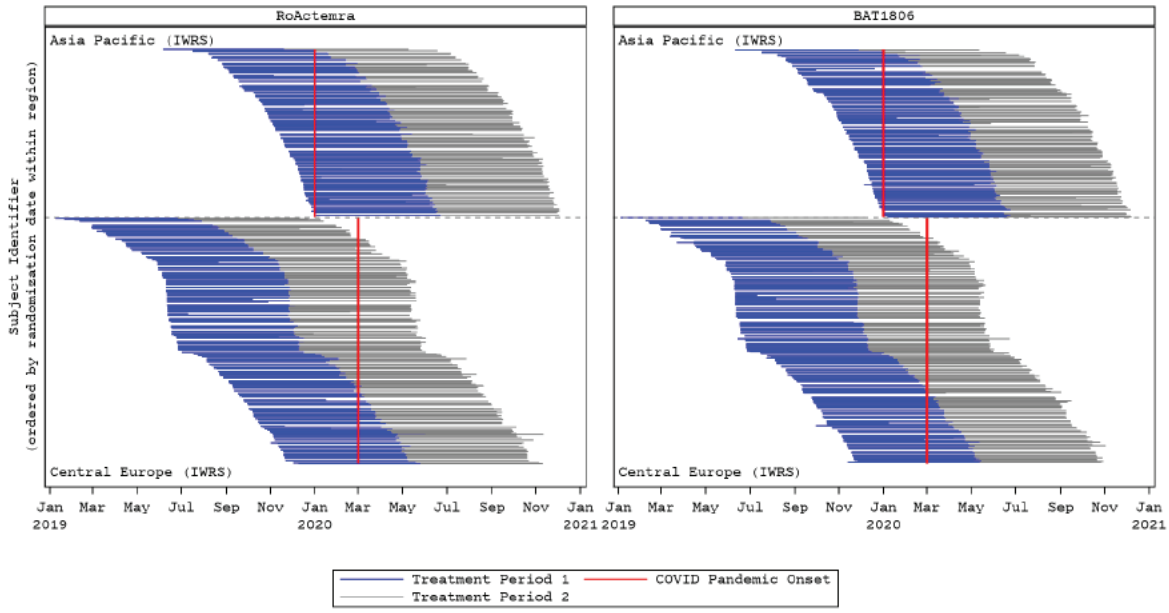
Table 34 summarizes the Biogen CSR's counts of subjects possibly affected by the COVID-19 pandemic. Based on the last row of the table, most of the subjects are in Asia Pacific and only slightly over a quarter of subjects in Central Europe were impacted by the pandemic.

Table 34. COVID-19 Impact

	Asia Pacific (n=252)		Central Europe (n=369)	
	EU-RoActemra	BAT1806	EU-RoActemra	BAT1806
Possibly Impacted by Pandemic	125	127	184	185
Pandemic onset before Week 24	118 (94.4)	122 (96.1)	49 (26.6)	53 (28.6)

Source: Reviewer's Table (Summary of Biogen CSR text)

Figure 23. COVID-19 Pandemic Impact by Treatment Group (FAS)



Abbreviations: COVID = coronavirus Disease 2019; IWRS = interactive web response system.
One subject from Poland was randomized with stratification factor 'Asia Pacific', 2 subjects from China were randomized with stratification factor 'Central Europe' in IWRS.
Source: Figure 4 of Biogen CSR, page 86

The impact of the COVID-19 pandemic did not appear to be disproportionate between the two study groups across the two geographical regions.

13.5.3. Additional Analyses

The following five (5) analyses were performed by the Reviewer: (1) Verification of subject responses from component datasets, (2) Reviewer's ACR20 response data findings versus the Applicants, (3) Verification of ICE status, (4) Secondary estimand ICE handling, and (5) Tipping point analysis.

<u>Verification of Subject Responses from Component Datasets</u>

Recall that the primary endpoint is the ACR20 response defined as:

1. ≥ 20% improvement from baseline in both tender joint count 68 joints, TJC68 and swollen joint count (66 joints, SJC66);
2. ≥ 20% improvement from baseline in at least 3 of the following 5 other specified ACR Core Data Set components:
   - Subject's assessment of pain VAS (0 to 100 mm, higher scale indicates worsen)

- Subject's Global Assessment of Disease Activity VAS (PtGA) (0 to 100 mm, higher scale indicates worsen)
- Physician's Global Assessment of Disease Activity VAS (PhGA) (0 to 100 mm, higher scale indicates worsen)
- Health Assessment Questionnaire – Disability Index (HAQ-DI)
- Acute phase reactant (CRP) level

If a subject's baseline value for a component is zero, the subject should be considered as not achieving 20% improvement from baseline for that component since there is no room for improvement.

In section 1.1 of the Applicant's complex-algorithms.pdf, items 1 and 2 above are referred to as the criteria for determining subject ACR20 response which is coded in the variable AVALC as either "Y" (responders) or "N" (non-responders). Joint count data can be found in the dataset, adjntsum.xpt, while data for criterion 2 are found in the following: advas.xpt (VAS), adhaqsum.xpt (HAQ-DI), and adlb.xpt (CRP).

When criteria 1 and 2 are applied to the respective datasets, the following ACR20 overall and component responses on evaluable subjects at Week 24 were obtained (Table 35).

Table 35. ACR20 Overall and Component Responses (Evaluable Subjects, Week 24)

	ACR20 Criteria						
	Criterion 1		Criterion 2				
	Joint Count		VAS				
Response	TJC68	SJC66	PTGADA	PHGADA	PTPAIN	HAQ-DI	CRP
	At least 20% improvement per Component						
Y	502	513	445	520	437	407	515
N	48	37	134	55	142	167	34
Total	550	550	579	575	579	574	549
	At least 20% improvement in joint counts		At least 20% improvement in each of at least 3 components				
Y	486		487				
N	64		92				
Total	550		579				
Combined Criterion 1 and Criterion 2							
Y	428						
N	122						
Total	550						

Source: Reviewer's Table

There were 550 subjects in the resulting dataset for criterion 1. Combining the component datasets for criterion 2 yielded 584 subjects but only 579 had at least three of the five components with available data. The overall ACR20 data (combining criteria 1 and 2) consisted of 550 subjects (Y: 428, N: 122).

