25 April 2024
EMA/227882/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tofidence

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/005984/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

%BLQ	percentage below the lower limit of quantification
ACR	American College of Rheumatology
ACR20/50/70	American College of Rheumatology 20%/50%/70% response criteria
ADA	antidrug antibody
AE	adverse event
AF	attributable fraction
AFj	attributable fraction up to timepoint j
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
APAC	Asia Pacific
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Class
bDMARD	biological disease-modifying antirheumatic drug
BDRM	Blinded Data Review Meeting
BLQ	below the lower limit of quantification
BW	body weight
CCP	cyclic citrullinated peptide
CI	confidence interval
Cj	compliance up to timepoint/visit
COX	cyclooxygenase
CRF	Case Report Form
CRO	contract research organization
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
Ctrough	trough serum concentration
CV	coefficient of variation
CV%	coefficient of variation percent
CYP450	cytochrome P450
DAS28	Disease Activity Score on 28 Joints
DAS28-CRP	Disease Activity Score on 28 Joints-C-reactive protein
DAS28-ESR	Disease Activity Score on 28 Joints-erythrocyte sedimentation rate
DMARD	disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EA	exploratory analysis
ECG	electrocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
EOS	End-of-Study
e-PRO	electronic subject reported outcome
ESR	erythrocyte sedimentation rate
ET	early termination
EULAR	European League Against Rheumatism

FAS	Full Analysis Set
FCS	fully conditional specification
GEE	generalized estimating equation
Geo	geometric
GLM	generalized linear model
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IEC	independent ethics committee
IgG	immunoglobulin
IGRA	interferon-gamma release assay
IL	interleukin
IL-6R	interleukin 6 receptor
IP	investigational product
IRB	institutional review board
IV	intravenous
IWRS	interactive web response system
LSM	least squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent-to-treat
Mj	total missed doses up to timepoint j
MMRM	mixed-effect models for repeated measures
MNAR	missing not at random
Mod	moderate
mrj	missed doses up to timepoint j due to remote visits
MTX	methotrexate
n	number of observations
N	number of subjects
NAb	neutralizing antibody
NHP	Non-human Primate
nj	administered dose up to timepoint j
Nj	planned
NRI	Non-Responder imputation
NSAID	nonsteroidal anti-inflammatory drug
PD	protocol deviation
PK	pharmacokinetic

PKS	Pharmacokinetic Set
PPS	Per Protocol Set
PT	preferred term
PtGA	Patient Global Assessment
RA	rheumatoid arthritis
Resp	response
RMP	Reference Medicinal Product
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SJC	swollen joint count
SJC28	Swollen Joint Count in 28 Joints
SJC66	Swollen Joint Count in 66 Joints
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TK	Toxicokinetics
TJC	tender joint count
TJC28	Tender Joint Count in 28 Joints
TJC68	Tender Joint Count in 68 Joints
TNF	tumor necrosis factor
TOST	two one-sided tests
TP	treatment period
TP1	initial treatment period
TP2	second treatment period
tsDMARD	targeted synthetic disease-modifying antirheumatic drug
ULN	upper limit of normal
VAS	visual analogue scale
W	week
w/o	without
WBC	white blood cell
β-HCG	beta human chorionic gonadotropin

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Netherlands B.V. submitted on 10 September 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Tofidence, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

- Rheumatoid arthritis (RA):
  - the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX) (monotherapy or in combination with MTX).
  - the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumor necrosis factor (TNF) antagonists (monotherapy or in combination with MTX).
- Coronavirus disease 2019 (COVID-19): the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.
- Polyarticular juvenile idiopathic arthritis (pJIA): the treatment of juvenile idiopathic polyarthritis (PJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX (monotherapy or in combination with MTX).
- Systemic juvenile idiopathic arthritis (sJIA): the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids (monotherapy or in combination with MTX).
- Cytokine release syndrome (CRS): the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal product.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA:

- Product name, strength, pharmaceutical form: RoActemra, 20 mg/ml, Concentrate for solution for

infusion

- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 16-01-2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/492/001-006

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: RoActemra, 20 mg/ml, Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 16-01-2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/492/001-006

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: RoActemra, 20 mg/ml, Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 16-01-2009
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/08/492/001-006
- Bioavailability study number(s): BAT1806-001-CR (a phase 1 randomised, double-blind, single-dose, 3-arm, parallel group study) and BAT1806-002-CR (a phase 3 randomised, double-blind, parallel group, active-control study)

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following Scientific Advice on the development relevant for the indications subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
28 February 2019	EMEA/H/SA/4052/1/2019/III	*Elena Wolff-Holz, Andrea Laslop*

The Scientific Advice pertained to the following quality, non-clinical, and clinical aspects:

- *Design of the characterisation studies for the cell bank system*
- *Comparability exercise for changes in the manufacturing process*
- *Strategy for demonstration of analytical biosimilarity*
- *Manufacturing process and process control and established DS and DP specifications to support a MAA*
- *Strategy for reduction of virus contamination*
- *Non-clinical comparability strategy*
- *Design of Phase 1 study in healthy Chinese male subjects, evaluating the PK profile, safety, tolerability and immunogenicity among BAT1806 and EU-sourced and US-licensed tocilizumab*
- *Design of the randomised, double-blind, multi-centre, multi-national clinical comparability Phase 3 study to compare the efficacy, safety and immunogenicity of BAT-1806 versus EU-sourced RoActemra in rheumatoid arthritis with inadequate response to methotrexate*
- *Agreement that the current comparability plan can support the same therapeutic indications for BAT1806 as those for RoActemra*

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Simona Badoi

The application was received by the EMA on	10 September 2022
Accelerated Assessment procedure was agreed-upon by CHMP on	N/A
The procedure started on	29 September 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 December 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 January 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 March 2023
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
A GMP inspection at Bio-Thera site (NO.155 YAOTIANHE STREET, YONGHE ZONE. 511356, HUANGPU DISTRICT, GUANGZHOU, GUANGDONG, China between 23-27/10/2023. The positive outcome of the inspection carried out was issued on 19/03/2024	19/03/2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	02 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 April 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tofidence on	25 April 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Not applicable for biosimilars.

2.1.2. Epidemiology

Not applicable for biosimilars.

2.1.3. Biologic features

Not applicable for biosimilars.

2.1.4. Clinical presentation, diagnosis

Not applicable for biosimilars.

2.1.5. Management

Not applicable for biosimilars.

2.2. About the product

Tocilizumab is a recombinant humanised IgG1 antibody directed against soluble and membrane-bound IL-6 receptors, thereby inhibiting IL-6-mediated signalling.

Tofidence (BAT1806, BIIB800) has been developed as a biosimilar to the reference product RoActemra.

The applicant is proposing BAT1806 IV infusion for marketing authorization for the following IV indications approved for the reference product that are currently eligible for biosimilar authorisation:

- Rheumatoid arthritis (RA):
    - the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX) (monotherapy or in combination with MTX).
    - the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more

disease-modifying anti-rheumatic drugs (DMARDs) or tumor necrosis factor (TNF) antagonists (monotherapy or in combination with MTX).

- Coronavirus disease 2019 (COVID-19): the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.
- Polyarticular juvenile idiopathic arthritis (pJIA): the treatment of juvenile idiopathic polyarthritis (PJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX (monotherapy or in combination with MTX).
- Systemic juvenile idiopathic arthritis (sJIA): the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids (monotherapy or in combination with MTX).

The indication for cytokine release syndrome (CRS) was claimed to at submission but withdrawn during the responses to D121.

2.3. Type of application and aspects on development

Tofidence (BAT1806, BIIB800) has been developed as a biosimilar to the reference product RoActemra.

The composition of the proposed biosimilar (Tofidence) differs from the one of the Reference Medicinal Product (RMP), in terms of buffer system used. RoActemra is buffered with sodium hydrogen phosphate, whereas the tocilizumab biosimilar uses a histidine buffer system and addition of arginine as stabiliser/tonicity agent. Currently only the three approved vial presentations (4ml, 10ml, and 20 ml at 20mg/ml) of RoActemra for intravenous use are the subject of this MAA.

Scientific advice was sought from European Medicines Agency (EMA) Committee for Human Medicinal Products (CHMP) (EMEA/H/SA/4052/1/2019/III, February 2019) regarding the analytical similarity data, and the quality, nonclinical and clinical development programs.

The company took the recommendations from applicable guidance (ICH, EMA, specific EMA biosimilar guidance, etc.) for the development of Tofidence (BAT1806, BIIB800) sufficiently into account.

The adequacy of the BAT1806 clinical program was discussed and was considered acceptable for a Marketing Authorisation Application (MAA). In general, the proposed design, study population, and immunogenicity timepoints selected for the pivotal Phase 3 study BAT-1806-002-CR were agreed with specific recommendations especially concerning the equivalence margin and the time point for the evaluation of the primary endpoint. The applicant initially planned the primary assessment at week 24, which was considered not optimal in the context of a biosimilar exercise per EMA Scientific Advice as in once weekly dosing a plateau could be reached at week 12. Therefore, measuring a response at week 24 may not be the most sensitive time point for detecting potential differences between biosimilar candidate and originator. The applicant changed the primary assessment for EMA (Week 12). Additionally, the Applicant was advised that an equivalence margin of [-15%, +15%] would not be acceptable, so the applicant introduced a revised margin of [-14,5%, +14,5%].

3. Quality aspects

3.1.1. Introduction

Tocilizumab, the active substance in Tofidence, also referred to as BIIB800, is a humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

The finished product is presented as a concentrate for solution for infusion in a vial containing 20 mg/mL of tocilizumab formulated with sucrose, polysorbate 80, L-histidine, L-histidine hydrochloride monohydrate, arginine hydrochloride and water for injections. Presentations include contents of 4 mL, 10 mL and 20 mL, with packs of 1 and 4 vials for each.

Tofidence was developed as biosimilar to the EU reference medicinal product RoActemra (EMEA/H/C/000955).

3.1.2. Active Substance

3.1.2.1. General information

Tocilizumab is a recombinant humanised IgG1 monoclonal antibody directed against soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), thereby inhibiting IL-6-mediated signalling. It harbours one single N-linked glycosylation site (Asp 299) and has a C-terminal lysine truncation in the heavy chain (HC). It further shows classical IgG1 post-translational modifications such as pyro-glutamate at position 1 in the HC, as well as oxidations, deamidations in both chains.

The active substance is composed of two HCs and two kappa light chains (LCs) connected by interchain disulfide bridges between the two HCs at the level of Cys 228 and Cys 231 and between the Cys214 of the LC and the Cys222 of the HC. There are four intramolecular disulphide bridges for the HC and two for the LC. The relative molecular mass is 149 kDa, including carbohydrate chains.

3.1.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Tocilizumab is manufactured at Bio-Thera Solutions, Ltd., 155 Yaotianhe Street, Yonghe Zone, Huangpu District, Guangzhou, 511356, China. All sites involved in manufacturing and control of the active substance operate in compliance with EU GMP.

The description of the active substance manufacturing process steps identifies all the steps per phase of manufacturing along with a more detailed description of each upstream and downstream steps (cell culture, harvest, and purification), which includes the assignment of the controlled process parameters of each unit operation and the associated in-process controls (IPCs) and tests, with the critical controls clearly highlighted. An overview of storage and shipping conditions is also provided.

A narrative description of the cell culture process is provided. The process starts with thawing of one vial of the working cell bank (WCB). Following production fermentation, the harvested cell culture supernatant is

further processed in downstream purification unit operations which include a series of chromatography, viral inactivation and filtration steps. IPCs and process parameters at each step have been defined as either critical or non-critical. Acceptable ranges and limits have been provided. Process holds have been indicated and is considered adequate.

There are no reprocessing steps for the active substance.

The unique current active substance batch numbering system is described and is considered acceptable.

Information on column dimensions as well as filters areas used for downstream process are included in the process description, as well as information on the corresponding materials.

The active substance manufacturing process description is acceptable with a sufficient level of details.

Control of materials

Raw materials

Raw materials used for cell bank generation or used in the active substance manufacturing process are provided. The compendial or non-compendial materials are sourced from qualified and approved sources, sampled and tested under appropriate conditions and according to the respective acceptance criteria. Based on a risk assessment raw materials are either considered critical or non-critical and may have a higher impact in the process performance and final product quality.

A list of materials of biological origin was also provided. Some of the raw materials listed as compendial do not comply with the European Pharmacopoeia. The applicant performed a gap analyses to identify the discrepancies for the compendial materials not meeting Ph. Eur. standards. Overall, the gap analyses can be accepted. As the gap analyses concern raw materials the risk to patients is considered low and the issue was considered addressed.

The internal specifications of the non-compendial raw materials used are presented. For all the raw materials described, the specification set can be considered acceptable.

The qualitative composition of the cell culture media and process solutions is provided. These do not include materials of human or animal origin.

The testing strategy in place for resins and filters used in the active substance manufacturing process is included.

Source, history and generation of cell substrate

The generation of the expression construct plasmid has been described in detail. Sufficient information on the transfection selection and primary cell bank generation have been presented.

The preparation, testing, storage, and release of the cell banks is sufficiently described. No evidence of microbial contamination was observed.

The acceptance criteria for the qualification of a new WCB are presented and found to be acceptable.

The banks are adequately characterised in line with ICH Q5A. The genetic characterisation of the MCB and EOPC involved the verification of the integrated sequences which were consistent with theoretical sequence of tocilizumab; and determination of the gene copy number. The results obtained support the genetic stability of the recombinant cell line and also the set limit of *in vitro* cell age (LIVCA).

Cell bank stability during storage in liquid nitrogen vapor phase is monitored over time. This is acceptable.

Control of Critical Steps and Intermediates

The control strategy for the tocilizumab active substance manufacturing process incorporates control of process parameters and in-process tests (IPCs). Based on a risk assessment the process parameters and IPCs were categorised as critical (CPP, CIPC) or non-critical (non-CPP, IPC). Other controlled process parameters and IPCs have been identified not to impact product quality but may impact process consistency. In general, the controlled parameters are considered adequate and the acceptance criteria (acceptable range, in-process specification) supported by development data.

Overall, the process parameters and IPCs in combination with the other control measures are harmonised with what is described in the process description and is sufficient to ensure quality and safety of tocilizumab active substance as well as to monitor process consistency. A description of the methods applied in the IPC controls which differ from the methods used for release and stability of the active substance has been provided.

Process Validation

The tocilizumab active substance manufacturing process has been validated by conducting process performance qualification (PPQ) batches. All CPPs as well as IPCs met their predefined acceptance criteria or ranges. Several non-CPPs exceeded their ranges and sufficient justifications were provided.

The PPQ results are in general adequately and thoroughly presented for CPP and non-CPP, IPC and performance attributes.

Extractables and leachables

A risk assessment with the outcome of a leachable risk rating of the potential extractables and leachables study was conducted focusing on pre-defined key points regarding technical process, exposure temperature and duration, extractability, and contact area. Process- and product-related impurity clearance to adequate levels was also demonstrated during the PPQ runs. Microbial control of the manufacturing process was shown to be effective as all bioburden and endotoxin IPC limits were met.

Chromatography resin and filtration membranes lifetime

Chromatography resin lifetimes have been established. In small scale studies, process intermediates obtained from representative GMP full scale batches were used as starting materials. The data support the claimed preliminary lifetimes. Final lifetimes will be defined after the finalisation of the full-scale process verification of column performance. The resin lifetime validation protocol is considered sufficient.

The membrane lifetime will be established at the commercial-scale. The final lifetime will be defined after the finalisation of the full-scale process verification of membrane performance. The provided protocol is mostly sufficient.

Hold times

Intermediate hold times were established using extended storage of PPQ batch materials. The provided results support the set hold conditions.

Shipping validation

Shipping validation of the active substance has not been performed, since active substance and finished product manufacturing take place at the same manufacturing plant, in two adjacent buildings.

The validation status of the manufacturing process during product lifecycle will be assured through a continued (ongoing) process verification program as required.

Overall, the active substance manufacturing process is considered adequately validated.

Manufacturing process development

The active substance manufacturing history has been described in sufficient detail. Altogether, the history of the active substance batches and their use during process development are considered sufficiently described.

To support comparability between the different manufacturing processes, a formal ICH Q5E compliant comparability evaluation was performed. Comparability of results from physicochemical, biochemical and biological assays were provided. For that matter, batches manufactured with the different processes were compared regarding results from quality attributes associated with protein structure, activity, purity/impurities, contaminants and stability profile (when appropriate) gathered through batch release testing, active substance characterisation between pre- and post-change material, stability studies at accelerated and stress conditions (to assess routes and rates of degradation), as well as forced degradation studies (to demonstrate a consistent pattern and rate of degradation under conditions expected to generate significant and specific degradation).

The materials from both processes are considered comparable.

A risk assessment has been performed to identify tocilizumab critical quality attributes (CQAs). The approach has been sufficiently described and is considered adequate. CQAs have been defined as mandatory by default due to compendial requirements or regulatory expectations or as non-mandatory using a scoring scheme. Impact and uncertainty scores were defined for four product impact categories including efficacy, pharmacokinetics/pharmacodynamics, immunogenicity, and safety. The final list of CQAs is considered acceptable.

Process characterisation is undertaken to assess the impact of medium or high risk process parameters and raw materials on product quality attributes and process consistency versus planned experimental input ranges. In summary, the studies are considered sufficiently well designed. The demonstrated impacts of process parameters on quality attributes and performance indicators have been adequately integrated into the final control strategy.

Characterisation

Elucidation of structure and other characteristics

Physicochemical and *in vitro* biological characterisation were performed and data are presented.

The attributes evaluated consisted in primary, secondary and higher order structures, in addition to carbohydrate structure and glycan distribution, as well as charge isoforms. Functional tests were used to confirm the activity of BIIB800 and included Fab- and Fc-related biological activity.

Higher order structure was studied , indicating that the secondary structures of different batches of samples were consistent.

Extensive *in vitro* Fab-related biological characterisation was performed.

The results demonstrate that the structure of BIIB800 is consistent among the batches manufactured and characterised. These features are consistent with the structures of human tocilizumab and Fc domains of a human IgG1. Functional characteristics of BIIB800 were found to be consistent with the expected IL-6R

binding functionalities and the inhibition of IL-6-mediated activity and potency to bind IL-6R were consistent across all the active substance batches. The results support the mechanism of action and clinical relevance of BIIB800.

The binding properties of the Fc part of BIIB800 have been extensively characterised, using a panel of different assays to evaluate the different functionalities. In relation to effector function analysis, ADCC and CDC are not part of mode of action for BIIB800.

Overall, the results of physiochemical and *in vitro* biological characterisation demonstrate the integrity and consistency of the structural, biochemical, and biological characteristics of the active substance manufactured using the proposed commercial process.

Impurities

The impurities of tocilizumab were divided into potential contaminants, process- and product-related impurities.

Data confirm sufficient clearance of the impurities during the manufacturing process. The levels detected are well below toxicology safety limits with high safety margins present.

The defined product-related impurities is considered adequate based on the characterisation studies.

3.1.2.3. Specification

Specifications

The active substance specifications include control of identity, purity and impurities, potency and other general tests.

The justification of specifications has been based on the results obtained for active substance batches at release. Based on the available data, the proposed acceptance criteria are acceptable.

The potency of active substance is verified by using two orthogonal test methods.

The specifications set for the tocilizumab active substance are considered adequate.

Analytical procedures

The test methods used for release and IPC testing consist of compendial and non-compendial methods which are state-of-the-art. The tests for appearance, pH, bioburden and bacterial endotoxins are stated to comply with Ph. Eur. and a non-detailed description is provided, which is acceptable. The description of the non-compendial methods is considered sufficient including the method principle, operating conditions, equipment. Additionally, the system suitability criteria and representative chromatogram/electropherogram/dose-response curve are provided.

Information on the validation status of the non-compendial test methods has been provided as well as a more detailed description for each method, this is considered acceptable. For compendial methods, only a demonstration of suitability for the intended use is presented.

Batch analysis

Batch release data are provided for tocilizumab manufactured from the commercial process. All test results are within specifications.

Reference Standards

An overview of the qualified product reference standards is provided. A two-tiered system with primary and working reference standards has been established for tocilizumab. The history of the reference standard used during development has been provided. The current primary reference standard will be used for the establishment of new working reference standards.

Both reference standards are requalified annually in line with a pre-defined stability protocol.

Qualification data demonstrated the suitability of the primary and working reference standards.

Container closure system

The container closure system (CCS) of tocilizumab active substance is a flexible bag composed by a product contact film of copolymer.

All incoming bags are checked. The primary container material complies with Ph. Eur. 3.1.7 and Ph. Eur. 3.2.2 as well as with Ph. Eur. 2.9.19. Its compatibility with the active substance is ensured by the data gathered container closure integrity and leachable and extractable studies. In conclusion, no risk from extractables and leachables was identified.

The suitability for the storage and transportation of active substance has also been verified over shipping qualification studies.

Overall, the suitability and safety of the CCS is described in sufficient detail and considered acceptable.

A potential future change in primary container closure supplier needs approval via a variation procedure.

3.1.2.4. Stability

The tocilizumab active substance stability program includes, in line with ICH Q5C, batches tested under long-term, accelerated and stressed conditions. The stability data obtained indicate that the active substance is stable in the proposed commercial container closure system at least up to the period and under conditions tested.

The data provided support the set shelf-life at the long-term storage condition.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and pharmaceutical development

Description of the product

The BIIB800 finished product is formulated for intravenous (IV) administration as a sterile 20 mg/mL concentrate for solution for infusion filled in Type I glass vials closed with a butyl rubber stopper and a seal with a flip-off cap. The finished product contains L-histidine, L-histidine hydrochloride monohydrate, arginine hydrochloride, sucrose, polysorbate 80, and water for injections. BIIB800 finished product 20 mg/mL is available in three configurations: content of 4 mL, 10 mL and 20 mL (packs of 1 vial and 4 vials each).

Excipients have Ph. Eur. grade and are commonly used in the formulation for monoclonal antibody finished products. There are no novel excipients and no excipients of animal or human grade. The formulation does

not follow the one from the reference medicinal product EU-RoActemra, with different salt in the buffer and pH.

The vial, stopper and seal components of the CCS for the finished product are compliant with the appropriate Ph. Eur. monographs for primary containers and closures.

The minimum fill volumes (overfill) are 4.25 mL, 10.25 mL and 20.80 mL for the 3 configurations, respectively. This is acceptable.

The description and composition of the finished product is acceptable.

Pharmaceutical development

The quality target product profile (QTPP) is presented.

Formulation development

The development of the commercial formulation has been sufficiently described. The excipients were selected after a series of screening studies A different formulation from the reference medicinal product formulation was chosen. In line with EMA/CHMP/BWP/247713/2012, the formulation of a biosimilar can differ from the reference medicinal product formulation. The BIIB800 formulation is considered adequate.

There are no overages of the active substance.

The information on physicochemical and biological properties is considered sufficient.

Manufacturing process development

The batch history was provided for process development together with the implemented changes (supported by additional process characterisation as needed), which all occurred before the Phase 1 and Phase 3 pivotal clinical studies with no major process changes between the process used to prepare the pivotal clinical material and the proposed commercial process. An ICH Q5E compliant comparability exercise is not considered necessary as the changes were made before entering clinical trials and the biosimilarity assessment.

To support the development of the finished product manufacturing process so that a finished product of a suitable and consistent quality is produced, a risk assessment following ICH Q8 and ICH Q9 guidance was performed during product development.

Container closure system

The CCS has been sufficiently described. The vial, stopper and seal components are standard materials used for the packaging of parenteral drugs, and are declared to be compliant with appropriate Ph. Eur. monographs for primary containers and closures.

The control strategy has been sufficiently described. The results reported indicate that container closure system ensure a hermetic seal and sterility maintenance of the finished product.

In-use

Tocilizumab is administered by infusion, diluted in 0.9% sodium chloride (NaCl). Compatibility of tocilizumab with standard infusion sets and in-line filters has been demonstrated. An in-use stability study shows that the diluted tocilizumab can be stored at room temperature (30±2°C) for up to 48 hours and 2°C to 8°C for up to 96 hours with light room exposure A dose accuracy verification study was also performed to confirm the

suitability of the infusion conditions to deliver the entire dose of the product. The compatibility studies support the instructions for use and handling in the proposed SmPC.

3.1.3.2. Manufacture of the product and process controls

Description of the manufacturing process

All sites involved in manufacturing and control of the finished product operate in compliance with EU GMP.

A flow diagram including process parameters and IPCs has been provided. Each step has been described in sufficient detail.

There are no reprocessing steps for the finished product manufacturing process.

The batch formula of tocilizumab finished product has been sufficiently provided.

Process Controls

Critical steps during the manufacturing of the tocilizumab finished product have been identified during manufacturing development. Adequate CPPs and IPCs are implemented to ensure a controlled state of the manufacturing process and of finished product quality attributes.

For each process step, a maximal processing time has been assigned. Process steps durations and hold times in the finished product manufacturing process together with their respective hold conditions and periods have been provided. The proposed holding times and temperature have been determined during process validation.

No intermediates are defined or controlled despite the definition of holding times for the various steps of the process.

Process validation

The validation of the tocilizumab finished product was performed covering all operations units. A bracketing approach was used. This is considered adequate.

The PPQ batches met the acceptable ranges with no trends observed, thereby showing consistency amongst each other, with no differences between batches treated as per routine or maximum processing conditions.

The aseptic filling process was validated via filter validation, component qualification, CCI testing, media fills and qualification of the sterilisation of the equipment and CCS. This is considered adequate.

Information on the validation of the shipping conditions for finished product were also provided and do not call for comments.

Overall, the finished product manufacturing process is considered adequately validated.

3.1.3.3. Product specification

Specifications

The finished product specifications include control of identity, purity and impurities, potency and other general tests.

The specification essentially free of particles complies with Ph. Eur 2.9.20 and 5.17.2.

CCI testing is performed during stability testing instead of sterility testing, which is acceptable.

The finished product specifications are considered acceptable.

Analytical procedures

The methods used for the release of the tocilizumab finished product are either compendial or identical to the ones used for active substance release, with the exception of polysorbate 80 testing. The method has been sufficiently described and adequately validated.

The suitability of the sterility method was adequately assessed.

The endotoxin test used for release of the finished product is compendial (Ph. Eur. 2.6.14 kinetic turbidimetric assay).

Batch analysis

Batch release data are provided for tocilizumab manufactured from the commercial process. All test results are within specifications.

Reference standard

The reference standards used for testing of the finished product are the same as those used for testing of the active substance.

Characterisation of impurities

The product-related impurities potentially present in tocilizumab finished product are the same as those potentially present in tocilizumab active substance, except sub-visible particulates.

Extractables and leachables have been investigated during manufacturing development (see above).

An elemental impurity assessment in line with ICH Q3D revealed no concern.

A nitrosamines risk assessment has been provided. No risk was identified as expected considering the nature and the manufacturing process of the product and no additional specific control is considered necessary.

Overall, the release and characterisation test results indicate that the levels of impurities in the tocilizumab finished product are low and consistent across finished product lots manufactured at the commercial site.

Container closures system

The tocilizumab finished product CCS consists of a glass vial made of type I clear borosilicate glass, a stopper made of rubber and an aluminium seal cap with a flip off button. For each component of the CCS, the respective material, quality standard/requirement, manufacturer/supplier, respective specifications, representative Certificate of Analysis and representative drawings are provided. The glass vial and stopper are in immediate contact with the finished product and comply with applicable compendial requirements. The components of the primary packaging material have been properly described and the materials of the containers and closures comply with the applicable quality requirements, furthermore in-house specification for each component of the CCS have been provided.

The CCS is considered to provide sufficient finished product protection against microbial contamination and adequate for long-term storage as supported by stability studies performed with identical CCS materials. The control strategy in place for the CCS qualification is sufficient.

3.1.3.4. Stability of the product

At least three batches from each presentation were enrolled on stability. A bracketing approach based on ICH Q1D was used.

In line with ICH Q5C, the batches were tested under long-term, accelerated and stress conditions in both upright and inverted positions. The batches were tested in the identical CCS used for commercial product. Furthermore, a photostability study in line with ICH Q1B was performed.

An adequate post-approval stability protocol has been provided and it has been committed that all stability studies will be completed and that a minimum of one batch of tocilizumab finished product will be put on long-term stability at the recommended storage condition every year that manufacturing of such batches occurs.

Considering the totality of the data, the acceptable shelf life when stored at 2°C-8°C protected from light (unopened vial) is 30 months for the 4 mL and 10 mL presentations and 27 months for the 20 mL presentations.

Chemical and physical in-use stability after dilution in 9 mg/mL sodium chloride solution has been demonstrated for 48 hours at 30 ºC and for up to 4 days in a refrigerator at 2°C -8°C.

From a microbiological point of view, the solution prepared in 9 mg/mL sodium chloride solution for injection should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C– 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

3.1.3.5. Biosimilarity

The EU-approved reference medicinal product, RoActemra (EU-RoActemra), has been used as the comparator throughout the biosimilarity program.

The quality attributes tested in the analytical biosimilarity study have been chosen based on a risk assessment by criticality score assignment. The CQAs were ranked using impact and uncertainty scores, which is commonly used, and a final criticality score of very high, high, moderate, low or very low, was assigned. The final list of CQAs and their criticality scores are considered adequate.

A tiered approach was used for the calculation of quality attribute acceptance criteria based on their criticality and method nature (quantitative or qualitative). The assessment is based on the provided raw data.

The batches used in the analytical biosimilarity study were presented.

EU-RoActemra batches, collected over a period, were used as reference medicinal product.

The primary structure was investigated using state-of-the-art methods.

Several binding studies including ELISA and SPR were used to investigate the binding properties of BIIB800 and EU-RoActemra. The reported data show comparable results with slightly higher potency values for BIIB800 in the competitive inhibition of IL-6 binding to sIL-6R ELISA assay. Additionally, several cell-based bioassays were employed to assess downstream effects of IL-6R binding (inhibition of proliferation, STAT3 activation, VEGF induction). Given the variability of bioassays, they show overall comparable results between BIIB800 and the reference medicinal product. In order to test the effect of shelf life, batches which were

stored at 4°C for several months (11-34 months) were included for BIIB800 and EU RoActemra (13-30 months). No significant effect was seen, which was further shown by forced degradation studies.

To further support biosimilarity, the degradation profiles of BIIB800 and EU-RoActemra were compared under accelerated and stress conditions. Under accelerated and high temperature conditions, BIIB800 shows overall slower degradation Potency was clearly affected by high temperatures but remained within acceptance criteria. These differences could be attributed to the different formulations of both products. At low pH comparable degradation profiles were reported.

Photostability studies showed that both products are photolabile and need protection from light. Agitation and freeze-thaw cycles (up to 5 cycles) did not show effects on the tested parameters.

Overall, biosimilarity with EU-RoActemra is considered demonstrated from a quality point of view.

Table 1 - Tofidence analytical biosimilarity assessment overview

Quality Attribute/Parameter		Tier	Key findings
Molecular Mass (LC-MS)	Intact masses (G0F/G0F)	3	Similar to reference product
	Intact deglycosylated masses	3	
	Reduced Heavy Chain (G0F)	3	
	Deglycosylated Heavy Chain	3	
	Reduced Light Chain	3	
Peptide Mapping (LC-MS/MS)	Reduced Peptide Map	3	Similar to reference product
	Primary amino acid sequence coverage, peptide assignment, N/C-terminal sequencing	3	Similar to reference product
	Oxidation HC M254	3	Similar amounts of oxidized variants
	Oxidation HC W279	3	
	Deamidation LC N137	3	Similar amounts of deamidated variants
	Deamidation HC N317	3	
	Deamidation HC N386	3	
	Deamidation HC N436	3	
	Non-reduced Peptide Map and disulfide bonds	3	Similar to reference product
Free thiol content (mol/mol) (DTNB-Ellman)		3	Similar to reference product
Glycosylation Heterogeneity (HILIC-HPLC LC-MS/MS)	Glycosylation site	3	Similar to reference product
	%High mannose	2	Quantitative differences in content of high mannose variants, outside quality range of the reference product. Differences could potentially impact PK, but were found to be not clinically meaningful in clinical studies.
	%aFucosylation	2	Quantitative differences in content of aFucosylation variants, outside quality range of the reference product. Differences not relevant for mechanism of action and expected to have no clinical impact .
	%Sialylation	2	Quantitative differences in content of sialylation, outside quality range of the reference product. Minor differences could potentially impact PK, but were found to be not clinically meaningful in clinical studies.
	%Galactosylation	2	Minor quantitative differences in content of galactosylation variants but within the quality range of the reference product. Differences not relevant for mechanism of action and expected to have no clinical impact.

Quality Attribute/Parameter		Tier	Key findings
Free Sialic Acid-NANA content (mol/mol) (DMB-RP-UPLC)		3	Similar NANA content.
Free Sialic Acid-NGNA content (mol/mol) (DMB-RP-UPLC)		3	Minor quantitative differences in NGNA content but within quality range of the reference product. Differences not relevant for mechanism of action and are expected to have no clinical impact.
Glycation Content (%) (LC-MS)		3	Quantitative differences in glycation content, outside quality range of the reference product. Differences demonstrated to have no impact on functional bioassay activity and demonstrated not to impact efficacy or safety in clinical studies.
Isoelectric point (cIEF)	Isoelectric profile	3	Consistent with reference product
	pI of main peak	2	Consistent with reference product
Extinction Coefficient ($mg^{-1}cm^{-1}mL$) (Edelhoch method)		3	Differences observed were within analytical variability Differences had no impact in protein concentration between innovator and biosimilar.
Secondary Structure: FTIR	FTIR profile	3	Visually similar to reference product
Secondary Structure: CD	Far UV CD profile	3	Visually similar to reference product
Tertiary Structure: CD	Near UV CD profile	3	Visually similar to reference product
Tertiary Structure: Fluorescence	Fluorescence profile	3	Visually similar to reference product
DSC	DSC profile	3	Visually similar to reference product
	T_{m1}	3	Similar to reference product
	T_{m2}	3	
	T_{m3}	3	
HIAC Subvisible particles	≥ 2µm	3	Similar to reference product
	≥ 5µm	3	
	≥ 10µm	3	
	≥ 25µm	3	
FlowCam Subvisible particles	Spherical particles (counts/mL)	3	Similar to reference product
	Non-spherical particles (counts/mL)	3	
DLS	Radius (nm)	3	Similar to reference product

Quality Attribute/Parameter		Tier	Key findings
SEC-MALS Molar mass	Profile	3	Visually similar to reference product
	Molar mass of main peak (kDa)	3	Similar to reference product
	Molar mass of aggregate (kDa)	3	Similar to reference product
SV-AUC	Average of sedimentation coefficient	3	Visually similar to reference product
	Average of monomer percentage (%)	3	Similar to reference product
SEC-HPLC	%HMW	2	Quantitative differences observed with lower HMW content in BIIB800, outside quality range of the reference product. Differences were found to be not clinically meaningful in clinical studies.
	%Monomer	2	Quantitative differences observed with higher main peak content in BIIB800, outside quality range of the reference product. Differences were found to be not clinically meaningful in clinical studies.
	Profile	3	Similar profiles with minor differences in peak height relating to lower HMW and LMW content in BIIB800.
rCE-SDS	%LC+HC	2	Similar LC and HC content to reference product
	%NGHC	2	Similar NGHC content to reference product
	Profile	3	Visually similar to reference product
nrCE-SDS	%Main peak	2	Similar main peak content to reference product
	%Pre peaks	2	Similar pre-peak content to reference product
	Profile	3	Visually similar to reference product
IEC-HPLC	%Acidic region	2	Minor quantitative differences observed with lower acidic region content in BIIB800, but within quality range of reference product. Differences were found to have no impact on functional bioassay activity and were not clinically meaningful in clinical studies.
	%Main peak	2	Minor quantitative differences observed with lower main peak content in BIIB800, but within quality range of reference product. Differences were found to have no impact on functional bioassay activity and were not clinically meaningful in clinical studies.
	%Basic region	2	Minor quantitative differences observed with lower basic region content in BIIB800, but within quality range of reference product. Differences were found to have no impact on functional bioassay activity and were not clinically meaningful in clinical studies.
	Profile	3	Similar profiles with minor differences in acid and basic peaks in BIIB800.

