11 December 2025
EMADOC-1829012207-39209
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gotenfia

International non-proprietary name: golimumab

Procedure No. EMEA/H/C/006621/0000

Note

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

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List of abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ACR20	ACR response of 20%
ADA	Anti-drug antibody
AEs	Adverse events
AS	Ankylosing spondylitis
AUC_1	Area under the curve after first dose
$AUC_{0-\infty}$	Area under the drug concentration-time curve from 0 to infinity (∞)
AUC_{0-t}	Area under the drug concentration-time curve from 0 to the sample collection time t
AUC_{0-672h}	Area under the drug concentration-time curve from 0 to 672 h
AUC_{ss}	Area under curve at steady state
BLQ	Number of subjects below the limit of quantification
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum drug concentration
C_{max1}	Maximum concentration after first dose
$C_{max,ss}$	Maximum concentration at steady state
C_{min1}	Minimum concentration after first dose
$C_{min,ss}$	Minimum concentration at steady state
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DAS28	28-joint disease activity score
DMARDs	Disease-Modifying Antirheumatic Drugs
ECG	Electrocardiography
ECL	Electrochemiluminescence
EMA	European Medicines Agency
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
Geo	Geometrix
GM	Geometric mean
GMR	Geometric mean ratio
HAQ-DI	Health Assessment Questionnaire Disability Index
IV	Intravenous
LCL	Lower confidence limit
MAA	Marketing authorisation application
Max	Maximum
MH	Mantel-Haenszel
Min	Minimum
MoA	Mechanism of action

MSD	Mesoscale Discovery
mTNFα	Transmembrane TNF-α
MTX	Methotrexate
NA	Not applicable
NAb	Neutralising antibody
NAPSI	Nail Psoriasis Severity Index
NC	Not calculated
PASI	Psoriasis area and severity index
pJIA	Polyarticular juvenile idiopathic arthritis
PD	Pharmacodynamic
PK	Pharmacokinetics
PKS	Per PK Analysis Set
PopPK	Population PK analysis
PPI	Plaque psoriatic involvement
PsA	Psoriatic arthritis
PT	Preferred term
RA	Rheumatic arthritis
RD	Common Risk Difference
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
sTNFα	Soluble TNF-α
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
TNF	Tumor necrosis factor
TNF α	Tumor necrosis factor alpha
TP	Treatment period
UC	Ulcerative colitis
UCL	Upper confidence limit
VAS	Visual analog scale

1. Executive Summary

On 11 December 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a marketing authorisation application for the medicinal product Gotenfia (golimumab) intended for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis and ulcerative colitis.

Gotenfia will be available as a 50 mg and 100 mg solution for injection in pre-filled syringes. The active substance of Gotenfia is golimumab, a tumour necrosis factor alpha (TNF-α) inhibitor (ATC code: L04AB06). Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors. By blocking TNF-α, golimumab reduces the inflammation and other symptoms of the diseases it is used for.

Gotenfia is a biosimilar medicinal product. It is highly similar to the reference product Simponi (golimumab), which was authorised in the EU on 1 October 2009. Data show that Gotenfia has comparable quality, safety and efficacy to Simponi.

The main evidence of bioequivalence of Gotenfia was based on a phase 1 study comparing the pharmacokinetics and safety between Gotenfia and Simponi in healthy subjects (BAT-2506-001-CR), a phase 3 study comparing the efficacy and safety between Gotenfia and Simponi in patients with active psoriatic arthritis (study BAT-2506-002-CR), and a supportive phase 1 study comparing the pharmacokinetics and safety of Gotenfia injection versus Simponi (and US-Simponi) in healthy subjects (BAT-2506-003-CR).

The full indications for Gotenfia are:

Rheumatoid arthritis (RA)

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

1. the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.