There were 34 (=584-550) subjects who had missing joint count data for criterion 1. Among the 34 subjects, 29 (=579-550) had at least three of the five components with data available for criterion 2. Based on the calculation rules for imputing missing ACR component data (Table 13), the 29 subjects fell under the following scenarios (Table 36):

Table 36. 29 Subjects with Missing Criterion 1 Data and Some Criterion 2 Components Data Available* (Week 24)

	Criterion 1		Criterion 2				
Scenario	**JC A**	**JC B**	**Comp A**	**Comp B**	**Comp C**	**ACR20**	**#Subjects**
J	Missing	Missing	Non-Resp	Non-Resp	Non-Resp	Non-Resp	7
O	Missing	Missing	Resp	Resp	Resp	Missing	16
Q	Missing	Missing	Resp	Resp	Non-Resp	Missing	6
Total							29

* At least three of the five components had data available for criterion 2

Source: Reviewer's Table

In Table 36, among the 29 subjects who had missing criterion 1 data but had data available for at least three of the five components for criterion 2, 7 subjects were considered as non-responders and 22 were considered as missing. The 22 missing subjects was determined by taking the sum of the last column in Table 36 for rows O and Q under the first column. Note that for scenario J, even though the joint count data are missing, it can be deduced from criterion 2 alone that these subjects are non-responders.

Reviewer's ACR20 Response Data Findings versus the Applicant's

This BLA's ACR20 data can be found in the adeffra.xpt dataset. The number of responders ("Y") and non-responders ("N") at Week 24 are presented in Table 37. The Applicant's ACR20NR refers to non-responder imputation applied to the "as observed" ACR20 data. The non-responder imputation is based on composite and treatment policy approaches under the primary estimand.

Table 37. Reviewer's and Applicant's ACR20 Response Data at Week 24

Source	Y	N	Total	Data Description
Reviewer's Findings	428	129	557	Crit1 data available, Crit2 data available

		22	22	Crit1 data missing, Crit2 data evaluable (scenarios O, Q: set to missing)
		5	42	Crit1 data missing and Crit2 not evaluable*
		37		Crit1 data missing and Crit2 data missing
Total	428	193	621	
Applicant's ACR20	428	129	557	Applicant's "as observed" dataset
Applicant's ACR20NR	428	193	621	Applicant's imputed dataset
Crit1=criterion 1; Crit2=criterion 2 * There were not at least three of the five components that had data available for criterion 2				

Source: Reviewer's Table

The reviewer identified 557 subjects with criteria 1 and 2 data available which can be used to assess ACR20 response, that matches the Applicant's ACR20 results. These are the 550 subjects with overall ACR20 response data identified previously plus the 7 subjects under scenario J. There were an additional 22 subjects that were considered as scenarios O and Q cases (set to missing ACR20).

Of the 621 subjects in the FAS, there were 42 (= 5+37) subjects that did not have sufficient data to verify the two criteria: 5 subjects had criterion 1 data missing and criterion 2 not evaluable, while 37 subjects had missing criteria 1 and 2 component data (at Week 24). Thus, there were 64 (=22+42 = 193-129 = 621-557) subjects whose ACR20 data at Week 24 were considered missing.

In summary, among 621 subjects in the FAS, 557 subjects had available criteria 1 and 2 data, with 428 responders and 129 non-responders (Applicant's ACR20). Twenty-two (22) subjects had evaluable criteria 1 and 2 data and were set to missing per the pre-specified calculation rules (Table 13). Forty-two (42) subjects had criterion 1 data missing and either criterion 2 data not evaluable (5 subjects) or criterion 2 data missing (37 subjects). Therefore, 64 (=22+42) subjects were considered as having missing response data and consequently imputed as non-responders (Applicant's ACR20NR) (Table 38):

Table 38. Available and Imputed Data Summary

	ACR20 Response		
	"Y"	**"N"**	**Total (%)**
Data Available	428	129	557 (90)
Data Imputed	-	64	64 (10)
Total	428	193	621 (100)

Source: Reviewer's Table

The Applicant's ACR20NR dataset was used in the analysis of the primary estimand.

Verification of ICE Status

The adeffra.xpt dataset includes ICE categories for all subjects. Table 39 categorizes the available and imputed ACR20 data in Table 38 by ICE status. The purpose of this table is to identify the numbers of subjects by ICE status that were imputed using the MAR or MNAR missing data approaches under the supplementary analysis of the secondary estimand (see next section).

Recall that in the primary analysis using the primary estimand, the strategies for handling ICEs were composite variable (ICE 1) and treatment policy (ICE 2-6). For the secondary estimand supplementary analysis, the strategies for handling ICEs were composite variable (ICE 1), hypothetical (ICE 2 and 4), and treatment policy (ICE 3, 5, and 6). In other words, the handling strategy for the secondary estimand were composite variable for death, hypothetical for ICE's related to COVID-19 pandemic, and treatment policy for the remaining ICE's (not related to COVID-19 pandemic).

In Table 39,

- Among a total of 557 subjects with data available to determine ACR response or non-response, 38 (=3+22+11+2) subjects had an ICE, mostly from missed study treatment at Week 20, and 519 had no ICE.
- Among a total of 64 subjects whose data were imputed as non-response, 46 (=4+5+26+11) had an ICE, mostly from discontinuation of study treatment up to Week 20, and 18 had no ICE.
- Approximately 86% of subjects in the FAS did not have an ICE. The majority of subjects who experienced an ICE (14%) were because of missed treatment infusion (~7%) or discontinuation of treatment (~6%). Most of the former were related to the COVID-19 pandemic.