Quality Attribute/Parameter		Tier	Key findings
IEC-HPLC-CpB	%Acidic region	2	Similar acidic peak content to reference product
	%Main peak	2	Similar main peak content to reference product
	%Basic region	2	Minor quantitative differences observed with lower basic region content in BIIB800, but within quality range of reference product. Differences were found to have no impact on functional bioassay activity and were not clinically meaningful in clinical studies.
	Profile	3	Similar profiles with minor differences in acid and basic peaks in BIIB800.
HIC-HPLC	%Pre-main peak	3	Minor quantitative differences observed with pre-peak content in BIIB800, but within quality range of reference product. Differences were found to be not clinically meaningful.
	%Main peak	3	Minor quantitative differences observed with main peak content in BIIB800, but within quality range of reference product. Differences were found to be not clinically meaningful.
	%Post-main peak	3	Minor quantitative differences observed with main peak content in BIIB800, but within quality range of reference product. Differences were found to be not clinically meaningful.
	Profile	3	Visually similar to reference product
RP-UPLC	%Pre-main peak	3	Minor quantitative differences observed with pre-peak content in BIIB800, but within quality range of reference product. Differences were found to be not clinically meaningful in clinical studies.
	%Main peak	3	Minor quantitative differences observed with main peak content in BIIB800, but within quality range of reference product. Differences were found to be not clinically meaningful in clinical studies.
	%Post-main peak	3	Minor quantitative differences observed with main peak content in BIIB800, but within quality range of reference product. Differences were found to be not clinically meaningful in clinical studies.
	Profile	3	Visually similar to reference product
General Properties	Protein concentration (mg/mL)	2	Similar to reference product

Quality Attribute/Parameter			Tier	Key findings
Fab-mediated Activities	Binding to soluble IL-6R (sIL-6R) (ELISA)	% Relative binding (EC_{50}) [a]	1	Similar % relative binding to the reference product
	Competitive Inhibition of sIL-6R binding to IL-6 (ELISA)	% Relative binding (EC_{50}) [a]	2	Similar % relative binding to the reference product
	Binding kinetics to sIL-6R (SPR)	On rates Ka(1/Ms) Off rates Kd (1/s) Equilibrium Constant K_D (M)	2	Similar binding kinetics to the reference product
	Binding to membrane bound IL-6R (mIL-6R) (Flow Cytometry)	% Relative binding activity (EC_{50}) [a]	3	Similar % relative binding to the reference product
	Inhibition of IL-6-mediated proliferation in TF-1 cells	% Relative Potency (EC_{50}) [a]	1	Similar % relative potency to the reference product
	IL-6 inhibition (SEAP Reporter Gene Assay)	% Relative Potency (EC_{50}) [a]	2	Similar % relative potency to the reference product
	Inhibition of STAT3 Phosphorylation	% Relative Potency (EC_{50}) [a]	3	Similar % relative potency to the reference product
	Inhibition of IL-6/sIL-6R induced VEGF release in HFLS-RA	% Relative Potency (EC_{50}) [a]	3	Similar % relative potency to the reference product

Quality Attribute/Parameter			Tier	Key findings
Fc Binding Affinity	C1q binding (BLI)	% Relative Binding Affinity (K_D) [a]	3	Similar % relative binding affinity to the reference product
	FcRn binding (BLI)	% Relative Binding Affinity (K_D) [a]	2	Similar % relative binding affinity to the reference product
	FcγRI binding (SPR)	% Relative Binding Affinity (K_D) [a]	3	Similar % relative binding affinity to the reference product
	FcγRIIa (131H) binding (BLI)	% Relative Binding Affinity (K_D) [a]	3	Similar % relative binding affinity to the reference product
	FcγRIIa (131R) binding (BLI)	% Relative Binding Affinity (K_D) [a]	3	Similar % relative binding affinity to the reference product
	FcγRIIb binding (BLI)	% Relative Binding Affinity (K_D) [a]	3	Similar % relative binding affinity to the reference product
	FcγRIIIa (158V) binding (BLI)	% Relative Binding Affinity (K_D) [a]	3	Similar % relative binding affinity to the reference product
	FcγRIIIa (158F) binding (BLI)	% Relative Binding Affinity (K_D) [a]	3	Similar % relative binding affinity to the reference product
	FcγRIIIb binding (SPR)	Affinity (K_D)	3	Similar K_D to the reference product
Fc-mediated Characterization	Lack of ADCC activity in TF-1 cells (Reporter gene assay)		3	Similar activity to the reference product
	Lack of ADCC activity in HEK-Blue IL-6™ cells (Reporter gene assay)		3	Similar activity to the reference product
	Lack of ADCC activity in TF-1 cells (PBMC-based LDH Cytotoxicity assay)		3	Similar activity to the reference product
	Lack of CDC activity in TF-1 cells (Cytotoxicity assay)		3	Similar activity to the reference product
	Lack of CDC activity in HEK-Blue IL-6™ cells (Cytotoxicity assay)		3	Similar activity to the reference product

[a] Reference standard B0520180301STD was used for all relative potency assays.

ADCC=Antibody-dependent cell mediated toxicity; BLI=Biolayer interferometry; C1q=Complement component 1q; CD=Circular dichroism; CDC=Complement-dependent cytotoxicity; cIEF=Capillary isoelectric focusing; CpB=Carboxypeptidase B; DLS=Dynamic light scattering; DMB=1,2-diamino-4,5-methylenedioxybenzene-2HCl; DTNB=5,5-dithio-bis-(2-nitrobenzoic acid) (Ellman's reagent); DSC=Differential scanning calorimetry; EC_{50}=Half maximal effective concentration; ELISA=Enzyme-linked immunosorbent assay; Fab=Antigen-binding fragment; Fc=Crystallizable fragment; FcRn=Neonatal Fc receptor; FcγR=Fc Gamma Receptor; FTIR=Fourier-transform infrared spectroscopy; HC=Heavy Chain; HEK=Human embryonic kidney; HIAC=High accuracy; HIC=Hydrophobic interaction chromatography; HILIC=Hydrophilic interaction chromatography; HFLS-RA=Human fibroblast-like synoviocytes-rheumatoid arthritis; HMW=High molecular weight; HPLC=High-performance liquid chromatography; IEC=Ion exchange chromatography; IL-6=Interleukin-6; IL-6R=Interleukin-6 receptor; Ka=Association constant; Kd=Disassociation constant; K_D=Equilibrium constant; kDa=kiloDalton; LC=Light Chain; LC=Liquid chromatography; LMW=low molecular weight; MALS=Multi-angle light scattering; MS=mass spectrometry; NANA=N-acetyl sialic acid; NGHC=Non-glycosylated heavy chain; NGNA=N-glycolyl sialic acid; nrCE-SDS=Non-reducing capillary electrophoresis- sodium dodecyl sulphate; pI=Isoelectric point; rCE-SDS=Reducing capillary electrophoresis- sodium dodecyl sulphate; RP=Reverse phase; SEAP=Secreted alkaline phosphatase; SEC=Size exclusion chromatography; sIL-6R=Soluble interleukin-6 receptor; SPR=Surface plasmon resonance; SV-AUC=Sedimentation velocity analytical ultracentrifugation; Tm=Melting temperature; UPLC=Ultra-performance liquid chromatography; UV=Ultraviolet; VEGF=Vascular endothelial growth factor.

3.1.3.6. Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – rev.3) has been sufficiently demonstrated. The active substance is produced in a serum- and protein-free culture medium. No animal-derived material is added during fermentation of tocilizumab. The MCB which has been established is free from TSE-risk substances.

Virus safety

The fermentation process of tocilizumab is in a serum- and protein-free medium. No animal-derived material is added during fermentation of tocilizumab minimising the possible contamination for adventitious viruses. The cells used for production of tocilizumab have been sufficiently screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB and EOPC of tocilizumab, with the exception of intracellular A-type and C-type retroviral particles which are well known to be present in murine cells. However, this is acceptable since there is sufficient capacity within the manufacturing procedure of tocilizumab for reduction of this type of viral particles.

The ability of the purification process to clear viruses was evaluated using the model viruses.

The purification process of tocilizumab includes two dedicated steps for inactivation/removal of enveloped viruses, with virus filtration having been sufficiently demonstrated to be efficient. In addition, the chromatography steps of tocilizumab also contribute to the virus safety.

In summary, virus safety of tocilizumab has been sufficiently demonstrated.

Overall, adventitious agents safety is considered demonstrated.

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

Module 3 provided in support of the Marketing Authorisation Application (MAA) for Tofidence is well structured and includes all essential information. The analytical biosimilarity study showed good comparability between the proposed biosimilar and its reference medicinal product EU-RoActemra. Biosimilarity is considered demonstrated. The MAA for Tofidence is considered approvable from the quality point of view.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Tofidence is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

Recommendations for future quality development have been agreed by the Applicant.

In conclusion, based on the review of the data provided, the MAA for Tofidence is considered approvable from the quality point of view.

3.1.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends points for investigation.

3.2. Non-clinical aspects

3.2.1. Introduction

BAT1806 is a recombinant humanized IgG1 monoclonal antibody, which can bind specifically to soluble and membrane-bound human interleukin-6 receptors and inhibit signaling mediated by these receptors. BAT1806 has been developed as a biosimilar to the European Medicines Agency (EMA) approved reference product RoActemra (EU-RoActemra), the United States Food and Drug Administration (FDA) approved and licensed reference product Actemra (US-Actemra), and the National Medical Products Administration (NMPA) approved reference product Actemra (CN-Actemra). EU-Actemra, US-RoActemra and CN-Actemra are all licensed tocilizumab products.

RoActemra and Actemra, administered via intravenous (IV) infusion, are marketed in Europe and the United States of America for the treatment of adult rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, pediatric juvenile idiopathic arthritis, giant cell arteritis, systemic sclerosis-associated interstitial lung disease, cytokine release syndrome (CRS) and coronavirus disease 2019 (COVID-19). EU-RoActemra and US-Actemra are also approved for subcutaneous administration, however this route of administration is not included in this application.

The non-clinical developmental program was performed to satisfy global requirements, therefore more non-clinical studies than the ones strictly required in the EU were performed and submitted. The "extra" studies were performed to satisfy marketing authorisation in US and China (e.g. in vivo PK and toxicity studies), but not strictly required by EMA (according to current guidelines, e.g. EMEA/CHMP/437/04 Rev 1, Guideline on similar biological medicinal products, EMEA/CHMP/42832/2005 Rev 1 Guideline on similar biological medicinal products containing biotechnology derived medicinal products as active substances: non-clinical and clinical issues, EMEA/CHMP/BWP/ /247713/2012 Rev. 1, Guideline on similar biological medicinal products containing Biotechnology- derived Proteins as Active Substance - Quality Issues) were not performed or repeated using an EU- sourced reference product, which can be accepted.

All the studies for the non-clinical package were performed in China, therefore in a NON-OECD MAD (Mutual Acceptance of Data) country. However, considering the non-pivotal nature of toxicology and PK in vivo studies, which would not be normally requested by EMA and are not deemed necessary for BAT 1806, the GLP aspects are not considered relevant, for this application.

3.2.2. Pharmacology

3.2.2.1. Primary pharmacodynamic studies

The Applicant performed a wide range of in vitro experiments comparing BAT1806 activities and modes of action and FcR binding to Actemra of different sources. Most of the experiments were performed for the similarity exercise already assessed in the quality part (please, refer to the quality section for details), but extra study reports were produced and submitted in Module 4.

The Applicant also performed an in vivo PD study (201501), comparing BAT1806 and US-Actemra efficacy in cynomolgus monkeys in a disease model of collagen- induced arthritis.

3.2.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were conducted, which is acceptable.

3.2.2.3. Safety pharmacology programme

Please refer to the toxicology section 3.2.4.

3.2.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted which is acceptable.

3.2.3. Pharmacokinetics

Pharmacokinetic (PK) and Toxicokinetic (TK) parameters were derived from four *in vivo* studies in Non-Human Primate (NHP) (single or repeat dose IV administrations). The most relevant study for this application is considered the single dose PK study (Report P17-S136-PK), which evaluated BAT1806 in comparison with US-Actemra and EU- RoActemra.

The validation results for all the methods used in the various studies were shown. Most relevant for this MAA is the method (report. P17-S136-MV) used for the PK study P17-S136-PK were BAT-1806 was compared to EU-RoActemra.

As already pointed out in the EMA Scientific Advice (EMEA/H/SA/4052/1/2019/III some differences in Maximum concentration in plasma (Cmax) and Exposure could be noticed between BAT-1806 and CN-Actemra (see section 3.2.4.6. Toxicokinetic data). However, the comparison between BAT 1806 and EU-Actemra in study P17-S136-PK showed similar PK parameters. Considering that, usually, no in vivo PK studies are requested for biosimilar applications and that the most relevant PK study showed acceptable results, the differences between BAT1806 and CN_Actemra detected in the PK/TK studies are not considered critical and relevant for this application.

No studies on distribution, metabolism, excretion and pharmacokinetic drug interactions were conducted, which is acceptable.

3.2.4. Toxicology

3.2.4.1. Single dose toxicity

Not performed, in line with guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010), as no concerns regarding toxicity were detected in the quality data. This is acceptable.

3.2.4.2. Repeat dose toxicity

The Applicant performed a repeat-dose toxicology study in cynomolgus monkeys dosed i.v. with three different concentrations of BAT-1806 (10, 30 or 100 mg/kg) or with CN-Actemra at 30 mg/kg once a week. The study included a 4-week treatment period (in total 5 doses) and a 4-week recovery period, a control group with animals dosed with normal saline solution was also included. In comparison with control animals a

decrease in complement levels, increase of IL-6 and IL-6R and changes in the spleen and thymus were observed in all the tocilizumab treated groups. The only marked differences between BAT-1806 and CN-Actemra treated groups were in the TK parameters as discussed in the PK section and here below. Overall, this study is not considered pivotal and of high relevance for this MAA.

3.2.4.3. Genotoxicity

Such studies are not required for similar biological medicinal products.

3.2.4.4. Carcinogenicity

Such studies are not required for similar biological medicinal products.

3.2.4.5. Reproductive and developmental toxicity

Such studies are not required for similar biological medicinal products.

3.2.4.6. Toxicokinetic data

PK and TK parameters were derived from several *in vivo* studies in NHP. The most relevant study for this application is the single PK study, P17-S136-PK which evaluated BAT1806 with US-Actemra and EU-RoActemra. As already pointed out in the EMA Scientific Advice (EMEA/H/SA/4052/1/2019/III), some differences in Cmax and Exposure could be noticed between BAT-1806 and CN-Actemra.
In particular, in study 2017021 substantial differences between BAT-1806 and CN-Actemra could be observed in female animals, where female animals from the reference group had the highest Cmax and exposure values. In contrast, in study N2015068 this latter group of animals had consistently the lowest Cmax and Exposure values of all groups, so that the observation appears not to be consistent between the studies. That considered, and also considering the not pivotal nature of these studies for the current MAA, these findings are overall considered of low relevance. Of note, antidrug antibody
(ADA) cannot be accountable for these differences, because no ADA were found in the 30mg/Kg groups for study 2017021 and for study N2015068 the parameters of the one ADA+ female animal were excluded from the calculations.

3.2.4.7. Tolerance

One stand-alone local tolerance study was conducted in rabbits. In the study two lots of BAT1806 from different manufacturing processes were tested and compared to EU-RoActemra. No local irritation was observed. No findings were also mentioned in the *in vitro* studies performed in cynomolgus monkeys. Stand-alone local tolerance studies are not normally requested and not encouraged for MAA of similar biological products, therefore these studies are not considered pivotal and of high relevance for this MAA.

3.2.4.8. Other toxicity studies

Two hemolysis assays were performed: one in rabbit RBCs and the other in human RBCs. In the latter study two lots of BAT1806 from different manufacturing processes were tested and compared to EU-RoActemra. In

none of the studies hemolysis was observed. These studies are not normally requested for MAA of similar biological products, therefore these studies are not considered pivotal and of high relevance for this MAA.

3.2.5. Ecotoxicity/environmental risk assessment

In the case of biosimilars, an environmental risk assessment is not needed, the Applicant's justification is acceptable.

3.2.6. Discussion on non-clinical aspects

The non-clinical developmental program was performed to satisfy global requirements, therefore more non-clinical studies than the ones strictly required in the EU were performed and submitted. The "extra" studies were performed to satisfy marketing authorisation in US and China (e.g. *in vivo* PK and toxicity studies), but not strictly required by EMA (according to current guidelines, e.g. EMEA/CHMP/437/04 Rev 1, Guideline on similar biological medicinal products, EMEA/CHMP/42832/2005 Rev 1 Guideline on similar biological medicinal products containing biotechnology derived medicinal products as active substances: non-clinical and clinical issues, EMEA/CHMP/BWP/ /247713/2012 Rev. 1, Guideline on similar biological medicinal products containing Biotechnology- derived Proteins as Active Substance - Quality Issues). Therefore, they were not performed or repeated using an EU- sourced reference product, which can be accepted.

All the studies for the non-clinical package were performed in China, therefore in a NON-OECD MAD (Mutual Acceptance of Data) country. However, considering the non-pivotal nature of toxicology and PK *in vivo* studies, which would not be normally requested by EMA and are not deemed necessary for BAT 1806, the GLP aspects are not considered relevant, for this application.

The Applicant performed a wide range of *in vitro* experiments comparing BAT1806 activities and modes of action and FcR binding to RoActemra of different sources. Most of the experiments were performed for the similarity exercise already assessed in the quality part (please, refer to the quality section for details), but extra study reports were produced to be submitted in Module 4. One minor clarification question on the methods was raised and was satisfactorily answered by the Applicant. Overall, the data show no unexpected results. The Applicant also performed an *in vivo* PD study (201501), comparing BAT1806 and US-Actemra efficacy in cynomolgus monkeys in a disease model of collagen- induced arthritis. From the data shown, it appears that if for some parameters (e.g. CRP and ESR) US-Actemra could be more or longer efficacious than BAT1806, for other parameters (e.g. middle finger width and clinical observation score), the opposite was noticed. However, these differences are not statistically significant and notably the study is not of high relevance for the current MAA. Batches used at different stages of development were mostly well indicated, when not a question was raised, which was satisfactorily answered by the Applicant.

PK and TK parameters were derived from four *in vivo* studies in NHP (single or repeat dose IV administrations). The most relevant study for this application is the single dose PK study (Report P17-S136-PK), which evaluated BAT1806 in comparison with US-Actemra and EU- RoActemra. As already pointed out in the EMA Scientific Advice (EMEA/H/SA/4052/1/2019/IIIEMA/CHMP/SAWP/116157/2019), some differences in Cmax and Exposure could be noticed between BAT-1806 and CN-Actemra (see section 3.2.4.6. Toxicokinetic data). However, the comparison between BAT 1806 and EU-Actemra in study P17-S136-PK showed similar PK parameters. Considering that, usually, no *in vivo* PK studies are requested for biosimilar applications and that the most relevant PK study showed acceptable results, the differences between BAT1806 and CN_Actemra detected in the PK/TK studies are not considered critical and relevant for this application. The

validation results for all the methods used in the various studies were shown. Most relevant for this MAA is the method (report. P17-S136-MV) used for the PK study P17-S136-PK were BAT-1806 was compared to EU-RoActemra. The results reported are found acceptable and the method considered validated. No studies on distribution, metabolism, excretion and pharmacokinetic drug interactions were conducted, which is acceptable.

The Applicant performed several *in vitro* and *in vivo* toxicological studies, none of which is considered pivotal and of high relevance for the current MAA. The studies are summarised and assessed above for information and completeness. Overall, no unexpected findings were observed. Given the non-pivotal nature of the studies and the absence of unexpected results or findings no questions were raised.

In the case of biosimilars, an environmental risk assessment is not needed, the Applicant's justification is acceptable.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Tocilizumab is not expected to pose a risk to the environment.

3.2.7. Conclusion on the non-clinical aspects

None of the in vivo and in vitro studies submitted exclusively in the nonclinical Module 4 is considered pivotal for this MAA. Pivotal studies are the same submitted in Module 3 and are assessed in detail in the quality part. Overall, the non-clinical package is considered acceptable, and no unexpected results were observed. From the non-clinical point of view, no major differences were observed between BAT 1806 and the EU-sourced comparator.

3.3. Clinical aspects

3.3.1. Introduction

GCP aspects

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2 - Overview of clinical studies

Study Number / Phase	Study Title	Study Objectives	Treatment Regimen	Study Population / Number of Randomized Subjects
BAT-1806-001-CR Phase 1	A randomized, double-blinded, single-dose, 3-arm parallel, comparative study to evaluate the pharmacokinetics and safety of BAT1806 Injection versus Actemra® in healthy Chinese male subjects	**Primary**: To establish pairwise PK biosimilarity between BAT1806 vs. EU-approved RoActemra, BAT1806 vs. US-licensed Actemra, US-licensed Actemra vs. EU-approved RoActemra in healthy Chinese male subjects. **Secondary**: To evaluate the clinical safety, tolerability, and immunogenicity of BAT1806 and EU- and US-licensed Actemra in healthy Chinese male subjects.	Single intravenous (IV) administration of 4 mg/kg of BAT1806 or tocilizumab reference medicinal product (EU-authorized RoActemra, and US-licensed Actemra) Eligible subjects were randomized in a 1:1:1 ratio to one of following treatment groups: (1) BAT1806; 4 mg/kg; IV (2) RoActemra; 4 mg/kg; IV (3) Actemra; 4 mg/kg; IV	Healthy volunteers N=138
BAT-1806-002-CR Phase 3	A randomized, double-blind, parallel group, active-control study to compare the efficacy and safety of BAT1806 to RoActemra in rheumatoid arthritis patients with inadequate response to methotrexate	**Primary**: To demonstrate equivalent efficacy of BAT1806 and RoActemra in subjects with RA that is inadequately controlled by MTX. **Secondary**: • To evaluate the efficacy profile of BAT1806 compared with RoActemra over time based on secondary efficacy endpoints • To evaluate the safety and tolerability profile of BAT1806 compared with RoActemra over the entire study period • To evaluate the immunogenicity profile of BAT1806 in terms of ADA production compared with RoActemra • To evaluate the steady-state PK of BAT1806	The study comprised Treatment Period 1 (TP1) (Weeks 0 to 24) followed by Treatment Period 2 (TP2) (Weeks 24 to 48). Eligible subjects were randomized in a 2:1:1 ratio to one of three treatment groups: (1) BAT1806 (TP1)/BAT1806 (TP2) (2) RoActemra (TP1)/RoActemra (TP2), or (3) RoActemra (TP1) followed by BAT1806 (TP2), administered intravenously every 4 weeks at a dose of 8 mg/kg	Patients with RA and inadequate response to MTX N=621

3.3.2. Clinical pharmacology

3.3.2.1. Pharmacokinetics

Two clinical studies were completed for BAT1806 from which PK data was obtained: a Phase 1 study in healthy volunteers and a Phase 3 study in subjects with RA with an inadequate response to methotrexate (MTX).

The Phase 1 study BAT1806-001-CR was a randomised, double-blind, single-dose, 3-arm, parallel group study to evaluate the PK and safety of BAT1806 versus Actemra and RoActemra in healthy Chinese male subjects. The primary endpoint of the study was area under the product concentration-time curve from time zero to infinity (AUC0-inf). Key PK secondary endpoints included area under the product concentration-time curve from time zero to time t (AUC0-t) and Cmax. Other secondary PK endpoints included time to maximum concentration (Tmax), half-life (t1/2), Volume of distribution at steady state (Vss), Volume of distribution at terminal state (Vz) and total clearance (CL).

The Phase 3 study BAT1806-002-CR was a randomised, double-blind, parallel group, active-control study conducted in Central Europe and Asia Pacific in RA subjects with an inadequate response to MTX to evaluate the efficacy, safety, immunogenicity, and PK parameters of BAT1806 and RoActemra. The primary objective of this study was to demonstrate equivalent efficacy of BAT1806 and RoActemra (see section 3.3.5. clinical efficacy). The PK secondary objective was to evaluate the steady-state PK of BAT1806 versus RoActemra with Ctrough as the PK endpoint.

A population PK model was developed based on serum concentration data collected following intravenous (IV) infusion of tocilizumab (and BAT1806) in 129 subjects in a Phase 1 study (BAT-1806-001-CR), and 614 subjects in a Phase 3 study (BAT-1806-002-CR). The aim of this analysis was to (1) develop a population PK model describing the PK of tocilizumab, and to (2) assess PK similarity of BAT1806 to RoActemra at 8 mg/kg in patients with Rheumatoid Arthritis (RA).

Analytical methods

Quantification of tocilizumab in human serum

The quantitation of BAT1806 and Actemra/RoActemra (tocilizumab) in human serum in clinical studies BAT-1806-001-CR and BAT-1806-002-CR was achieved using an ELISA method validated by Covance Pharmaceutical R&D (Shanghai) Co. Ltd. The concentration of tocilizumab in serum is determined using a sandwich ELISA. BAT1806 and/or tocilizumab in human serum samples, quality controls (QCs) and standard calibrators are captured onto 96-well microtiter plates pre-coated with recombinant IL-6R. Bound BAT1806 or tocilizumab was subsequently detected with horseradish peroxidase (HRP) conjugated anti-tocilizumab non-paratope specific, anti-idiotype monoclonal antibody. Tetramethylbenzidine (TMB) substrate reactive with HRP is used to generate a colorimetric signal that is proportional to the amount of tocilizumab in the sample. The colour development is stopped with sulfuric acid and the optical density (OD) is measured at 450 nm with a reference at 630 nm subtracted. Tocilizumab concentrations in samples are interpolated from a calibration curve generated using a 4-parameter logistic regression model, weighted 1/Y2.

The bioanalytical method used in the clinical studies has been validated according to EMA guideline EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**.

Immunogenicity

Immunogenicity analysis consists of a tiered testing approach that includes a screening assay, a confirmation assay and a titration assay for the detection of anti-drug antibodies as well as a neutralizing antibody assay to further characterize a positive antibody response. The detection of the ADA and neutralizing antibody (NAb) in human serum was achieved using ECL immunoassays. Both methods were developed and validated by Covance Pharmaceutical R&D (Shanghai) Co., Ltd.

Two (2) analytical procedures were established for the detection of ADA in study BAT-1806-001-CR (healthy volunteers) and study BAT-1806-002-CR (RA patients). Each assay method consisted of pooled human serum negative control and positive control prepared with anti-BAT1806 polyclonal antibody spiked in pooled human serum. The positive control, negative controls and samples were pre-treated with acid and incubated on a 96 well ELISA plate pre-coated with BAT1806. ADA bound to the immobilized BAT1806 was subsequently eluted with acid prior to being tested in the ADA bridging assay. The pre-treated samples were mixed with equimolar concentrations of biotinylated-BAT1806/tocilizumab (EU & US) and sulfo-tagged-BAT1806/tocilizumab (EU & US), to be neutralized and incubated forming an immune complex. The immune complex was added to a streptavidin-coated Meso Scale Discovery (MSD) plate and incubated during which, the immune complex binds to the pre-coated streptavidin. After incubation, read buffer was added to the plate in the MSD reader and generates an electrochemiluminescence signal, which was positively correlated with the content of ADA in the sample.

The methods were validated for sensitivity, specificity, selectivity, drug tolerance, within-run and between-run precision, system suitability, interference, haemolysis and lipemic effect, hook effect, bench-top stability, freeze-thaw stability, and long-term stability.

The neutralizing antibody assay method consisted of pooled human serum negative control and positive control prepared with anti-BAT1806 polyclonal antibody spiked in pooled human serum. The positive control, negative controls and samples were pre-treated with acid and incubated on a 96 well ELISA plate pre-coated with BAT1806. ADA bound to the immobilized BAT1806 was subsequently eluted with acid prior to being tested in the NAb competitive ligand binding assay. The pre-treated samples were incubated with the pre-prepared sulfo-tag-drug to form an immune complex, then added to the MSD plate pre-coated with IL-6R for incubation. During this process, the sulfo-tag-drug binds to the pre-coated IL-6R on the well. Following incubation and washing, read buffer was added to the wells and the plate was read in the MSD plate reader triggering an electrocatalytic chemiluminescence reaction to generate a luminescence signal. The intensity of the luminescent signal was inversely proportional with the content of neutralizing antibody in the sample.

The assay was validated for its precision, selectivity, drug tolerance, matrix effect, interference and specificity, haemolysis effect, lipemic effect, bench-top/process stability, freeze-thaw stability, and long-term stability.

Population Pharmacokinetic Analysis

A population PK model was established describing the PK of tocilizumab, and to assess PK similarity of BAT1806 to RoActemra in the study BAT1806-002-CR in subjects with RA.

A two-compartmental model with mixed (linear + Michaelis-Menten non-linear) elimination with additive and proportional residual error models was used to describe the observed concentration-time profiles of tocilizumab and BAT1806.

A population PK dataset was initially built with the data of BAT1806, Actemra, and RoActemra from study BAT-1806-001-CR (Phase 1) and formatted according to the requirements for the posterior population PK analysis using NONMEM software. The dataset was later updated with the addition of data of BAT1806 and RoActemra formulations from study BAT-1806-002-CR (Phase 3). The dataset included study (phase) number, period, subject ID (SUBJID), visit identifier, drug administration information (dates, times, dose levels), time of blood sample collection (nominal and actual), serum concentration values of BAT1806, Actemra, and RoActemra as well as intrinsic covariates (e.g., body weight, age, age group, race, sex, Anti-drug Antibody (ADA), Neutralizing Antibody (nAB), RAF (Rheumatoid factor) and extrinsic covariates (e.g., dose levels, country, concomitant methotrexate intake or not).

For updated base structural model including pooled phase 1 and phase 3 data, a step-wise approach was used for the covariate analysis.

None of the Treatment, ADA, nAB covariates was found to be statistically significant. In addition, no significant relationships were observed in Treatment, Ethnicity, Race, Region, and "Treatment by Region" groups with the corresponding PK parameters.

The PK model with estimated effect of DOSEL on CL and estimated effect of continuous covariate (Weight) on CL and V1 was selected as the Final PK model.

Phase 1 Study: Study BAT-1806-001-CR in healthy volunteers

Study design

It was a randomised, double-blinded, single-dose, 3-arm parallel Phase I clinical study to establish pairwise PK biosimilarity between BAT1806 vs EU-licensed RoActemra, BAT1806 vs US-licensed Actemra, US-licensed Actemra vs EU-licensed Actemra in healthy Chinese male subjects and to evaluate the clinical safety, tolerability and immunogenicity of 3 groups.

A total of 138 eligible healthy male subjects were planned to be enrolled and randomised at a ratio of 1:1:1 to receive single IV drip of BAT1806 or RoActemra-EU or Actemra- US. Sentinel staggered dosing was introduced to the study.

The planned primary PK endpoint was AUC0-inf. Secondary PK endpoints included: AUC0-t, Cmax, Tmax, t1/2, Vss, Vz and CL. The drug was administered through IV administration over 60±6 minutes.

The time points for PK sampling were as follows: prior to infusion of investigational product (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.

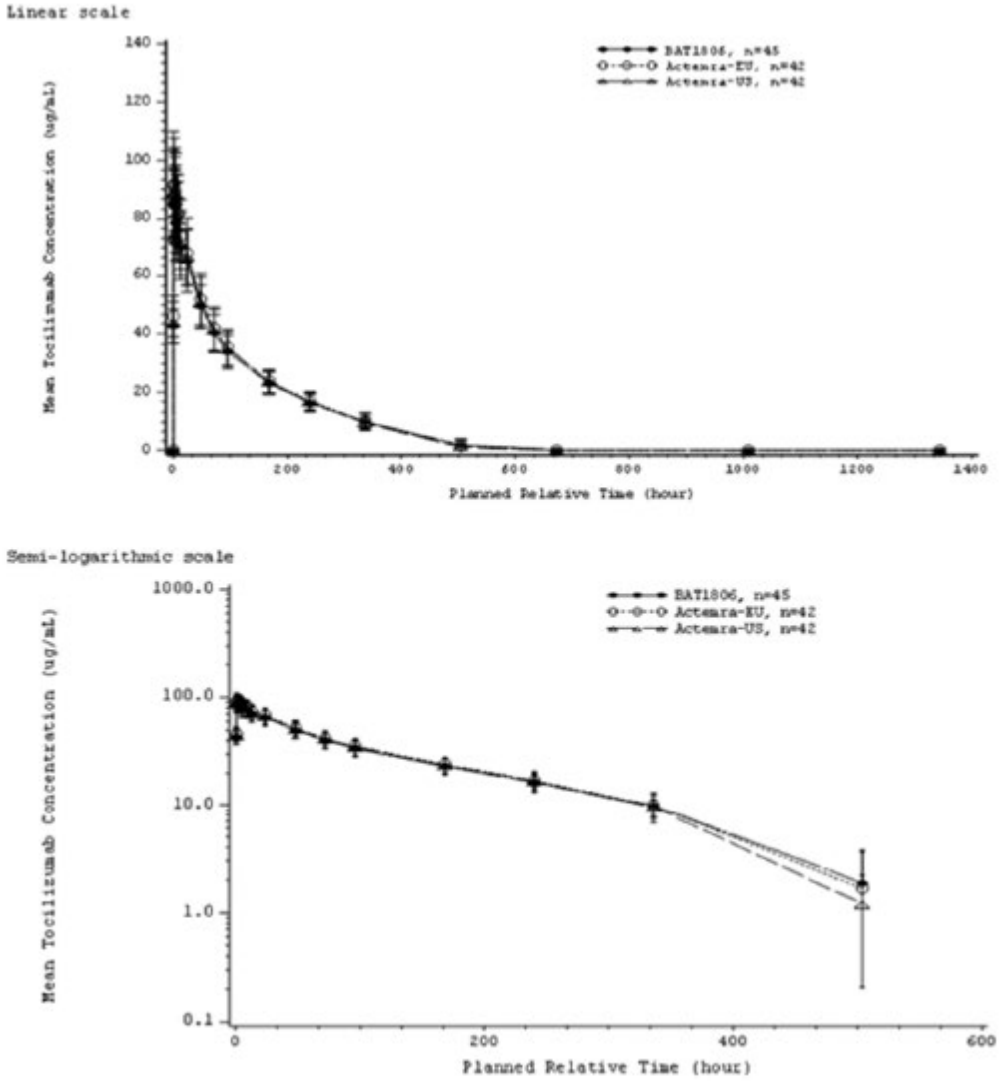
A blinded PK interim analysis was conducted after 50% subjects (69 subjects) had completed the study to assess evaluability of primary PK parameters and the geometric coefficient of variation (geo CV) was calculated to re-assess sample size. Both the observed CV (%) for the primary PK parameter AUC0-inf (17.8 %) and the largest observed CV (%) across the primary and secondary PK parameters (19.4%) were lower than expected (ie, original CV estimate of 25%). Based on these results, the recruitment of subjects followed the original plan of 123 evaluable subjects was sufficient and no additional subject recruitment was required.