2. the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

Golimumab, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Gotenfia in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

Psoriatic arthritis (PsA)

Gotenfia, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Golimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Gotenfia is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)

Gotenfia is indicated for the treatment of adults with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative colitis (UC)

Gotenfia is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Treatment with Gotenfia is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis. Patients treated with Gotenfia should be given the Patient Card.

Detailed recommendations for the use of this product are described in the summary of product characteristics (SmPC), which will be published on the EMA website in all official European Union languages after the marketing authorisation has been granted by the European Commission.

This report summarises the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).

1.1. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
25 June 2020	Quality, non-clinical, clinical	EMEA/H/SA/4480/1/2020/III Juha Kolehmainen, Andrea Laslop	The Scientific advice pertained to the following quality, non-clinical, and clinical aspects: • The characterisation studies for the primary cell bank (PCB), master cell bank (MCB) and working cell bank. The Virus Clearance studies. The studies to demonstrate comparability between process A and B batches. The proposed biosimilarity assessment strategy. • Adequacy of the non-clinical program to support the Marketing Authorisation Application. • The PK equivalence study with EU-approved Simponi including discussion on the population, primary and secondary endpoint, selected dose, sample size calculation, equivalence margin and Ethnicity. The Phase 3 efficacy and safety study to compare BAT2506 versus EU Simponi in patients with active psoriatic arthritis. Aspects discussed include population, primary and secondary endpoint, sample size calculation, equivalence margin, considerations for assessment of the effects of COVID-19 and/or related measures, including data handling for missing data. The extrapolation to all indication granted for the reference medicinal product.
25 March 2021	Clinical	EMA/SA/0000050874 Juha Kolehmainen, Anna Vikerfors	The Scientific advice pertained to the following clinical aspects: • Patient population and equivalence margin of the proposed phase 3 efficacy and safety study.

1.2. Eligibility to the centralised procedure

The applicant STADA Arzneimittel AG submitted on 28 December 2024 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Gotenfia (Golimumab), 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 indication:

Rheumatoid arthritis (RA)

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

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

Golimumab, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

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Gotenfia is indicated for the treatment of adults with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative colitis (UC)

Gotenfia is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

1.3. Legal basis and 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 European Union provisions in force for not less than 8 years in the EEA:

Product name, strength, pharmaceutical form:	Simponi, 50 mg solution for injection in prefilled syringe and prefilled pen Simponi, 100 mg, solution for injection in prefilled syringe and prefilled pen Simponi 45 mg/ 0.45ml, solution for injection in prefilled pen
Marketing authorisation holder:	Janssen Cilag International
Date of authorisation:	01 October 2009 (50 mg) 03 September 2013 (100 mg) 18 February 2019 (45 mg/ 0.45 ml)
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/09/546/001-004 (50 mg) EU/1/09/546/005-008 (100 mg) EU/1/09/546/009 (45 mg/ 0.45 ml)

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

Product name, strength, pharmaceutical form:	Simponi, 50 mg solution for injection in prefilled syringe Simponi, 100 mg, solution for injection in prefilled syringe
Marketing authorisation holder:	Janssen Cilag International
Date of authorisation:	01 October 2009 (50 mg) 03 September 2013 (100 mg)
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/09/546/003-004 (50 mg) EU/1/09/546/007-008 (100 mg)

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

Product name, strength, pharmaceutical form:	Simponi, 50 mg solution for injection in prefilled syringe Simponi, 100 mg, solution for injection in prefilled syringe
Marketing authorisation holder:	Janssen Cilag International
Date of authorisation:	01 October 2009 (50 mg) 03 September 2013 (100mg)
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/09/546/003 EU/1/09/546/007
Bioavailability studies numbers:	BAT-2506-001 and BAT-2506-002

1.4. Information on paediatrics

Not applicable.