Table 39. Data Categories by ICE and Data Handling under Primary Analysis

Data Category			Data Available	Data Imputed As NR	Total (%)
ICE	Death	ICE1:	0	4	4 (1)
	Discontinuation of Treatment	ICE2:	0	5	5 (1)
		ICE3:	3	26	29 (5)
	Missed Treatment Infusion	ICE4:	22	11	33 (5)
		ICE5:	11	0	11 (2)
	Rescue Medication	ICE6:	2	0	2 (0)
No ICE	No ICE	No ICE	519	18	537 (86)
Total	**Total**		**557**	**64**	**621 (100)**

ICE1: Death prior to assessment
ICE2: Discontinuation of study treatment (up to Week 20 dosing) related to the COVID-19 pandemic

ICE3: Discontinuation of study treatment (up to Week 20 dosing) not related to the COVID-19 pandemic
ICE4: Missed study treatment infusion (at Week 20) related to the COVID-19 pandemic
ICE5: Missed study treatment infusion (at Week 20) not related to the COVID-19 pandemic
ICE6: Administration of rescue medication within 1 day prior to an ACR assessment
NR: non-response

Source: Reviewer's Table

The reviewer verified that the responses (variable "AVALC") of the 64 subjects were set by the Applicant to "N" by "DTYPE" = NRI, where NRI=non-responder imputation. Note that although there are pre-specified non-responder imputation rules for ICE1-6, there do not appear to be pre-specified rules for the 18 subjects with missing data who had no ICE.

Lastly, the Applicant's Table 14.2.1.1.2 (Bio-Thera CSR, page 639 of 3002) presented the total number of subjects in (last column) by treatment group (table not shown here). The numbers of ICEs did not appear to be disproportionate between the two groups.

Secondary Estimand ICE Handling

As described in Section 9.3.1.3 of the SAP, the following steps were taken (in order) for handling ICE data under the secondary estimand:

1. Any missing data (other than missing data due to death) will be multiple imputed using a MAR approach (any available data occurring under influence of an ICE will be analyzed as observed under the treatment policy approach).
2. Next, any (observed or imputed) data occurring under influence of an ICE related to the COVID-19 pandemic will be considered as missing and multiple imputed using a MNAR approach for the applied hypothetical strategy for those ICEs. Multiple imputations on component level will be binary (i.e., Response vs Non-Response).

It appears that step 1 is first applied to all missing data ICEs (2-6) except for the ICE for death. Thus, in the 42 (=5+26+11+0) subjects with ICEs 2-4, will have ACR20 responses imputed under the MAR approach. Subsequently, the 38 (=0+5+22+11) subjects with ICE2 and ICE4 (i.e., ICEs with hypothetical strategy) will be considered missing and imputation will be performed under the MNAR approach. Note that 22 subjects with ICE4 had ACR20 data available but were set to missing and multiple imputed per step 2.

Per the SAP, the number of imputations was 25. A total of 625 (=25x25) point estimates for the response probability difference and standard errors were calculated. These estimates were combined using SAS Proc MIANALYZE and consequently, the 2-sided 90% CI was obtained.

These are additional details identified by the Reviewer for the supplementary analysis using the secondary estimand.

Tipping Point Analysis

The reviewer verified the Applicant's TPA results using Table 41 shown below. These tables present the actual values of the lower and upper bounds of the 90% CI, respectively, when gradually switching the number of ACR20 non-responders to responder in each group. The cells in green correspond to the cases when there is no longer equivalence between the two study groups. In the Applicant's TPA analysis results section, explanation (a) is consistent with Table 40 and (b) with Table 41.

Table 40. TPA for the Upper Bound of the 90% CI

		Number of Missing BAT1806 Subjects Imputed as Responder				
		22	**23**	**24**	**25**	**26**
Number of Missing RoActemra Subjects Imputed as Responder	**0**	14.79	15.1	15.4	15.71	16.01
	1	14.45	14.76	15.07	15.37	15.67
	2	14.12	14.43	14.73	15.04	15.34
	3	13.79	14.1	14.4	14.71	15.01
	4	13.46	13.77	14.07	14.37	14.68

Source: Reviewer's Table

Table 41. TPA for the Lower Bound of 90% CI

		Number of Missing BAT1806 Subjects Imputed as Responder									
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Number of Missing RoActemra Subjects Imputed as Responder	**25**	-11.96	-11.63	-11.3	-10.97	-10.64	-10.32	-9.99	-9.66	-9.33	-9.00
	26	-12.28	-11.94	-11.62	-11.29	-10.96	-10.63	-10.3	-9.98	-9.65	-9.32
	27	-12.59	-12.25	-11.93	-11.6	-11.27	-10.94	-10.62	-10.29	-9.96	-9.63
	28	-12.89	-12.56	-12.23	-11.91	-11.58	-11.25	-10.92	-10.59	-10.27	-9.94
	29	-13.2	-12.87	-12.54	-12.21	-11.89	-11.56	-11.23	-10.9	-10.58	-10.25
	30	-13.51	-13.18	-12.85	-12.52	-12.2	-11.87	-11.54	-11.21	-10.88	-10.56
	31	-13.82	-13.48	-13.16	-12.83	-12.5	-12.18	-11.85	-11.52	-11.19	-10.86
	32	-14.12	-13.79	-13.47	-13.14	-12.81	-12.48	-12.16	-11.83	-11.5	-11.17
	33	-14.43	-14.1	-13.77	-13.44	-13.12	-12.79	-12.46	-12.13	-11.81	-11.48
	34	-14.74	-14.4	-14.08	-13.75	-13.42	-13.1	-12.77	-12.44	-12.11	-11.78

Source: Reviewer's Table

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/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA ASSESSMENT AND EVALUATION

Application Number*:	761354
Supporting Document Number/s:	SDN 1, 18, 21, and 33
CDER Receipt Date:	9/29/2022
Sponsor:	Biogen Inc.
Product:	Tofidence (tocilizumab biosimilar)
Pharmacologic Class:	anti-interleukin-6 receptor (IL-6R) monoclonal antibody
Indication:	Rheumatoid Arthritis (RA), Polyarticular juvenile idiopathic arthritis (PJIA), Systemic juvenile idiopathic arthritis (SJIA)
Therapeutic area:	Rheumatology
Clinical Review Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Pharm/Tox Division	Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer:	Yu-Chen Tsai, PhD
Supervisor/Team Leader:	Timothy Robison, PhD, D.A.B.T.
Project Manager:	Susie Choi, Pharm.D.
Purpose of Review:	Other Safety assessment of Extractables and Leachables
Reviewer Completion Date:	August 22, 2023

Template Version: Sep 11, 2020

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APPEARS THIS WAY ON ORIGINAL

1 Executive Summary

1.2 Brief Discussion of Nonclinical Findings

An Information Request was sent to the Sponsor on August 2, 2023, to request justification that the Sponsor's analytical methods used in leachables studies were adequate to exclude the potential presence of [redacted]. The Sponsor responded on August 2, 2023 (as SDN 33).