Comparisons between treatments were evaluated by an analysis of the PK parameters in the PKAS by performing an analysis of variance (ANOVA), with fixed effects for treatment and BW group, on the log-transformed values of AUC0-inf, AUC0-t, and Cmax. From these analyses, least squares (LS) means, LS treatment differences, and 90% CIs for the treatment differences on log-scale were obtained. The results were transformed back to the original scale by exponentiation to provide treatment geometric LS means, point estimates of the geometric test/reference LS mean ratios, and 90% CI for these ratios for the following treatment comparisons: BAT1806/Actemra-US, BAT1806/RoActemra-EU and Actemra-US/RoActemra-EU. The 90% CI of the ratio of geometric means of log-transformed AUC0-inf, AUC0-t, and Cmax was used to assess bioequivalence between the test and reference using the bioequivalence interval of 80.00% to 125.00%. Bioequivalence was declared if the 90% CI for the ratio fell within 80.00% and 125.00% for the primary PK parameter AUC0-inf.

Study results

Male subjects were screened according to the inclusion and exclusion criteria of the study protocol for eligibility. Their age range was 18-51 years old, the BMI was between 18.6-27.8 kg/m2, and the BW was between 55.1-84.7 kg. A total of 138 subjects were randomised and assigned into each treatment group (46 subjects to BAT1806 group, 44 subjects to RoActemra-EU group, and 48 subjects to Actemra-US group). Excluding 9 subjects prematurely withdrawn from the study, 129 subjects were included in the PKAS (45 subjects in the BAT1806 group, 42 subjects in the RoActemra-EU group, and 42 subjects in the Actemra-US group).

Figure 1 - Mean (±SD) Tocilizumab Serum Concentration-time Profiles for All Treatments on Linear and Semi-logarithmic Scales (Pharmacokinetic Analysis Set) – study BAT-1806-001-CR



Note: If lower SD bar was negative, it was not displayed.

Source: Figure 14.2.1

Table 3 - Descriptive Statistics for Tocilizumab Serum PK Parameters for Each Treatment Group (PKAS) – study BAT-1806-001-CR

Parameter	Statistic	BAT1806 (n=45)	RoActemra (n=42)	Actemra (n=42)
$AUC_{0\text{-}inf}$ (µg*h/mL)	Geo Mean (GCV%)	10840 (16.6)	11080 (19.5)	10690 (15.4)
	Mean (SD)	10980 (1867.8)	11290 (2167.3)	10810 (1661.3)
	Median (min, max)	10900 (7570, 17600)	11000 (6760, 17100)	10800 (7280, 14800)
C_{max} (µg/mL)	Geo Mean (GCV%)	88.28 (14.5)	96.28 (17.6)	91.29 (16.4)
	Mean (SD)	89.19 (13.16)	97.72 (17.11)	92.49 (15.39)
	Median (min, max)	87.4 (65.7, 129.0)	98.7 (66.0, 146.0)	91.6 (62.6, 132.0)
T_{max} (h)	Median (min, max)	2.00 (1.00, 9.00)	2.00 (1.00, 5.00)	2.00 (0.98, 9.02)
$AUC_{0\text{-}t}$ (µg*h/mL)	Geo Mean (GCV%)	10260 (17.8)	10580 (21.5)	10390 (16.4)
	Mean (SD)	10420 (1890.8)	10800 (2147.7)	10530 (1713.0)
	Median (min, max)	10200 (6820, 16800)	10700 (5610, 15900)	10700 (6880, 14700)
$t_{1/2}$ (h)	Geo Mean (GCV%)	89.81 (32.4)	82.08 (33.5)	72.57 (30.7)
	Mean (SD)	93.97 (26.830)	86.23 (26.162)	75.85 (22.978)
	Median (min, max)	101 (44.7, 156)	90.0 (40.2, 135)	74.3 (43.7, 130)
CL (L/h)	Geo Mean (GCV%)	0.02457 (16.4)	0.02421 (18.8)	0.02482 (13.0)
	Mean (SD)	0.02489 (0.0040581)	0.02461 (0.0045317)	0.02503 (0.0032767)
	Median (min, max)	0.0240 (0.0178, 0.0339)	0.0244 (0.0132, 0.0384)	0.0245 (0.0191, 0.0324)
V_z (L)	Geo Mean (GCV%)	3.184 (32.9)	2.867 (32.6)	2.599 (32.4)
	Mean (SD)	2.730 (0.88744)	3.341 (1.0149)	3.009 (0.95072)
	Median (min, max)	3.27 (1.64, 5.33)	2.95 (1.35, 5.32)	2.72 (1.42, 5.22)
V_{ss} (L)	Geo Mean (GCV%)	3.748 (16.4)	3.528 (17.0)	3.453 (14.3)
	Mean (SD)	3.797 (0.61373)	3.579 (0.62136)	3.487 (0.49004)
	Median (min, max)	3.74 (2.63, 5.14)	3.53 (2.46, 5.25)	3.49 (2.59, 4.76)

Abbreviations: GCV% = Geometric coefficient of variation in percent; Geo = Geometric; Max = Maximum; Min = Minimum; N = sample size; n = available data; SD = standard deviation.
Source: BAT-1806-001-CR CSR Table 14.2.2

Table 4 - Statistical Comparison of PK Parameters (PKAS) – study BAT-1806-001-CR

Parameter (units)	Treatment	n	GLS Mean	Statistical Comparisons GLS Mean Ratio (90% CI) (%)		
				BAT1806/ RoActemra	BAT1806/ Actemra	Actemra/ RoActemra
Primary Endpoint						
$AUC_{0\text{-}inf}$ (µg·h/mL)	BAT1806	45	11100	98.06 (92.10, 104.41)	100.82 (95.76, 106.15)	97.26 (91.75, 103.10)
	RoActemra	42	11320			
	Actemra	42	11010			
Key Secondary Endpoints						
$AUC_{0\text{-}t}$ (µg·h/mL)	BAT1806	45	10540	97.39 (91.01, 104.20)	98.18 (92.89, 103.78)	99.19 (93.22, 105.53)
	RoActemra	42	10820			
	Actemra	42	10730			
C_{max} (µg/mL)	BAT1806	45	89.57	91.71 (86.90, 96.79)	96.25 (91.70, 101.03)	95.28 (90.04, 100.82)
	RoActemra	42	97.67			
	Actemra	42	93.06			

Abbreviations: BW = Body weight; CI = Confidence interval; GLS = Geometric least squares; n = available data
Results based on ANOVA model with fixed effects of treatment and body weight group, with residual variance per treatment.
Source: BAT-1806-001-CR CSR Table 14.2.3

Pharmacokinetic comparability has been demonstrated for all comparisons (BAT1806 versus RoActemra-EU, BAT1806 versus Actemra-US, and Actemra-US versus RoActemra-EU). For all comparisons, the 90% CIs of the primary parameter (AUC0-inf) and secondary parameters (Cmax and AUC0-t) were contained within the predefined 80.00% to 125.00% bioequivalence limits.

Pharmacokinetics in target population

Phase 3 Study: Study BAT-1806-002-CR in RA subjects with moderate-to-severe disease

Study BAT-1806-002-CR was a Phase 3, double-blind, randomised, parallel-group, active-control study to compare the efficacy and safety of BAT1806 to RoActemra in subjects with RA with an inadequate response to MTX.

The study comprised a screening period, a 24-week initial treatment period (TP1), a 24-week secondary treatment period (TP2), and a 4-week follow-up period. Subjects were randomised in a 2:1:1 ratio to one of three treatment groups:

1. BAT1806 (TP1)/BAT1806 (TP2) (BAT1806 → BAT1806),
2. RoActemra (TP1)/ RoActemra (TP2) (RoActemra → RoActemra), or
3. RoActemra up to Week 24 (TP1) followed by BAT1806 (TP2) (RoActemra → BAT1806)

Both BAT1806 and RoActemra were administered intravenously every 4 weeks at a dose of 8 mg/kg. A maximum dose of 800 mg was allowed for each infusion. The dose of study treatment may have been reduced to 4 mg/kg body weight during the study because of laboratory abnormalities.

The time points for PK sampling were as follows: prior to infusion of treatment (BAT1806/RoActemra) on Days 0, 28, 84, 140, 168, 196, 252, 308, 336 (end of study), and 8 weeks after the last dose (follow-up visit).

The PK endpoint was Ctrough at predose over the course of the study for both study arms.

Study results

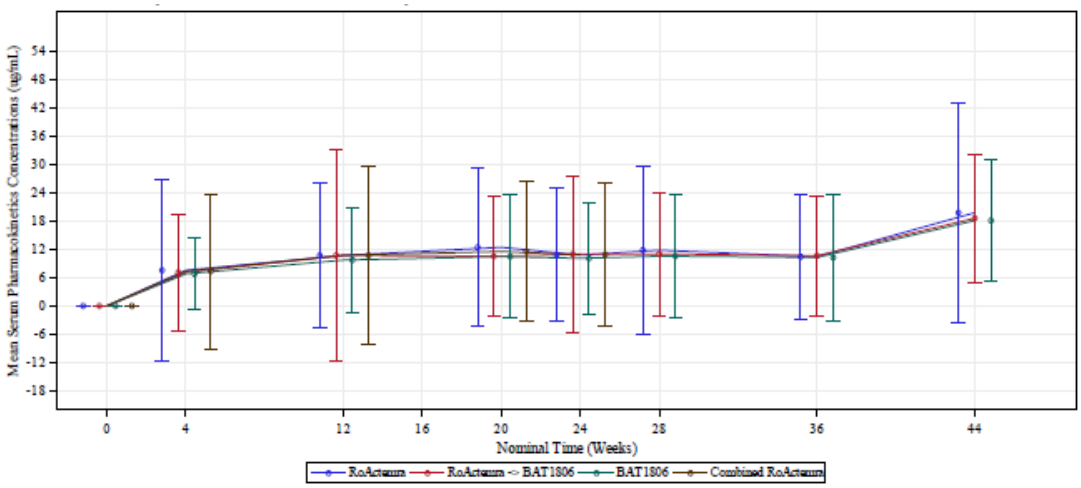
Comparative repeat-dose PK was investigated in RA subjects with moderate-to-severe disease. The mean (SD) age was 50.5 (11.98) years (range of 20 to 76 years), mean (SD) height was 163.31 (7.663) cm, and the mean (SD) weight was 66.40 (14.262) kg. Most subjects were female (534 subjects, 86.0%), from Central Europe (368 subjects, 59.3%), White (368 subjects, 59.3%), and not Hispanic or Latino (610 subjects, 98.2%). Most subjects did not have previous biologic or targeted synthetic DMARD (tsDMARD) usage (412 subjects, 66.3%). Similar results can be seen over the populations PPS at Week 12, PPS at Week 24, and subjects who entered TP2. Overall, there were no notable differences between the RoActemra and BAT1806 groups with regard to the demographic and baseline characteristics. The demographic and baseline characteristics for subjects who entered TP2 are also similar across the groups.

Table 5 - Serum Ctrough of Tocilizumab by Scheduled Visit – Overall (PKAS) - study BAT-1806-002-CR

Visit	Statistic	RoActemra			BAT1806 N=310
		RoActemra →RoActemra N=167	RoActemra →BAT1806 N=142	Combined N=309	
Baseline	n	167	142	309	310
	Geo Mean	-	-	-	-
	Geo CV%	-	-	-	-
	BLQ, n (%)	167 (100)	142 (100)	309 (100)	310 (100)
Week 4	n	163	140	303	302
	Geo Mean	6.2973	5.5772	5.9594	5.8228
	Geo CV%	117.7	139.6	127.5	144.3
	BLQ, n (%)	20 (12.3)	21 (15)	41 (13.5)	36 (11.9)
Week 12	n	145	133	278	288
	Geo Mean	10.8187	12.5253	11.5920	11.9650
	Geo CV%	156.0	111.2	134.5	113.3
	BLQ, n (%)	25 (17.2)	26 (19.5)	51 (18.3)	44 (15.3)
Week 20	n	137	130	267	278
	Geo Mean	14.4531	13.2710	13.8789	12.1911
	Geo CV%	140.5	111.0	126.0	146.8
	BLQ, n (%)	21 (15.3)	25 (19.2)	46 (17.2)	35 (12.6)
Week 24	n	137	134	271	276
	Geo Mean	11.6519	12.9307	12.2579	12.8822
	Geo CV%	156.2	124.6	140.3	121.3
	BLQ, n (%)	20 (14.6)	23 (17.2)	43 (15.9)	28 (10.1)
Week 28	n	141	133	274	280
	Geo Mean	12.4398	12.6589	12.5440	13.0740
	Geo CV%	180.7	157.0	168.5	126.5
	BLQ, n (%)	23 (16.3)	25 (18.8)	48 (17.5)	33 (11.8)
Week 36	n	141	136	277	283
	Geo Mean	12.7412	13.9536	13.2926	13.0658
	Geo CV%	137.4	121.8	129.8	115.5
	BLQ, n (%)	15 (10.6)	26 (19.1)	41 (14.8)	25 (8.8)
Week 44	n	138	134	272	282
	Geo Mean	13.5014	13.3536	13.4291	12.2718
	Geo CV%	121.0	125.1	122.6	150.6
	BLQ, n (%)	17 (12.3)	19 (14.2)	36 (13.2)	31 (11)

Abbreviations: BLQ = below the lower limit of quantification; CV% = coefficient of variation percent; Geo = Geometric; N = number of subjects; n = number of subjects in the specified category.
Note 1: Concentration values are in µg/mL.
Note 2: Concentration values below the lower limit of quantification (BLQ) were not included in the calculation of geometric mean and geometric CV%.
Note 3: For subjects who discontinued study treatment early but continued to have pharmacokinetics assessment more than 4 weeks after the last dose, the concentration data were excluded from summaries.

Figure 2 - Linear Mean (±SD) Serum Ctrough Concentrations (µg/mL) of Tocilizumab (Pharmacokinetic Set) - study BAT-1806-002-CR



Source: Figure 14.3.4.4.2

Table 6 - Comparison of Ctrough Data from RA Subjects Receiving 8 mg/kg Doses of Intravenous Tocilizumab over 24 Weeks - study BAT-1806-002-CR

	Study BAT1806-002-CR		RoActemra (SmPC, 2022)*	MUSASHI (Ogata et al., 2014) N=173	SUMMACTA (Burmester et al., 2014) N=493
	BAT1806 N=310	RoActemra N=309			
Mean C_{trough} ± SD (µg/mL) at Week 24	15.80 ± 12.3	13.38 ± 17.1	15.9 ± 13.1	12.4 ± 7.9	18.0 ± 14.2

Abbreviations: C_{trough} = serum trough concentration; SD = standard deviation
*Data obtained from population PK analysis of a database composed of 3552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg RoActemra every 4 weeks for 24 weeks or with 162 mg RoActemra given subcutaneously either once a week or every other week for 24 weeks. Data presented for RoActemra 8 mg/kg IV infusion only.
Source: Study BAT1806-002-CR CSR Table 14.3.4.4.1; RoActemra SmPC, 2022; Ogata et al., 2014; Burmester et al., 2014

Supportive Population PK analysis

PK-similarity was assessed by graphical (CL and V1) and statistical (AUClast (Week 44) and AUClast (Week 20)) comparison of BAT1806 to RoActemra exclusively in the Phase 3 study.

Table 7 - Summary statistics of model-derived AUClast at Week 20 of Phase 3 at two dose levels (with no effect of Treatment by Region)

	4 mg/kg		8 mg/kg	
	RoActemra (N=35)	BAT1806 (N=25)	RoActemra (N=228)	BAT1806 (N=248)
AUC_{last} (µg.h/mL)				
Mean (CV%)	16900 (54.8%)	21100 (49.1%)	41500 (42.5%)	41500 (40.6%)
Median (Min, Max)	16400 (5820, 44900)	19500 (9590, 53400)	38100 (10000, 121000)	39100 (13900, 134000)
Geo Mean (Geo CV%)	14900 (53.9%)	19000 (48.5%)	38300 (42.0%)	38600 (39.6%)
90% CI	7130-36100	10300-36000	19900-73400	20500-70400

AUC_{last}= Area under the concentration-time curve after last dosing event at steady state (linear trapezoidal rule); CV= Coefficient of variation expressed as a percentage, ratio of standard deviation to mean; Min= minimum; Max= maximum; N= number of subjects; 90% CI= 90% Confidence Interval; Geo Mean = Geometric Mean; Geo CV% = Geometric CV%.
Source: Population PK Report, Module 5.3.3.5, Table 10

Table 8 - Summary statistics of model-derived AUClast at week 44 of Phase 3 at two dose levels (with no effect of Treatment by Region)

	4 mg/kg		8 mg/kg	
	RoActemra (N=25)	BAT1806 (N=48)	RoActemra (N=115)	BAT1806 (N=363)
AUC_{Last} (µg.h/mL)				
Mean [CV%]	19700 [63.7%]	18300 [69.9%]	43900 [39.6%]	43000 [41.0%]
Median [Min, Max]	14600 [5410, 52600]	16000 [5900, 90800]	43200 [17000, 116000]	39000 [1080, 120000]
Geo Mean [Geo CV%]	16400 [68.7%]	16000 [49.7%]	40600 [41.1%]	39500 [45.3%]
90% CI	6360-43700	8170-29800	21500-71800	21300-76300

AUC_{Last}= Area under the concentration-time curve after last dosing event at steady state (linear trapezoidal rule); CV= Coefficient of variation expressed as a percentage, ratio of standard deviation to mean; Min= minimum; Max= maximum; N= number of subjects; 90% CI= 90% Confidence Interval; Geo Mean = Geometric Mean; Geo CV% = Geometric CV%.

Table 9 - GMR (BAT1806/RoActemra) and 90% CI of predicted AUClast at 8 mg/kg dose level with no effect of Treatment by Region

PK Parameter	Dose Level	Week	N	GMR (Test/Ref) (%)	90% CI (%)
AUC_{Last} (h.µg/mL)	8 mg/kg	20	N=228 (RoActemra) N=248 (BAT1806)	100.78	94.98-106.9
	8 mg/kg	44	N=115 (RoActemra) N=363 (BAT1806)	97.26	90.27-104.8

GMR = Geometric Mean Ratio; Test = Test formulation (BAT1806); Ref = Reference formulation (RoActemra®); 90% CI = 90% Confidence Interval; N = Number of subjects.

The Point Estimate (Geometric Mean Ratio) and 90% Confidence Interval (CI) of prediction-based AUCLast at Weeks 20 and 44 of the Phase 3 study at 8 mg/kg dose level were within the equivalence range of 80.00-

125.00%. Estimated CL (L/h) (0.00797 [0.00525-0.0123]) and V1 (L) (3.15 [2.68-3.67]) of BAT1806 were also found to be considerably close to the CL (L/h) (0.00780 [0.00452-0.0131]) and V1 (L) (3.11 [2.51-3.73]) of RoActemra in the Phase 3 study. Hence, the PK-similarity of BAT1806 to RoActemra in the Phase 3 study was demonstrated with model-predicted PK parameters.

Special populations

No tocilizumab study has been performed in patients with hepatic and severe renal impairment. Tocilizumab is a monoclonal antibody and no influence of renal or hepatic failure on the PK is expected. Weight-based dosing is intended, with a dose limit of 800 mg. For adults no dose adjustment is recommended by age, gender and ethnicity.

3.3.2.2. Pharmacodynamics

Mechanism of action

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

Primary and Secondary pharmacology

Validated PD markers do not exist for the efficacy of IL-6 receptor inhibitors. No studies on secondary PD have been provided. Regarding the primary PD, a set of non-clinical in vitro studies have been performed (see section 3.2. non-clinical aspects).

Immunogenicity

Clinical immunogenicity was evaluated by monitoring the humoral immune response (anti-drug antibodies [ADA] and neutralizing ADA [NAb]) reactive with BAT1806, RoActemra (European Union [EU]-licensed) and Actemra (United States [US]-licensed) respectively, allied to assessment of impact on clinical parameters (pharmacokinetic [PK], drug trough concentration, efficacy and treatment-related adverse events).

The evaluable population of clinical immunogenicity comprises the 2 studies BAT1806-001-CR (phase 1 in healthy volunteers) and BAT1806-002-CR (Phase 3 in RA patients).

Table 10 - Endpoints for Assessment of Relative Immunogenicity

Endpoint	Study	
	BAT1806-001-CR	BAT1806-002-CR
Immunogenicity		
ADA	X	X
ADA titer	X	X
NAb	X	X
Serum tocilizumab concentration/PK parameters		
Serum tocilizumab concentration [µg/mL]	X	X (Serum tocilizumab trough concentration)
Serum tocilizumab PK parameters: C_{max} [µg/mL] AUC_{0-t} [µg*h/mL] AUC_{0-inf} [µg*h/mL]	X	N/A
Efficacy		
ACR20, ACR50, ACR70	N/A	X
DAS28 ESR	N/A	X
Safety		
AE (including related AEs)	X	X

ACR20/50/70 = American College of Rheumatology 20/50/70% response, ADA = anti-drug antibody, AE = adverse event, AUC_{0-inf} = area under the concentration time-curve from time zero to infinity, AUC_{0-t} = area under the concentration-time curve from time 0 to time t, C_{max} = maximum concentration, N/A = not applicable, NAb = neutralizing antibody, PK = pharmacokinetic, SAE = serious adverse event.
Source: Table 3, ISI SAP

Phase 1 study BAT1806-001-CR in healthy volunteers

The timepoints of ADA/NAb blood sample collection during the study were before administration (within 1 h before study drug administration), 336 h±1 day (Day 15), 1008 h±1 day (Day 43), and 1344 h± 2 day (Day 57).

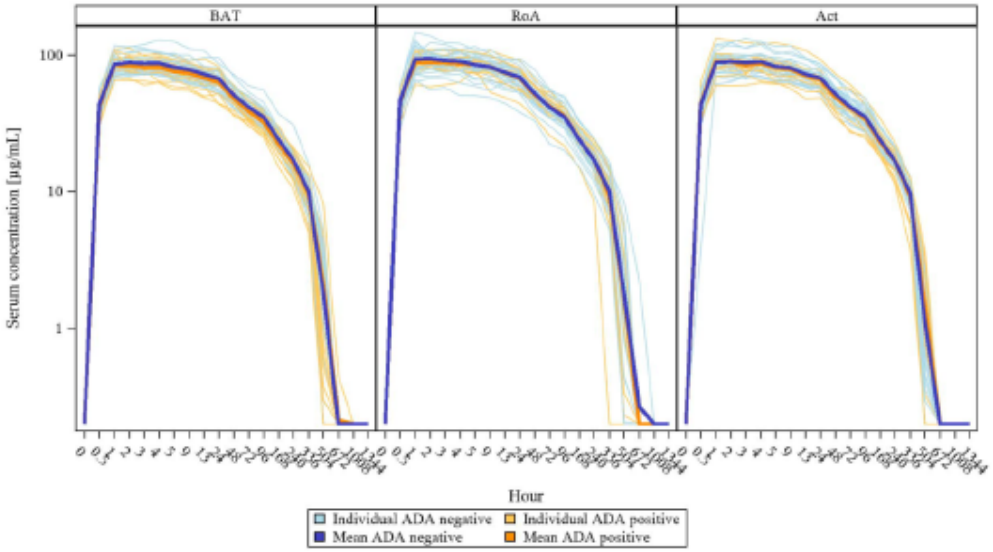
Table 11 - Summary of ADA/NAb Results in Study BAT1806-001-CR (SAS)

Subject ADA/NAb status	BAT1806 (N=45)	RoActemra (N=42)	Actemra (N=42)
Pre-existing (baseline) ADA-positive			
n (%)	2 (4.4)	0	0
Maximal ADA titer			
Geo Mean	38.95		
GCV (%)	1.271		
Median (range)	38.95 (38.6, 39.3)		
Treatment-induced ADA-positive			
n (%)	17 (37.8)	12 (28.6)	13 (31.0)
Maximal ADA titer			
Geo Mean	77.44	40.09	42.58
GCV (%)	212.904	174.217	176.447
Median (range)	67.80 (10.0, 1140.0)	42.80 (10.0, 380.0)	38.90 (10.0, 512.0)
ADA-negative			
n (%)	26 (57.8%)	30 (71.4%)	29 (69.0)
NAb-positive			
n (%)	16 (35.6)	10 (23.8)	13 (31.0)
% of ADA-positive subjects	84.2	83.3	100.0

ADA = anti-drug antibody, NAb = neutralizing antibody, N = number of subjects in the SAF, n=number of subjects, % = n/N expressed as percentage.
ADA Titer: A quasi-quantitative expression of the level of ADA in a sample.
Maximal ADA titer represents the subject's highest ADA titer value within the study (including baseline and post baseline samples).
ADA-negative: denominator = Number of subjects in the Safety Analysis Set.
NAb positive: denominator 1 = Number of subjects in the Safety Analysis Set.
NAb positive: denominator 2 = (Number of subjects with pre-existing ADA + Number of subjects with treatment induced ADA).
Source: Table 73, ISI TFLs

Impact of ADA status on clinical parameters

Figure 3 - Spaghetti Plot of Serum Tocilizumab Concentration Over Time by ADA Status in Study BAT1806-001-CR (PKC)



BAT=BAT1806, RoA=RoActemra-EU, Act=Actemra, ADA=anti-drug antibody.
Concentration levels below limit of quantification (BLQ), recorded as '0', were imputed as 0.2 (µg/mL), which is the lower limit of quantification (LLOQ).
Source: Figure 8, ISI TFLs

Table 12 - Serum Tocilizumab Pharmacokinetics Parameters by ADA Status in Study BAT1806-001-CR (PKAS)

	BAT1806		RoActemra		Actemra	
Pharmacokinetics parameter / Statistics	**ADA positive (N=19)**	**ADA negative (N=26)**	**ADA positive (N=12)**	**ADA negative (N=30)**	**ADA positive (N=13)**	**ADA negative (N=29)**
C_{max}						
n	19	26	12	30	13	29
Geo Mean	86.43	89.66	93.68	97.33	90.03	91.85
GCV (%)	14.9	14.2	12.0	19.5	18.4	15.7
Median (range)	85.50 (65.7, 112)	88.90 (72.0, 129)	92.60 (78.4, 110)	100.5 (66.0, 146)	92.60 (62.6, 132)	90.50 (69.9, 132)
AUC_{0-t} [µg*h/mL]						
n	19	26	12	30	13	29
Geo Mean	9932	10510	10420	10650	10120	10520
GCV (%)	19.5	16.2	25.7	20.0	21.9	13.7
Median (range)	10200 (6820, 14300)	10500 (7910, 16800)	10630 (5610, 14300)	10700 (5920, 15900)	10800 (6880, 14700)	10700 (8570, 14100)
AUC_{0-inf} [µg*h/mL]						
n	19	26	12	30	13	29
Geo Mean	10410	11160	10970	11130	10520	10770
GCV (%)	18.6	14.7	22.1	18.8	20.1	13.1
Median (range)	10700 (7570, 14400)	11200 (8900, 17600)	10950 (6900, 15400)	11050 (6760, 17100)	11100 (7280, 14800)	10800 (8660, 14500)

ADA = antidrug antibody, AUC_{0-inf} = Area under the concentration-time curve in serum from time X extrapolated to infinity, AUC_{0-t} = Area under the serum concentration-time curve from time X to the time of last measurable concentration, C_{max} = Maximum concentration, Geo Mean = geometric mean, GCV% = geometric coefficient of variation, N = Number of subjects in Pharmacokinetics Analysis Set, n = number of subjects with data available.
The analysis values were rounded to specific significant digits prior to calculating summary statistics.
Source: Table 77a, ISI TFLs

Phase 3 study BAT1806-002-CR in RA subjects with moderate-to-severe disease

The time points for ADA/Nab sampling were as follows: prior to infusion of treatment (BAT1806/RoActemra) on day 0 (baseline) and at weeks 4, 12, 24, 28, 36, 48 (end of study), and 8 weeks after the last dose (follow-up visit).

Table 13 - Summary of ADA and NAb response parameters vs. clinical impact treatment period 1 in study BAT1806-002-CR

Parameter		
ADA/NAb dynamics	**BAT1806** (N=312) (SAF)	**RoActemra Combined** (N=309) (SAF)
ADA positive in TP1, n (%): • Total treatment-emergent • Transient • Persistent	 62 (19.9) 45 (72.6) 17 (27.4)	 39 (12.6) 31 (79.5) 8 (20.5)
Geometric mean of maximal ADA titer in TP1 for treatment-induced ADA	20.9	20.0
NAb positive at Week 24, %	98.5	97.7
Trough concentrations	**BAT1806** (ADA-, N=266; ADA+, N=42) (PKS)	**RoActemra** (ADA-, N=246; ADA+, N=64) (PKS)
Geometric mean drug tough concentration at Week 24, µg/ml: • ADA negative (95% CI) • ADA positive (95% CI) • NAb negative • NAb positive	 9.1674 (7.4292, 11.3123) 6.2760 (4.3093, 9.1401) 9.1154 6.3675	 7.3765 (5.9137, 9.2011) 2.6902 (1.4085, 5.1384) 7.3765 2.6902
Efficacy at week 24	**BAT1806** (ADA-, N=246; ADA+, N=64) (FAS)	**RoActemra** (ADA-, N=266; ADA+, N=42) (FAS)
ACR20 responders at Week 24, n (%): • ADA negative • ADA positive	 171 (77.0) 47 (77.0)	 182 (77.4) 28 (71.8)
ACR50 responders at Week 24, n (%): • ADA negative • ADA positive	 100 (44.4) 32 (52.5)	 111 (45.7) 21 (52.5)
ACR70 responders at Week 24, n (%): • ADA negative • ADA positive	 51 (22.2) 13 (21.3)	 57 (23.4) 12 (30.0)
DAS28-ESR at Week 24, mean (SD): • ADA negative • ADA positive	 3.13 (1.45) 3.35 (1.35)	 3.34 (1.52) 3.45 (1.32)

ACR20/50/70 = American College of Rheumatology 20/50/70% response, ADA = anti-drug antibody, ADA- = ADA negative, ADA+ = ADA positive, CI = confidence interval, DAS28 = disease activity score in 28 joints, ESR = erythrocyte sedimentation rate,
FAS = full analysis set, NAb = neutralizing antibody, PKS = pharmacokinetic analysis set, SAF = safety analysis set, TP = Treatment Period.
NAb-positive subjects both include positive at baseline.
Source: Table 11, Table 15, Table 19, Table 34, Table 49, ISI TFLs

Table 14 - Summary of ADA and NAb Response Parameters vs. Clinical Impact in TP1 and TP2 Combined in Study BAT1806-002-CR

Parameter			
ADA/NAb dynamics	**BAT1806** (N=312) (SAF)	**RoActemra only** (N=167) (SAF)	**RoActemra-BAT1806** (N=142) (SAF)
ADA positive in TP1 and TP2 combined, n (%): • Total treatment-emergent • Transient • Persistent	88 (28.2) 48 (54.5) 40 (45.5)	40 (24.0) 22 (55.0) 18 (45.0)	28 (19.7) 19 (67.9) 9 (32.1)
Geometric mean of maximal ADA titer in TP1 and TP2 combined	21.0	20.0	20.0
NAb positive in TP1 and TP2 combined , %	98.9	95.2	100.0
Trough concentrations	**BAT1806** (ADA-, N=219; ADA+, N=91) (PKS)	**RoActemra only** (ADA-, N=125; ADA+, N=41) (PKS)	**RoActemra-BAT1806** (ADA-, N=111; ADA+, N=31) (PKS)
Geometric mean drug tough concentration at Week 48, µg/ml: • ADA negative (95% CI) • ADA positive (95% CI) • NAb negative • NAb positive	 10.0313 (8.1069, 12.4124) 6.9941 (4.7663, 10.2631) 10.0365 6.9553	 9.5341 (6.9913, 13.0017) 5.8368 (3.2840, 10.3741) 9.6311 5.6030	 10.0880 (7.5007, 13.5677) 3.8228 (1.6686, 8.7582) 10.0880 3.8228
Efficacy	**BAT1806** (ADA-, N=219; ADA+, N=91) (FAS)	**RoActemra only** (ADA-, N=116; ADA+, N=39) (FAS)	**RoActemra-BAT1806** (ADA-, N=120; ADA+, N=33) (FAS)
ACR20 responders at Week 48, n (%): • ADA negative • ADA positive	 176 (90.3) 77 (90.6)	 89 (88.1) 33 (86.8)	 96 (92.3) 25 (83.3)
ACR50 responders at Week 48, n (%): • ADA negative • ADA positive	 139 (71.3) 58 (68.2)	 63 (62.4) 23 (60.5)	 72 (69.2) 22 (73.3)
ACR70 responders at Week 48, n (%): • ADA negative	 87 (44.6)	 38 (37.6)	 48 (46.2)
• ADA positive	42 (49.4)	16 (42.1)	18 (60.0)
DAS28-ESR at Week 48, mean (SD) • ADA negative • ADA positive	 2.45 (1.39) 2.53 (1.33)	 2.87 (1.55) 3.20 (1.78)	 2.59 (1.28) 2.83 (0.95)

ACR20/50/70 = American College of Rheumatology 20/50/70% response, ADA = anti-drug antibody, ADA- = ADA negative, ADA+ = ADA positive, CI = confidence interval, DAS28 = disease activity score in 28 joints, ESR = erythrocyte sedimentation rate, FAS = full analysis set, NAb = neutralizing antibody, PKS = pharmacokinetic analysis set, SAF = safety analysis set, TP = Treatment Period.
NAb-positive subjects both include positive at baseline.
Source: Table 13, Table 17, Table 23, Table 38, Table 53, ISI TFLs

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

Biogen is proposing BAT1806 as RoActemra biosimilar for IV infusion only. Two (2) clinical studies were completed for BAT1806 from which PK data was obtained: a Phase 1 study in healthy volunteers and a Phase 3 study in subjects with RA with an inadequate response to methotrexate (MTX). Furthermore, a population PK model was developed based on serum concentration data collected from both studies and aimed to (1) further describe the PK of tocilizumab, and to (2) assess PK similarity of BAT1806 to RoActemra at 8 mg/kg in patients with Rheumatoid Arthritis (RA). The resulting PK database is deemed sufficient for a biosimilar development.