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

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 from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

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:	Tomas Radimersky

The application was received by the EMA on	28 December 2024
The procedure started on	23 January 2025
The CHMP Rapporteur's first Assessment Report was received on	14 April 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	16 April 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	28 April 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	15 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 May 2025
The Biologics Working Party agreed on the Assessment Overview during their meeting on	13 May 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 May 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 August 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	22 September 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 October 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	16 October 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 November 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 November 2025

The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	04 December 2025
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 Gotenfia on	11 December 2025

1.7. Final CHMP outcome

1.7.1. Final opinion

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

Rheumatoid arthritis (RA)

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

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

Golimumab, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

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Ulcerative colitis (UC)

Gotenfia is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.7.2. Conclusions on biosimilarity and benefit risk balance

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

1.7.3. Conditions or restrictions regarding supply and use

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

1.7.4. Other conditions and requirements of the marketing authorisation

1.7.4.1. Periodic safety update reports

The requirements for submission of PSURs 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.

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

1.7.5.1. 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.

1.7.5.2. Additional risk minimisation measures

The educational programme consists of a Patient Card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professional(s) treating the patient about

ongoing treatment with the product.

The Patient Card shall contain the following key messages:

- A reminder to patients to show the Patient Card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using Gotenfia.
- A statement that the brand name and batch number should be recorded.
- Provision to record the type, date, and result of TB screenings.
- That treatment with Gotenfia may increase the risks of serious infection, opportunistic infections, tuberculosis, hepatitis B reactivation and breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero; and when to seek attention from a HCP.
- Contact details of the prescriber.

1.7.6. Proposed list of recommendations

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

2. Introduction

2.1. Therapeutic Context

Not applicable.

2.2. Aspects of development

Gotenfia (company code BAT2506) has been developed as a biosimilar to the reference medicinal product Simponi.

The applicant is seeking approval for all indications currently approved for Simponi, which are: the treatment of rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, ulcerative colitis, and juvenile idiopathic arthritis.

The application covers the 50 mg and 100 mg solution for injection in prefilled syringe presentations. However, the applicant has not applied for the 50 mg and 100 mg solution for injection in prefilled pen format. Additionally, the paediatric strength (45 mg/0.45 ml solution for injection), indicated for the treatment of juvenile idiopathic arthritis in children weighing less than 40 kg, is not included in the application.

The applicant received an EMA scientific advice on 25 June 2020 (EMEA/H/SA/4480/1/2020/III) and on 25 March 2021 (EMA/SA/0000050874) (see section 2.2.).

The clinical development programme was designed to compare the pharmacokinetics and safety of BAT2506 and Simponi in healthy male subjects (BAT-2506-001-CR phase 1), and to compare the efficacy and safety of BAT2506 versus Simponi in patients with active psoriatic arthritis (BAT-2506-002-CR phase 3). A supportive phase 1 study (BAT2506-003-CR) was also conducted to compare the pharmacokinetics and safety of BAT2506 injection versus the EU-approved and US-licensed Simponi in healthy male subjects.

All three studies were conducted in adherence to requirements of ICH GCP, IRB/IEC, and all other applicable local regulations.