Although [redacted] has not been shown to have carcinogenic potential, a safe exposure limit could be determined using [redacted] which is a known human carcinogen of the same general chemical class. The lowest published TD_{50} (doses giving a 50 percent tumor incidence equivalent to a cancer risk probability level of 1:2) for [redacted] ICH M7 (R2) details an alternative method for calculating an acceptable level of a known carcinogen (Note 4) using linear extrapolation to a level with no more than a 1:100,000 risk of cancer in humans. Using this methodology, [redacted] mg/kg/day TD_{50} in mice would calculate to a dose in mice of [redacted] µg/kg/day. Calculated to a 50 kg representative patient would yield an acceptable daily intake of [redacted] µg/person/day for adult humans (also known as Safety Concern Threshold (SCT)).

To derive a dose to cause tumors in 1 in 100,000 animals, divide by 50,000:
[redacted] mg/kg/day ÷ 50,000 = [redacted] µg/kg/day

To derive a total human daily dose:
[redacted] µg/kg/day x 50 kg body weight = [redacted] µg/person/day

This methodology is conservative in that it is meant to extrapolate to daily exposure over a lifetime (defined as 70 years) to a known carcinogen. The drug, BIIB800, is to be administered once a month which calculates to less than 3 years of total dosing days over a 70-year period.

The calculation is based on the TTC level for life-long treatment at 1.5 µg/person/day using the formula:

Less-than-lifetime AI = 1.5 µg x (365 days x 70 years lifetime = 25550) / 1095 days (3 years) = 35 µg

[redacted] µg/day is less than the Less-than-lifetime AI of 35 µg/day.

The analytical concentration (also known as Analytical Evaluation Threshold (AET)) that would need to be detectable to observe [redacted] when accounting for monthly dosing, is [redacted] µg/mL based on an SCT of [redacted] µg/day, using the following equation and worst-case assumptions: 1 dose per month, 2 containers per month, and 20 mL per container.

AET-
(b) (4) (ug/month) x 1 (dose/month) / 2 (container/month) x 20 (mL/container) = ~ (b) (4) ug/mL

The GCMS targets used by the Sponsor in the leachables study have a lower Limit of Quantitation of 0.1 µg/mL, meaning it can detect the presence of (b) (4) at concentrations corresponding to ≥ (b) (4) µg/day.

(b) (4) The BIIB800 drug product is an aqueous solution which is not amenable to extraction of (b) (4) Additionally, the extraction time and temperature used during the extractables study are much higher than actual process conditions. The study conditions were intentionally selected to force extractables in higher quantities than will be present during actual manufacturing conditions to adequately characterize the equipment. In the extractable and leachable studies analyzing the final drug product, (b) (4) was not detected. The materials used for primary packaging components of BIIB800 were used for other FDA-approved drugs.

Overall, the detection of (b) (4) as an extractable from materials used in the manufacturer line for the BIIB800 drug product does not pose a safety concern.

(b) (4)

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I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA ASSESSMENT AND EVALUATION

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Therapeutic area:	Rheumatology
Clinical Review Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Pharm/Tox Division	Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer:	Yu-Chen Tsai, PhD
Supervisor/Team Leader:	Timothy Robison, PhD, D.A.B.T.
Project Manager:	Susie Choi, Pharm.D.
Purpose of Review:	Other Safety assessment of Extractables and Leachables
Reviewer Completion Date:	July 27, 2023

Template Version: Sep 11, 2020

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1 Executive Summary

1.1 Introduction

The Sponsor is developing BAT1806, a recombinant humanized anti-human interleukin-6 receptor monoclonal antibody, as a biosimilar to US licensed Actemra (tocilizumab). The drug product, presented at three strengths (80 mg/4 mL [6 mL vial], 200 mg/10 mL [15 mL vial], and 400 mg/20 mL [25 mL vial]) is stored in (b) (4) clear glass vials. Each vial is closed with a (b) (4) rubber. The stoppered vial is sealed with an aluminum crimp seal with (b) (4) flip off button. Extractable studies were performed on the product-contact materials used in the DP manufacturing process. The studies were evaluated in the present review.

1.2 Brief Discussion of Nonclinical Findings

Extractable studies were performed on the product-contact materials (filter and manufacturing line) used in the DP manufacturing process. The two major extractables, (b) (4), were identified and found to have levels close to or exceeding the qualification threshold (QT) of 5 µg/day for non-genotoxic extractables or leachables. However, (b) (4) were not found in extractables studies with the container closure system or leachables studies with the drug product in the container closure system that human subjects would directly use. There were no leachables in the analysis of the drug product in the container closure system that corresponded to extractables identified from the filter or manufacturing line. The levels of these two extractables from the product-contacting materials of BIIB800 DP do not appear to pose any safety concerns.