Bioanalytical methods

A quantitative sandwich ELISA method was utilised for the quantification of BAT1806 and originators EU-RoActemra and US-Actemra concentrations in healthy human serum (clinical study BAT-1806-CR-001) and in

RA human serum samples (clinical study BAT-1806-CR-002). The bioanalytical method used in the clinical studies has been validated according to EMA guideline EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**. Bioanalytical similarity between BAT1806, EU-tocilizumab and US-tocilizumab analysis standard was confirmed during method validation. Method validation revealed that the assay performs with adequate accuracy and precision for BAT1806, EU-tocilizumab and US-tocilizumab (within- and between-run). Upon successful completion of precision and accuracy tests, BAT1806 was used for batch control sample preparation, which is deemed acceptable. Method interference from free IL-6R was investigated. No potential interference of concomitant medication and possible earlier anti-IL6 medications was assessed during validation. However, as in both clinical studies participants who had prior use of any authorised or investigational IL-6 /IL-6R inhibitors were excluded and since the pre-dose samples in both studies had results that were below the limit of Quantification (BLQ), an interference with earlier anti-IL-6 medications seems to be unlikely. Overall, the bioanalytical method met the requirements of the validation plan and is considered suitable for quantification of BAT1806, Tocilizumab EU and Tocilizumab US in human serum. Method performance in studies BAT-1806-001-CR and BAT-1806-002-CR was deemed appropriate. Furthermore, the incurred sample analysis performed on 209 samples was considered adequate and was in accordance with the EMA guideline.

Immunogenicity testing of BAT1806 (biosimilar) and tocilizumab (reference product) in the clinical studies was conducted by using a single assay approach with BAT1806 (biosimilar) used as antigen for both, ADA and NAbs analysis. An ECL method has been validated for the detection of anti- tocilizumab antibodies in human serum. The validation data demonstrate that the assay is suitable of reliably detecting the presence of specific anti-tocilizumab antibodies in human serum. The drug tolerance is considered sufficient. No potential interference of Rheumatoid Factor with ECL ADA Assay Method ICSH 20-048 has been investigated/discussed during method validation. However, upon request the applicant provided a post-hoc selectivity study to demonstrate the absence of interference of Rheumatoid Factor with ECL ADA Assay Method ICSH 20-048. An interference of Rheumatoid Factor is unlikely based on the data provided.

A non-cell based ECL competitive ligand binding assay (CLB) has been utilised for determination of neutralising anti-dug antibodies in both pivotal clinical trials. As none of the 3 products applied in the clinical trials (BAT1806, EU-RoActemra, US-Actemra) exhibits FC effector functions, this assay type may be appropriate. The validation data demonstrate that the applied assays are sufficiently capable to detect neutralizing anti-tocilizumab antibodies in human serum. For samples with 10% haemolysis the results did not meet acceptance criteria. However, the selectivity in haemolysed matrices has been investigated with at least 2% haemolysed samples and this experiment passed the acceptance criteria. In addition, based on the information provided by the applicant, none of the samples were haemolytic during nAb sample analysis of studies BAT-1806-001-CR and BAT-1806-002-CR. Thus, an impact of haemolysis on the reported Nab results can be excluded.

Method ICSH-18-032 used in the phase 3 study BAT-1806-002-CR has not been validated for RA patient serum. Upon request a post-hoc study has been provided by the applicant and based on the provided post-hoc analysis data the absence of matrix interference in RA patient serum samples is demonstrated.

Population PK analysis

For population PK model development, the model was informed by intensive PK sampling data from the phase 1 study and sparse PK data from the phase 3 study. The population PK analysis dataset consisted of a total of 129 subjects from the Phase 1 study and 615 subjects in TP1 (the first 6 months) from the Phase 3 study, and 596 subjects from TP2 (the second 6 months) of the Phase 3 study. In the respective studies, tocilizumab was solely administered via IV route. As serum BLQ concentrations of tocilizumab were >10% of

the concentrations, they were set to 0 and included in the analysis, which is deemed appropriate. Four (4) subjects were excluded from the analysis for acceptable reasons. Handling of missing data is acceptable.

A 2-compartment model with mixed (linear + Michaelis-Menten non-linear) elimination has been established, which is endorsed. Patient factors were investigated for their potential influence on the PK of tocilizumab, including ADA positivity, nAb positivity, Treatment, Ethnicity, Race, Region, and "Treatment by Region". None of them was found to be statistically significant. Overall, model development is considered adequate.

For the final model, interpatient variability was included on both CL and V1. The final PK model considered the estimated effect of dose level on CL and the estimated effect of weight on CL and V1. Weight was centered to the median value from the Phase 1 and Phase 3 studies as a reference value, which is endorsed. Parameter estimates were reported with associated uncertainty, with between subject variability reported as the coefficient of variation (CV%) and precision reported as the percent relative standard error (RSE%) and the 90% CI. Shrinkage of ETAs of the model parameters was below 30% for all parameters.

The pop PK model was evaluated at all stages of development by multiple diagnostics. Overall, plots for the final model show good agreement between the observed and the simulated exposure, supporting the structural model.

The pop PK model was applied to provide supportive evidence on PK similarity only; it was not applied to simulate exposure in unexplored dosing regimens or to otherwise generate pivotal data. Overall, the population PK model is deemed to be valid for its intended purpose.

Based on population PK model, clearance was estimated to 0.0082 L/h (CV%: 26.4%), V1 was calculated to be 3.21 L (14.4 %) and V2 to 3.27 L (47.2%). Parameters are in line with those expected for a monoclonal antibody and with values reported in RoActemra SmPC (CL: 9.5 mL/h; central volume of distribution: 3.72 L; peripheral volume of distribution: 3.35 L).

PK in healthy volunteers

Study **BAT-1806-001-CR** was a randomised, double-blinded, single-dose, 3-arm parallel Phase I clinical study to establish pairwise PK biosimilarity between BAT1806 vs EU-RoActemra, BAT1806 vs US-Actemra, US-Actemra vs EU-RoActemra in healthy Chinese male subjects and to evaluate the clinical safety, tolerability and immunogenicity of 3 groups. The general study design is acceptable to establish pairwise PK biosimilarity. The parallel group design is acceptable considering the half-life and immunogenic potential of tocilizumab. The chosen 4 mg/kg dose (half of therapeutic dose) is considered to be acceptable for the following reasons: a) Based on available PK data of tocilizumab it is assumed that the proposed dose of 4 mg/kg would be within the non-linear dose range associated with a greater sensitivity to detect difference between products compared to the 8mg/kg dose. b) Additional PK data were collected for the 8 mg/kg IV dose in RA patients in the phase III trial. c) A population PK analysis including 4mg/kg and 8mg/kg data was conducted to further establish PK similarity. d) The 4mg/kg dose is within the therapeutic range and may provide better safety in healthy volunteers.

The primary and secondary PK endpoints are in line with EMA guideline (EMA/CHMP/BMWP/403543/2010) and acceptable. However, it should be noted that in the Phase 1 clinical trial the demonstration of biosimilarity is based on PK parameters only and no PD parameters have been assessed in order to contribute to the comparability exercise.

The protein concentration of BAT1806 batch No. A0520180402 is 20.0 mg/mL and of RoActemra batch No. B2065 is 19.8 mg/mL. The applicant was asked information whether/how the products were normalised to ensure administration of equal amounts of protein. In response to the Day 120 LoQ, the Applicant clarified

that drug product batches with closely matching nominal protein concentrations were selected, but no correction or normalisation for differences in protein concentration have been applied. Although a correction/normalisation to ensure administration of equal amounts of protein should have been applied. The issue was not further pursued.

Although, drug product batches with closely matching nominal protein concentrations were selected, it could not be excluded with certainty that unequal amounts of protein were possibly administered, since no correction or normalisation for differences in protein concentration was performed by the applicant.

A blinded PK interim analysis was conducted after 50% subjects had completed the study to re-assess sample size. Other than in superiority trials, a blinded sample size re-estimation may inflate the type-I-error rate in the equivalence setting. While there might be a potential for type-1-error inflation, this was considered very likely to be "negligible" by the Applicant. No further justification was provided to support this claim. In the given situation (i.e. post hoc), this might indeed be correct (given a relatively large sample size at the interim analysis, no adjustment of the sample size and 90% CIs far away from the equivalence margins), but it is not considered true in the general (a priori) case. The PK statistical analysis is in accordance with the recommendations in the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010). Moreover, for the PK biosimilarity demonstration the conventional equivalence margin 80-125% was used which is in accordance with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010). The randomisation scheme is considered adequate. Moreover, the stratification at randomisation by body weight is considered appropriate as body weight was identified as major factor in the variability of the PK parameters.

Neither critical exclusions of subjects/samples nor critical protocol deviations were reported.

The included population was restricted in sex (male), age (18-55 years), weight (55-85 kg) and BMI (18-28 kg/m2) and the study was conducted at a single site in China. This is acceptable for the purpose of PK biosimilarity testing, where a homogenous population is intended in order to detect potential product differences in PK characteristics. Demographic information for the Safety Analysis Set (identical to PK analysis set) of study BAT-1806-001-CR by treatment group shows comparable age, weight and BMI distribution. There was no relevant medical history reported and no prior medications received for subjects in the SAS. No prohibited medications were administered.

BAT1806, EU-RoActemra, and US-Actemra exhibited nearly superimposable mean tocilizumab serum concentration-time profiles. Descriptive statistics for tocilizumab demonstrate that determined PK parameters were similar for all treatment groups. More importantly, the 90% CIs for test to reference ratios of AUC0-inf were contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for all of the pair-wise comparisons among the 3 study drugs, demonstrating PK similarity among BAT1806, EU-RoActemra, and US-Actemra. Furthermore, the key secondary endpoints AUC0-t and Cmax showed PK biosimilarity (90% confidence intervals contained within 80.00% to 125.00%). Thus, based on the PK results of study BAT-1806-001-CR it may be concluded that BAT-1806 and EU-RoActemra are biosimilar from a PK point of view.

PK in target population

In the phase III RA patient trial **BAT-1806-002-CR**, EU approved RoActemra and BAT1806 were administered intravenously every 4 weeks at a dose level of 8 mg/kg, limited at 800mg and with the possibility to reduce to 4mg/kg, which is in line with RoActemra approval. The PK secondary objective was to evaluate the steady-state PK of BAT1806 versus RoActemra with Ctrough as the PK endpoint.

Prior to the 4th dose (at week 12), the geometric mean of tocilizumab Ctrough was 11.97 µg/mL and 11.59 µg/mL and for the BAT1806 and RoActemra groups, respectively. The geometric mean Ctrough remained similar for both products during treatment period 1 (up to week 24). Switching from RoActemra to BAT1806 had no relevant impact on Ctrough values; Ctrough level remained comparable between switch and non-switch group until week 44. Ctrough values obtained for both, BAT1806 and RoActemra at week 24 were comparable to published data on RoActemtra.

The population PK model was additionally applied to provide supportive evidence on PK similarity at the 8 mg/kg therapeutic dose level in RA. Model-based AUClast at weeks 20 and 44 of BAT1806 was compared to RoActemra for biosimilarity assessment purposes. The geometric mean ratio (BAT1806/RoActemra) of AUClast and its 90% CIs were within the equivalence interval of 80.00 to 125.00% at dose level of 8 mg/kg in the Phase 3 study under all tested scenarios, i.e., at Week 20 and 44, in the absence and presence of Treatment by Region effect, and when two formulations were compared in each region. The CL and V1 of tocilizumab in BAT1806 and RoActemra in the Phase 3 study were compared graphically and were found to be comparable. Overall, PK results from study BAT-1806-002-CR and population PK analysis support the conclusion that BAT1806 and EU-RoActemra are PK biosimilar.

Pharmacodynamics

The mode of action of tocilizumab is established. No pharmacodynamic endpoints were included in any clinical study.

Clinical immunogenicity was evaluated by monitoring the humoral immune response (anti-drug antibodies [ADA] and neutralizing ADA [NAb]) reactive with BAT1806, EU-RoActemra and US-Actemra respectively. The immunogenic profile and the impact on clinical parameters (PK, efficacy and safety) was assessed in both clinical trials (BAT1806-001-CR and BAT1806-002-CR).

In phase 1 **study BAT1806-001-CR**, the incidence of treatment-induced ADA-positivity was higher in the biosimilar group (37.8%) as compared to the comparator groups (28.6% for EU-RoActemra and 31.0% for US-Actemra). Geometric mean titers were generally low with the highest maximum titer seen in the biosimilar group (1140.0). The majority of TE-ADA positive subjects in all 3 treatment groups had antibodies with neutralising capacity (nAb positive). ADA samples were tested positive as early as at day 15. However, incidence of ADA increased with time; highest incidence was seen at day 57. The presence of ADAs and NAbs had no obvious influence on concentration-time-profiles and PK parameters (Cmax, AUC) of BAT1806, EU-RoActemra and US-Actemra, respectively.

In phase 3 **study BAT1806-002-CR**, the percentage of ADA positive subjects at baseline was generally low (<2%). In both treatment groups, TE-ADAs occurred at week 4 (first sample post dose) and prevalence remained approximately the same over time, with no increase with ongoing treatment. TE-ADA for the 24-week treatment period (T1) was higher for BAT1806 (19.9%) compared with the RoActemra combined group (12.6%). Considering the overall 52-weeks study period, overall incidence of treatment-induced ADA positive subjects was slightly higher in the BAT1806-only treated group (28.2%) as compared to the RoActemra-only treated group (24.0%). For the switched group (treated with RoActemra followed by BAT1806), the incidence of ADA positive subjects was the lowest (19.7%). Thus, a switch from RoActemra to BAT1806 does not appear to be associated with an increased risk of Immunogenicity.

Geometric mean ADA titer were rather low for RoActemra and BAT1806 treated subjects. The large majority of ADAs in all treatment groups had drug neutralizing activity (nAB positivity), with potential impact on PK and efficacy. During the 24-weeks treatment period (TP1), the geometric mean serum tocilizumab trough concentration (Ctrough) for ADA positive subjects was lower than for ADA negative subjects at each

timepoint in both treatment groups. The higher ADA incidence detected for the BAT1806 group was not associated with a higher reduction in Ctrough in ADA positive subjects compared to the RoActemra group. The impact of ADA status on efficacy was investigated and analysed for ACR20, ACR50, and ACR70 as well as DAS28-ESR. For discussion see section 3.3.5. clinical efficacy

Overall, the presented database is deemed sufficient for analysis of immunogenicity of BAT1806. Compared to information given in RoActemra SmPC (1.6% of subjects developed anti-tocilizumab antibodies within 6 months), the incidence of TE-ADAs found in study BAT1806-001-CR is remarkably high (28.6% positivity after single dose application). The rationale provided by the applicant, that differences in the assays used, may have led to the differences between the information provided in the SmPC and the study data collected, given the sensitivity of the assays, is acknowledged and understandable. However, biosimilarity between originator and biosimilar should be granted. Based on the data provided by the applicant, some numerical differences in ADA occurrence and the False Positive Error Rate (FPER) between BAT1806 and RoActemra have been observed, especially in the Study BAT1806-001-CR. In addition, the False Positive Error Rate (FPER) calculated for the samples analysed in Study BAT1806-001-CR were generally quite high and numerical differences have been observed between the biosimilar and the comparators. However, the high rate of false positives could be due to the different sensitivities of the tier 1 screening assay and tier 2 confirmation assay. In addition, although the cut point established for Study BAT-1806-001-CR is considered to be not fully appropriate for all study samples (the in-study population), the discrepancies and differences observed for the FPER in study BAT1806-001-CR are not considered to overall question the similarity between the products.

Nevertheless, the incidence of TE-ADAs was lower in the phase 3 patient study vs phase 1 single dose study for both, RoActemra (12.6% vs 28.6%) and BAT1806 (19.9% vs. 37.8%). However, this observed difference is likely due to different levels of immune competence in RA patients (concomitant administration of immune-suppressive medications) compared to the healthy volunteers. Concomitant use of MTX and other immunomodulators may reduce the formation of antibodies against Tocilizumab.

Throughout the clinical trials, the overall incidence of treatment-induced ADA positive subjects was higher in the BAT1806-treated groups as compared to the RoActemra-treated groups. The potential causes that may have contributed to this finding is still unclear. No methodological bias could be clearly identified so far. However, based on the provided data, it is currently not considered that the slight differences between the ADA status and between the treatment groups alter the benefit-risk ratio to an extent that would suggest major efficacy/safety concerns and thus dissimilarity between both products.

Furthermore, an (almost) identical number of participants with ADA and NAbs results were identified. Although, this might be due to the relatively high sensitivity and drug tolerance of the two methods used, a slightly lower number of NAbs would still have been expected compared to ADAs. However, since an (almost) identical number of participants with ADA and NAbs results were identified in both the biosimilar and the originator treatment group, no biosimilarity concerns are anticipated. In addition, the ADA-positive status does not appear to affect efficacy compared to ADA-negative subjects in either treatment group.

SmPC

With regard to Clinical Pharmacology, Tofidence SmPC is in line with EU-RoActemra SmPC, which is appropriate.

3.3.4. Conclusions on clinical pharmacology

The available clinical pharmacology data overall support PK biosimilarity of BAT1806 versus EU-RoActemra in the healthy subjects and RA patients.

No PD parameters have been assessed to contribute to the comparability exercise. Thus, PD comparability cannot be concluded. However, the mechanism of action of tocilizumab is established, and based on all the data provided, there are no concerns in this case, and it is considered that the absence of the PD parameters has no negative impact on the benefit/risk ratio of the biosimilar.

Although, throughout the clinical trials, the overall incidence of treatment-induced ADA positive subjects was higher in the BAT1806-treated groups as compared to the RoActemra-treated groups, the potential causes that may have contributed to this finding are still not entirely clear. However, based on the provided data, it is not considered that the differences between the ADA status and between the treatment groups alter the benefit-risk ratio to an extent that would suggest major efficacy/safety concerns and thus dissimilarity between both products.

3.3.5. Clinical efficacy

3.3.5.1. Dose response study(ies)

Not applicable for biosimilars.

3.3.5.2. Main study

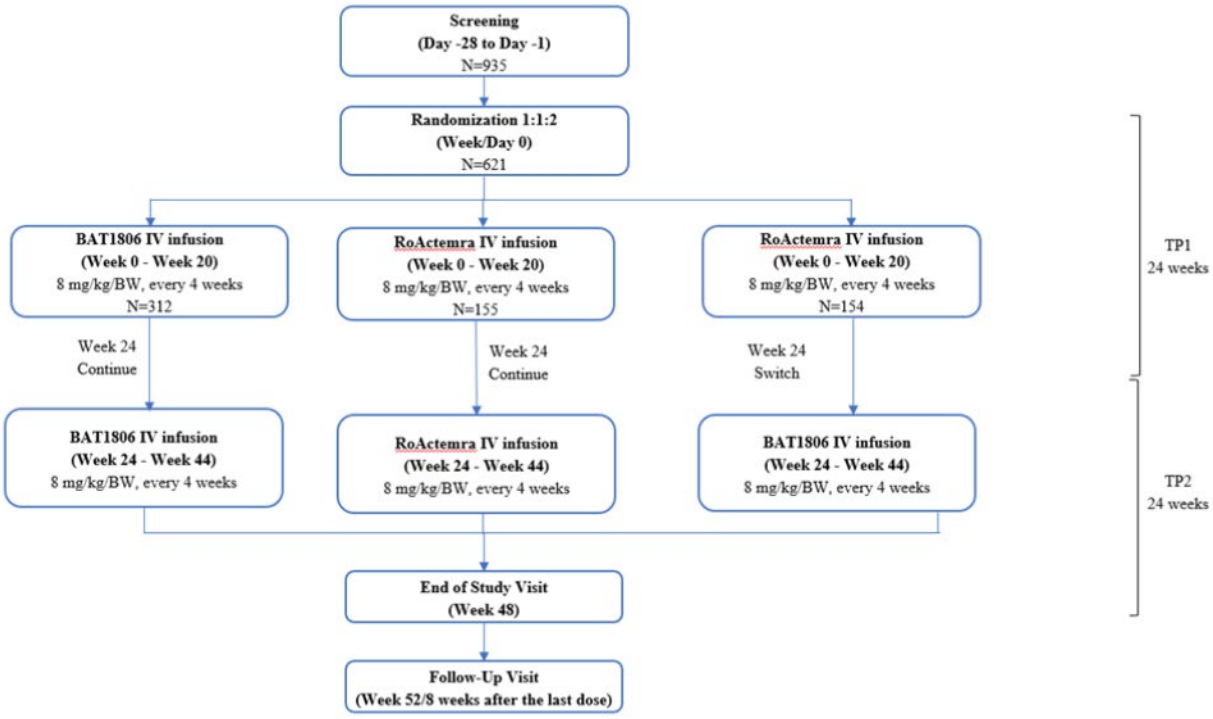
BAT-1806-002-CR

Methods

Study BAT-1806-002-CR was a Phase 3, multicenter, multinational, randomised, double-blind, active-control study to compare efficacy, safety, immunogenicity and PK of BAT1806 compared with RoActemra in participants with RA that was 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 an extra 4-week follow-up period. After completion of screening procedures, eligible participants were to be randomised in a 1:1:2 ratio to receive either RoActemra or BAT1806by intravenous (IV) infusion every 4 weeks until Week 20 in a double-blind fashion. The time points of the primary efficacy endpoint analysis depended on the regulatory authority requirement of the respective region (ie, for the EMA Week 12 and for the US FDA and China NMPA Week 24). From Week 24, the participants continued study treatment in a double-blind fashion with IV infusions every 4 weeks until Week 44. Participants originally randomised to BAT1806 continued treatment with BAT1806. Participants randomised to one of the RoActemra groups were switched to BAT1806 treatment, the other RoActemra group continue treatment with RoActemra.

Figure 4 - Study design BAT-1806-002CR



Study Participants

Eligible were male or female patients who were 18 years of age or older who fulfilled the ACR/EULAR 2010 revised classification criteria for RA diagnosis for at least 6 months before screening with active RA per prespecified criteria. Patients were required to have received MTX therapy for at least 12 weeks before randomisation, with at least the last 4 weeks before randomisation on a stable dose and had to continue on their stable MTX dose and route of administration throughout the study. If patients were using oral corticosteroids and/or nonsteroidal anti-inflammatory drugs, they had to be on a stable dose for at least 4 and 2 consecutive weeks, respectively, before randomisation and had to continue at this level throughout the study. Patients were also required to have received not more than 2 biological agents other than IL-6 inhibitors or targeted synthetic DMARDs in total for RA treatment.

Excluded were patients who had RA of ACR functional class IV or were wheelchair/bed bound, with known hypersensitivity to tocilizumab or to study treatment excipients, and/or previous exposure to any authorized or investigational IL-6 inhibitor and/or alkylating agents or concomitant medications like any biological agents or any targeted synthetic, any cell-depleting therapy ≤12 months before randomisation, investigational drug or device ≤8 weeks or 5 half- lives before randomisation or any conventional DMARDs other than MTX ≤4 weeks before randomisation.

Treatments

Table 15 - Treatments for study BAT-1806-002CR

	Preparations to be Administered	
	BAT1806	**RoActemra**
Manufacturer	Bio-Thera Solutions, Ltd	Roche
Active ingredient	Tocilizumab	
Dosage	8 mg/kg	
Route	Intravenous infusion	
Formulation	80 mg/4 mL injection vials	
Batch number(s)	Supplier Lot/Original batch: A0520180402; A0520190401	Supplier Lot/Original batch: B2070H09; B3024H15; B3024H21; B2081H11; B2081H18; B2091H07
	Blinded Lots: 18000300B1; 18000300B2; 18000300B3; 18000300B4; 18000300B5; 18000300B6; 18000300B7; 18000300B8; 18000300B9	

In both parts of the study, 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 could be reduced to 4 mg/kg body weight or interrupted in accordance with the recommendations of the RoActemra label in case of laboratory abnormalities.

During TP1, subjects received a total of 6 doses of either BAT1806 or RoActemra. During TP2, subjects received another 6 doses of either BAT1806 or RoActemra. During the study, all subjects continued taking their regular MTX therapy at a stable dose.

Permitted as concomitant medication were MTX on a stable dose at least the last 4 consecutive weeks prior to randomisation, continuation of existent Folic acid supplementation as per local standard for the duration of the study, Oral corticosteroids on a stable ≤ 10 mg dose of prednisone/day or equivalent for at least 4 consecutive weeks prior to randomisation and throughout the study, NSAIDs cyclooxygenase [COX] inhibitors) on a stable dose for at least 2 consecutive weeks before randomisation and throughout the study.

Prohibited were any biological agents for treatment of RA or any tsDMARDs, any conventional DMARDs other than MTX, high potency opioids, alkylating agents, IV immunoglobulins or plasmapheresis and intra-articular or parenteral corticosteroids.

Furthermore, an increase in dose of NSAIDs if a participant was on stable NSAIDs therapy or initiation of NSAIDs without exceeding the maximum approved dose was allowed as rescue treatment to treat a flare for no more than 2 consecutive weeks.

Objectives

The primary objective of the study was to demonstrate equivalent efficacy of BAT1806 and RoActemra in subjects with RA that was inadequately controlled by MTX.

The secondary objectives of the study were:

- To evaluate the efficacy profile of BAT1806 compared with RoActemra over time based on secondary efficacy endpoints
- To evaluate the safety and tolerability profile of BAT1806 compared with RoActemra over the entire study period
- To evaluate the immunogenicity profile of BAT1806 in terms of antidrug antibody (ADA) production compared with RoActemra
- To evaluate the steady-state pharmacokinetics (PK) of BAT1806 compared with RoActemra
- To assess safety and immunogenicity following transition from RoActemra to BAT1806

Outcomes/endpoints

The primary endpoint for the study was the percentage of subjects achieving an American College of Rheumatology 20% (ACR20) response. Two time points (Week 12 or Week 24) were analysed independently as primary for this measure, depending on the regulatory agency for submission.

The secondary endpoints included 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 SJC66, TJC68, VAS, HAQ-DI, Subject's Global Assessment of VAS, Physician's Global Assessment of VAS, CRP, and ESR. The immunogenicity endpoint for the study was the proportion of subjects developing ADAs to RoActemra or BAT1806 over the course of the study. The safety endpoints included all Adverse events (TEAEs, SAEs, related AEs, and related SAEs), Laboratory parameters, Vital signs, Physical examination and ECG.

Sample size

A total of approximately 770 subjects were planned to be screened to ensure that a total of 612 subjects are randomised, with the aim of having 598 evaluable subjects completing Week 12 of TP1 (assuming approximate dropout rate of 2% to Week 12). Using a 2-sided 95% CI ($\alpha = 0.025$), a reference proportion of 52.7%, a true difference of zero, and an equivalence margin of [-14.5%, +14.5%], 598 evaluable subjects total (299 per arm) were planned to provide over 89% power to show equivalence of BAT1806 with RoActemra for the difference in proportion of ACR20 responders at Week 12.

For the derivation of the equivalence margin, data on ACR20 response at Week 12 from the OPTION trial as well as data on the incidence of onset by visit from the TOWARD and the LITHE trial was used. Based on a fixed effects meta-analysis (as I2 = 0%, Cochran-Q = 1.780, P value = 0.41) resulting in a 95% CI around the point estimate of the risk difference of 32.7% is (29.0%, 36.3%) and the planning to retain 50% of the treatment effect, an equivalence margin of [-14.5%, +14.5%] was deemed appropriate as a clinically relevant margin for assessing similarity at Week 12.

Randomisation and blinding (masking)

Eligible subjects were planned to be randomised in a 1:1 ratio at the Baseline Visit according to a prespecified randomisation scheme. Upon qualification for the study, subjects were planned to be randomised using a computerised Interactive Voice and Web Response System (IXRS) system to receive either BAT1806 or

RoActemra during TP1, and further to this, to randomize additionally for TP2 (randomisation for both TP1 and TP2 will be done at the beginning of TP1) for subjects receiving RoActemra during TP1. Randomisation was planned to be stratified by region and previous biologic or targeted synthetic DMARD use (Yes/No).

The trial was planned to be a randomised, double-blind study. The investigators, site staff assessing the safety and efficacy, other related study staff (including contract research organization and sponsor), all subjects, and central laboratories were planned to remain blinded to the study treatment assignment throughout the study. Laboratory staff performing evaluation of PK and immunogenicity assessments were also planned to be blinded to conduct the bioanalysis. The unblinded site staff who were not involved in any study treatment administration or assessment were responsible for preparing the infusion solution according to the treatment allocation via IWRS. It was planned that if the investigator or sponsor considers an emergency unblinding is necessary, treatment could be unblinded for an individual subject via the IXRS. In case of unblinding (intentional or accidental), it was planned that the Medical Monitor should be notified immediately in writing. No Data Safety Monitoring Board (DSMB)/ Data Monitoring Committee (DMC) was set up.

Statistical methods

Analysis Populations/Sets

The primary analysis was based on the full analysis set. In this equivalence setting however, the Per Protocol Set (PPS) could be the most sensitive population and hence should show consistent results. The primary endpoint was analysed on the PPS set as supplementary analysis and showed consistent results. Due to the last version of the study protocol, it was planned to conduct a further analysis on a pre-defined modified intent-to-treat (ITT) set, which was removed from the statistical analysis plan (SAP) V3.0 due to the fact that the modified intent-to-treat (mITT) set and ITT set were close and due to the additional intercurrent event (ICE) handling for subjects in the Full Analysis Set (FAS) who did not achieve dosing and/or at least 1 postbaseline efficacy assessment.

Primary Endpoint / Primary Estimand

The primary endpoint was ACR at week 12 for the EMA, and was changed from week 24 to week 12 based on an EMA Scientific Advice (EMEA/H/SA/4052/1/2019/III, February 2019). The primary estimand and especially the intercurrent event handling was changed in the last Version of the SAP (V3.0, dated 21 Apr 2021) and hence is not in line with which was planned due to the last Version of the Study Protocol (V6.0, dated 2 Sep 2020). The SAP was updated after a couple of Blinded Data Review Meetings (BDRM) and discussions on the handling of COVID-19-related effects.

For the primary estimand, the ICE (Death prior to assessment of ACR20 at week 12) was handled per composite variable (Death was handled as ACR20 non-response) and all other ICEs "Discontinuation of study treatment related to COVID-19", "Discontinuation of study treatment not related to COVID-19", "Missed study treatment infusion related to COVID-19", "Missed study treatment infusion not related to COVID-19" as well as "Administration of rescue medication within 1 day prior to an assessment of ACR up to Week 12" were handled with a hypothetical strategy. The use of the hypothetical strategy for the not COVID-19 related ICEs "Discontinuation of study treatment not related to COVID-19", "Missed study treatment infusion not related to COVID-19" as well as "Administration of rescue medication within 1 day prior to an assessment of ACR up to Week 12" is debatable. However, for the Secondary Estimand these three not COVID-19 related ICEs were handled as per Treatment policy strategy.

Overall, the conducted sensitivity analyses (including a tipping point analysis) show more or less consistent results with the primary analysis.

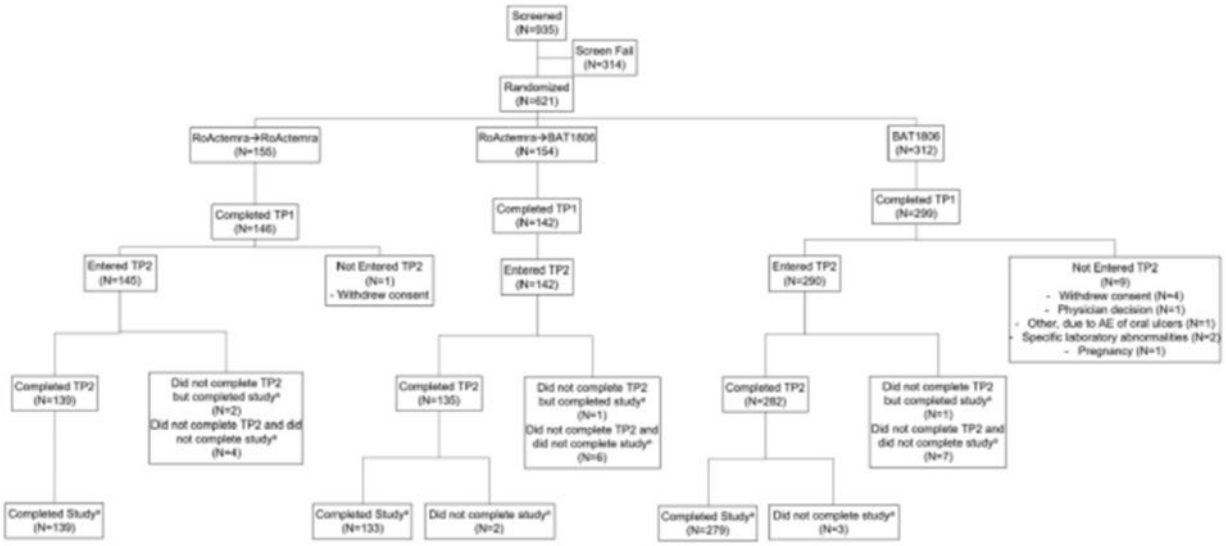
Secondary Endpoints / Secondary Estimand(s)

The analysis strategies as well as sensitivity analyses for the secondary endpoints were provided. Please refer to section 3.3.6. discussion on clinical efficacy.

Results

Participant flow

Figure 5 - Schematic of Subject Disposition



Abbreviations: AE, adverse event; N, number of subjects; TP1, Treatment Period 1; TP2, Treatment Period 2.
[a] Subject is noted as completed study if s/he completed the Follow-Up Visit, regardless of whether s/he completed TP2 (defined as completing Week 48/End-of-Study visit).

Recruitment

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 End-of-Study (EOS) Visit performed at Week 48) and a 4-week follow-up period.

Date of First Observation: 19 Dec 2018

Date of Last Observation: 05 Jan 2021

Conduct of the study

Amendments

The original protocol (v1.0, 15 June 2018) was amended 5 times. The last version was version 6 dated 02 September 2020. Major introduced changes were e.g. the time-points for the primary analysis based on the recommendations from EMA, US FDA, and China NMPA. The amendments are considered to not have negatively impacted the outcome of the study.