Table 2: Summary of Clinical Studies in the BAT2506 Development Program

Study Number / Phase		**Study Title**	**Study Objectives**	**Treatment Regimen**	**Study Population / Number of Randomised Subjects**
		Pivotal PK and efficacy studies			
BAT-2506-001-CR Phase 1		A Randomised, Double-blind, Single-dose, Parallel Two-arm Study to Compare the Pharmacokinetics and Safety of BAT2506 and Simponi in Healthy Chinese Male Subjects	**Primary:** To compare the pharmacokinetic (PK) similarity between BAT2506 and Simponi after a single subcutaneous injection in healthy Chinese male subjects. **Secondary:** To evaluate the safety and immunogenicity of BAT2506 and Simponi in healthy Chinese male subjects.	Single SC administration of 50 mg BAT2506 or golimumab reference medicinal product (EU-authorized Simponi) Eligible subjects were randomised in a 1:1 ratio to one of following treatment groups: (1) BAT2506: 50 mg; SC (2) EU-Simponi: 50 mg; SC	Healthy volunteers N=182
BAT-2506-002-CR Phase 3		A Multicenter, Double-blind, Randomised, Parallel-group Study to Compare the Efficacy and Safety of BAT2506 Versus Simponi in Participants with Active Psoriatic Arthritis	**Primary:** To demonstrate the equivalence of BAT2506 and Simponi on American College of Rheumatology (ACR) 20 response in subjects with active PsA **Secondary**: To compare the efficacy of BAT2506 with Simponi on additional efficacy parameters in subjects with active PsA To compare the PK of BAT2506 with Simponi in subjects with active PsA To compare PD parameter of BAT2506 with Simponi in subjects with active PsA To compare the safety of BAT2506 with Simponi in subjects with active PsA To compare the immunogenicity of BAT2506 with Simponi in subjects with active PsA To assess safety and immunogenicity following transition from Simponi to BAT2506	Multiple SC administrations of 50 mg BAT2506 or golimumab reference medicinal product (EU-authorized Simponi) for around one year period. Eligible subjects were randomised in a 1:2:1 ration to one of the following treatment groups: Simponi (EU-approved) 50 mg (Week 0 to Week 48) BAT2506 50 mg (Week 0 to Week 48) Simponi→BAT2506: Administered with Simponi 50 mg (Week 0 to Week 20) followed by BAT2506 50 mg	Subjects with active PsA N=704

Study Number / Phase		Study Title	Study Objectives	Treatment Regimen	Study Population / Number of Randomised Subjects
				(Week 24 to Week 48) Study drugs administered once every 4 weeks.	
		Supportive PK study			
BAT-2506-003-CR Phase 1		A randomised, double-blind, single-dose, parallel three-arm comparative study on pharmacokinetics and safety of BAT2506 Injection versus the EU-approved and US-licensed Simponi in healthy Chinese male subjects	**Primary:** To compare the similarity of pharmacokinetics (PK) between BAT2506 Injection and Simponi (EU-approved and US-licensed) after a single subcutaneous injection in healthy Chinese male subjects **Secondary:** To evaluate the safety, tolerability and immunogenicity of BAT2506 Injection with EU-approved Simponi and US-licensed Simponi in healthy Chinese male subjects	Single SC administration of 50 mg BAT2506 or golimumab reference product (EU- or US-authorized Simponi) Eligible subjects were randomised in a 1:1:1 ratio to one of the following treatment groups: (1) BAT2506: 50 mg; SC (2) EU-Simponi: 50 mg; SC (3) US-Simponi: 50 mg SC	Healthy Chinese male volunteers N=375

2.3. Description of the product

Gotenfia (BAT2506) contains the active substance, golimumab, a recombinant, fully human immunoglobulin G1 (IgG1) monoclonal antibody that binds to both soluble and membrane-bound TNF-α, blocks TNF-α binding to its receptor (TNFR), and inhibits TNF-α mediated signalling. Golimumab belongs to the pharmacological class of TNF-α inhibitors.

2.4. Inspection issues

2.4.1. GMP inspection(s)

No inspection required.

2.4.2. GLP inspection(s)

No inspection required.

2.4.3. GCP inspection

Based on the review of clinical data, the need for a GCP inspection for the clinical trials included in

this dossier was not identified. No inspection required.

3. Quality aspects

3.1. Introduction

Golimumab, the active substance contained in Gotenfia, also referred to as BAT2506, is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (MAb) produced by a Chinese hamster Ovary (CHO) cell line with recombinant DNA technology. Golimumab forms high affinity, stable complexes with both the soluble (s) and transmembrane (tm) bioactive forms of human tumour necrosis factor (TNF)-α, which prevents the binding of TNF-α to its receptors.

The finished product is formulated with L-histidine, L-histidine monohydrochloride monohydrate, trehalose, polysorbate 80 (PS80) and water for injections.