Additional extractables of potential note included (b) (4) None of these extractables were observed in extraction studies with the container closure system or leachable studies with the drug product with the container closure system. However, the potential presence of (b) (4), a human carcinogen, raises significant safety concerns. As noted in a previous information request dated May 19, 2023, we have concerns regarding reporting limits for analytical methods used in leachables studies given that they were higher than the Analytical Evaluation Threshold (AET) of 0.0375 µg/mL, indicating that the methods did not possess sufficient sensitivity. The Sponsor should provide justification that analytical methods used in leachables studies were adequate to exclude the potential presence of (b) (4)

1.3 Nonclinical Comments to Sponsor

Your extractable studies conducted with product-contact materials identified (b) (4) at a level of (b) (4) µg/day (under Module 3.2.P.2.3, Section 2.8). (b) (4) is regarded as a potential human carcinogen. Its presence in the final

drug product would be unacceptable. As noted in a previous information request dated May 19, 2023, we have concerns that your reporting limits for analytical methods used in leachables studies were higher than the Analytical Evaluation Threshold (AET) of 0.0375 µg/mL, indicating that the methods did not possess sufficient sensitivity. Provide justification that your analytical methods used in leachables studies were adequate to exclude the potential presence of (b) (4). A response should be provided by August 3, 2023.

2 Drug Information

2.1 Drug

Product name: tocilizumab, BIIB800 (also referred to as “BAT1806”)

Molecular Weight: Approximately 149 kDa including carbohydrate chains.

Structure or Biochemical Description: Consisting of two heavy and two kappa light chains connected by inter-chain disulfide bonds.

Pharmacologic Class: Recombinant humanized monoclonal immunoglobulin (Ig)G1 anti-interleukin-6 receptor (IL-6R) antibody.

2.2 Relevant IND

IND 142381 (BAT1806, for treatment of rheumatoid arthritis)

2.3 Drug Formulation

The drug product is a concentrate for solution for infusion that is intended for intravenous infusion. The quantitative composition, function, and quality standard of each component in the finished drug product are provided in the table below. All excipients are compendial grade (see the table below). No novel excipients are used for the manufacture of the drug product and proposed levels are less than or equal to FDA-approved IV products.

Table 1. Quantitative Composition of Drug Product

Component	Function	Quality Standard	Amount per mL	Nominal Concentration	Nominal Amount (mg) per Vial [a]		
					80 mg	200 mg	400 mg
Tocilizumab	Active Ingredient	See 3.2.S.4.1; *Specifications*	20mg	20 mg/mL	80	200	400
L-Histidine	(b) (4)	Compendial	0.81mg	5.2 mM	3.24	8.10	16.20
L-Histidine hydrochloride monohydrate		Compendial	1.01 mg	4.8 mM	4.04	10.10	20.20
Arginine hydrochloride		Compendial	10.53 mg	50 mM	42.12	105.30	210.60
Sucrose		Compendial	20 mg	20 mg/mL	80.0	200.0	400.0
Polysorbate 80		Compendial	0.5 mg	0.5 mg/mL	2.0	5.0	10.0
Water for injection		Compendial	QS to final volume	QS to final volume	QS to (b) (4)	QS to	QS to

[a] Nominal quantity excludes overfill, see Module 3, 3.2.P.2.3 *Manufacturing Development Studies*.
QS = Quantum sufficit

(Excerpted from Sponsor submission)

The product, presented at three strengths (80 mg/4 mL [6 mL vial], 200 mg/10 mL [15 mL vial], and 400 mg/20 mL [20 mL vial]), is supplied in a (b) (4) glass vial closed with a stopper and seal with a flip off cap. The Sponsor reported that all packaging components are suitable for pharmaceutical use, and the materials of construction of the container components are compliant with compendial regulations (see the table below).

Table 2. Description of the Primary Container Closure

Table 1: Description of the Primary Container Closure

Item	Description	Supplier
Vial	Nominal size: 6 mL, 15 mL, 25 mL Material: (b) (4) clear glass compliant with USP/Ph.Eur./JP	(b) (4)
Stopper	Nominal Size: 20mm Material: (b) (4) rubber compliant with USP/Ph.Eur.	
Seal	Material: Aluminum crimp seal with (b) (4) flip off button	

(Excerpted from Sponsor submission)

2.4 Comments on Impurities/Degradants of Concern

Extractable studies were performed on the product-contact materials (filter and manufacturing line) used in the DP manufacturing process that consisted of (b) (4) and worst-case temperature condition relative to routine processing conditions.

The safety assessment of extractables from the filter and manufacturing line are described in Section 11.

2.5 Proposed Clinical Population and Dosing Regimen

Indications:

1) Rheumatoid arthritis (RA): Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
2) Systemic Juvenile Idiopathic Arthritis (SJIA): Treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
3) Polyarticular Juvenile Arthritis (PJIA): Treatment of patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

For intravenous infusion:

• Injection: in 80 mg/4mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) single-dose vials for further dilution prior to intravenous (IV) infusion

2.6 Regulatory Background

BLA 761354 is for BIIB800, a proposed biosimilar product to US-licensed Actemra® (tocilizumab). US-licensed Actemra® was approved by the FDA in 2010 for the IV route (BLA 125276). BLA 761354 was submitted to the FDA on September 29, 2022.

3 Studies Submitted

3.1 Studies Reviewed

The Sponsor's summaries as well as laboratory reports of the extractables studies with the product-contact materials used in the DP manufacturing process were reviewed to conduct safety assessments of the levels of extractables.

3.2 Previous Reviews Referenced

BLA 761354, Pharmacology/Toxicology BLA Assessment and Evaluation, Safety Assessment of Extractables and Leachables, Dated June 16, 2023.

11 Integrated Summary and Safety Evaluation

The drug product, presented at three strengths (80 mg/4 mL [6 mL vial], 200 mg/10 mL [15 mL vial], and 400 mg/20 mL [25 mL vial]) is stored in (b) (4) clear glass vials. Each vial is closed with a (b) (4) rubber. The stoppered vial is sealed with an aluminum crimp seal with (b) (4) flip off button. Based on a Safety Concern Threshold (SCT) of 1.5 µg/day, the Analytical Evaluation Threshold (AET) was calculated as 0.0375 µg/mL.

Extractable Assessment (product-contacting materials)

Extractable studies were performed on the product-contact materials (filter and manufacturing line) used in the DP manufacturing process using a harsh model solvent (b) (4) and worst-case temperature condition relative to routine processing conditions. The extractable study results from product-contacting materials are provided in the table.