Deviations

Overall, 38,3% of the participants had at least 1 major protocol deviation. In the RoActemra/RoActemra group 36,1% had at least 1 major protocol deviation compared to 35,1% in the RoActemra/BAT1806 and 40,1% in the BAT1806/BAT1806 group. No specific pattern of difference has been identified. As a result of the COVID-19 pandemic, some patients were unable to attend study visits on site, which were replaced with remote visits. Consequently, some patients missed study drug administration, joint counts, and laboratory assessments. Remote visits occurred only in China and their incidence was balanced between the treatment arms. Discontinuation of study treatment related to the COVID-19 pandemic was low. In conclusion, the described protocol deviations are considered to have had no major impact on the study results.

Baseline data

Table 16 - Demographic and Other Baseline Characteristics (Full Analysis Set)

Characteristic	RoActemra			BAT1806	Total
	RoActemra →RoActemra N=155	RoActemra →BAT1806 N=154	Combined N=309	N=312	N=621
Age (years)					
Mean (SD)	50.7 (12.37)	49.4 (11.66)	50.1 (12.02)	50.9 (11.93)	50.5 (11.98)
Sex, n (%)					
Male	20 (12.9%)	24 (15.6%)	44 (14.2%)	43 (13.8%)	87 (14.0%)
Female	135 (87.1%)	130 (84.4%)	265 (85.8%)	269 (86.2%)	534 (86.0%)
Race, n (%)					
White	91 (58.7%)	91 (59.1%)	182 (58.9%)	186 (59.6%)	368 (59.3%)
Black	0	0	0	0	0
Asian	64 (41.3%)	63 (40.9%)	127 (41.1%)	126 (40.4%)	253 (40.7%)
Native Hawaiian or Pacific Islander	0	0	0	0	0
Other	0	0	0	0	0
Ethnicity, n (%)					
Hispanic or Latino	4 (2.6%)	3 (1.9%)	7 (2.3%)	4 (1.3%)	11 (1.8%)
Not Hispanic or Latino	151 (97.4%)	151 (98.1%)	302 (97.7%)	308 (98.7%)	610 (98.2%)
Height (cm)					
Mean (SD)	163.40 (8.034)	163.58 (7.865)	163.49 (7.938)	163.12 (7.389)	163.31 (7.663)
Weight (kg)					
Mean (SD)	67.35 (14.340)	65.89 (15.506)	66.62 (14.926)	66.18 (13.592)	66.40 (14.262)
Body mass index (kg/m^2)					
Mean (SD)	25.141 (4.6869)	24.548 (4.8072)	24.845 (4.7488)	24.777 (4.3556)	24.811 (4.5519)
Region, n (%)					
Central Europe	91 (58.7%)	91 (59.1%)	182 (58.9%)	186 (59.6%)	368 (59.3%)
Asia Pacific	64 (41.3%)	63 (40.9%)	127 (41.1%)	126 (40.4%)	253 (40.7%)
Previous biologic or tsDMARD use, n (%)					
Yes	53 (34.2%)	57 (37.0%)	110 (35.6%)	99 (31.7%)	209 (33.7%)
No	102 (65.8%)	97 (63.0%)	199 (64.4%)	213 (68.3%)	412 (66.3%)

Abbreviations: N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

Overall, there were no notable differences between the RoActemra and BAT1806 groups with regard to the demographic and baseline characteristics. The demographic and baseline characteristics for subjects who entered TP2 are also similar across the groups.

The most common medical histories by PT included hypertension (25.6%), menopause (13.4%), osteoporosis (9.8%) and anaemia (9.2%). There were no major differences in medical history between the treatment groups.

The most common concomitant medications used throughout the study were other immunosuppressants (99.8%), folic acid and derivatives (92.9%) and glucocorticoids (58.0%). The most common concomitant medications used throughout the study by preferred name were methotrexate (methotrexate 92.1%; methotrexate sodium 7.7%), folic acid (92.8%) and methylprednisolone (35.1%). Throughout the study, 79 (12.7%) participants underwent concomitant procedures. The most common concomitant procedure was intrauterine contraceptive device insertion (1.8%) followed by ultrasound abdomen (1.4%).

The proportion of participants who underwent concomitant procedures in TP1 was slightly higher in the BAT1806 group with 10.6% compared to 6.5% in the combined RoActemra group but mostly unrelated to the study indication. No notable differences between treatment groups were observed in TP2.

Numbers analysed

A total of 621 participants were randomised thus included in the FAS. Overall, the PPS at Week 12 and Week 24 included 596 (96.0%) and 601 (96.8%) participants, respectively. A total of 619 participants with postbaseline PK assessments were included for PK analyses for TP1/throughout the study.

Table 17 - Subject Disposition: Study BAT-1806-002-CR

	RoActemra				
	RoActemra →RoActemra	RoActemra →BAT1806	Combined	BAT1806	Total
Subjects screened					935
Screen failures					314
FAS	155	154	309	312	621
PPS at Week 12	151	150	301	295	596
PPS at Week 24	151	151	302	299	601
SAF as Received During TP1	NA	NA	309	312	621
SAF as Received During TP2	145	142	287	290	577
SAF Throughout the Study	167	142	309	312	621
PKS as Received During TP1	NA	NA	309	310	619
PKS as Received During TP2	145	142	287	290	577
PKS Throughout the Study	167	142	309	310	619
Subjects completed TP1	146 (94.2%)	142 (92.2%)	288 (93.2%)	299 (95.8%)	587 (94.5%)
Subjects completed TP1 not entering TP2	1 (0.6%)	0	1 (0.3%)	9 (2.9%)	10 (1.6%)
Subjects entering TP2	145 (93.5%)	142 (92.2%)	287 (92.9%)	290 (92.9%)	577 (92.9%)

Subjects entering and completed TP2[a]	139 (89.7%)	135 (87.7%)	274 (88.7%)	282 (90.4%)	556 (89.5%)
Subjects completed the study	141 (91.0%)	134 (87.0%)	275 (89.0%)	280 (89.7%)	555 (89.4%)
Subjects withdrawn from the study	26 (16.8%)	8 (5.2%)	34 (11.0%)	32 (10.3%)	66 (10.6%)
Reason for study withdrawal					
Subject withdrew consent	9 (5.8%)	1 (0.6%)	10 (3.2%)	12 (3.8%)	22 (3.5%)
Other	6 (3.9%)	5 (3.2%)	11 (3.6%)	10 (3.2%)	21 (3.4%)
Specific laboratory abnormalities	2 (1.3%)	0	2 (0.6%)	6 (1.9%)	8 (1.3%)
Anaphylactic reaction or other serious hypersensitivity or infusion-related reaction (as per label)	3 (1.9%)	0	3 (1.0%)	1 (0.3%)	4 (0.6%)
Pregnancy	2 (1.3%)	0	2 (0.6%)	1 (0.3%)	3 (0.5%)
Physician decision	2 (1.3%)	0	2 (0.6%)	1 (0.3%)	3 (0.5%)
Malignancy	0	0	0	1 (0.3%)	1 (0.2%)
Serious or opportunistic infection, including TB	1 (0.6%)	0	1 (0.3%)	0	1 (0.2%)
Confirmed diverticulitis or any gastrointestinally active ulcerative condition	1 (0.6%)	0	1 (0.3%)	0	1 (0.2%)
Subjects who were consistently noncompliant with study treatment	0	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Sponsor request	0	1 (0.6%)	1 (0.3%)	0	1 (0.2%)

Abbreviations: EOS = End-of-Study; FAS = Full Analysis Set; NA = not applicable; PKS = Pharmacokinetics Set; PPS = Per Protocol Set = SAF = Safety Set; TB = tuberculosis; TP = Treatment Period; W = week.
Note: See Section 9.7.1.2 for definitions of the analysis sets.
Note: For 'Throughout the study' analyses, 12 subjects were randomized to RoActemra→BAT1806 at the beginning of TP1 (Day 0) but did not enter TP2, and were grouped into RoActemra for SAF. Throughout the Study and PKS Throughout the Study based on the treatment administered.
[a] For subjects discontinuing at Week 44 but provided data at EOS Visit, the EOS Visit was mapped to Week 48 and the subject was considered as completed TP2. Subject was considered as completed the 24-week initial TP (TP1) if the Week 24 study visit was completed, and subject was considered as completed the 24-week secondary TP (TP2) if the Week 48 study visit was completed.

Outcomes and estimation

- **Primary Efficacy Endpoint**

The primary endpoint was the **percentage of subjects achieving an ACR20 response**. Two analysis time points (Week 12 or Week 24) were analysed as primary for this measure, depending on the regulatory agency for submission.

The applicant initially planned the primary assessment at week 24, which was considered not optimal in the context of a biosimilar exercise per EMA Scientific Advice as in once weekly dosing a plateau could be reached at week 12. Therefore, measuring a response at week 24 may not be the most sensitive time point for detecting potential differences between biosimilar candidate and originator. The applicant changed the primary assessment for EMA (Week 12). Additionally, the Applicant was advised that an equivalence margin of [-15%, +15%] would not be acceptable, so the applicant followed the advice and introduced a revised margin of [-14,5%, +14,5%].

ACR20 Response at Week 12

Table 18 - Proportion of Subjects Achieving ACR20 Response at Week 12 (Full Analysis Set)

Statistic	RoActemra N=309	BAT1806 N=312
Number of subjects evaluable for ACR response	285 (92.2%)	292 (93.6%)
Subjects achieving ACR20 response (observed data)	182 (58.9%)	205 (65.7%)
Primary Estimand EMA[b]		
Adjusted ACR20 response rate[a]	64.82%	68.97%
% Estimated treatment difference (SE)		4.15 (3.970)
95% CI		(-3.63, 11.93)
Secondary Estimand EMA[c]		
Adjusted ACR20 response rate[a]	63.49%	68.51%
% Estimated treatment difference (SE)		5.02 (3.969)
95% CI		(-2.76, 12.80)

Abbreviations: ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drug; EMA, European Medicines Agency; ICE, intercurrent event; N, number of subjects; W, Week.

Note 1: Multiple imputation was applied to the binary responder status of each ACR20 component, and ACR20 was then subsequently derived.

Note 2: Logistic regression model was applied with treatment arm (BAT1806 versus RoActemra, reference RoActemra), and randomized strata (region and previous biologic or targeted synthetic DMARD use) as terms in the model.

[a] For adjusted ACR20 response rate, the mean value of the adjusted response rates over all imputations is presented.

[b] The hypothetical strategy was applied for all ICEs other than death (composite approach). Where the assessment was affected by an ICE, the full set of components was considered missing, and subsequently multiple imputed using the Missing Not at Random (MNAR) approach.

[c] Hypothetical strategy was applied to the COVID-19 pandemic-related ICEs, the treatment policy approach was applied for all the rest of the ICEs other than death (composite approach).

At Week 12, a higher proportion of participants in the BAT1806 group achieved ACR20 response compared with the RoActemra group (65.7% versus 58.9%). This response rate is based on the observed data, with no imputation of missing data. The responses observed are generally in line with the ACR20 response reported at Week 12 in the OPTION study, that was used for sample size derivation (61.5%).

Once multiple imputation was applied for the EMA primary estimand, the adjusted ACR20 response rate was 68.97% and 64.82% in the BAT1806 and RoActemra groups, respectively, with an estimated treatment difference of 4.15% and 95% CI of (-3.63%, 11.93%), which was contained entirely within the predefined equivalence margin of [-14.5%, +14.5%].

The adjusted ACR20 response rate for the EMA secondary estimand was 68.51% and 63.49% in the BAT1806 and RoActemra groups, respectively, with an estimated treatment difference of 5.02% and 95% CI of (-2.76%, 12.80%). This was also contained within the predefined equivalence margin. As the results of the primary and secondary estimands are comparable (within approximately 1%), there appears to be limited effect of missing or discontinued study treatment not related to the COVID-19 pandemic or receipt of rescue medication on the outcomes at Week 12.

Sensitivity analyses were conducted by the applicant based on Week 12 FAS using actual stratification factors. The results are comparable to those using randomised stratification factors. The 2-sided 95% CIs for both estimands of this sensitivity analysis were contained entirely within the predefined equivalence margin.

Supportive analysis for the main estimand was performed using the PPS at Week 12. The results were similar to those of the main analysis and the sensitivity analyses, and again the respective 2-sided 95% CIs for both the primary and secondary estimands are entirely contained within the predefined equivalence margin for EMA.

ACR20 at Week 24

Table 19 - Proportion of Subjects Achieving ACR20 Response at Week 24 (Full Analysis Set)

Statistic	RoActemra N=309	BAT1806 N=312
Primary Estimand EMA[b]		
Adjusted ACR20 response rate[a]	64.85%	68.94%
% Estimated treatment difference (SE)		4.09 (3.970)
95% CI		(-3.70, 11.87)
Secondary Estimand EMA[c]		
Adjusted ACR20 response rate[a]	63.53%	68.48%
% Estimated treatment difference (SE)		4.95 (3.971)
95% CI		(-2.83, 12.73)

Abbreviations: ACR, American College of Rheumatology; EMA, European Medicines Agency; ICE, intercurrent event; MNAR, Missing Not at Random; N, number of subjects.

Note: Multiple imputation was applied to the binary responder status of each ACR20 component, and ACR20 was then subsequently derived. Logistic regression model was applied with treatment arm (BAT1806 versus RoActemra, reference RoActemra), and actual strata (region and previous biologic or targeted synthetic disease-modifying antirheumatic drug [DMARD] use) as terms in the model.

[a] For adjusted ACR20 response rate, the mean value of the adjusted response rates over all imputations is presented.

[b] The hypothetical strategy was applied for all ICEs other than death (composite approach). Where the assessment was affected by an ICE, the full set of components was considered missing, and subsequently multiple imputed using the MNAR approach.

[c] Hypothetical strategy was applied to the binary responder status of each ACR20 component, and ACR20 was then subsequently derived.

At Week 24, a similar proportion of participants in both groups achieved ACR20 response based on observed data (BAT1806 69.9%, RoActemra 68.0%). The responses observed for both treatment groups are around 10% higher than the meta-analysis of the historical studies used for sample size derivation based on Week 24 ACR20 response (58.6%).

Supportive/Supplemental Analyses of the proportions of participants achieving ACR20 response up to Week 24 are summarized below (FDA/NMPA). The proportions of ACR20 responders in both treatment groups were similar at Weeks 4, 8, 12, 16, and 20.

- **Secondary Efficacy Endpoints**

Percentage of Subjects Achieving ACR20, ACR50 and ACR70 Responses over time

The proportions of responders increased over time as expected. The proportions of ACR50 and ACR70 responders in both treatment groups were comparable at Weeks 4, 8, 12, 20, and 24. The proportion of responders continued to increase further after Week 24. In general, the results were comparable across the 3 treatment groups in TP2 for ACR20 and ACR50, with a slightly higher response in the BAT1806 arm, consistent with the findings from ACR20 in TP1. However, the results of ACR 20 over time show a decrease in efficacy of BAT1806 from 205 (65.7%) responder vs RoActemra with 182 (58.9%) in week 12 to 198 (63.5%) responder in the BAT1806 and 200 (64.7%) in the RoActemra group at week 16.

Change From Baseline in DAS28 CRP and ESR

DAS28 CRP and ESR both showed comparable reductions from baseline at all visits for both treatment groups, with BAT1806 providing a generally greater reduction. The differences in LS Means for both parameters up to Week 24 were generally within 0.15 points, showing high comparability.

Additionally, DAS28 CRP and ESR were analysed for EMA at Week 12 and FDA/NMPA at Week 24 using the estimands framework. The primary estimand for EMA was based on hypothetical strategies for all ICEs except death (composite variable strategy: return-to-baseline multiple imputation approach).

The secondary estimand for EMA, FDA, and NMPA was based on a similar composite approach for death, treatment policy approach for ICEs of rescue medication, discontinuation of study treatment or missed study treatment for reasons not related to COVID-19 and a hypothetical strategy for discontinuation of study treatment or missed study treatment for reasons related to the COVID-19 pandemic. The primary and secondary estimands were analysed at each visit using an ANCOVA model.

The results at week 12 are similar to those for the observed data above. For DAS28 CRP for the primary and secondary estimands at all visits up to Week 12, the treatment groups are comparable, and all 95% CIs contain zero. For DAS28 ESR the same applies for Week 4 and Week 8. However, at Week 12 there is a slight trend towards greater BAT1806 activity, although still comparable.

Table 20 - Change From Baseline in DAS28 (CRP and ESR) Through Week 24 Using Observed Values (Full Analysis Set)

		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.

Proportion of Subjects Achieving DAS28 CRP and ESR EULAR Remission at Week 12 and Week 24

EULAR remission response was generally similar between the 2 treatment groups across all visits for both DAS28 CRP and ESR, with a similar slight divergence in favour of BAT1806 at Week 12 for DAS28 ESR, as observed in the continuous analysis presented under the next point.

Change From Baseline in DAS28 CRP and ESR Post-Week 24 Through Week 48

After Week 24, DAS28 CRP and ESR remained generally comparable, although similar to DAS28 CRP and ESR during TP1, there was a higher remission response in the continued BAT1806 group. No major differences were identified in the response of the RoActemra/BAT1806 group compared with the RoActemra group, although DAS response did increase over the response for those subjects that remained on RoActemra in TP2.

Table 21 - DAS28 (CRP and ESR) Changes From Baseline and Remission Frequencies Post-Week 24 Through Week 48 (Full Analysis Set)

Visit/Parameter	Statistic	RoActemra N=155	RoActemra →BAT1806 N=154	BAT1806 N=312
Week 28/DAS28 CRP	n	140	135	282
	Mean (SD)	-2.760 (1.0562)	-2.838 (1.2236)	-2.929 (1.1900)
	EULAR Remission	47 (30.3%)	50 (32.5%)	123 (39.4%)
Week 32/DAS28 CRP	n	140	133	284
	Mean (SD)	-2.929 (1.0345)	-3.070 (1.3016)	-3.028 (1.2096)
	EULAR Remission	54 (34.8%)	60 (39.0%)	125 (40.1%)
Week 36/DAS28 CRP	n	141	137	284
	Mean (SD)	-3.041 (1.1267)	-3.091 (1.2710)	-3.113 (1.1805)
	EULAR Remission	64 (41.3%)	58 (37.7%)	141 (45.2%)
Week 40/DAS28 CRP	n	137	135	278
	Mean (SD)	-3.085 (1.0773)	-3.154 (1.2766)	-3.174 (1.2239)
	EULAR Remission	62 (40.0%)	65 (42.2%)	144 (46.2%)
Week 44/DAS28 CRP	n	140	134	282
	Mean (SD)	-3.070 (1.0468)	-3.259 (1.1856)	-3.285 (1.2126)
	EULAR Remission	63 (40.6%)	71 (46.1%)	158 (50.6%)
Week 48/DAS28 CRP	n	139	133	279
	Mean (SD)	-3.128 (1.0936)	-3.394 (1.2062)	-3.388 (1.2273)
	EULAR Remission	68 (43.9%)	80 (51.9%)	174 (55.8%)
Week 28/DAS28 ESR	n	141	134	281
	Mean (SD)	-3.365 (1.4427)	-3.462 (1.5100)	-3.686 (1.5270)
	EULAR Remission	39 (25.2%)	43 (27.9%)	99 (31.7%)
Week 32/DAS28 ESR	n	142	133	286
	Mean (SD)	-3.492 (1.3720)	-3.708 (1.6171)	-3.753 (1.4822)
	EULAR Remission	44 (28.4%)	52 (33.8%)	121 (38.8%)
Week 36/DAS28 ESR	n	141	137	283
	Mean (SD)	-3.728 (1.6895)	-3.829 (1.6922)	-3.896 (1.5346)
	EULAR Remission	50 (32.3%)	57 (37.0%)	123 (39.4%)
Week 40/DAS28 ESR	n	135	132	276
	Mean (SD)	-3.680 (1.4298)	-3.754 (1.5245)	-3.915 (1.4726)
	EULAR Remission	51 (32.9%)	55 (35.7%)	119 (38.1%)
Week 44/DAS28 ESR	n	140	133	282
	Mean (SD)	-3.729 (1.4462)	-3.858 (1.2710)	-4.062 (1.5063)
	EULAR Remission	54 (34.8%)	56 (36.4%)	137 (43.9%)
Week 48/DAS28 ESR	n	137	130	279
	Mean (SD)	-3.738 (1.4868)	-4.061 (1.4139)	-4.183 (1.5182)
	EULAR Remission	56 (36.1%)	67 (43.5%)	151 (48.4%)

Abbreviations: CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; N, number of subjects; n, number of subjects in the specified category.

Change From Baseline in ACR and DAS28 Components

Descriptive summaries of the changes from baseline in ACR and DAS28 components through Week 24 and post-Week 24 through Week 48 in the FAS have been provided. Parameters assessed are Tender Joint Count in 28 Joints (TJC68), Swollen Joint Count in 66 Joints (SJC66), Tender Joint Count in 28 Joints (TJC28), Swollen Joint Count in 28 Joints (SJC28), pain visual analogue scale (VAS), subject and physician global assessment of disease activity, HAQ-DI, CRP, and ESR. The outcomes during TP1, are in general comparable between the 2 treatment groups. For nearly all visits up to Week 24 for all ACR and DAS28 components, no major differences were observed. There were a small number of components at specific visits where some minimal difference was observed, which are considered not meaningful. Nearly all 95% CIs for the treatment difference include zero, further confirming the outcome of similarity between the treatments. During TP2, overall results were comparable at each visit for all parameters. However, there was a trend of higher response occurring in the BAT1806 and RoActemra/BAT1806 groups.

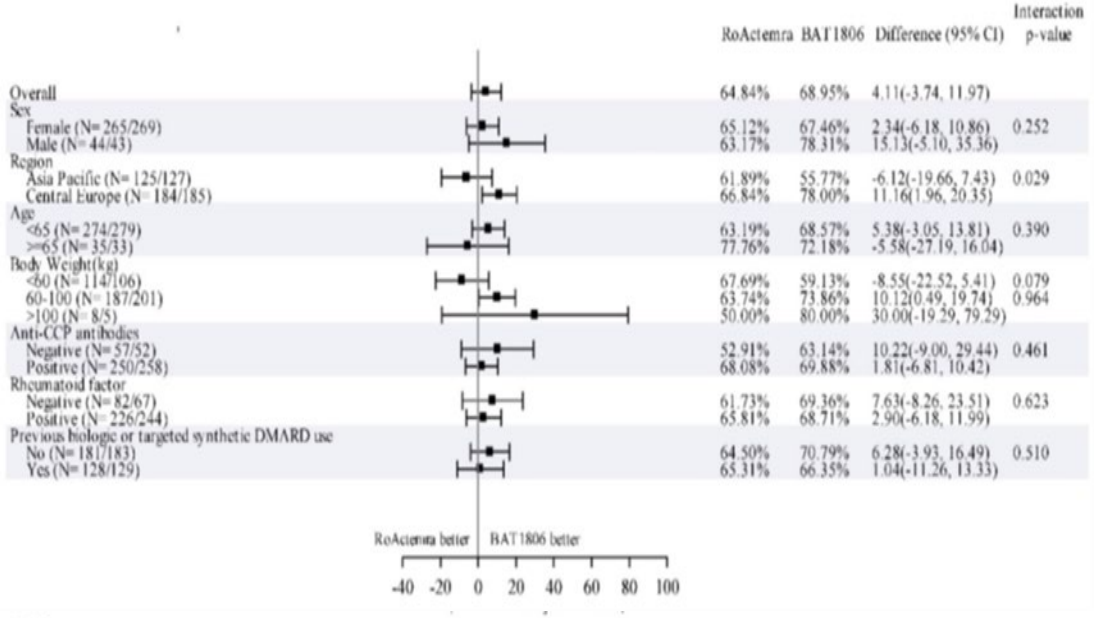
Ancillary analyses

- **Subgroup analyses**

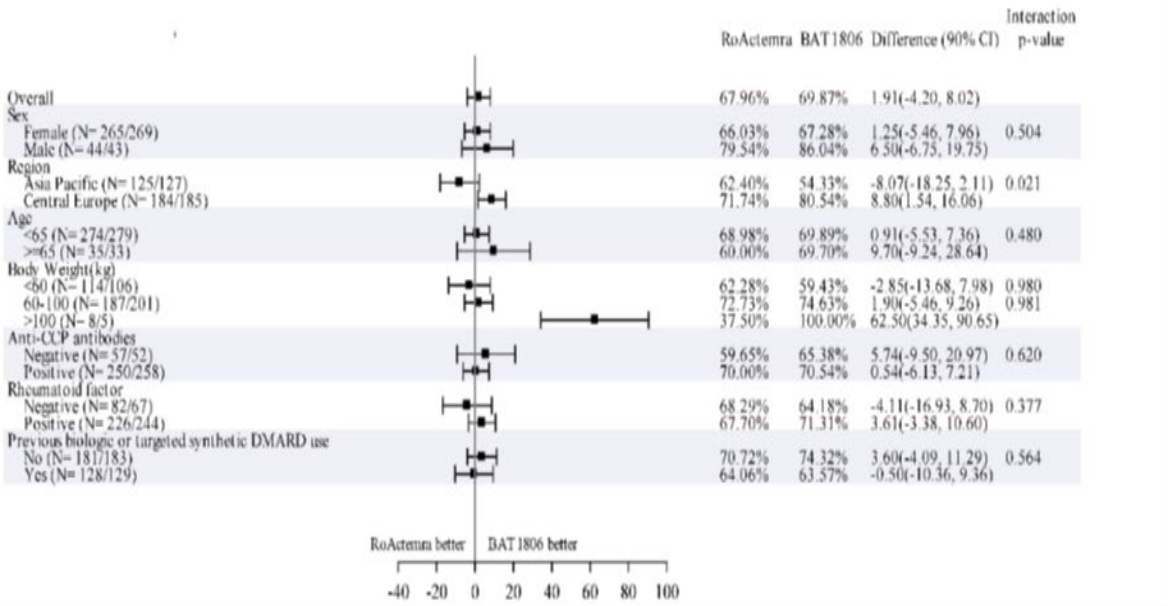
To evaluate the consistency of the primary efficacy analysis results over stratification factors, demographics, baseline characteristics, and prior medication use, subgroup analyses were conducted by the applicant.

Table 22 - Subgroup Analysis – Proportion of Subjects Achieving ACR20 Response at Week 12 and Week 24 (Primary Estimand) (Full Analysis Set)

Visit: Week 12



Visit: Week 24



When assessing the strata used in the randomisation, the proportion of subjects achieving ACR20 response was comparable in those with or without prior biologics use. However, an impact of region favouring BAT1806 in Central Europe (treatment-by-region interaction p-value at Week 12 = 0.029, treatment-by-region interaction p-value at Week 24 = 0.021 following primary estimands for EMA and FDA/NMPA, respectively) was observed.

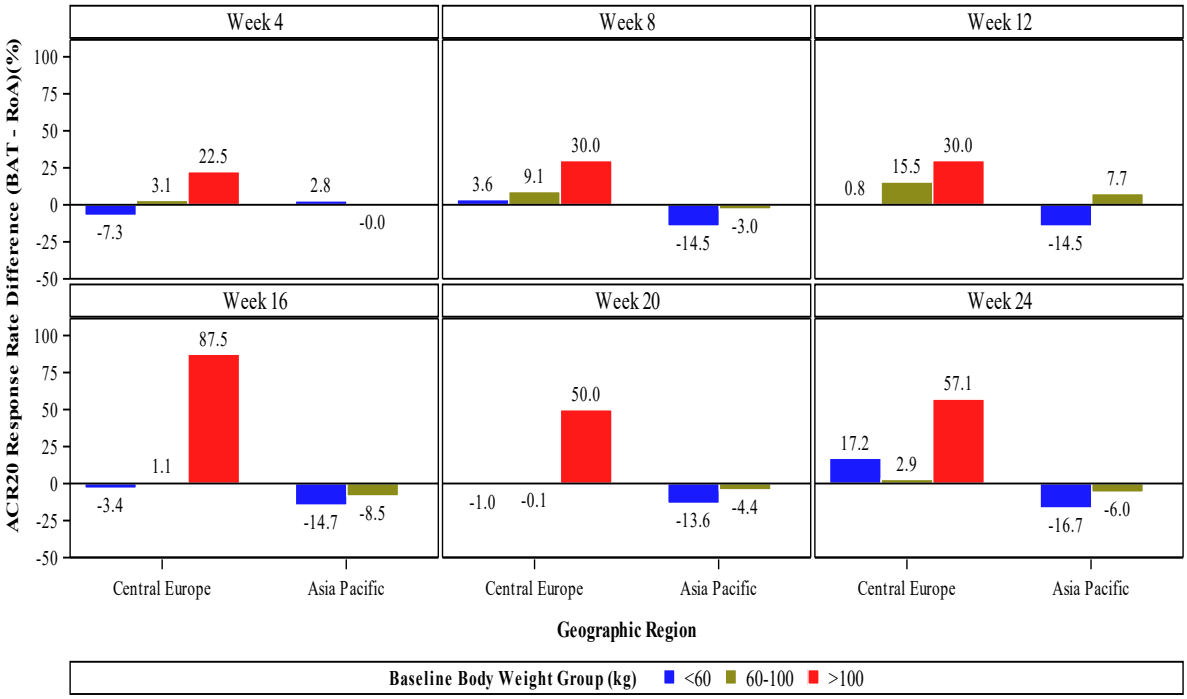
The data provided with the D180 response showed that there is a significant difference in body weight between regions (see Table 23 below) potentially explaining part of the observed regional differences in the outcome.

Table 23 - Body weight by region (Assessor's own computation based on Table 5 and Figure 31 provided in the D180 response)

	Asia Pacific	Central Europe	Fisher's exact test
n	253	368	
Weight (cutoff 60)			
<60	149 (58.9)	71 (19.2)	
>60	103 (41.1)	297 (80.7)	p < 0.0001
Weight (cutoffs 60 and 100)			
<60	149 (58.9)	71 (19.2)	
>60 to 100	103 (41.1)	285 (77.4)	
>100	0 (0.0)	13 (3.5)	p < 0.0001

• Percentages are given in brackets and are computed within region;
• Note: Figure 31 and Table 5 show differences in for the number of subjects in Asia Pacific with body weight ≥ 60 kg. We have used the data from Table 5

Figure 6 - Bar chart of observed ACR20 response rate difference by randomised region and baseline body weight at each visit (full analysis set)



- **Proportion of Subjects Achieving ACR20 Response by ADA Status**

Table 24 - Proportion of Subjects Achieving ACR20 Response at Week 12 by ADA status (Safety Set)

	ADA positive		ADA negative	
Statistic	**RoActemra**	**BAT1806**	**RoActemra**	**BAT1806**
Number of ADA positive or negative subjects up to Week 12	33	48	275	261
Number of subjects evaluable for ACR response	33 (100.0%)	48 (100.0%)	252(91.6%)	243(93.1%)
Subjects achieving ACR20 response (observed data)	25 (75.8%)	35 (72.9%)	157(57.1%)	170(65.1%)
Primary Estimand EMA[b]				
ACR20 response probabilities[a]	74.91%	71.80%	63.87%	69.00%
% Estimated treatment difference (SE)		-3.10 (10.242)		5.13 (4.301)
95% CI		(-23.18, 16.97)		(-3.30, 13.56)
Secondary Estimand EMA[c]				
ACR20 response probabilities[a]	76.13%	71.24%	62.32%	68.47%
% Estimated treatment difference (SE)		-4.89 (9.839)		6.15 (4.303)
95% CI		(-24.17, 14.40)		(-2.28, 14.59)

Abbreviations: ACR20 = American College of Rheumatology 20% response criteria; ADA = antidrug antibody; CI = confidence interval; COVID-19 = coronavirus disease 2019; EMA = European Medicines Agency; MNAR = Missing Not at Random; SE = standard error; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

There was a slightly higher proportion of participants in the BAT1806 group with 65,1% compared to 57,1% in the RoActemra group achieving ACR20 in the ADA negative subgroup and the applicant was asked to discuss this difference. The applicant discussed the difference and concluded that the modest treatment group difference in the proportion of patients achieving ACR20 at Week 12 in the ADA negative subgroup was not associated with any difference in serum tocilizumab concentration measured at Week 12. In addition, there was a very similar proportion of patients in the ADA negative subgroup achieving ACR20 at Week 24: 68.57% for RoActemra compared to 69.35% for BAT-1806. Therefore, the conclusion made by the applicant that the difference observed at Week 12 represents a chance finding is considered likely. The clarification was adequate and accepted.