Gotenfia is presented as a solution for subcutaneous (SC) injection in single use pre-filled syringe (PFS): 50 mg in 0.5 mL and 100 mg in 1 mL.

Gotenfia is a proposed biosimilar to the reference medicinal product Simponi (EMA/H/C/00992).

3.2. Active substance

3.2.1. General information

BAT2506 is a recombinant human IgG1κ MAb consisting of two heavy chains (HC) and two kappa light chains (LC) connected by inter-chain disulfide bonds. The relative molecular weight (MW) of the molecule is approximately 147 kDa not including the mass of the sugar moieties of the glycan structure. BAT2506 contains a single N-linked glycosylation site: asparagine 306 in the heavy chain. Post-translational modifications (PTMs) are presented and include C-terminal lysine truncation and pyroglutamate in the heavy chain.

Sufficient general information was provided.

3.2.2. Manufacture, characterisation, and process controls

Description of manufacturing process and process controls

The active substance is manufactured at Bio-Thera Solutions, Ltd., 155 Yaotianhe Street, Huangpu District, Guangzhou, Guangdong, China, 511356. All sites involved in manufacturing and controls of the active substance operate in accordance with EU GMP.

The active substance is manufactured using a recombinant CHO cell line. The manufacturing process of BAT2506 active substance includes upstream manufacturing (USP) and downstream manufacturing (DSP).

Overall, the manufacturing process for the active substance has been clearly defined and the purpose of each manufacturing step has been discussed in sufficient detail. The overall manufacturing process has been outlined in high-level flow-diagrams and separate descriptions. Critical process parameters (CPP) and in-process tests have been provided for each manufacturing step. The overall control strategy is further detailed and justified in CTD sections S.2.5 and S.2.6.

Reprocessing is not permitted during the manufacture of BAT2506 active substance.

Control of materials

Sufficient information on compendial and non-compendial materials (certificates of analysis and controls) as well as the preparation of cell culture media, feeds and buffers, is provided.

Source, History and Generation of the cell Substrate

The host cell line used for the production is derived from Chinese Hamster Ovarian cells

The host cell line was tested for identity and it was characterised to assure the absence of microbial contaminants, endogenous and adventitious agents

Overall, the description of the development of the host cell line was provided and it is considered sufficient.

Cell banking system, characterisation and testing

A Primary Cell Bank (PCB)/Master Cell Bank (MCB)/WCB system has been established by the Applicant. Cell banks viability and a test for identity were performed, and the cell bank was characterised to assure the absence of microbial contaminants, endogenous and adventitious agents.

Control of critical steps and intermediates

The parameter criticality assessment and classification are adequate. Proven acceptable ranges (PARs) are defined and justified by data presented. When the process parameters fall outside the PAR, an investigation is conducted and actions are taken to assess any potential negative impact on product quality. In the case of safety-related critical IPCs for unprocessed bulk, failure to meet the acceptance criteria would lead to batch rejection.

Overall, the process control strategy is deemed adequate.

Process Validation

Process validation of the BAT2506 active substance manufacturing process followed a 3-stage lifecycle approach, which included Process Design, Process Validation and Continued (Ongoing) Process Verification.

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

Manufacturing process development

Process characterisation

Overall, the process control strategy is found acceptable. Process characterisation studies have been sufficiently described.

The approach used for selecting and evaluating process parameters for both upstream and downstream unit operations demonstrates a structured and risk-based methodology, consistent with the principles outlined in ICH Q8(R2). For upstream processes, a decision tree was employed to assess each parameter's potential impact on product quality and process performance. This assessment was grounded on prior knowledge, including development studies, manufacturing experience, platform knowledge, literature, and the understanding of critical quality attributes (CQAs) as identified in the Product Risk Assessment.

In downstream processing, a severity scoring system was applied to each input parameter. This system considered both the main effect - defined as the parameter's potential impact on CQAs - and the interaction effect, which reflects the parameter's potential to influence or be influenced by other

parameters. The final severity score was calculated as the product of the highest main effect score and the highest interaction score. This score was then used to determine the minimum level of experimental complexity required for process characterisation.