The two major extractables, (b) (4), were found to have the values close to or above the qualification threshold (QT) of 5 µg/day, which is applicable for non-genotoxic extractables and leachables (i.e., (b) (4) y, as the drug will be given one dose). However, per ICH Q3C, (b) (4) are classified as Class 3 residual solvents (i.e., solvents with low toxic potential). Quantities of these residual solvents at 50 mg/day or less are acceptable without justification.

More importantly, (b) (4) were not found in extractables and leachables studies with the container closure system (see referenced review) that is used with the final drug product administered to patients. There were no corresponding leachables in the analysis of the drug product in the final container closure system that could be attributed to the filter or manufacturing line. All the observed leachables in the drug product in the final container closure system appeared to be from the rubber stopper.

Additional extractables of potential note included (b) (4) hat were observed at levels of (b) (4) µg/day, respectively. None of these extractables were observed in extraction studies with the container closure system or leachable studies with the drug product with the container closure system. The QT of 5 µg/day can cover (b) (4).

(b) (4)

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(b) (4)

In conclusion, the levels of extractables from the product-contacting materials of BIIB800 DP did not appear to pose any safety concern with the exception of (b) (4) The potential presence of (b) (4) a human carcinogen, raises significant safety concerns. As noted in a previous information request dated May 19, 2023, we have concerns regarding reporting limits for analytical methods used in leachables studies given that they were higher than the Analytical Evaluation Threshold (AET) of 0.0375 µg/mL, indicating that the methods did not possess sufficient sensitivity. The Sponsor should provide justification that analytical methods used in leachables studies were adequate to exclude the potential presence of (b) (4)

(b) (4)

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/s/

YU-CHEN TSAI
07/27/2023 02:51:48 PM

TIMOTHY W ROBISON
07/27/2023 07:35:29 PM
I concur. The review contains a comment to the Sponsor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA ASSESSMENT AND EVALUATION

Application Number*:	761354
Supporting Document Number/s:	SDN 1, 18, and 21
CDER Receipt Date:	9/29/2022
Sponsor:	Biogen Inc.
Product:	Tofidence (tocilizumab biosimilar)
Pharmacologic Class:	anti-interleukin-6 receptor (IL-6R) monoclonal antibody
Indication:	Rheumatoid Arthritis (RA), Polyarticular juvenile idiopathic arthritis (PJIA), Systemic juvenile idiopathic arthritis (SJIA)
Therapeutic area:	Rheumatology
Clinical Review Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Pharm/Tox Division	Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer:	Yu-Chen Tsai, PhD
Supervisor/Team Leader:	Timothy Robison, PhD, D.A.B.T.
Project Manager:	Susie Choi, Pharm.D.
Purpose of Review:	Other Safety assessment of Extractables and Leachables
Reviewer Completion Date:	June 16, 2023

Template Version: Sep 11, 2020

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

The Sponsor is developing BAT1806, a recombinant humanized anti-human interleukin-6 receptor monoclonal antibody, as a biosimilar to US licensed Actemra (tocilizumab). The drug product, presented at three strengths (80 mg/4 mL [6 mL vial], 200 mg/10 mL [15 mL vial], and 400 mg/20 mL [25 mL vial]) is stored in (b) (4) clear glass vials. Each vial is closed with a (b) (4) rubber. The stoppered vial is sealed with an aluminum crimp seal with (b) (4) flip off button. Extractables and leachables studies were conducted with the container closure system that were evaluated in the present review.

1.2 Brief Discussion of Nonclinical Findings

Based on a Safety Concern Threshold (SCT) of 1.5 µg/day, the Analytical Evaluation Threshold (AET) for the CCS was calculated as 0.0375 µg/mL.

With a focus toward organic (non-metal) extractables, under aggressive extraction conditions, (b) (4) In a rubber stopper extraction study and simulated leachables study, (b) (4) exceeded the AET of 0.0375 µg/mL. These 7 chemicals were used targeted potential leachables.

In the long-term leachable/migration study, three batches of BIIB800 DP (as 80 mg/4 mL presentation (worst-case contact surface area to volume ratio)) were evaluated under the accelerated storage condition (25±2°C) through 6 months and under the long-term storage condition (5±3°C) through 30 months. The 6 mL vial with a 4-mL fill was used a worst-case scenario. No leachables were identified that exceeded reporting limits. However, when multiplying the reporting limits by the maximum volume (40 mL), quantities of two leachables, (b) (4) were potentially greater than the qualification threshold (QT) of 5 µg/day. Levels of the two compounds were assessed for toxicological risks. The toxicological risk assessment determined PDEs for each compound and determined that the potential levels of (b) (4) did not pose any safety concerns.

It was noted that the Sponsor's reporting limits were higher than the AET of 0.0375 µg/mL indicating that the methods did not possess sufficient sensitivity. Given that the CCS, consisting of a (b) (4) clear glass vials and (b) (4) rubber stopper was considered of low risk, it was considered unnecessary at this time to request that the Sponsor improve the sensitivity of methods used for measurements of leachables. Further, all observed leachables were typically of (b) (4) rubber stoppers.

Levels of elemental (metal) leachables were also determined to pose no safety concerns.

1.3.1 Recommendations

Approval of the BLA is recommended from the nonclinical perspective.

1.3.2 Nonclinical Comments to Sponsor

Your reporting limits for analytical methods used in extractables and leachables studies were higher than the AET of 0.0375 µg/mL indicating that the methods did not possess sufficient sensitivity. Sensitivity of methods should be improved to at least match the AET of 0.0375 µg/mL for extractables and leachables studies conducted with future container closure systems used with the BIIB800 drug product.

2 Drug Information

2.1 Drug

Product name: tocilizumab, BIIB800 (also referred to as “BAT1806”)

Molecular Weight: Approximately 149 kDa including carbohydrate chains.

Structure or Biochemical Description: Consisting of two heavy and two kappa light chains connected by inter-chain disulfide bonds.