3.3.5.3. Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 25 - Summary of efficacy for trial BAT-1806-002-CR

Title: A Randomised, 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		
Study identifier	EudraCT number: 2018-002202-31	
Design	Phase 3, multicentre, multinational, randomised, double-blind, parallel-group, active-control study	
	Duration of main phase:	56 weeks including a screening period of up to 4 weeks, a 24-week initial treatment period (TP1), a 24-week secondary treatment period (TP2), and a 4-week safety follow-up period
Hypothesis	Equivalence to be achieved between BAT1806 and RoActemra if the two-sided 95%CI for the difference in response probabilities of ACR20 is contained within the pre-specified equivalence margin (-14.5%, +14.5%).	
Treatments groups	Treatment Period 1: Day/Week 0 - Week 24	
	RoActemra	RoActemra administered by IV infusion at a dose of 8 mg/kg body weight once every 4 weeks up to Week 24, 309 subjects were randomised in this group
	BAT1806	BAT1806 administered by IV infusion at a dose of 8 mg/kg body weight once every 4 weeks up to Week 24, 312 subjects were randomised in this group
	Treatment Period 2: Week 24 through Week 48	
	RoActemra->RoActemra	RoActemra administered by IV infusion at a dose of 8 mg/kg body weight once every 4 weeks up to Week 48, 145 subjects were randomised in this group
	RoActemra->BAT1806	BAT1806 administered by IV infusion at a dose of 8 mg/kg body weight once every 4 weeks up to Week 48, 142 subjects were randomised in this group
	BAT1806->BAT1806	BAT1806 administered by IV infusion at a dose of 8 mg/kg body weight once every 4 weeks up to Week 48, 290 subjects were randomised in this group

Endpoints and definitions	Primary endpoint	ACR20	Percentage of patients achieving an American College of Rheumatology 20% (ACR20) response defined as at least 20% improvement in both the tender joint count and the swollen joint count and at least 20% improvement in three of the other 5 ACR core measures.
	Secondary endpoint	DAS28-ESR	Change from baseline in Disease Activity Score on 28 Joints (DAS28) calculated using erythrocyte sedimentation rate (DAS28-ESR) over the course of the study
	Secondary endpoint	ACR50	Percentage of patients achieving an American College of Rheumatology 50% (ACR50) response defined as the ACR50 response indicates at least 50% improvement in both the Total Joint Count (TJC) and the Swollen Joint Count (SJC) and at least 50%improvement in 3 of the 5 other ACR core set measures
	Secondary endpoint	ACR70	Percentage of patients achieving an American College of Rheumatology 70% (ACR50) response defined as the ACR70 response indicates at least 50% improvement in both the Total Joint Count (TJC) and the Swollen Joint Count (SJC) and at least 70%improvement in 3 of the 5 other ACR core set measures
Database lock	22 April 2021		
Results and Analysis			
Analysis description	**Primary Analysis** A logistic regression model was conducted on the FAS. The model includes treatment arm (BAT1806 versus RoActemra, reference RoActemra), and randomised strata (geographical region and previous biologic or targeted synthetic DMARD use). The estimated response rate for each treatment arm, and the corresponding difference in rates along with the 2-sided 95% CIs for the difference were derived using the procedure described in the SAP.		
Analysis population and time point description	The Full Analysis Set (FAS) included all subjects randomised in the study. Timepoint was at week 12		
	Treatment group	RoActemra	BAT1806

Descriptive statistics and estimate variability	Number of subjects	309	312
	Number of subjects evaluable for ACR response	285 (92.2%)	292 (93.6%)
	Subjects achieving ACR20 response (observed data)	182 (58.9%)	205 (65.7%)
	Adjusted ACR20 response rate (primary estimand)	64.82%	68.97%
	Adjusted ACR20 response rate (Secondary estimand)	63.49%	68.51%
Effect estimate per comparison	Primary endpoint as per the primary estimand	Comparison groups	BAT1806 vs RoActemra
		treatment difference in percentage of subjects achieving ACR20 (%) (SE)	4.15 (3.970)
		95% Confidence interval (%)	(-3.63, 11.93)
	Primary endpoint as per the secondary estimand	Comparison groups	BAT1806 vs RoActemra
		treatment difference in percentage of subjects achieving ACR20 (%) (SE)	5.02 (3.969)
		95% Confidence interval (%)	(-2.76,12.80)
Analysis description	**Secondary Analysis: ACR50** The same methods used for ACR20 were used for ACR50 analyses.		
Analysis population and time point description	The Full Analysis Set (FAS) included all subjects randomised in the study. Timepoint was at week 12.		
	Treatment group	RoActemra	BAT1806

Descriptive statistics and estimate variability	Number of subjects	309	312
	Number of subjects evaluable for ACR50 response	291 (94.2%)	298 (95.5%)
	Subjects achieving ACR50 response (observed data)	91 (29.4%)	78 (25.0%)
	Adjusted ACR50 response rate (primary estimand)	32.53%	27.14%
	Adjusted ACR50 response rate (Secondary estimand)	31.82%	26.90%
Effect estimate per comparison	Primary estimand (as defined for primary endpoint)	Comparison groups	BAT1806 vs RoActemra
		treatment difference in percentage of subject achieving ACR50 (%) (SE)	-5.39 (3.846)
		95% Confidence interval (%)	(-12.93, 2.15)
	Secondary estimand (as defined for primary endpoint)	Comparison groups	BAT1806 vs RoActemra
		treatment difference in percentage of subject achieving ACR50(%) (SE)	-4.92 (3.743)
		95% Confidence interval (%)	(-12.26, 2.42)
Analysis description	**Secondary Analysis: ACR70** The same methods used for ACR20 were used for ACR70 analyses		
Analysis population and time point description	The Full Analysis Set (FAS) included all subjects randomised in the study. Timepoint was at week 12.		
Descriptive statistics and estimate variability	Treatment group	RoActemra	BAT1806
	Number of subjects	309	312

	Number of subjects evaluable for ACR70 response	292 (94.5%)	298 (95.5%)
	Subjects achieving ACR70 response (observed data)	29 (9.4%)	26 (8.3%)
	Adjusted ACR70 response rate (primary estimand)	11.30%	10.21%
	Adjusted ACR70 response rate (Secondary estimand)	10.58%	9.82%
Effect estimate per comparison	Primary estimand (as defined for primary endpoint)	Comparison groups	BAT1806 vs RoActemra
		treatment difference in percentage of subject achieving ACR70 (%)(SE)	-1.09 (2.659)
		95% Confidence interval (%)	(-6.30, 4.13)
	Secondary estimand (as defined for primary endpoint)	Comparison groups	BAT1806 vs RoActemra
		treatment difference in percentage of subject achieving ACR70 (%) (SE)	-0.76 (2.540)
		95% Confidence interval (%)	(-5.74, 4.21)
Analysis description	**Secondary Analysis: DAS28-ESR** An ANCOVA model was employed. The treatment group, strata as used in the stratified randomisation procedure (region and previous biologic or tsDMARD use), and baseline value were included in the model.		
Analysis population and time point description	The Full Analysis Set (FAS) included all subjects randomised in the study. Timepoint was at week 12		
Descriptive statistics and estimate variability	Treatment group	RoActemra	BAT1806
	Number of subjects	309	312

	DAS28-ESR Primary Estimand (LS Mean)	-2.744	-3.012
	Standard Error	0.1062	0.1070
	DAS28-ESR Secondary Estimand LS Mean	-2.635	-2.958
	Standard Error	0.1001	0.1002
Effect estimate per comparison	Primary estimand (as defined for primary endpoint)	Comparison groups	BAT1806 vs RoActemra
		treatment difference in DAS28-ESR LS Mean (SE)	-0.268 (0.1466)
		95% Confidence interval	(-0.555, 0.020)
	Secondary estimand (as defined for primary endpoint)	Comparison groups	BAT1806 vs RoActemra
		treatment difference in DAS28-ESR LS Mean (SE)	-0.323 (0.1369)
		95% Confidence interval (%)	(-0.592, -0.055)

3.3.5.4. Clinical studies in special populations

Age group and gender

Table 26 - Subjects per age group and gender

Age group (Safety Analysis Set)	Study Identifier	Treatment group	Patients		Person-time	
			M (N, %)	F (N, %)	M	F
18-55 years	BAT1806-001-CR	Tofidence	45 (100%)	0	-[1]	0
		Actemra US	42 (100%)	0	-[1]	0
		RoActemra EU	42 (100%)	0	-[1]	0
18-64 years		Tofidence	37 (13.3)	242 (86.7)	29.45	192.82
		RoActemra EU-> Tofidence	21 (16.3)	108 (83.7)	17.24	90.51
		RoActemra EU	19 (13.1)	126 (86.9)	15.24	94.24
65-74 years		Tofidence	6 (18.8)	26 (81.3)	4.05	22.12
		RoActemra EU-> Tofidence	2 (18.2)	9 (81.8)	1.71	7.67
		RoActemra EU	2 (9.1)	20 (90.9)	0.98	15.75
75-84 years		Tofidence	0	1 (100.0)		0.85
		RoActemra EU-> Tofidence	0	2 (100.0)		1.71
		RoActemra EU	0	0		
≥85 years		Tofidence	0	0		
		RoActemra EU-> Tofidence	0	0		
		RoActemra EU	0	0		
Total			87 (14.0)	534 (86.0)	68.67	425.67

[1] A single administration of investigational or reference product was given in Study BAT1806-001-CR.

Person-time is expressed in years.

3.3.5.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

3.3.5.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

3.3.5.7. Supportive study(ies)

Not applicable.

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Study BAT-1806-002-CR was a Phase 3, multicentre, multinational, randomised, double-blind, parallel-group, active-control study to compare efficacy, safety, immunogenicity, and pharmacokinetics of BAT1806 to RoActemra (dose of 8 mg/kg) in participants with rheumatoid arthritis with inadequate response to methotrexate. At the time of the submission of the MAA, the study was finalised. This submission contains efficacy, safety, immunogenicity, and PK results up to Week 56 covering both the 24-week TP1 and 24-wek TP2 and the follow-up period of 4 weeks.

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 an extra 4-week follow-up period. After screening, eligible subjects were randomised in a 1:1:2 ratio to receive either RoActemra or BAT1806by intravenous (IV) infusion every 4 weeks in a double-blind fashion. From Week 24, the participants continued study treatment in a double-blind fashion with IV infusions every 4 weeks until Week 44. Participants originally randomised to BAT1806 continued treatment with BAT1806. Participants of one RoActemra groups were switched to BAT1806 treatment, the other RoActemra group continue treatment with RoActemra.

The design of the study is considered generally acceptable as pointed out in the EMA/CHMP scientific advice. However, the switch from RoActemra to BAT1806 was not requested by the EMA/CHMP scientific advice and it is not in line with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010)".

According to the main inclusion criteria, participants should have fulfilled the ACR/EULAR 2010 revised classification criteria for RA diagnosis for at least 6 months before screening, based on the medical history record and present with active RA, as defined by: ≥6 out of 68 tender joints (at screening and randomisation) AND ≥6 out of 66 swollen joints (at screening and randomisation) AND Serum CRP > upper limit of normal (ULN) value, i.e., CRP ≥1 mg/dL (≥10 mg/L) or ESR ≥28 mm/hour at screening. Patients were required to receive MTX therapy for at least 12 weeks before randomisation, with at least 4 consecutive weeks before randomisation on a stable dose ranging between 10 to 25 mg/week, which had to be continued throughout the study. If patients were using oral corticosteroids and/or nonsteroidal anti-inflammatory drugs, they had to be on a stable dose (≤10 mg prednisone/day or equivalent for corticosteroids) for at least 4 and 2 consecutive weeks, respectively, before randomisation, and must have been willing to continue at this level throughout the study. Patients were eligible if they had received no more than 2 biological agents other than IL-6 inhibitors or targeted synthetic DMARDs (e.g., tofacitinib) in total for RA treatment.

Excluded were patients who had RA of ACR functional class IV or were wheelchair/bed bound, with known hypersensitivity to tocilizumab or to study treatment excipients, and/or previous exposure to any authorized or investigational IL-6 inhibitor and/or alkylating agents or concomitant medications like any biological agents or any targeted synthetic, any cell-depleting therapy ≤12 months before randomisation, investigational drug or device ≤8 weeks or 5 half- lives before randomisation or any conventional DMARDs other than MTX ≤4 weeks before randomisation.

The study population of patients with RA with active RA with MTX background treatment selected for this study is considered adequate for a pivotal study of a biosimilar of TNF-inhibitors, which have similar treatment recommendations. Furthermore, this patient population has been extensively studied and reliable historical data is available for the reference product in controlled clinical studies.

A total of 621 participants were randomised, with 309 randomised to receive RoActemra in TP1 and 312 randomised to receive BAT1806. Of this 621, 587 (94.5%) completed TP1 (288/309 who were randomised to RoActemra and 299/312 who were randomised to BAT1806). Of the 621 randomised participants, 253 were from China, 169 were from Poland, 100 were from Ukraine, 57 were from Georgia and 42 were from Bulgaria. A total of 577 (92.9%) participants entered TP2, 290 who were randomised to BAT1806 in TP1. Of the 287 participants who were randomised to RoActemra in TP1, 145 continued to receive RoActemra in TP2 and 142 subjects received BAT1806 in TP2.

The tocilizumab dose selected for this study was 8 mg/kg body weight Q4W, which is the recommended starting dose in the Summary of Products Characteristics (SmPC) of RoActemra. The dose could be reduced to 4 mg/kg body weight or interrupted in accordance with the recommendations of the RoActemra label in case of laboratory abnormalities, which is appropriate. Furthermore, an increase in dose of NSAIDs if a participant was on stable NSAIDs therapy or initiation of NSAIDs without exceeding the maximum approved dose was allowed as rescue treatment to treat a flare for not more than 2 consecutive weeks.

The primary objective of the study was to demonstrate equivalent efficacy of BAT1806 and RoActemra in participants with RA who were inadequately controlled by MTX. Secondary objectives were to evaluate the efficacy, safety, tolerability and immunogenicity profile of BAT1806 compared with RoActemra over the entire study period.

The primary endpoint was the American College of Rheumatology 20% response (ACR20). The ACR20 is considered an appropriate endpoint for a valid and reliable estimate of the margin of equivalence for this study. The ACR20 response has been used in many clinical studies to assess efficacy of biological agents for the treatment of RA and also in RA clinical studies of biosimilars. In the EMA scientific advice (EMEA/H/SA/4052/1/2019/III), the MAA was advised that a primary endpoint of ACR20 at Week 12 may be a more sensitive endpoint. Therefore, ACR20 was assessed as time points for the primary analysis for the EMA at Week 12 and for the FDA and NMPA at Week 24. Additionally, the Applicant was advised that an equivalence margin of [-15%, +15%] would not be acceptable, so the applicant introduced a revised margin of [-14,5%, +14,5%]. Given the results of the trial and putting this into the context of experience with other development programs no further justification of the selected equivalence margin will be sought even though the provided documentation is not considered fully satisfactory.

The primary estimand and especially the intercurrent event handling was changed in the last Version of the SAP (V3.0, dated 21 Apr 2021) and hence is not in line with which was planned due to the last Version of the Study Protocol (V6.0, dated 2 Sep 2020). The SAP was updated after a couple of Blinded Data Review Meetings (BDRM) and discussions on the handling of COVID-19-related effects. These late changes are of course not optimal. However, a couple of sensitivity analyses have been conducted which all show more or less consistent results, which is reassuring.

For the primary estimand, the ICE (Death prior to assessment of ACR20 at week 12) was handled per composite variable (Death was handled as ACR20 non-response) and all other ICEs "Discontinuation of study treatment related to COVID-19", "Discontinuation of study treatment not related to COVID-19", "Missed study treatment infusion related to COVID-19", "Missed study treatment infusion not related to COVID-19" as well as "Administration of rescue medication within 1 day prior to an assessment of ACR up to Week 12" were handled with a hypothetical strategy. The use of the hypothetical strategy for the not COVID-19 related ICEs "Discontinuation of study treatment not related to COVID-19", "Missed study treatment infusion not related to COVID-19" as well as "Administration of rescue medication within 1 day prior to an assessment of ACR up to Week 12" is debatable. However, for the Secondary Estimand these three not COVID-19 related ICEs were

handled as per Treatment policy strategy. The results based on the secondary estimand are consistent with the results of the primary estimand, which is reassuring. Hence this raises no further concerns.

Secondary endpoints included change in DAS28 (both CRP and ESR), ACR 20/50/70 and in the individual components of the DAS28 and ACR response throughout the study to monitor and compare the time course of the response to study treatment. DAS28-ESR and DAS28-CRP were analysed, although in the EMA/CHMP scientific advice it was emphasised that DAS28-ESR should be preferred over DAS28-CRP, since RoActemra/Actemra induces a rapid drop in CRP levels, which is not related to a clinical response, whereas DAS28-ESR is considered more sensitive to detect differences following treatment as compared to DAS28-CRP since ESR is being not impacted by this pharmacodynamic effect.

The primary and secondary efficacy objectives of the clinical trial BAT-1806-002-CR are considered adequate and in line with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010)".

As a result of the COVID-19 pandemic, some patients were unable to attend study visits on site, which were replaced with remote visits. Consequently, some patients missed study drug administration, joint counts, and laboratory assessments. Remote visits occurred only in China and their incidence was balanced between the treatment arms. Discontinuation of study treatment related to the COVID-19 pandemic was low. In conclusion, the described protocol deviations are considered to have had no major impact on the study results.

The analysis strategies as well as sensitivity analyses fir the secondary endpoints seem to be acceptable. However, hypotheses belonging to the endpoints as well as equivalence margins are not defined. It is just shown that there is no significant difference between the two groups (95% CIs contain zero) and whether the estimates between the two groups are "comparable" (leaving open what is considered "comparable). A non-significant test result is not a proof that the null hypothesis is true (i.e. that the two groups are equivalent). Hence the results of the Secondary endpoints can only be considered descriptive.

For randomisation and blinding (masking) the choice and number of stratification factors seem to be appropriate. Given the planned sample size, more stratifying variables would have been feasible, but no abnormalities are observed with respect to the balance of other baseline factors. Hence this is acceptable. There were quite a few number of subjects (75 subjects) who had a different electronic data capture (EDC) stratum than that to which the subject was randomised. The applicant argued that misclassification primarily occurred due to a misunderstanding of the meaning of prior biologic treatment. This sheds some doubts on the training of study personal and hence on the conduct of trial. Nevertheless, the strata seem to be balanced also in terms of the actual factors as captured in EDC. Furthermore, in the analysis, the randomised stratum (as captured in the interactive web response system (IWRS)) was used as covariates in the statistical model for the efficacy analysis, and a sensitivity analysis was conducted using the actual stratum (as captured in EDC). Both analyses showed consistent results, which is reassuring.

Efficacy data and additional analyses

The demographic and baseline characteristics were generally similar across groups.

The mean age of the participants was 50.5 years, ranging from 20 to 76 years. The mean height was 163.31 cm, and the mean weight was 66.40 kg. Most were female (86.0%, from Central Europe (59.3%), White (59.3%) and not Hispanic or Latino (98.2%). The majority (66.3%) did not have previous biologic or targeted synthetic DMARD usage. In the BAT1806 group 32 participants between 65 and 74 years were enrolled

compared to 11 in the RoActemra/BAT1806 and 22 in the RoActemra group. In the age group over 75 years 1 participant in BAT1806 and 2 in the RoActemra/BAT1806 group were enrolled. Although the numbers are rather low, it is acceptable for the MAA of a biosimilar. Overall, there were no notable differences between the RoActemra and BAT1806 groups with regard to the demographic and baseline characteristics.

Rheumatoid Arthritis Disease Characteristics at Baseline per FAS have been summarised descriptively. According to the inclusion criteria, a subject should have active RA, as defined by ≥6 out of 68 tender joints (at screening and randomisation) and ≥6 out of 66 swollen joints (at screening and randomisation), serum CRP ≥upper limit of normal (ULN), i.e., ≥1 mg/dl (≥10 mg/L) or ESR ≥28 mm/hour.

According to the Final CSR Version 2.0, all 621 participants in the FAS were randomised and received their first study treatment under protocol Version 4.0 dated 17 September 2018 and the Version 5.0 of the protocol from 27 April 2020 introduced major changes concerning the timepoint for analysis of the primary endpoint according to the EMA/CHMP scientific advice received, i.e., at Week 12 instead of Week 24, and consequently update of the primary efficacy analysis. However, as the schedule of assessment was not modified and the study was double-blind, it is not expected that these changes impacted the results of the study.

Efficacy analyses

At Week 12, a higher proportion of participants in the BAT1806 group achieved ACR20 response compared with the RoActemra group (65.7% versus 58.9%). This response rate is based on the observed data, with no imputation of missing data. The responses observed are generally in line with the ACR20 response reported at Week 12 in the OPTION study, that was used for sample size derivation with 61.5%.

Once multiple imputation was applied for the EMA primary estimand, the adjusted ACR20 response rate was 68.97% and 64.82% in the BAT1806 and RoActemra groups, respectively, with an estimated treatment difference of 4.15% and 95% CI of (-3.63%, 11.93%), which was contained entirely within the predefined equivalence margin of [-14.5%, +14.5 %]. In conclusion, based on the results of the confirmatory testing conducted using the primary estimand, equivalence between BAT1806 and RoActemra was shown.

For the secondary estimand, the ACR20 response probabilities were 68.51% and 63.49% in the BAT1806- and RoActemra groups, respectively, with an estimated treatment difference of 5.02% and 95%CI of (-2.76, 12.80%), which was contained entirely within the predefined equivalence margin of [-14.5%, +14.5%]. Thus, results from the secondary estimand showed equivalence between BAT1806 and RoActemra.

All sensitivity and supportive analyses (including PPS analyses) of the primary efficacy endpoint were consistent with the primary and secondary estimands of the primary efficacy analyses. All corresponding CIs were contained within the predefined equivalence margins.

The primary and secondary estimands for the primary and secondary efficacy endpoints were defined in the Statistical Analysis Plan (SAP) Version 3.0 from 21 April 2021 with all their attributes, including intercurrent events.

DAS28-CRP and DAS28-ESR both showed comparable reductions from baseline at all visits for both treatment groups. For DAS28-CRP for the primary and secondary estimands at all visits up to Week 12, the treatment groups were similar, and all 95% CIs contain zero. However, it should be noted that no equivalence margins were pre-specified in the protocol and in the SAP for the secondary endpoints. For DAS28-ESR the same conclusion applies for Week 4 and Week 8. However, at Week 12 a higher reduction from baseline was observed in the BAT1806 group, although the 95%CI for LS mean difference was lower than 0.6.

The subgroup analyses show a difference (95% CI) in the Proportion of Subjects Achieving ACR20 Response at Week 12 for the region Central Europe of 11.09 (1.89,20.29) in favour of BAT1806, whereas a difference of -6.12 (-19.66, 7.43) in favour of RoActemra was observed for the Asia Pacific region. The interaction p-value for region was nominally significant (p = 0.029), which is remarkable as usually there is a lack of power to detect differential effects in subgroups. The average difference in ACR20 response between regions is hence 17.21%. The subgroup with a bodyweight of 60 to 100 kg shows a higher difference (95% CI) of 10.12 (0.49,19.74) also in favour of BAT1806, whereas subjects below 60kg show a difference of -8.55 (-22.52, 5.41) in favour of RoActemra. The average difference in ACR20 response between these weight cohorts is hence 18.67%. This seems to be of a similar magnitude as the regional differences. Both region and body weight impact ACR20 in a way that even the difference in point estimates is substantially larger than the equivalence margin (not to speak of confidence intervals) and hence a clinically meaningful impact is assumed. The outcome data presented in the D180 response additionally shows that there is a pattern (especially for the primary analysis of ACR20 at week 12) that there is an increasing response with body weight in both regions in subjects treated with BAT1806. In contrast, the effect is reversed in the RoActemra arm where in both regions the response decreases with body weight. Similar patterns are also apparent at other time points, although not always as pronounced as at week 12. The differences in ACR20 between BAT1806 and RoAcemra reflect this pattern as well. In almost all cases the pattern is reproduced that the differences in response increases with increasing body weight independently in both regions. The same is true if we look at the regions: within each body weight group, subjects in Central Europe have a larger difference in ACR20 response to BAT1806 compared to RoActemra than in Asia Pacific. The only exceptions to this pattern are very early measurements (ACR20 at week 4) and very late measurements (ACR20 at week 24), which is in line with the consideration that these time points might be less sensitive to differences. The data seems to show, though, that there is an additional regional difference *beyond* the effect of body weight.

The applicant states that there are no reasons to expect an actual/true difference given the CMC, PK and quality attributes data for the proposed biosimilar. Furthermore, based on the totality of the data clinical, analytical, functional and non-clinical data, the applicant deems the observation to be a chance finding. Overall, differences in the efficacy / biosimilarity in different regions and based on different weight cannot be fully excluded based on the provided data. However, it also could not be substantiated. The issue is not further pursued as it is considered to have no major impact on the biosimilarity assessment.

Similarly, for both the primary and secondary estimands, the 95%CI of the estimated treatment difference up to Week 12 was outside the equivalence margin in Nab positive subjects. In Nab negative subjects it was contained in the equivalence margin for the primary estimand whereas for the secondary estimand was slightly outside the upper limit of the equivalence margin. Overall, no clinically relevant differences between the 2 treatment groups were observed for the ACR20 responses at Week 24 by ADA status.

The CRS indication initially applied for was removed during the submission of the D121 responses due to commercial reasons.

3.3.7. Conclusions on the clinical efficacy

The primary endpoint of study BAT-1806-002-CR was the American College of Rheumatology 20% response (ACR20).

The data submitted show that the results of the primary endpoint are contained within the prespecified equivalence margin. All sensitivity and supportive analyses (including PPS analyses) of the primary efficacy

endpoint were consistent with the primary and secondary estimands of the primary efficacy analyses. All corresponding CIs were contained within the predefined equivalence margins.

The secondary efficacy analyses for endpoints including ACR20, ACR50, ACR70, DAS28 and other ACR components and EULAR response were generally comparable between the treatment groups. DAS28-CRP and DAS28-ESR both showed comparable reductions from baseline at all visits for both treatment groups. For DAS28-CRP for the primary and secondary estimands at all visits up to Week 12, the treatment groups were similar, and all 95% CIs contain zero.

The submitted efficacy data support biosimilarity with regards to efficacy of BAT1806 and RoActemra.

3.3.8. Clinical safety

In the clinical development program for BAT1806. The comparability of the safety profile from BAT1806 compared to RoActemra was evaluated in 2 clinical studies: BAT-1806-001-CR and BAT-1806-002-CR.

Table 27 - Clinical studies for the comparability of the safety profile

Study Number / Phase	Study Title	Study Objectives	Treatment Regimen	Study Population / Number of Randomized Subjects
BAT-1806-001-CR Phase 1	A randomized, double-blinded, single-dose, 3-arm parallel, comparative study to evaluate the pharmacokinetics and safety of BAT1806 Injection versus Actemra® in healthy Chinese male subjects	**Primary**: To establish pairwise PK biosimilarity between BAT1806 vs. EU-approved RoActemra, BAT1806 vs. US-licensed Actemra, US-licensed Actemra vs. EU-approved RoActemra in healthy Chinese male subjects. **Secondary**: To evaluate the clinical safety, tolerability, and immunogenicity of BAT1806 and EU- and US-licensed Actemra in healthy Chinese male subjects.	Single intravenous (IV) administration of 4 mg/kg of BAT1806 or tocilizumab reference medicinal product (EU-authorized RoActemra, and US-licensed Actemra) Eligible subjects were randomized in a 1:1:1 ratio to one of following treatment groups: (1) BAT1806; 4 mg/kg; IV (2) RoActemra; 4 mg/kg; IV (3) Actemra; 4 mg/kg; IV	Healthy volunteers N=138
BAT-1806-002-CR Phase 3	A randomized, double-blind, parallel group, active-control study to compare the efficacy and safety of BAT1806 to RoActemra in rheumatoid arthritis patients with inadequate response to methotrexate	**Primary**: To demonstrate equivalent efficacy of BAT1806 and RoActemra in subjects with RA that is inadequately controlled by MTX. **Secondary**: • To evaluate the efficacy profile of BAT1806 compared with RoActemra over time based on secondary efficacy endpoints • To evaluate the safety and tolerability profile of BAT1806 compared with RoActemra over the entire study period • To evaluate the immunogenicity profile of BAT1806 in terms of ADA production compared with RoActemra • To evaluate the steady-state PK of BAT1806	The study comprised Treatment Period 1 (TP1) (Weeks 0 to 24) followed by Treatment Period 2 (TP2) (Weeks 24 to 48). Eligible subjects were randomized in a 2:1:1 ratio to one of three treatment groups: (1) BAT1806 (TP1)/BAT1806 (TP2) (2) RoActemra (TP1)/RoActemra (TP2), or (3) RoActemra (TP1) followed by BAT1806 (TP2), administered intravenously every 4 weeks at a dose of 8 mg/kg	Patients with RA and inadequate response to MTX N=621

BAT-1806-001-CR evaluated PK bio-similarity and safety in comparison with EU-licensed RoActemra and EU-licensed RoActemra. However, only a single dose administration of 4 mg/kg body weight was administered to 138 Chinese male healthy subjects and the data were not pooled. Therefore, the main safety results reported for this study are discussed in section 3.3.8.8. Study BAT-1806-001-CR.

BAT-1806-002-CR was a Phase 3, multicentre, multinational, randomised, double-blind, parallel-group, active-control study to compare efficacy, safety, immunogenicity, and PK of BAT1806 compared with

RoActemra in subjects with RA that was inadequately controlled by MTX. 621 participants were enrolled in this study.

3.3.8.1. Patient exposure

In healthy subjects (Study BAT-1806-001-CR), all individuals in the SAS received a single, full dose of BAT1806 (N = 45) or tocilizumab (RoActemra: N = 42; Actemra: N = 42) as a 1-hour IV infusion at 4 mg/kg of body weight. The mean (SD) dose administered was 268 (32) mg, 270 (33) mg and 267 (30) mg for BAT1806, RoActemra and Actemra, respectively.

Of the 621 participants randomised into Study BAT-1806-002-CR, 587 of the 621 (94.5%) completed TP1, 577 (92.9%) entered TP2. Of the subjects who continued in TP 2, 556/577 (89.5%) completed all study drug administrations and a total of 555/577 (89.4%) completed the entire study duration. In the safety analysis set received IV infusions (Q4W, 8 mg/kg body weight) of either BAT1806 only (n = 312), RoActemra only (n = 167) or switched from RoActemra to BAT1806 (n = 142).

Participants received up to 12 doses total, 6 doses per treatment period. Participants allocated to the switch arm received 6 doses of RoActemra in TP1 and 6 doses of BAT1806 in TP2. There were no meaningful differences across treatment groups in the number of doses or cumulative doses administered.

Due to the COVID-19 pandemic and remote visits introduced in Asia Pacific, the fraction of missed doses attributable to remote visits increased over the course, consistent with the increasing number of participants affected by the COVID-19 pandemic. However, the fraction of missed doses was similar between the treatment groups. Remote visits did not occur in Central Europe region.

Table 28 - Duration of exposure

Duration of exposure (Safety Analysis Set)			
Study Identifier	**Treatment Group**	**Number of Patients**	**Person-time**
BAT1806-001-CR	Tofidence	45	-[1]
	Actemra US	42	-[1]
	RoActemra EU	42	-[1]
BAT1806-002-CR			
(T1 and T2 combined)	Tofidence	312	249.29
	RoActemra EU-> Tofidence	142	118.84
	RoActemra EU	167	126.21
1 to <3 m	Tofidence	9	1.62
	RoActemra EU-> Tofidence	0	0
	RoActemra EU	7	1.31
3 to <6 m	Tofidence	10	3.79
	RoActemra EU-> Tofidence	2	0.94
	RoActemra EU	5	1.71
≥6 m	Tofidence	288	243.64
	RoActemra EU-> Tofidence	140	117.90
	RoActemra EU	145	122.63
Total		621	494.34

[1] A single administration of investigational or reference product was given in Study BAT1806-001-CR.
T1 = treatment period 1; T2 = treatment period 2
Person-time is expressed in years.

3.3.8.2. Adverse events

Overview

Of the 621 randomised participants enrolled in study BAT-1806-002-CR, a total of 471 (75.8%) participants experienced a total of 2519 AEs, of whom 467 (75.2%) experienced 2424 TEAEs. Of the 2424 TEAEs, 51 were serious and experienced by 41 (6.6%) participants. A total of 350 (56.4%) participants experienced 1539 TEAEs related to study treatment, of whom 13 (2.1%) had 18 serious TEAEs related to study treatment. A total of 196 (31.6%) participants experienced 363 TEAEs leading to action taken with study drug. A total of 17 (2.7%) experienced 20 non-TEAEs that occurred > 8 weeks after last dose of study drug. Thirty-four (5.5%) participants experienced 46 TEAEs which led to the study drug being stopped. Four (0.6%) participants experienced 8 TEAEs which led to death and 5 (0.8%) participants experienced 9 AEs leading to death.

Table 29 - Overall Summary of Adverse Events (Safety Set)

Number of Subjects With	TP1		TP2[a]			Throughout the Study		
	RoActemra N=309 n (%)	BAT1806 N=312 n (%)	RoActemra→ RoActemra N=145 n (%)	RoActemra→BAT180 N=142 n (%)	BAT1806 N=290 n (%)	RoActemra→ RoActemra N=167 n (%)	RoActemra→BAT1806 N=142 n (%)	BAT1806 N=312 n (%)
Any AE	201 (65.0)	206 (66.0)	91 (62.8)	92 (64.8)	162 (55.9)	131 (78.4)	108 (76.1)	232 (74.4)
Any TEAE	196 (63.4)	201 (64.4)	90 (62.1)	92 (64.8)	162 (55.9)	129 (77.2)	107 (75.4)	231 (74.0)
Any serious TEAE	13 (4.2)	11 (3.5)	4 (2.8)	5 (3.5)	8 (2.8)	12 (7.2)	10 (7.0)	19 (6.1)
Any related TEAE	151 (48.9)	148 (47.4)	59 (40.7)	64 (45.1)	112 (38.6)	96 (57.5)	81 (57.0)	173 (55.4)
Any related serious TEAE	7 (2.3)	2 (0.6)	1 (0.7)	1 (0.7)	2 (0.7)	6 (3.6)	3 (2.1)	4 (1.3)
Any TEAE leading to action taken with study drug	81 (26.2)	58 (18.6)	27 (18.6)	26 (18.3)	45 (15.5)	61 (36.5	47 (33.1)	88 (28.2)
Any TEAE leading to study drug stopped	16 (5.2)	11 (3.5)	1 (0.7)	1 (0.7)	5 (1.7)	16 (9.6)	2 (1.4)	16 (5.1)
Any non-TEAE > 8 weeks after last dose of study drug	1 (0.3)	3 (1.0)	4 (2.8)	1 (0.7)	8 (2.8)	5 (3.0)	1 (0.7)	11 (3.5)
Any TEAE leading to death	1 (0.3)	3 (1.0)	0	0	0	1 (0.6)	0	3 (1.0)
Any AE leading to death	1 (0.3)	4 (1.3)	0	0	0	1 (0.6)	0	4 (1.3)

Abbreviations: AE = adverse event; N = number of subjects; n = number of subjects in the specified category; SAF = Safety Set; TEAE = treatment-emergent adverse event; TP1 = Treatment Period 1; TP2 = Treatment Period 2.
Note: The SAF included all randomized subjects that were administered any treatment with study drug. Subjects were analyzed according to treatment administered at the start of TP1 and TP2.
[a] The N for summary in TP2 only included subjects who were administered study treatment in TP2.

Treatment-Emergent Adverse Events

The most frequent TEAEs by SOC were Investigations (27.1% of participants in TP1, 25.3% in TP2 and 36.9% throughout the study), Infections and infestations (21.7% of participants in TP1, 22.9% in TP2, 36.2% throughout the study), and Metabolism and nutrition disorders (16.1% of participants in TP1, 14.6% in TP2, 21.3% throughout the study).