This methodology offers several strengths. It ensures that parameters with the greatest potential to affect product quality are prioritised for further study, and it provides a transparent, reproducible framework for decision-making. The use of prior knowledge to inform risk assessments is in line with regulatory expectations and supports efficient development.

For the process characterisation of upstream and downstream processes, scale-down models (SDM) were used. Comparison between commercial scale and SDM is provided.

Process comparability

During the clinical stage of process development, the active substance facility was optimised and reconstructed and was requalified after the reconstruction activities were completed. In the period of reconstruction, all the critical and major process equipment were relocated to another manufacturing line in the same site. The batches manufactured during this period were used for process characterisation and were also included in the stability and similarity studies. After the reconstruction, active substance facility was fully re-qualified, BAT2506 PPQ and post PPQ active substance batches were manufactured. The process versions are overall comparable.

Process A was used to establish the end-of-production cell (EPC) bank, the interim reference standard (IRS) as well as to manufacture batches for preclinical toxicological studies. All critical studies have been conducted using material from the commercial scale. Initial EPC studies performed have been replaced by the determination of LIVCA, evaluated using process B2, which was used to establish the maximum allowed cell age for commercial manufacturing. This supports the reduced relevance of the initial EPC studies.

The IRS, manufactured using the smaller scale process, was used to calibrate the current PRS obtained from the larger scale, which is now used for routine control of BAT2506 and will be used for future working reference standard (WRS) establishment and characterisation. Both IRS and primary reference standard (PRS) meet the same release and stability specifications and exhibit the same product profile. Therefore, the reduced relevance of the IRS is justified, considering its demonstrated equivalence to the PRS.

The Applicant also mentioned that the initial preclinical toxicological studies which were performed using products manufactured at smaller scale are of less importance as they were submitted only as supportive information. The pivotal non-clinical studies to support this registration are the *in vitro* comparative pharmacology studies with product manufactured at larger scale. Also, the final evaluation of product's safety and efficacy was obtained from clinical studies which used the product manufactured at larger scale.

Therefore, the omission of detailed information on the smaller scale process from the dossier is considered appropriately justified.

Characterisation

Elucidation of structure and other characteristics

BAT2506 has been analysed using orthogonal, state-of-the-art analytical methods. Data on primary, secondary, and higher-order structures, post-translational modifications, biological and functional activity, purity, and immunochemical properties have been collected and evaluated.

Impurities

Product-related impurities

A discussion of the potential impurities in BAT2506 active substance has been provided. The impact of different levels of these impurities on biological activity was discussed in the dossier and supported by appropriate data. Product-related impurities are controlled as part of batch release testing and have been sufficiently characterised.

Process-related impurities

Process-related impurities are part of the routine release testing. For process-related impurities were analysed. In addition, elemental impurities in BAT2506 samples were evaluated, and no related risk was detected.

Nitrosamine assessment was discussed and the comprehensive risk analysis was. It was concluded that there is a negligible risk of the presence of nitrosamines in the active substance, which is endorsed.

3.2.3. Specification

Specification and justification of specification

Specifications for the active substance include control of identity, purity and impurities, potency and other general tests.

Considering the totality of the data, the active substance specifications are considered acceptable.

Analytical procedures and validation of analytical procedures

Use of compendial and non-compendial methods is described. The Applicant performed extensive testing demonstrating equivalence or superiority of their own analytical methods compared to the Ph. Eur. methods described in monograph 3103. Therefore, it is agreed that the Applicant's own methods should be maintained.

Comparison with golimumab Chemical Reference Standard (CRS) and Biological Reference Preparation (BRP) was performed. The use of BRP is implemented and described in the protocol for qualification of future primary reference standard material.