Pharmacologic Class: Recombinant humanized monoclonal immunoglobulin (Ig)G1 anti-interleukin-6 receptor (IL-6R) antibody.

2.2 Relevant IND

IND 142381 (BAT1806, for treatment of rheumatoid arthritis)

2.3 Drug Formulation

The drug product is a concentrate for solution for infusion that is intended for intravenous infusion. The quantitative composition, function, and quality standard of each component in the finished drug product are provided in the table below. All excipients are compendial grade (see the table below). No novel excipients are used for the manufacture of the drug product and proposed levels are less than or equal to FDA-approved IV products.

Table 1. Quantitative Composition of Drug Product

Component	Function	Quality Standard	Amount per mL	Nominal Concentration	Nominal Amount (mg) per Vial [a]		
					80 mg	200 mg	400 mg
Tocilizumab	Active Ingredient	See 3.2.S.4.1; *Specifications*	20mg	20 mg/mL	80	200	400
L-Histidine	(b) (4)	Compendial	0.81mg	5.2 mM	3.24	8.10	16.20
L-Histidine hydrochloride monohydrate		Compendial	1.01 mg	4.8 mM	4.04	10.10	20.20
Arginine hydrochloride		Compendial	10.53 mg	50 mM	42.12	105.30	210.60
Sucrose		Compendial	20 mg	20 mg/mL	80.0	200.0	400.0
Polysorbate 80		Compendial	0.5 mg	0.5 mg/mL	2.0	5.0	10.0
Water for injection		Compendial	QS to final volume	QS to final volume	QS to (b) (4)	QS to	QS to

[a] Nominal quantity excludes overfill, see Module 3, 3.2.P.2.3 *Manufacturing Development Studies*.
QS = Quantum sufficit

(Excerpted from Sponsor submission)

The product, presented at three strengths (80 mg/4 mL [6 mL vial], 200 mg/10 mL [15 mL vial], and 400 mg/20 mL [20 mL vial]), is supplied in a (b) (4) glass vial closed with a stopper and seal with a flip off cap. The Sponsor reported that all packaging components are suitable for pharmaceutical use, and the materials of construction of the container components are compliant with compendial regulations (see the table below).

Table 2. Description of the Primary Container Closure

Table 1: Description of the Primary Container Closure

Item	Description	Supplier
Vial	Nominal size: 6 mL, 15 mL, 25 mL Material: (b) (4) clear glass compliant with USP/Ph.Eur./JP	(b) (4)
Stopper	Nominal Size: 20mm Material: (b) (4) rubber compliant with USP/Ph.Eur.	
Seal	Material: Aluminum crimp seal with (b) (4) flip off button	

(Excerpted from Sponsor submission)

2.4 Comments on Impurities/Degradants of Concern

Extractable studies on individual primary container components ((b) (4) glass vial and (b) (4) rubber stopper) with various solvents were performed to identify potential leachable compounds. A simulated leachables study was also performed. Identified extractables were used as potential target leachables. Long-term leachable/migration studies were conducted with the CCS (80 mg/4 mL vial presentation) using accelerated conditions of 25°C for 6 months and long-term storage conditions of 5°C for up to 30 months.

The safety assessment of extractables and leachables from the primary container is described in Section 11.

2.5 Proposed Clinical Population and Dosing Regimen

Indications:

1) Rheumatoid arthritis (RA): Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
2) Systemic Juvenile Idiopathic Arthritis (SJIA): Treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
3) Polyarticular Juvenile Arthritis (PJIA): Treatment of patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

For intravenous infusion:

• Injection: in 80 mg/4mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) single-dose vials for further dilution prior to intravenous (IV) infusion

2.6 Regulatory Background

BLA 761354 is for BIIB800, a proposed biosimilar product to US-licensed Actemra® (tocilizumab). US-licensed Actemra® was approved by the FDA in 2010 for the IV route (BLA 125276). BLA 761354 was submitted to the FDA on September 29, 2022. Upon reviewing the extractable and leachable information, two information requests were sent to the Sponsor on April 12, 2023, and May 19, 2023, respectively. The responses from the Sponsor were included in the current review.

1. IR dated 04/12/2023
Your BLA is under review, and we request the following information regarding the container closure system:

In Section 3.2.P.2.4, Container Closure System, results of extractable and leachable studies were summarized. After reviewing the summary, we request the following:

1) Provide reports of extractable and leachable studies

2) Provide information of maximum patient exposure on a µg/day or µg/dose basis for each identified extractable and leachable,

Submit your responses to the BLA, no later than close of business April 21, 2023.

2. IR dated 05/19/2023
We are reviewing your BLA and April 21, 2023, submissions (latter being the response to our April 17, 2023, nonclinical information request) and request additional information:

In section 3.2.P.2.4, Container Closure System and section 1.11.1, Quality Information Amendment – FDA Information Request 2, it appears that you may have followed the ICH Q3D(R1) guidance to calculate individual Analytical Evaluation Thresholds (AETs) for organic extractables and leachables. However, ICH Q3D (R1) is limited to controlling elemental impurities (i.e., metals) and does not apply to the control of organic extractables and leachables. The method of calculating AETs, described in your submissions, was not appropriate for organic extractables and leachables. Provide the identities and quantities of all organic (non-elemental) extractables and leachables exceeding an AET based on the Safety Concern Threshold (SCT) of 1.5 µg/day. Reference 1 below has examples of AET calculations using the SCT of 1.5 µg/day. In addition, for organic extractables and leachables exceeding the qualification threshold (QT) of 5 µg/day and are not genotoxic, provide risk assessments for each compound.

We have provided publications below for your reference. Submit the requested information to the BLA by 5:00 PM Eastern Time on Thursday, May 25, 2023.

3 Studies Submitted

3.1 Studies Reviewed

The Sponsor's summaries as well as laboratory reports of the extractables and leachables studies with the primary container system were reviewed to conduct safety assessments of the levels of leachables (and extractables).

3.2 Previous Reviews Referenced

None.