Table 30 - Treatment-Emergent Adverse Events That Occurred in ⩾2% of All Subjects by SOC and PT (Safety Set)

	TP1		TP2[a]			Throughout the Study		
SOC (in bold) PT	RoActemra N=309 n (%)	BAT180 N=312 n (%)	RoActemra →RoActemra N=145 n (%)	RoActemra →BAT1806 N=142 n (%)	BAT180 N=290 n (%)	RoActemra →RoActemra N=167 n (%)	RoActemra →BAT180 N=142 n (%)	BAT180 N=312 n (%)
At least 1 TEAE	196 (63.4)	201 (64.4)	90 (62.1)	92 (64.8)	162 (55.9)	129 (77.2)	107 (75.4)	231 (74.0)
Investigations	89 (28.8)	79 (25.3)	34 (23.4)	45 (31.7)	67 (23.1)	63 (37.7)	61 (43.0)	105 (33.7)
ALT increased	36 (11.7)	26 (8.3)	7 (4.8)	15 (10.6)	13 (4.5)	23 (13.8)	24 (16.9)	32 (10.3)
AST increased	19 (6.1)	14 (4.5)	5 (3.4)	6 (4.2)	9 (3.1)	11 (6.6)	13 (9.2)	19 (6.1)
LDL increased	15 (4.9)	8 (2.6)	7 (4.8)	5 (3.5)	7 (2.4)	13 (7.8)	7 (4.9)	10 (3.2)
Blood bilirubin increased	3 (1.0)	9 (2.9)	4 (2.8)	5 (3.5)	13 (4.5)	6 (3.6)	5 (3.5)	17 (5.4)
WBC count decreased	7 (2.3)	4 (1.3)	4 (2.8)	6 (4.2)	12 (4.1)	7 (4.2)	6 (4.2)	13 (4.2)
Blood LDH increased	8 (2.6)	9 (2.9)	6 (4.1)	4 (2.8)	8 (2.8)	7 (4.2)	5 (3.5)	12 (3.8)
Transaminases increased	5 (1.6)	5 (1.6)	3 (2.1)	3 (2.1)	6 (2.1)	4 (2.4)	6 (4.2)	10 (3.2)
GGT increased	2 (0.6)	6 (1.9)	1 (0.7)	3 (2.1)	6 (2.1)	2 (1.2)	4 (2.8)	10 (3.2)
BP increased	7 (2.3)	4 (1.3)	2 (1.4)	1 (0.7)	2 (0.7)	6 (3.6)	4 (2.8)	5 (1.6)
Blood cholesterol increased	4 (1.3)	4 (1.3)	2 (1.4)	4 (2.8)	4 (1.4)	3 (1.8)	4 (2.8)	6 (1.9)
Neutrophil count decreased	6 (1.9)	2 (0.6)	3 (2.1)	0	5 (1.7)	6 (3.6)	2 (1.4)	5 (1.6)
Infections and infestations	69 (22.3)	66 (21.2)	41 (28.3)	32 (22.5)	59 (20.3)	70 (41.9)	49 (34.5)	106 (34.0)
Upper respiratory tract infection	32 (10.4)	29 (9.3)	15 (10.3)	6 (4.2)	20 (6.9)	34 (20.4)	14 (9.9)	44 (14.1)
Nasopharyngitis	6 (1.9)	10 (3.2)	2 (1.4)	7 (4.9)	7 (2.4)	5 (3.0)	8 (5.6)	17 (5.4)
Urinary tract infection	4 (1.3)	6 (1.9)	7 (4.8)	6 (4.2)	7 (2.4)	9 (5.4)	7 (4.9)	13 (4.2)
Bronchitis	4 (1.3)	4 (1.3)	3 (2.1)	2 (1.4)	4 (1.4)	4 (2.4)	5 (3.5)	7 (2.2)
Metabolism and nutrition disorders	47 (15.2)	53 (17.0)	19 (13.1)	21 (14.8)	44 (15.2)	32 (19.2)	31 (21.8)	69 (22.1)
Hyperlipidaemia	18 (5.8)	22 (7.1)	6 (4.1)	7 (4.9)	21 (7.2)	12 (7.2)	11 (7.7)	31 (9.9)
Hypercholesterolaemia	16 (5.2)	10 (3.2)	5 (3.4)	1 (0.7)	8 (2.8)	12 (7.2)	5 (3.5)	14 (4.5)
Hypertriglyceridaemia	7 (2.3)	11 (3.5)	6 (4.1)	3 (2.1)	12 (4.1)	7 (4.2)	4 (2.8)	18 (5.8)
Hypokalaemia	5 (1.6)	9 (2.9)	3 (2.1)	5 (3.5)	6 (2.1)	4 (2.4)	7 (4.9)	12 (3.8)
Hyperuricaemia	5 (1.6)	2 (0.6)	6 (4.1)	2 (1.4)	5 (1.7)	7 (4.2)	4 (2.8)	6 (1.9)
Blood and lymphatic system disorders	43 (13.9)	33 (10.6)	25 (17.2)	22 (15.5)	35 (12.1)	37 (22.2)	26 (18.3)	55 (17.6)
Leukopenia	28 (9.1)	12 (3.8)	15 (10.3)	10 (7.0)	15 (5.2)	24 (14.4)	13 (9.2)	20 (6.4)
Neutropenia	23 (7.4)	16 (5.1)	7 (4.8)	9 (6.3)	12 (4.1)	15 (9.0)	13 (9.2)	26 (8.3)
Anaemia	2 (0.6)	3 (1.0)	4 (2.8)	8 (5.6)	5 (1.7)	6 (3.6)	8 (5.6)	8 (2.6)
Thrombocytopenia	6 (1.9)	6 (1.9)	3 (2.1)	5 (3.5)	7 (2.4)	6 (3.6)	6 (4.2)	10 (3.2)
Lymphopenia	0	5 (1.6)	2 (1.4)	0	9 (3.1)	2 (1.2)	0	13 (4.2)
Gastrointestinal disorders	28 (9.1)	35 (11.2)	15 (10.3)	10 (7.0)	25 (8.6)	25 (15.0)	17 (12.0)	51 (16.3)

Mouth ulceration	8 (2.6)	4 (1.3)	3 (2.1)	3 (2.1)	6 (2.1)	6 (3.6)	5 (3.5)	9 (2.9)
Abdominal pain upper	3 (1.0)	8 (2.6)	3 (2.1)	1 (0.7)	1 (0.3)	3 (1.8)	3 (2.1)	9 (2.9)
Abdominal discomfort	1 (0.3)	5 (1.6)	1 (0.7)	1 (0.7)	6 (2.1)	2 (1.2)	1 (0.7)	10 (3.2)
Diarrhoea	1 (0.3)	6 (1.9)	3 (2.1)	0	5 (1.7)	4 (2.4)	0	9 (2.9)
Hepatobiliary disorders	29 (9.4)	34 (10.9)	16 (11.0)	13 (9.2)	26 (9.0)	20 (12.0)	23 (16.2)	49 (15.7)
Hepatic function abnormal	17 (5.5)	14 (4.5)	9 (6.2)	10 (7.0)	10 (3.4)	13 (7.8)	14 (9.9)	22 (7.1)
Liver injury	5 (1.6)	13 (4.2)	3 (2.1)	2 (1.4)	14 (4.8)	4 (2.4)	4 (2.8)	20 (6.4)
Musculoskeletal and connective tissue disorders	13 (4.2)	23 (7.4)	2 (1.4)	4 (2.8)	15 (5.2)	10 (6.0)	9 (6.3)	36 (11.5)
Arthralgia	9 (2.9)	6 (1.9)	0	0	1 (0.3)	5 (3.0)	4 (2.8)	7 (2.2)
Respiratory, thoracic and mediastinal disorders	16 (5.2)	19 (6.1)	6 (4.1)	5 (3.5)	10 (3.4)	16 (9.6)	11 (7.7)	28 (9.0)
Nervous system disorders	11 (3.6)	14 (4.5)	5 (3.4)	7 (4.9)	13 (4.5)	11 (6.6)	11 (7.7)	27 (8.7)
Headache	3 (1.0)	2 (0.6)	2 (1.4)	4 (2.8)	5 (1.7)	5 (3.0)	4 (2.8)	7 (2.2)
Dizziness	3 (1.0)	4 (1.3)	3 (2.1)	2 (1.4)	3 (1.0)	5 (3.0)	3 (2.1)	7 (2.2)
Skin and subcutaneous disorders	12 (3.9)	12 (3.8)	2 (1.4)	9 (6.3)	11 (3.8)	10 (6.0)	13 (9.2)	21 (6.7)
Rash	2 (0.6)	2 (0.6)	0	4 (2.8)	6 (2.1)	2 (1.2)	4 (2.8)	8 (2.6)
General disorders and administration site conditions	8 (2.6)	21 (6.7)	3 (2.1)	2 (1.4)	6 (2.1)	7 (4.2)	6 (4.2)	24 (7.7)
Injury, poisoning and procedural complications	5 (1.6)	9 (2.9)	7 (4.8)	4 (2.8)	6 (2.1)	7 (4.2)	9 (6.3)	15 (4.8)
Cardiac disorders	5 (1.6)	10 (3.2)	4 (2.8)	3 (2.1)	6 (2.1)	8 (4.8)	4 (2.8)	15 (4.8)
Vascular disorders	13 (4.2)	8 (2.6)	1 (0.7)	6 (4.2)	4 (1.4)	4 (2.4)	11 (7.7)	12 (3.8)
Hypertension	8 (2.6)	4 (1.3)	0	5 (3.5)	3 (1.0)	3 (1.8)	7 (4.9)	7 (2.2)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects in the specified category; PT = preferred term; SAF = Safety Set; SOC = system organ class; TEAE = treatment-emergent adverse event; TP1 = Treatment Period 1; TP2 = Treatment Period 2; WBC = white blood cell.
Note: MedDRA v23.1 coding dictionary applied. The SAF included all randomized subjects that were administered any treatment with study drug. Subjects were analyzed according to treatment administered at the start of TP1 and TP2.

The most frequent TEAEs by PT were upper respiratory tract infection (9.8% of participants in TP1, 7.1% in TP2, 14.8% throughout the study), ALT increased (10.0% of participants in TP1, 6.1% in TP2, 12.7% throughout the study), and leukopenia (6.4% of participants in TP1, 6.9% in TP2, 9.2% throughout the study). In TP1 TEAEs of General disorders and administration site conditions were slightly increased in the BAT1806 group.

The most frequent treatment-related TEAEs by SOC were Investigations (23.5% of participants in TP1, 20.8% in TP2 and 31.4% throughout the study), Infections and infestations (12.6% of participants in TP1, 13.9% in TP2, 21.7% throughout the study) and Blood and lymphatic system disorders (10.5% of participants in TP1, 11.4% in TP2, 15.6% throughout the study). The most frequent treatment-related TEAEs by PT were ALT increased (9.0% of participants in TP1, 5.2% in TP2, 11.4% throughout the study), upper respiratory tract infection (6.6% of participants in TP1, 4.9% in TP2, 9.8% throughout the study), and leukopenia (5.8% of participants in TP1, 6.2% in TP2, 8.5% throughout the study).

Most TEAEs were mild. A total 34.3% of the participants experienced moderate TEAEs and 3.9% experienced severe TEAEs throughout the study. Similarly for related TEAEs, most were mild with a total 20.6% who experienced moderate related TEAEs and 2.6% who experienced severe related TEAEs throughout the study.

No significant differences were reported between the treatment groups. It appears that in almost all severity categories BAT1806 is slightly below the rates of AEs reported for RoActemra.

A total of 17 participants (2.7%) experienced AEs occurring >8 weeks after last dose of study drug which was defined as non-TEAEs. Four participants (0.6%) experienced 4 non-TEAEs in TP1 and 13 (2.3%) experienced 16 non-TEAEs in TP2. No notable differences were observed between the RoActemra and BAT1806 groups. Most of the non-TEAEs occurred in 1 subject each, except for the following: hypertriglyceridemia (3 BAT1806 participants, 0.5%), hyperlipidaemia (2 RoActemra/RoActemra participants, 0.3%), platelet count increased (2 BAT1806 participants, 0.3%) and upper respiratory tract infection (1 BAT1806 participant and 1 RoActemra participant, 0.3%).

One fatal non-TEAE occurred in the BAT1806 group: 1 participant experienced a serious AE of cardiopulmonary failure of severe intensity about 2.5 months after the last dose of study drug and died. (see also below)

3.3.8.3. Serious adverse events, deaths, and other significant events

The rate of serious adverse events was generally low and comparable between the treatment groups and no trends were observed. Overall, 41 (6.6%) participants experienced 51 serious TEAEs throughout the study, 12 (7.2%) from the RoActemra/RoActemra group, 10 (7.0%) from the RoActemra/BAT1806 group, and 19 (6.1%) from the BAT1806 group. Serious TEAEs that occurred in > 1 subject include pneumonia, lumbar spinal stenosis, and abortion spontaneous.

Table 31 - Serious Treatment-Emergent Adverse Events (Safety Set)

SOC PT	TP1		TP2[a]			Throughout the Study		
	RoActemra N=309 n (%)	BAT1806 N=312 n (%)	RoActemra → RoActemra N=145 n (%)	RoActemra → BAT1806 N=142 n (%)	BAT1806 N=290 n (%)	RoActemra → RoActemra N=167 n (%)	RoActemra → BAT1806 N=142 n (%)	BAT1806 N=312 n (%)
At least 1 serious TEAE	13 (4.2)	11 (3.5)	4 (2.8)	5 (3.5)	8 (2.8)	12 (7.2)	10 (7.0)	19 (6.1)
Infections and infestations	5 (1.6)	3 (1.0)	2 (1.4)	2 (1.4)	2 (0.7)	5 (3.0)	4 (2.8)	5 (1.6)
Pneumonia	1 (0.3)	1 (0.3)	1 (0.7)	0 (0.0)	1 (0.3)	2 (1.2)	0 (0.0)	2 (0.6)
Appendicitis	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Arthritis infective	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Bronchitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Laryngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Localized infection	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Mediastinitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Pancreatic abscess	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Peritonitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Salpingo-oophoritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Septic shock	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Tooth abscess	1 (0.3)	0 (0.0)	2 (1.4)	2 (1.4)	2 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)

Injury, poisoning and procedural complication	1 (0.3)	1 (0.3)	3 (2.1)	0 (0.0)	1 (0.3)	3 (1.8)	1 (0.7)	2 (0.6)
Contusion	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Joint dislocation	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Joint injury	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Patella fracture	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Rib fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Spinal cord injury cervical	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Nervous system disorders	2 (0.6)	2 (0.6)	0 (0.0)	1 (0.7)	1 (0.3)	2 (1.2)	1 (0.7)	3 (1.0)
Cerebral haemorrhage	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Lacunar infarction	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Memory impairment	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Ruptured cerebral aneurysm	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Transient ischaemic attack	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.7)	2 (0.7)	0 (0.0)	1 (0.7)	3 (1.0)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.3)	0 (0.0)	1 (0.7)	1 (0.3)
Osteoporosis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pathological fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Spondylolisthesis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Cardiac disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	3 (1.0)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Coronary artery disease	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Coronary artery disease	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Reproductive system and breast disorders	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.4)	0 (0.0)
Adenomyosis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Uterine haemorrhage	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Uterine polyp	1 (0.3)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.3)
Ovarian cancer stage III	0 (0.0)	1 (0.3)	0 (0.0)	0	0 (0.0)	0 (0.0)	0	1 (0.3)
Renal hamartoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
Abortion spontaneous	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Diverticular perforation	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Death	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hepatobiliary disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Cholangitis acute	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Cholecystitis acute	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Immune system disorders	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Drug hypersensitivity	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Respiratory failure	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Vascular disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Thrombophlebitis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Abbreviations: COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects in the specified category; PT = preferred term; SAF = Safety Set; SOC = system organ class; TEAE = treatment-emergent adverse event; TP1 = Treatment Period 1; TP2 = Treatment Period 2.

Note: MedDRA v23.1 coding dictionary applied. The SAF included all randomized subjects that were administered any treatment with study drug. Subjects were analyzed according to treatment administered at the start of TP1 and TP2.

[a] The N for summary in TP2 only included subjects who were administered study treatment in TP2.

Deaths

Five deaths were reported during study BAT-1806-002-CR. One participant received RoActemra and experienced a serious TEAEs of deep neck space infection and mediastinitis and furthermore serious TEAEs of septic shock and cerebral haemorrhage leading to death. The TEAEs of localised infection, mediastinitis and the 2 events of septic shock were considered as possibly related to study drug, while the event of cerebral haemorrhage was considered as unlikely related. Four died in the BAT1806 group, one serious TEAE of ovarian cancer stage III of severe intensity, one serious TEAE of ruptured cerebral aneurysm of severe intensity, one serious TEAE of death reason unknown and one serious AE about 2.5 months after the last dose of BAT1806, of cardiopulmonary failure of severe intensity. These four events were considered unrelated to the study treatment.

3.3.8.4. Laboratory findings

The most frequent clinical laboratory abnormalities reported as TEAEs in clinical trial BAT-1806-002-CR were ALT increased reported with 11.7% in the RoActemra group and 8.3% in BAT1806 group in TP1 and 4.8% in the RoActemra group, 10.6% in the RoActemra – BAT1806 group and 4.5% in the BAT1806 group in TP2. AST increased was reported in 6.1% in RoActemra group and 4.5% in BAT1806 group in TP1 and in 3.4% in RoActemra group, 4.2% in RoActemra – BAT1806 group and 3.1% in BAT1806 group in TP2. LDL increased was reported in 4.9% in RoActemra group and 2.6% in BAT1806 group in TP1 and in 4.8% in RoActemra group, 3.5% in RoActemra – BAT1806 group and 2.4% in BAT1806 group in TP2. Majority of clinical laboratory abnormalities were reported numerically more frequent in RoActemra group than in BAT1806, except blood bilirubin increased and anaemia.

Table 32 - Clinical Laboratory Abnormalities Reported as TEAEs (SAF)

PT	TP1		TP2[a]			Throughout the Study		
	RoActemra N=309 n (%)	BAT1806 N=312 n (%)	RoActemra N=145 n (%)	RoActemra →BAT1806 N=142 n (%)	BAT1806 N=290 n (%)	RoActemra N=167 n (%)	RoActemra →BAT1806 N=142 n (%)	BAT1806 N=312 n (%)
ALT increased	36 (11.7)	26 (8.3)	7 (4.8)	15 (10.6)	13 (4.5)	23 (13.8)	24 (16.9)	32 (10.3)
AST increased	19 (6.1)	14 (4.5)	5 (3.4)	6 (4.2)	9 (3.1)	11 (6.6)	13 (9.2)	19 (6.1)
LDL increased	15 (4.9)	8 (2.6)	7 (4.8)	5 (3.5)	7 (2.4)	13 (7.8)	7 (4.9)	10 (3.2)
Blood bilirubin increased	3 (1.0)	9 (2.9)	4 (2.8)	5 (3.5)	13 (4.5)	6 (3.6)	5 (3.5)	17 (5.4)
Leukopenia	28 (9.1)	12 (3.8)	15 (10.3)	10 (7.0)	15 (5.2)	24 (14.4)	13 (9.2)	20 (6.4)
Neutropenia	23 (7.4)	16 (5.1)	7 (4.8)	9 (6.3)	12 (4.1)	15 (9.0)	13 (9.2)	26 (8.3)
Anemia	2 (0.6)	3 (1.0)	4 (2.8)	8 (5.6)	5 (1.7)	6 (3.6)	8 (5.6)	8 (2.6)

Abbreviations: ALT = Alanine transaminase; AST = Aspartate aminotransferase; LDL = Low-density lipoprotein; n = Number of subjects in group; N = Number of subjects; PT = Preferred term; TP =Treatment phase

Overall, there were no clinically meaningful differences in haematology between BAT1806 and tocilizumab for either study population. The most prevalent laboratory-related TEAE was 'ALT increased' (>10.3%, overall). No TEAEs of 'LDL increased' or urinalysis were observed for either BAT1806 or reference product.

The proportion of subjects with increase to high CRP and ESR as worst postbaseline grade appeared to be slightly higher in the RoActemra groups. However, the differences in ESR are 0,7% in TP1 between the treatment groups and the incidence in TP2 was 1.4%, 1.4%, and 0% of participants in the RoActemra, RoActemra/BAT1806 and BAT1806 groups, respectively, had increase to high worst postbaseline ESR. Through TP1, 6.1% and 3.5% of the participants in the RoActemra and the BAT1806 group, respectively, had increase to high worst postbaseline CRP. Through TP2, 6.9%, 2.8%, and 3.4% of participants in the

RoActemra, RoActemra/BAT1806, and BAT1806 groups, respectively, had increase to high worst postbaseline CRP.

The proportion of subjects that demonstrated ECG-related TEAEs was generally low (~1 to 4%) across all treatment groups. There were no clinically meaningful differences or trends in ECG parameters between BAT1806 and the reference product.

3.3.8.5. In vitro biomarker test for patient selection for safety

Not Applicable.

3.3.8.6. Safety in special populations

Not applicable for biosimilars.

3.3.8.7. Immunological events

During all periods of Study BAT-1806-002-CR ADAs were assessed.

Throughout the study, all ADA positive participants were tested positive for NAbs except for 1 patient in each group.

During TP1, of the 42 participants in the RoActemra combined group who were assessed as ADA positive, 33 developed ADA positivity during the first 12 weeks. Similarly, for the BAT1806 group, of the 64 subjects who were assessed as ADA positive during TP1, 48 developed ADA positivity during the first 12 weeks. During TP2, the level of ADA positivity among the RoActemra and BAT1806 groups was consistent with that during TP1. There were no major differences observed in the level of ADA positivity during TP2 for the RoActemra/BAT1806 group compared with the continued RoActemra group.

Table 33 - Overall Summary of Antidrug Antibody Incidence (Safety Set)

	RoActemra			
	RoActemra N=167	RoActemra →BAT1806 N=142	Combined N=309	BAT1806 N=312
Subjects with no postbaseline ADA result	1 (0.6%)	0	1 (0.3%)	2 (0.6%)
Within the first 12 weeks				
ADA positive at any time	19 (11.4%)	14 (9.9%)	33 (10.7%)	48 (15.4%)
ADA negative	147 (88.0%)	128 (90.1%)	275 (89.0%)	261 (83.7%)
NAb positive	19 (11.4%)	14 (9.9%)	33 (10.7%)	47 (15.1%)
NAb negative	147 (88.0%)	128 (90.1%)	275 (89.0%)	262 (84.0%)
Within TP1				
ADA positive at any time	26 (15.6%)	16 (11.3%)	42 (13.6%)	64 (20.5%)
ADA negative	140 (83.8%)	126 (88.7%)	266 (86.1%)	246 (78.8%)
NAb positive	26 (15.6%)	16 (11.3%)	42 (13.6%)	63 (20.2%)
NAb negative	140 (83.8%)	126 (88.7%)	266 (86.1%)	247 (79.2%)
Within TP2				
Subjects entered TP2	145	142	NA	290
ADA positive at any point	27 (18.6%)	23 (16.2%)		61 (21.0%)
ADA negative	118 (81.4%)	118 (83.1%)		229 (79.0%)
NAb positive	26 (17.9%)	23 (16.2%)		61 (21.0%)
NAb negative	119 (82.1%)	118 (83.1%)		229 (79.0%)
Overall (postbaseline)				
ADA positive at any time	41 (24.6%)	31 (21.8%)	72 (23.3%)	91 (29.2%)
ADA negative	125 (74.9%)	111 (78.2%)	236 (76.4%)	219 (70.2%)
NAb positive	40 (24.0%)	31 (21.8%)	71 (23.0%)	90 (28.8%)
NAb negative	126 (75.4%)	111 (78.2%)	237 (76.7%)	220 (70.5%)

Abbreviations: ADA = antidrug antibody; N = number of subjects; NA = not applicable; NAb = neutralizing antibody; SAF = Safety Set; TP1 = Treatment Period 1; TP2 = Treatment Period 2.
Note: The SAF included all randomized subjects that were administered any treatment with study drug. Subjects were analyzed according to treatment administered at the start of TP1 and TP2.

In all treatment groups, ADA negative participants experienced a higher incidence of treatment-related adverse events compared to ADA positive participants during the 52-week treatment period. AEs in the SMQ Hypersensitivity in patients receiving BAT1806 occurred predominantly in the ADA-negative subgroup. One AE with the PT 'infusion reaction' was reported in an ADA-negative subject from the RoActemra group during TP1, the event was recorded as non-serious and the patient continued treatment without changing the dose.

Table 34 - 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.

Hypersensitivity reactions were assessed using the broad SMQ of "hypersensitivity". The proportion of participants with at least 1 TEAE in the SMQ Hypersensitivity during TP1 + TP2 combined was 4.8% in the RoActemra-RoActemra group, 10.6% in the RoActemra-BAT1806 group and 6.1% in the BAT1806 group. Of these 42 participants, 6 (1.0% of total) were ADA positive at any time during TP1 + TP2 combined compared to 36 (5.8% of total) who were ADA negative. These results suggest that that ADA positive status did not influence incidence of hypersensitivity reactions in any treatment group, a result that was consistent with the relatively low ADA titer levels (geometric mean and median ADA titer was approximately 20) detected in this study. Therefore, ADA positive status is considered not to have influenced the incidence of hypersensitivity reactions in any treatment group.

3.3.8.8. Safety related to drug-drug interactions and other interactions

Not applicable for biosimilars.

3.3.8.9. Discontinuation due to adverse events

The proportion of participants who experienced a TEAE leading to action taken with study drug was higher in those who received RoActemra with 26.2% compared to BAT1806 with 18.6% in TP1 and RoActemra with 18.6%, RoActemra/BAT1806 with 18.3% and BAT1806 with 15.5% in TP2. The most frequent action taken was dose reduction, followed by temporary interruptions. The reported events were comparable between the treatment groups.

3.3.8.10. Post marketing experience

BAT1806 is not marketed in any country.

3.3.8.11. Study BAT-1806-001-CR

Study BAT-1806-001-CR was a randomised, double-blinded, single-dose, 3-arm parallel Phase I clinical study to establish pairwise PK biosimilarity between BAT1806 vs EU-licensed Actemra, BAT1806 vs US-licensed Actemra, US-licensed Actemra vs EU-licensed Actemra in healthy Chinese male subjects and to evaluate the clinical safety, tolerability and immunogenicity of 3 groups. In this study BAT1806 or RoActemra-EU or Actemra-US were administered via single-dose intravenous injection at a dose of 4 mg/kg. Therefore, the safety data from this study are summarized in this section.

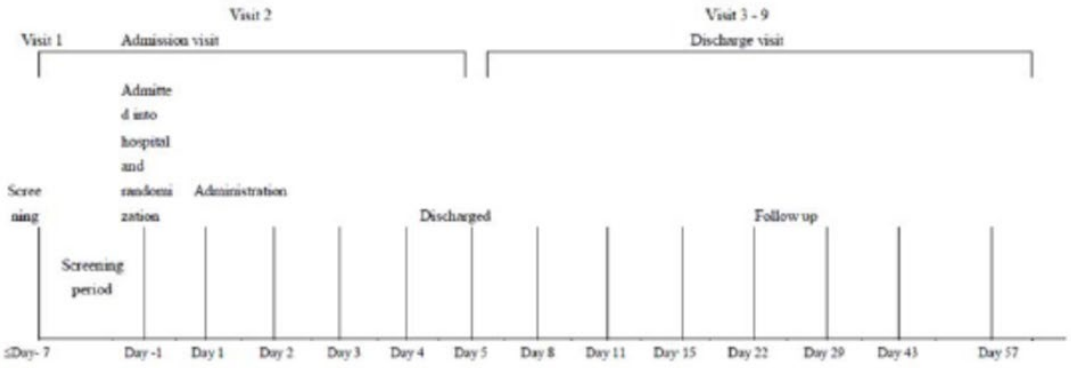
First participant enrolled: 06 June 2018

Last visit last participant: 08 November 2018

Study Overview

A total of 138 eligible healthy male subjects were planned to be enrolled and randomised at a ratio of 1:1:1 to receive single IV drip of BAT1806 or RoActemra-EU or Actemra- US.

Figure 7 - Flow Chart of Study Visit



Of the total 129 participants in SAS, all were Asian males, 121 (93.8%) with their ethnicity as Han and 8 (6.2%) subjects with their ethnicity as Other (Manchu or Mongolia). The overall mean age was 36.2 years. The overall minimum age was 18 years, the overall maximum age was 51 years, which met the inclusion criteria in protocol as "healthy male subjects at age of 18-55 years (inclusive for both)".

The mean weight of all participants was 67.11 kg, with minimum weight of 55.1 kg and maximum weight of 84.7 kg. The mean BMI was 23.37 kg/m2, with minimum BMI of 18.6 kg/m2 and maximum BMI of 27.8 kg/m2, both weight and BMI met the inclusion criteria in protocol as "BMI between 18-28 kg/m2 and BW between 55-85 kg". The mean height of all subjects was 169.44 cm, with minimum height of 152.7 cm and maximum height of 184.0 cm. Participants weight, BMI and height were well balanced among BAT1806, RoActemra-EU and Actemra-US treatment groups. There was no relevant medical history reported and no prior medications received for participants in the SAS.

All safety analyses were carried out using the SAS, which was defined as all participants who have received IP i.e. in the SAS, all participants received a single dosage of IP (all IP infused).

Adverse events

Overall, 77.5% of the participants experienced TEAEs with 68.9% in BAT1806 group, 85.7% in RoActemra-EU group and 78.6% in Actemra-US group.

A total of 72.1% of the participants experienced treatment-related TEAEs with 60.0% in BAT1806 group, 34 81.0% in RoActemra-EU group and 76.2% in Actemra-US group.

The incidence of TEAEs and treatment-related TEAEs in the BAT1806 group were numerically lower than in RoActemra-EU group and in Actemra-US group. Incidence of CTCAE Grade IV TEAEs in BAT1806 group was also lower than RoActemra-EU group and Actemra-US group. However, the overall number of participants is low in this data-set compared to study BAT-1806-002-CR.

There were no serious TEAEs, deaths, or TEAEs leading to study discontinuation reported in this study.

Table 35 - Overview of Treatment Emergent Adverse Events (Safety Analysis Set)

	Number (%) of Subjects			
Number of Subjects with	**BAT1806 (N = 45)**	**RoActemra-EU (N = 42)**	**Actemra-US (N = 42)**	**Overall (N = 129)**
Any TEAE	31 (68.9)	36 (85.7)	33 (78.6)	100 (77.5)
Any treatment-related TEAE	27 (60.0)	34 (81.0)	32 (76.2)	93 (72.1)
Any serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any treatment-related serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade I: Mild	15 (33.3)	9 (21.4)	14 (33.3)	38 (29.5)
Grade II: Moderate	12 (26.7)	17 (40.5)	11 (26.2)	40 (31.0)
Grade III: Severe	3 (6.7)	2 (4.8)	5 (11.9)	10 (7.8)
Grade IV: Life-Threatening	1 (2.2)	8 (19.0)	3 (7.1)	12 (9.3)
Grade V: Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAE leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: TEAE = treatment emergent adverse event.

The most common SOCs (reported in ≥4%) were investigations with 68.3%, metabolism and nutrition disorders with 30.2% and blood and lymphatic system disorders with 4.7%, infections and infestations 4.7%.

The most common TEAEs by PT (reported in ≥10% of all participants) included neutrophil count decreased with 44.2%, white blood cell count decreased with 27.1%, alanine aminotransferase (ALT) increased with 21.7% participants, hypertriglyceridemia with 21.7%, aspartate aminotransferase (AST) increased with 18.6 % participants and hyperuricaemia with 12.4 % participants.

Furthermore, the incidence of TEAEs including neutrophil count decreased and white blood cell count decreased in BAT1806 were significantly lower than in RoActemra-EU and Actemra-US groups (neutrophil count decreased: 26.7% vs 47.6% vs 59.5%; white blood cell count decreased: 15.6% vs 28.6% vs 38.1%) and most of these TEAEs (about 80%) were CTCAE Grade I or II and all were recovered at the Final Visit with about 90% recovered within one-week duration since TEAE onset.

Table 36 -Summary of Common Treatment Emergent Adverse Events (⩾ 4%) by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class/ Preferred Term	Number (%) of Subjects BAT1806 (N = 45)	RoActemra-EU (N = 42)	Actemra-US (N = 42)	Overall (N = 129)
Number of subjects with TEAEs	31 (68.9)	36 (85.7)	33 (78.6)	100 (77.5)
Investigations	24 (53.3)	29 (69.0)	29 (69.0)	82 (63.6)
Neutrophil count decreased	12 (26.7)	20 (47.6)	25 (59.5)	57 (44.2)
White blood cell count decreased	7 (15.6)	12 (28.6)	16 (38.1)	35 (27.1)
Alanine aminotransferase increased	9 (20.0)	11 (26.2)	8 (19.0)	28 (21.7)
Aspartate aminotransferase increased	9 (20.0)	10 (23.8)	5 (11.9)	24 (18.6)
Blood bilirubin increased	0 (0.0)	5 (11.9)	5 (11.9)	10 (7.8)
Blood creatine phosphokinase increased	1 (2.2)	4 (9.5)	3 (7.1)	8 (6.2)
Neutrophil count increased	2 (4.4)	3 (7.1)	0 (0.0)	5 (3.9)
Metabolism and nutrition disorders	12 (26.7)	18 (42.9)	9 (21.4)	39 (30.2)
Hypertriglyceridaemia	10 (22.2)	12 (28.6)	6 (14.3)	28 (21.7)
Hyperuricaemia	4 (8.9)	7 (16.7)	5 (11.9)	16 (12.4)
Blood and lymphatic system disorders	2 (4.4)	4 (9.5)	0 (0.0)	6 (4.7)
Leukocytosis	2 (4.4)	3 (7.1)	0 (0.0)	5 (3.9)
Infections and Infestations	2 (4.4)	3 (7.1)	1 (2.4)	6 (4.7)
Cardiac disorders	0 (0.0)	4 (9.5)	1 (2.4)	5 (3.9)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.

Overall, no major differences in occurrence of TEAEs between 3 groups were observed, but the incidence of most common TEAEs were numerically lower in BAT1806 group than in reference groups.

Concerning TEAEs, 72.1% of the participants experienced treatment-related TEAEs. The most common treatment-related TEAEs by SOC were investigations with 57.4% and metabolism and nutrition disorders with26.4%.

The most common treatment-related TEAEs by PT included neutrophil count decreased (44.2%), white blood cell count decreased (27.1%), hypertriglyceridemia (20.2%), ALT increased (17.8%) and AST increased (14.0%).

No Deaths, SAEs or TEAEs leading to study discontinuation were reported in this study.

In study BAT-1806-001-CR, the frequency of and the number of clinical laboratory abnormalities reported as TEAEs was numerically higher in RoActemra - EU group than in BAT1806 group. TEAEs reported more frequently were neutrophil count decreased, white blood cell count decreased, ALT increased, AST increased, blood CRP increased, neutrophil count increased. However, due to the small sample size and small differences between groups no conclusion can be drawn.

Grade IV TEAEs (life-threatening) laboratory abnormalities were reported in 1 participant treated with BAT1806, i.e., hyperuricemia, 8 (19%) participants treated with RoActemra, i.e., hyperuricemia in 5 participants, neutrophil count decreased 2 participants, CPK increased 1 participant, and 3 (7.1%) participants treated with Actemra, i.e., hyperuricemia 1 subject, hypertriglyceridemia 1 subject, CPK increased 1 subject. These TEAEs were blood creatinine phosphokinase increased, neutrophil count

decreased, hyperuricemia and hypertriglyceridemia. All these Grade IV TEAEs reported were resolved within 35 days at latest.