Batch analysis

Information of active substance batches including manufacturing date and use of batch was provided. The results in this section are presented alongside the current specification. All batches were released according to the specifications effective at the time of release; any differences were indicated in footnotes.

A summary of the evolution of active substance release specification was provided, along with information on which batches were used in clinical trials.

Reference standards or materials

A two-tiered system for reference material is foreseen. PRS, WRS and IRS development and qualification were adequately described. IRS was calibrated against US Simponi batch FGS3XMF. Comparison of currently established PRS with golimumab CRS and BRP was performed. The protocol for the qualification of future reference standard materials is considered acceptable. Calibration against the official Ph. Eur. BRP has been implemented, additionally to the calibration and comparison with the IRS, in the protocol for the qualification of future PRS**.**

Container closure system (CCS)

Description and choice of the CCS is considered acceptable. The primary container closure complies with Ph. Eur. and USP requirements.

Extractable and leachable studies for BAT2506 active substance were performed using representative bags.

3.2.4. Stability

A shelf life of 24 months is proposed for active substance when stored at -60±10°C. This claim is based on stability data from long-term conditions. Stability studies were conducted in the proposed CCS and in line with ICH guidelines. More data was submitted during the procedure and now the shelf life claim of 24 months (-60±10°C) is accepted.

Accelerated stability studies (5±3°C) have been performed. Slight trends were detected for stability sensitive purity attributes. So far, all quality attributes remained inside the specifications during the whole study duration. Studies in stressed conditions (25±2°C) were also shown, results indicate changes, however within the acceptance criteria.

In a freeze-thaw study freeze-thaw cycles (-60°C freezing for 24 h and then 25°C condition of rethawing for 24h), the quality of the product was basically not affected.

The stability of BAT2506 active substance was also tested under mechanical shaking (200 rpm, up to 48h protected from light): no detectible changes in the quality parameters were identified.

The post-approval stability protocol has been revised and now found acceptable.

Section 3.2.S.7.1 has been amended with the specification that BAT2506 active substance should be stored protected from light.

3.3. Finished medicinal product

3.3.1 Description of the product and pharmaceutical development

Components of the finished product

The finished product is formulated with L-histidine, L-histidine monohydrochloride monohydrate, trehalose, PS80 and water for injections. It is presented as a solution for SC injection in single use PFS with 2 strengths of 50 mg (in 0.5 mL) and 100 mg (in 1 mL).

The composition of Gotenfia (Table 3) is different to the one of EU-Simponi with two strengths 50 mg and 100 mg at the same concentration of 100 mg/mL. Sorbitol has been replaced with trehalose in Gotenfia. All excipients used for the manufacture of BAT2506 finished product are of compendial grade. No excipients of human or animal origin or novel excipients are used.

A formulation study was performed. Data have been provided to support the change in formulation (replacing sorbitol with trehalose and a slight increase in PS80 concentration). The information is considered sufficient to guarantee the quality of the finished product.

The Gotenfia finished product does not include overages. Overfills are used to guarantee the extractable volume are met for the required doses, which is considered adequate.

Table 3: – Composition of BAT2506 finished product

Component	Amount per mL	Amount per PFS		Function	Quality Standard
		50 mg/0.5 mL[1]	100 mg/1mL[2]		
BAT2506	100 mg	50 mg	100 mg	Active ingredient	In-house standard
L-Histidine	0.28 mg	0.14 mg	0.28 mg	Buffer, pH adjuster	USP/NF, Ph Eur.
L-Histidine monohydrochloride monohydrate	1.72 mg	0.86 mg	1.72 mg	Buffer, pH adjuster	USP/NF, IPh Eur.
Trehalose	85mg	42.5mg	85mg	Stabilizer	USP/NF, Ph Eur.
Polysorbate 80	0.20 mg	0.10 mg	0.20 mg	Surfactant	USP/NF, Ph. Eur.
Water for injections	q.s. to 1 mL	q.s. to 0.5 mL	q.s. to 1 mL	Solvent	USP/NF, Ph. Eur.
[1] Overfill to a target volume of 0.50-0.54 mL to guarantee the delivery of the labelled volume. [2] Overfill to a target volume of 1.00-1.04 mL to guarantee the delivery of the labelled volume.					