11 Integrated Summary and Safety Evaluation

The drug product, presented at three strengths (80 mg/4 mL [6 mL vial], 200 mg/10 mL [15 mL vial], and 400 mg/20 mL [25 mL vial]) is stored in (b) (4) clear glass vials. Each vial is closed with a (b) (4) rubber. The stoppered vial is sealed with an aluminum crimp seal with (b) (4) flip off button. Based on a Safety Concern Threshold (SCT) of 1.5 µg/day, the Analytical Evaluation Threshold (AET) was calculated as 0.0375 µg/mL.

Extractables

Extractable characterization was performed for the individual primary container closure materials ((b) (4) glass vial and (b) (4) rubber stopper) using aggressive extraction conditions that are extreme relative to intended use conditions.

Extractable characterization was performed by incubating representative vials in four model solvents (b) (4)

(b) (4) for 72 hours at 70°C using a worst-case contact surface area to volume ratio of approximately 36 cm^2/mL (4 ml fill in 6 mL vial).

The elemental impurities (metals) reported for the glass vial extracts are shown in the table below. Two of the metals, (b) (4), are essential components for normal human physiology and the exposures per dose are well below amounts present in human serum. The other two metals detected, (b) (4), are below established reference limits in ICH Q3D.

Table 3. Glass Vial Extractable Results

(b) (4)

Per PQRI (Product Quality Research Institute) guidelines, an Analytical Evaluation Threshold (AET) for organic extractables and leachables in the BIIB800 drug product was calculated to be 0.0375 µg/mL using the SCT of 1.5 µg/day using the following equation and worst-case assumptions: 1 labeled dose per container, 2 containers per day, and 20 mL per container.

$$\text{Estimated AET} = \frac{1.5\ \mu g/day\ (SCT) * 1\ dose/container}{2\ containers/day * 20\ mL/container} = 0.0375\ \mu g/mL$$

Extractable characterization of (b) (4) rubber stoppers was performed by incubating stoppers in (b) (4) at 70°C for 24 hours. In addition, a simulated leachable study was performed under accelerated conditions with the assembled primary packaging components ((b) (4) glass vial and (b) (4) rubber stopper) filled with two solvents: (b) (4) and BIIB800 DP solution. The 6-mL vial with a 4 mL fill was used as a worst-case contact surface area to volume ratio at approximately 36 cm^2/mL. The filled containers were stored inverted at 60°C for 24 hours and then sonicated for 30 minutes. For these studies, qualified UPLC-MS/MS (Liquid Chromatography with diode array detector-mass spectroscopy) and GC-MS (Gas Chromatography-Mass Spectrometry) analytical methods were used. The table below summarizes the organic extractables that exceeded the estimated AET (0.0375 µg/mL) from the rubber stopper extraction and simulated leachable studies.

Table 4. Summary of Organic Compounds from Rubber Stopper Extraction and Simulated Leachable Studies exceeding the estimated AET

(b) (4)

Other organic compounds detected by GC-MS under aggressive extraction conditions included: (b) (4) These compounds were identified based on confirmed matches against a NIST spectral database. (b) (4) exceeded the AET of 0.0375 µg/mL. These compounds were included in the subsequent targeted long-term leachable/migration study, along with (b) (4)

Leachables

The seven organic compounds identified in the rubber stopper extraction and simulated leachable studies were considered potential leachables and were monitored in the long-term leachable/migration study. In the study, three batches of BIIB800 DP (as 80 mg/4 mL presentation (worst-case contact surface area to volume ratio)) were evaluated under the accelerated (25±2°C) storage condition through 6 months and under the long-term (5±3°C) storage condition through 30 months (see the table below for study design).

Table 5. Long-Term Leachable/ Migration Study Design

Test Material	Storage Condition	Time points (months)	Orientation	Analytical Methods/ Compound Type Detected
DP(80mg/4mL)[a]	N/A	0	N/A	ICP-MS: Metals UPLC-MS/MS: NVOC GC-MS: SVOC
	5±3°C (Long-term)	3, 6, 12, 24, 30	Upright, Inverted	
	25±2°C (Accelerated)	3, 6	Upright, Inverted	

[a] DP batches A0520180402, A0520180503, A0520180604

(Excerpted from Sponsor submission)

As shown in the table below, values of Maximum Exposure per Dose of all metal leachables were below their respective reference limits, and values of Maximum Concentration were below their respective AETs.

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The table below summarizes results of the seven target compounds from the study, along with corresponding analytical method reporting limit (RL), and potential maximum quantity administered per day (µg/day). No compounds were detected through 30 months at 5±3°C or 6 months at 25°C using the reporting limits. It was noted that the Sponsor's reporting limits were higher than the AET of 0.0375 µg/mL indicating that the methods did not possess sufficient sensitivity. Given that the CCS, consisting of a (b) (4) clear glass vials and (b) (4) rubber stopper was considered of low risk, it was considered unnecessary at this time to request that the Sponsor improve the sensitivity of methods used for measurements of leachables. Further, all observed leachables were typically of (b) (4) rubber stoppers.

Potential maximum quantities of leachables (µg/day) were determined based on the method reporting limit multiplied by the worst-case 40 mL dose volume (associated with 800 mg, which is the maximum adult dose for rheumatoid arthritis indication).

None of the seven targeted organic compounds from leachable/ migration study was classified as genotoxic. Five of seven targeted organic compounds remained below the 5 µg/day qualification threshold (QT) which is applicable for non-genotoxic compounds. Potential maximum quantities for the two compounds monitored by UPLC (i.e., (b) (4)) were quantified as <(b) (4) µg/day and < (b) (4) µg/day, respectively, based on analytical method reporting limits and exceeded the qualification threshold of 5 µg/day.

(b) (4)

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(b) (4)

In conclusion, the levels of leachables from the primary container closure of BIIB800 DP did not appear to pose any safety concern.

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/s/

YU-CHEN TSAI
06/16/2023 10:52:20 AM

TIMOTHY W ROBISON
06/16/2023 11:40:54 AM
I concur.