Immunogenicity

At baseline, 2 participants in BAT1806 group had positive ADA results and one participant presented positive nAb result. A total of 9 (7.0%), 29 (22.5%), and 41(31.8%) participants reported ADA-positive results on Day 15, Day 43 and Day 57, respectively. Similar ADA incidence rate was observed among 3 groups on Day 15 and Day 43. The ADA-positive results on Day 57 (Final Visit) was reported by 19 (42.2%), 10 (23.8%), and 12 (28.6%) participants in BAT1806, RoActemra-EU, and Actemra-US groups, respectively.

Regarding to nAb incidence, a total of 9 (7.0%), 24 (18.6%), and 35 (27.1%) participants reported positive results on Day 15, Day 43, and Day 57, respectively. The nAb-positive results on Day 57 (Final Visit) were reported by 14 (31.1%), 9 (21.4%) and 12 (28.6%) participants in BAT1806, RoActemra-EU, and Actemra-US groups, respectively.

However, the study results revealed that the immunogenic response over time did not appear to correlate well with serum drug concentrations. As for all 3 products, tocilizumab serum levels were non-quantifiable in the majority of participants by Day 29. However, there were still many subjects with newly observed positive ADA/nAb results on Days 43 and 57 when drug levels were not detectable. Overall, no confirmed impact of these immunogenic responses to tocilizumab PK was identified in this study. No clear correlation of ADA development to AEs was observed in this study. No participant had clinically significant hypersensitivity or serious hypersensitivity or anaphylaxis or injection site reaction after IP administration.

3.3.9. Discussion on clinical safety

In the clinical development program for BAT1806, two studies were conducted.

BAT-1806-001-CR evaluated PK bio-similarity and safety in comparison with EU-licensed RoActemra and EU-licensed RoActemra. However, only a single dose administration of 4 mg/kg body weight was administered to 138 Chinese male healthy subjects and the data were not pooled.

BAT-1806-002-CR was a Phase 3, multicentre, multinational, randomised, double-blind, parallel-group, active-control study to compare efficacy, safety, immunogenicity and PK of BAT1806 compared with RoActemra in subjects with RA that was inadequately controlled by MTX. A number of 621 participants were enrolled in this study.

This is in accordance with the "Guideline on similar biological products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010). All the studies have been completed at the time of submission.

Secondary objectives of the Phase 1 study (BAT-1806-001-CR) and Phase 3 study (BAT-1806-002-CR) was to compare the clinical safety, tolerability and immunogenicity between the biosimilar BAT1806 and the reference product, RoActemra. An additional secondary objective in study BAT-1806-002 was to assess safety and immunogenicity following transition from RoActemra to BAT1806.

BAT-1806-001-CR

Study BAT-1806-001-CR was a single-dose study in healthy volunteers. The overall number of healthy volunteers exposed to the study drugs as well as the dose levels administered are considered adequate.

There were no serious TEAE, death or TEAE leading to study discontinuation and no unexpected AEs reported. Overall, 77.5% of the participants experienced TEAE with 68.9% participants in BAT1806 group, 85.7% in RoActemra-EU group and 78.6% in Actemra-US group. A total of 72.1% participants experienced treatment-related TEAE with 60.0% in BAT1806 group, 81.0% in RoActemra-EU group and 76.2% in Actemra-US group. The overall incidence of TEAEs and treatment-related TEAEs was slightly lower in BAT1806 group compared to the other groups.

The most common SOCs involved with treatment-related TEAEs in all 3 treatment groups were investigations (57.4%) and metabolism and nutrition disorders (26.4%), the most common treatment-related TEAEs by PT in all 3 treatment groups were neutrophil count decreased (44.2%) and white blood cell count decreased (27.1%). Most of these TEAEs (about 80%) were CTCAE Grade I or II, and all of them recovered at the Final Visit. The most frequent laboratory abnormalities related TEAEs were neutrophil count decreased, white blood cell count decreased and ALT increased.

12 (26.7%) of participants in BAT1806 group experienced Grade I (mild) treatment-related TEAEs, 9 (21.4%) participants in RoActemra-EU group and 14 (33.3%) in Actemra-US group. 11 (24.4%) of participants in BAT1806 group experienced Grade II (moderate) treatment-related TEAEs, 18 (42.9%) of participants from RoActemra-EU group and 12 (28.6%) from Actemra-US group. 3 (6.7%) participants from BAT1806 group experienced Grade IV (severe) treatment-related TEAEs, 3 (7.1%) participants in RoActemra-EU group and 5 (11.9%) participants from Actemra-US group. Among participants who reported Grade IV (life-threatening) treatment-related TEAEs, 1 (2.2%) participant was in BAT1806 group, 4 (9.5%) participants were in RoActemra-EU group, and 1 (2.4%) participant were in Actemra-US group. No Grade V TEAEs have been reported in the study. Severity of treatment-related TEAEs appears to favour BAT1806.

The overall incidences of ADA- and nAb-positive results appeared to increase with time for all 3 IPs. At baseline, 2 participants in BAT1806 group had positive ADA results and one participant presented positive nAb result. The ADA-positive results on Day 57 (Final Visit) were reported with 42.2%, 23.8% and 28.6% of the participants in BAT1806, RoActemra-EU and Actemra-US groups, respectively.

Regarding to nAb incidence, a total of 9 (7.0%), 24 (18.6%), and 35 (27.1%) participants reported positive results on Day 15, Day 43, and Day 57, respectively. The nAb-positive results on Day 57 (Final Visit) were reported by 14 (31.1%), 9 (21.4%) and 12 (28.6%) participants in BAT1806, RoActemra-EU, and Actemra-US groups, respectively.

In study BAT-1806-001-CR, the incidence of ADA- and Nab-positive increase over time, with the appearance of ADA- and Nab-positive at Day 15. At Day 57, the proportion of participants ADA positive was higher in BAT1806 group 42.2% than in RoActemra EU 23.8% and Actemra US 28.6%. The proportion of participants Nab positive was higher at Day 43 and Day 57 in BAT1806 group, 22.2% and 31.1%, respectively, as compared to 14.3% and 21.4%, respectively in RoActemra EU group and 19.0% and 28.6%, respectively, in Actemra US group. No hypersensitivity or anaphylaxis or injection site reaction were reported in study BAT-1806-001-CR. No clear correlation of ADA development to AEs was observed in this study. However, it should be mentioned that the mode of reporting of injection site examination results as “normal” or “abnormal” is rather unusual.

Although, the differences seen in ADA positivity described above, no confirmed impact of these immunogenic responses to tocilizumab PK was identified in this study. No clear correlation of ADA development to AEs was observed in this study. No subject had clinically significant hypersensitivity or serious hypersensitivity or anaphylaxis or injection site reaction after IP administration.

BAT-1806-002-CR

In study BAT-1806-002-CR conducted in subjects with RA, 621 participants in the safety analysis set received IV infusions (Q4W, 8 mg/kg body weight) of either BAT1806 only (n = 312), RoActemra only (n = 167), or switched between both (n = 142). Participants received up to 12 doses of total, 6 doses per treatment period. Participants allocated to the switch arm received up to 6 doses of RoActemra in TP1 and up to 6 doses of BAT1806 in TP2.

Of the 621 randomised participants enrolled in study BAT-186-002-CR, a total of 75.8% experienced Adverse events. Of these 75.2% experienced Treatment-Emergent Adverse Events and for 6.6% of the participants serious TEAEs were reported. Furthermore, 56.4% of the participants experienced TEAEs related to study treatment and 2.1% were serious TEAEs related to study treatment. TEAEs leading to action taken with study drug were reported for 31.6%. Non-TEAEs that occurred > 8 weeks after last dose of study drug were reported for 2.7%. TEAEs which led to the study drug discontinuation were reported for 5.5% of the participants. A 5 (0.8%) participants experienced AEs leading to death.

The most frequent TEAEs by SOC were Investigations with 27.1% of participants in TP1, 25.3% in TP2 and 36.9% throughout the study, followed by Infections and infestations with 21.7% of participants in TP1, 22.9% in TP2, 36.2% throughout the study and Metabolism and nutrition disorders with 16.1% of participants in TP1, 14.6% in TP2, 21.3% throughout the study.

The most frequent TEAEs by PT were upper respiratory tract infection (9.8% in TP1, 7.1% in TP2 and 14.8% throughout the study), followed by ALT increased (10.0% in TP1, 6.1% in TP2 and 12.7% throughout the study) and leukopenia (6.4% in TP1, 6.9% in TP2 and 9.2% throughout the study). No notable differences were observed between the treatment groups.

The most frequent treatment-related TEAEs by SOC were Investigations (23.5% of participants in TP1, 20.8% in TP2 and 31.4% throughout the study), Infections and infestations (12.6% of participants in TP1, 13.9% in TP2, 21.7% throughout the study) and Blood and lymphatic system disorders (10.5% of participants in TP1, 11.4% in TP2, 15.6% throughout the study).

The most frequent treatment-related TEAEs by PT were ALT increased (9.0% of participants in TP1, 5.2% in TP2, 11.4% throughout the study), upper respiratory tract infection (6.6% of participants in TP1, 4.9% in TP2, 9.8% throughout the study), and leukopenia (5.8% of participants in TP1, 6.2% in TP2, 8.5% throughout the study). The reported differences are not considered clinically relevant.

Most TEAEs were mild, 34.3% of the participants experienced moderate TEAEs and 3.9% experienced severe TEAEs throughout the study. Similarly, for related TEAEs most were mild, 20.6% of the participants experienced moderate related TEAEs and 2.6% experienced severe related TEAEs throughout the study. No notable differences between the treatment groups were reported.

There were 5 (five) hypersensitivity reactions reported as TEAEs during study BAT-1806-002: one in RoActemra group during TP1, two in RoActemra – BAT1806 during TP1 and two in BAT1806 during TP1. Except one hypersensitivity TEAE which was considered unrelated, three of them were considered probable related and one possible related to the study drug. One of the hypersensitivity reactions was reported as a serious AE/other medically important condition. All hypersensitivity reactions have recovered/resolved. In addition, skin reactions such as rash and urticaria, and hypertension have been reported.

The rate of serious adverse events was generally low and comparable between the treatment groups with no trends observed. Overall, 6.6% of the participants experienced serious TEAEs, 7.2% from the RoActemra/RoActemra group, 7.0% from the RoActemra/BAT1806 group and 6.1% from the BAT1806 group.

Serious TEAEs that occurred in > 1 subject include pneumonia, lumbar spinal stenosis, and abortion spontaneous.

Five deaths were reported during study BAT-1806-002-CR. One participant received RoActemra and experienced a serious TEAEs of deep neck space infection and mediastinitis and furthermore serious TEAEs of septic shock and cerebral haemorrhage leading to death. The TEAEs of localised infection, mediastinitis and the 2 events of septic shock were considered as possibly related to study drug, while the event of cerebral haemorrhage was considered as unlikely related. Four participants died in the BAT1806 group due to an AE i.e. one serious TEAE of ovarian cancer stage III of severe intensity, one serious TEAE of ruptured cerebral aneurysm of severe intensity, one serious TEAE of death reason unknown and one serious AE about 2.5 months after the last dose of BAT1806, of cardiopulmonary failure of severe intensity. These four events were considered unrelated to the study treatment. Based on the narratives presented by the applicant this can be agreed.

AEs occurring >8 weeks after last dose of study drug defined as non-TEAEs were reported for 2.7% of the participants with 0.6% in TP1 and 2.3% experiencing non-TEAEs in TP2. No notable differences were observed between the RoActemra and BAT1806 groups.

The proportion of participants who experienced a TEAE leading to action taken with study drug was higher in those who received RoActemra with 26.2% compared to BAT1806 with 18.6% in TP1. In TP2 the rates were comparable with 18.6% in the RoActemra, 18.3% in the RoActemra/BAT1806 and with 15.5% in the BAT1806 group. The most frequent action taken was dose reduction, followed by temporary interruptions.

In RA subjects, the proportion of subjects that demonstrated ECG-related TEAEs was generally low (~1 to 4%) across all treatment groups. There were no clinically meaningful differences or trends in ECG parameters between BAT1806 and the reference product.

Overall, ADA negative participants experienced a higher incidence of treatment-related adverse events compared to ADA positive participants in all treatment groups during the 52-week treatment period.

ADA negative participants experienced a higher incidence of treatment-related adverse events compared to ADA positive participants in all treatment groups during the 52-week treatment period.

Hypersensitivity reactions were assessed using the broad SMQ of "hypersensitivity". The proportion of participants with at least 1 TEAE in the SMQ Hypersensitivity during TP1 + TP2 combined was 4.8% in the RoActemra-RoActemra group, 10.6% in the RoActemra-BAT1806 group and 6.1% in the BAT1806 group. Of these 42 participants, 6 (1.0% of total) were ADA positive at any time during TP1 + TP2 combined compared to 36 (5.8% of total) who were ADA negative. These results suggest that ADA positive status did not influence incidence of hypersensitivity reactions in any treatment group, a result that was consistent with the relatively low ADA titer levels (geometric mean and median ADA titer was approximately 20) detected in this study. Therefore, ADA positive status is considered not to have influenced the incidence of hypersensitivity reactions in any treatment group.

3.3.10. Conclusions on clinical safety

Safety data for 499 participants from the two biosimilarity Studies BAT-1806-001-CR and BAT-1806-002-CR, who received BAT1806 as single (4 mg/kg) or multiple (8 mg/kg, maximum of 800 mg) IV infusions, respectively, were submitted.

The safety profile of BAT1806 was generally consistent with the mechanism of action and with the safety profile of the reference product and the rates of AEs, Grade ≥ 3 AEs, SAEs, and AEs leading to dose reduction or discontinuation appear comparable.

3.4. Risk Management Plan

3.4.1. Safety concerns

Table 37 - Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Serious infection* • Complications of diverticulitis* • Neutropenia • Hepatotoxicity
Important potential risks	• Thrombocytopenia and the potential risk of bleeding • Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events • Malignancies • Demyelinating disorders • Immunogenicity
Missing information	None

*The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic tocilizumab dosing, and are assessed as important potential risks for the indication of COVID-19.

The safety specification is aligned with RoActemra and thus acceptable.

3.4.2. Pharmacovigilance plan

The applicant states that it employs routine pharmacovigilance activities in order to further characterise all of the safety concerns discussed in its European Union (EU) risk management plan (RMP). As a routine pharmacovigilance activity in addition to adverse reactions reporting and signal detection, specific adverse reaction follow-up questionnaires for malignancies are used.

The applicant does not plan any additional pharmacovigilance activities.

3.4.3. Risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Table 38 - Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Serious infections *	***Routine risk minimisation measures:*** SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Complications of diverticulitis *	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects) Legal status: Tofidence is a prescription only medicine ***Additional risk minimisation measures:*** Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Neutropenia	***Routine risk minimisation measures:*** SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Dosing Guide	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Hepatotoxicity	***Routine risk minimisation measures:*** SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Patient Alert Card DHPC	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Important potential risks		
Thrombocytopenia and the potential risk of bleeding	***Routine risk minimisation measures:*** SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use).	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC Section 4.8 (Undesirable effects). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure	***Additional pharmacovigilance activities:*** None
Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Dosing Guide	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Malignancies	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given [Tofidence]). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Dosing Guide	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** AE follow-up form for malignancy ***Additional pharmacovigilance activities:*** None
Demyelinating disorders	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use).	***Routine pharmacovigilance activities beyond adverse***

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Healthcare Provider Brochure	***reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Immunogenicity	***Routine risk minimisation measures:*** SmPC Section 4.8 (Undesirable effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** No additional risk minimisation activities.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Missing information		
Not applicable.		

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic Tocilizumab dosing but are assessed as important potential risks for the indication of COVID-19.

3.4.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3.6. Product information

3.6.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Roactemra. The bridging report submitted by the applicant has been found acceptable.

3.6.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons: the product is intended to be administered by a healthcare provider. Therefore, the QRD Group agreed with the use of the minimum particulars on the 20 mL vial.

3.6.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tofidence (Tocilizumab) is included in the additional monitoring list as it is a biological product that does not contain a new active substance and is authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

4. Biosimilarity assessment

4.1. Comparability exercise and indications claimed

The approach for demonstrating biosimilarity was in accordance with the current EMA guidelines. The EU-approved reference product, RoActemra, has been used as the comparator throughout the biosimilarity program for assessment of quality, safety and efficacy of BAT1806. The biosimilarity assessment consisted of:

- The analytical similarity assessment, encompassing physicochemical and biological testing, comparing BAT1806 to RoActemra.
- The pivotal nonclinical in-vitro studies, including Fab-mediated functional activity studies, Fc-related binding studies and ADCC and CDC activity studies and in-vivo animal studies including single-dose PK, local tolerance testing and RBC haemolysis or aggregation study, compared BAT1806 with RoActemra. Studies were also conducted comparing BAT1806 with US-licensed Actemra (US-Actemra) and Chinese-licensed Actemra (CN-Actemra) to support registration in those respective territories and are considered as supportive only for Europe.
- The Phase 1 PK study was a 3-arm study comparing BAT1806 with EU-RoActemra and US-Actemra at a ratio of 1:1:1.

- The Phase 3 safety and efficacy study was a 2-arm study comparing BAT1806 with RoActemra.

Indications claimed

The applicant is proposing BAT1806 IV infusion for marketing authorization for the IV indications approved for the reference product that are currently eligible for biosimilar authorisation:

- Rheumatoid arthritis (RA):
    - the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX) (monotherapy or in combination with MTX).
    - the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumor necrosis factor (TNF) antagonists (monotherapy or in combination with MTX).
- Coronavirus disease 2019 (COVID-19): the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.
- Polyarticular juvenile idiopathic arthritis (pJIA): the treatment of juvenile idiopathic polyarthritis (PJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX (monotherapy or in combination with MTX).
- Systemic juvenile idiopathic arthritis (sJIA): the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids (monotherapy or in combination with MTX).

4.2. Results supporting biosimilarity

Quality

Reference is made to section 3.1.3.5. To support biosimilarity an analytical comparability study in line with EMA/CHMP/BWP/247713/2012 has been performed using suitable state-of-the art methods. The quality attributes were defined using a suitable risk assessment and are considered to cover all attributes important for tocilizumab in terms of safety, purity and modes of action (including potency). In conclusion, the biosimilarity between Tofidence to its reference medicinal product EU-RoActemra has been sufficiently demonstrated from a quality point of view.

Pharmacokinetics

The pivotal data for demonstrating PK similarity with the EU reference product are obtained from a single-dose study in healthy volunteers (BAT1806-001-CR): Pharmacokinetic comparability has been demonstrated for BAT1806 versus EU-RoActemra. The 90% CIs of the primary parameter (AUC0-inf) and secondary parameters (Cmax and AUC0-t) were contained within the predefined 80.00% to 125.00% bioequivalence limits.

In the pivotal efficacy and safety study BAT1806-002-CR, PK trough concentration samples were collected from all study patients at scheduled visits.

Efficacy

Study BAT-1806-002-CR was a randomised, double-blind, parallel group, active-control study to compare the efficacy and safety of BAT1806 to RoActemra in RA patients with inadequate response to methotrexate (8 mg/kg Q4W, 6 doses per treatment period).

The primary endpoint was the percentage of subjects achieving an ACR20 response assessed at Week 12. The results of the primary efficacy endpoint, support equivalence and clinical similarity between BAT1806 and RoActemra. The estimated 95% CIs of the treatment difference at Week 12 were contained within the predefined equivalence margins, as confirmed by the corresponding primary and secondary estimands. All sensitivity and supportive analyses of the primary efficacy endpoint were consistent with primary and secondary estimands of the primary efficacy analyses. Secondary efficacy endpoints of ACR20 at timepoints other than Week 12 or Week 24, ACR50, ACR70, DAS28 and other ACR components and EULAR response, were generally comparable between the treatment groups throughout the study, providing further evidence of clinical similarity.

Safety

The safety outcomes following BAT1806 treatment were in general comparable with those of the reference product RoActemra. No new safety signals were identified. The incidence, frequency and severity of treatment-related adverse events reported in Study BAT-1806-002-CR was in line with the established safety profile of RoActemra.

Immunogenicity:

In Study BAT-1806-002-CR, similar proportions of ADA-positive participants in the BAT1806 and RoActemra treatment groups achieved responses for the primary and secondary endpoints across both parts of the study. The ADA incidence in the RoActemra/BAT1806 switch group was lower compared to the BAT1806 and the RoActemra group, which indicates that switching from RoActemra to BAT1806 did not seem to be associated with higher rates in immunogenicity. There was no apparent increased risk of treatment-related hypersensitivity reactions for BAT1806 compared with RoActemra.

4.3. Uncertainties and limitations about biosimilarity

Efficacy

The subgroup analyses show a difference in the Proportion of Subjects Achieving ACR20 Response at Week 12 for the region Central Europe in favour of BAT1806, whereas a difference of in favour of RoActemra was observed for the Asia Pacific region. The interaction p-value for region was nominally significant ($p = 0.029$), which is remarkable as usually there is a lack of power to detect differential effects in subgroups. The average difference in ACR20 response between regions is hence 17.21%.

The subgroup with a bodyweight of 60 to 100 kg shows a higher difference also in favour of BAT1806, whereas subjects below 60kg show a difference in favour of RoActemra. The average difference in ACR20 response between these weight cohorts is hence 18.67%. This seems to be of a similar magnitude as the regional differences. Both region and body weight impact ACR20 in a way that even the difference in point estimates is substantially larger than the equivalence margin (not to speak of confidence intervals) and hence a clinically meaningful impact is assumed.

The outcome data presented in the response to the LoOI additionally shows that there indeed is a pattern that (especially for the primary analysis of ACR20 at week 12) there is an increasing response with body weight in both regions in subjects treated with BAT1806. In contrast, the effect is reversed in the RoActemra arm were in both regions the response decreases with body weight. Similar patterns are also apparent at other time points, although not always as pronounced as at week 12. Furthermore, the data seems to show, though, that there is an additional regional difference beyond the effect of body weight.

The applicant states that there are no reasons to expect an actual/true difference given the CMC, PK and quality attributes data for the proposed biosimilar. Furthermore, based on the totality of the data clinical, analytical, functional and non-clinical data, the applicant deems the observation to be a chance finding. Overall, differences in the efficacy / biosimilarity in different regions and based on different weight cannot be fully excluded based on the provided data. However, it also could not be substantiated.

Immunogenicity

Throughout the clinical trials, the overall incidence of treatment-induced ADA positive participants was higher in the BAT1806-treated groups as compared to the RoActemra-treated groups. In Study BAT-1806-001-CR the incidence of ADA positive participants was over 15% higher in BAT1806 group compared to EU-RoActemra. However, the difference of 4.6% in study BAT-1806-002-CR in the proportion of ADA-positive patients between the BAT1806 and RoActemra group was lower but also seen and it is unclear which impact the background treatment (99,8% received MTX and 58% received corticosteroids) on the incidence had.

4.4. Discussion on biosimilarity

From a pharmacokinetic perspective, the available data overall support biosimilarity versus the EU reference product in the healthy subjects and RA patients.

The analytical biosimilarity study showed in general good comparability between the proposed biosimilar and its reference medicinal product. In summary, the biosimilarity between BAT1806 to its RMP EU-RoActemra has been sufficiently demonstrated from a quality point of view.

In Study BAT-1806-002-CR the efficacy and safety of BAT1806 was compared to RoActemra in RA patients with inadequate response to methotrexate (8 mg/kg Q4W, 6 doses per treatment period). The primary endpoint was the percentage of subjects achieving an ACR20 response assessed at Week 12.

No significant difference was reported between the BAT1806 and RoActemra group for proportion of subjects achieving ACR20, ACR50 and ACR70 over time and these results were similar to those for the historic RoActemra studies, although most of these studies used a primary endpoint at week 24.

However, concerning the subgroup analyses a difference (95% CI) in the Proportion of Subjects Achieving ACR20 Response at Week 12 for the region Central Europe in favour of BAT1806, and a difference in favour of RoActemra was observed for the Asia Pacific region. The interaction p-value for region was nominally significant. The subgroup with a bodyweight of 60 to 100 kg shows a higher difference also in favour of BAT1806, whereas subjects below 60kg show a difference in favour of RoActemra. The average seems to be of a similar magnitude as the regional differences. The outcome data presented in the response to the LoOI additionally shows that there indeed is a pattern that (especially for the primary analysis of ACR20 at week 12) there is an increasing response with body weight in both regions in subjects treated with BAT1806. In contrast, the effect is reversed in the RoActemra arm were in both regions the response decreases with body weight. Similar patterns are also apparent at other time points, although not always as pronounced as at

week 12. The differences reflect this pattern as well. Overall, differences in the efficacy / biosimilarity in different regions and based on different weight cannot be fully excluded based on the provided data. However, it also could not be substantiated. The issue is not further pursued as it is considered to have no major impact on the biosimilarity assessment.

The safety data of BAT1806 reported for study BAT-1806-001-CR and BAT-1806-002-CR showed no significant differences between the treatment groups of healthy volunteers and RA patients.

The proportion of ADA-positive patients in BAT1806 group was 29.2% and therefore 4.6% higher than in the RoActemra group with 24.6%. Additionally, it has to be noted that the ADA incidence in the RoActemra/BAT1806 switch group was markedly lower with 21.8% compared to the BAT1806 and the RoActemra group.

4.5. Extrapolation of safety and efficacy

BAT1806 is intended for administration as an IV infusion and is available as an injectable solution at a strength of 80 mg/4 mL, which is consistent with the EU summary of product characteristics (SmPC) for intravenously formulated tocilizumab (RoActemra SmPC, 2022). The Applicant, Biogen, is proposing BAT1806 IV infusion for marketing authorization for the indications approved for the reference product that are currently eligible for biosimilar authorisation.

The development program of BAT1806 evaluating the biosimilarity between BAT1806 and RoActemra are in line with the EMA guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance (EMEA/CHMP/BMWP/42832/2005) and similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

Safety and Efficacy of BAT1806 in comparison to those of Actemra and RoActemra were evaluated in 2 clinical trials: Study BAT-1806-001-CR evaluating PK and Safety of a single administration of 4mg/kg of BAT1806 vs US-licensed Actemra vs EU-approved RoActemra in 138 healthy male Chinese subjects and Study BAT-1806-002-CR evaluating Efficacy, Safety and Immunogenicity in of BAT1806 to EU-approved RoActemra in subjects with RA with an inadequate response to MTX.

In the clinical studies conducted, the PK equivalence of IV infusion of BAT1806 to the reference products RoActemra was met and no significant differences in safety or immunogenicity were observed. Furthermore, equivalence with regards to efficacy between BAT1806 and RoActemra in RA patients has been demonstrated.

EMA guidelines state, if biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification (FDA, 2015; EMA/CHMP/BWMP/403543/2010). On the basis of the commonality of mechanism of action, an extrapolation of equivalent efficacy demonstrated in RA to the other approved indications of Actemra and RoActemra can be justified.

Interleukin-6 (IL-6) is a multifunctional proinflammatory cytokine produced by various types of cells (Preuss & Anjum, 2022) and has a pleiotropic effect on inflammation, immune response, and haematopoiesis (Tanaka et al., 2014). IL-6 is overexpressed in multiple inflammatory diseases, including PJIA, sJIA, and plays an important role in the pathogenesis of these types of diseases. During inflammation, it has been shown that IL-6 can up-regulate T helper 17 cell (Th17)/regulatory T cell (Treg) balance, promote T-follicular helper-cell

differentiation, induce differentiation of CD8+ T-cells into cytotoxic T-cells, and activate B-cells into antibody-producing plasma cells (Kimura & Kishimoto, 2010; Okada et al., 1988).

All approved indications for Actemra (US) and RoActemra (EU) applied for by the applicant share the common feature that they are associated with elevated levels of IL-6.

BAT1806 has a similar primary structure as the reference product and was found to be similar to the reference product in terms of higher order structure, particles and aggregates, purity and product-related substances profiles, and in vitro biological activities. Where differences were observed, additional structure-activity analyses were conducted to demonstrate that the differences would have no clinical impact.

Tocilizumab exerts its therapeutic effect through neutralizing IL-6R and no differences were observed between BAT1806 and both EU and US sourced reference product that may affect potency or PK. Therefore, BAT1806 is expected to display similar therapeutic effect to the reference product for all its authorized indications.

Pharmacokinetic Similarity

BAT1806 shows no structural differences from RoActemra that might impact PK across the indications approved for RoActemra. BAT1806 demonstrated a comparable PK profile to RoActemra when given as a single dose of 4 mg/kg to healthy subjects and in RA patients at dose of 8 mg/kg Q4W. The dose of 8 mg/kg Q4W is generally adopted across all indications.

No clinically meaningful and significant differences in PK parameters have been reported across all of the approved EU indications for RoActemra. Therefore, it is reasonable to expect that BAT1806 will demonstrate similar PK values and safety profile in patients with pJIA, sJIA or COVID-19 who have not been directly studied within the clinical development program of BAT1806.

Based on the totality of evidence it is reasonable to conclude that BAT1806 will display a similar PK profile in all the approved EU indications for RoActemra.

Efficacy Similarity

The binding and neutralization of IL-6R is associated with treatment efficacy within all indications approved for RoActemra. The clinical equivalence Study BAT-1806-002-CR was conducted in RA patients as they are considered to be an adequately sensitive population to study efficacy, safety and immunogenicity for the following reasons. Among all licensed RoActemra indications, RA is the most extensively studied one. RA is the most prevalent of all indications. The magnitude of effect versus placebo is relatively large in RA patients. The ACR20 is an easily calculated score and able to demonstrate treatment efficacy within 12 weeks.

Study BAT-1806-002-CR was a randomised, double-blind, parallel group, active-control study to compare the efficacy and safety of BAT1806 to RoActemra in RA patients with inadequate response to methotrexate (8 mg/kg Q4W, 6 doses per treatment period). The primary endpoint was the percentage of subjects achieving an ACR20 response assessed at Week 12. No significant difference was reported between the BAT1806 and RoActemra group for proportion of subjects achieving ACR20 (65% and 69 % respectively), ACR50 (29% and 25% respectively) and ACR70 (9% and 8% respectively) and these results were similar to those for the historic RoActemra studies, although most of these studies used a primary endpoint at week 24.

The clinical development program of BAT1806 demonstrated similar efficacy between BAT1806 and RoActemra in a controlled, randomised, double-blind study in RA patients. Taking into consideration the structural, biological, PK/PD similarity, equivalent PK in RA patients that is considered also demonstrated, the

totality of evidence indicate that BAT1806 is a biosimilar to RoActemra. Based on the results presented, BAT1806 is expected to demonstrate similar treatment efficacy in patients with pJIA, sJIA, CRS or COVID-19.

Safety Considerations

The safety data of BAT1806 reported for study BAT-1806-001-CR and BAT-1806-002-CR showed no significant differences between the treatment groups of healthy volunteers and RA patients.

No substantial differences in the safety profile have been found in clinical studies across different EU and US-approved indications for Actemra/RoActemra conducted to date. Therefore, it is reasonable to expect that the similarity in terms of safety that was observed between BAT1806 and the reference product in healthy volunteers and RA patients can be extrapolated to patients with pJIA, sJIAor COVID-19.

Immunogenicity Considerations

In historical data from pooled Phase 1 and Phase 3 data from adult RA patients (N=5875), 1.2% of patients administered IV tocilizumab developed ADAs and there was no difference in patients receiving tocilizumab monotherapy and those who received concomitant conventional synthetic DMARDs (0.7-1.3%) (Burmester et al., 2017). In addition, ADA development did not correlate with PK or safety events, including anaphylaxis, hypersensitivity or injection-site reactions, and no patients who developed ADAs had loss of efficacy. In paediatric patients with pJIA, out of 167 patients who had a negative ADA result at baseline 4 (2.4%) developed positive ADA results during the study and only 1 (0.6%) had a positive confirmation and neutralizing assay result (Brunner et al., 2021). Of 75 paediatric patients with sJIA treated with tocilizumab, ADAs developed in 2 (2.7%) patients. Both patients withdrew from the study (De Benedetti et al., 2012).

In Study BAT-1806-001-CR in healthy subjects receiving a single dose of 4 mg/kg, the overall incidences of ADA- and NAb-positive results appeared to increase with time for all treatments. The results of ADA-positive, nAb-positive participants at the Final Visit (Day 57) in BAT1806, RoActemra- EU, and Actemra-US groups were 19 (42.2%) vs 10 (23.8%) vs 12 (28.6%) participants, 14 (31.1%) vs 9 (21.4%) vs 12 (28.6%) subjects, respectively. Overall, no confirmed impact of these immunogenic responses to tocilizumab PK was identified in this study.

These results show a higher incidence of ADA in the BAT1806 compared to the RoActemra group of 18.4%. However, it has to be noted that the numbers were rather low and the immunogenicity data from the larger data set reported BAT-1806-002-CR have to be considered. Additionally, the higher incidence of ADAs was not correlated to a higher rate of AEs which were similar or even lower in the BAT1806.

In Study BAT-1806-002-CR in RA patients receiving 8 mg/kg IV, generally, the incidence of ADAs in the BAT1806, RoActemra and RoActemra/BAT1806 groups were 29.2%, 24.6% and 21.8% respectively, the majority of ADA positive subjects reported titers of < 20, or 20.

4.6. Additional considerations

None.

4.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Tofidence is considered biosimilar to Roactemra. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

5. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tofidence is favourable in the following indication(s):

Tofidence, in combination with methotrexate (MTX), is indicated for:

• the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.

• the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease- modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Tofidence can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tofidence has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Tofidence is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Tofidence is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Tofidence can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Tofidence in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tofidence can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA, sJIA, and pJIA targeting all physicians who are expected to prescribe/use Tofidence containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack

The MAH must agree the content and format of the educational material, together with a communication plan (including means of distribution), with the national competent authority prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- Reference to the Summary of Product Characteristics (e.g., link to EMA website)
- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
- The product must not be given to patients with active or suspected infection
- The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Risk of Hepatotoxicity
- Caution should be exercised when considering initiation of tocilizumab treatment in patients with elevated transaminases ALT or AST above 1.5 x ULN. In patients with elevated ALT or AST above 5 x ULN treatment is not recommended.
- In RA, pJIA and sJIA, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. The recommended dose modifications, including tocilizumab discontinuation, based on transaminases levels, in line with SmPC section 4.2.
- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or

intestinal ulcerations

- Details on how to report serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Guidance on how to diagnose Macrophage Activation Syndrome in sJIA patients
- Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and infusion reactions
- Preparation of infusion
- Infusion rate
- Monitoring of the patient for infusion reactions
- Details on how to report serious adverse reactions

The patient Information Pack should contain the following key elements:

- Package leaflet (e.g., link to EMA website)
- Patient alert card
- to address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.
- to address the risk that patients using Tofidence may develop complications of diverticulitis which can become serious if not treated.
- to address the risk that patients using Tofidence may develop serious hepatic injury. Patients would be monitored for liver function tests. Patients should inform their doctor immediately if they experience signs and symptoms of liver toxicity including tiredness, abdominal pain and jaundice.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.