Manufacturing process development

The development of the manufacturing process of Gotenfia started with a pilot process and was subsequently validated at commercial scale. The manufacturing processes for the two strengths differ only in the filling volume (1 mL vs 0.5 mL). In summary, the pilot and commercial batches are considered comparable.

Container closure system

The Gotenfia finished product CCS consists of a PFS. An elemental impurity assessment in line with ICH Q3D revealed no concern. A Notified Body Opinion (NBOp) was provided confirming full compliance of the pre-filled syringe with the relevant General Safety and Performance Requirements (GSPRs).

Microbial attributes

The microbiological control strategy of BAT2506 finished product is adequate.

Compatibility

Compatibility of Gotenfia with its primary CCS was evaluated. The indicators of the finished product passed the relevant tests.

3.3.2. Manufacture of the product and process controls

Manufacturing process and controls

The Gotenfia finished product manufacturing takes place at Bio-Thera Solutions, Ltd site located at 155 Yaotianhe Street, Huangpu District, Guangzhou, Guangdong, China, 511356. The manufacturer responsible for EU release is STADA Arzneimittel AG, Stadastrasse 2–18, 61118 Bad Vilbel, Germany. All sites involved in manufacturing and controls of the finished product operate in accordance with EU GMP.

The batch formulas of Gotenfia finished product for the 50 mg and 100 mg strength have been sufficiently provided.

The Gotenfia finished product manufacturing process consists of thawing of active substance, active

substance pooling, two steps of sterile filtration, aseptic filling, 100% inspection and release sampling of filled syringes. The filled syringes are assembled with a plunger-rod and labelled by automatic syringe labelling line, and then automatically inserted into the needle safety device (NSD). A flow-diagram including material inputs, process parameters and IPCs has been provided.

A brief description of each step has been included, which is considered adequate. IPCs are indicated and the processing times and storage conditions are stated.

Reprocessing of a manufacturing step is not permitted.

The control strategy has been briefly described. Control strategy parameters CQA, CPP, IPC have been defined. OOSs are reported when the results exceed its acceptance criteria. In this case, a thorough investigation is carried out in accordance with internal procedures taking into consideration also the criticality of the affected IPC and the stage inside the process. Corrective and preventive measures are taken when necessary, to avoid the recurrence.

Process validation

PPQ batches were included into the process validation. The batches cover the stated batch sizes in Section P.3.2. The data provided including additional validation tests complied with the predefined acceptance criteria. The assembly and labelling as well as the secondary packaging process were sufficiently validated. Filling interventions were performed. After the hold-times the examination showed no drying on the needle tips and no impact on the quality (filling volume or visible particles) of the finished product.

A filter validation study demonstrated sufficient bacterial contamination retention as well as compatibility with finished product including tubing and storage bags. Extractable and leachable studies were performed. No extractable/leachable (including elemental impurities) above a value of toxicology concern was identified taking the calculated permitted daily exposure (PDE) into account.

Media fills have been performed, which support the conclusion that the line is capable to aseptically fill a sufficient amount of PFS for Gotenfia finished product.

Sterilisation of equipment and packaging components is considered sufficient.

Shipping qualification is based on verification of the transport equipment to keep the required temperature range. Given the representative shipping equipment, the information provided can be accepted.

3.3.3. Product specification

Specification and justification of specification

Specifications for the finished product include control of identity, purity and impurities, potency and other general tests.

The specifications have been set based the principles of ICH Q6B. Furthermore, for some acceptance criteria the limits from the EU reference medicinal product have been considered. During the procedure, the Applicant was asked to tighten certain acceptance criteria. The finally assigned acceptance criteria are considered acceptable.

Analytical procedures and validation of analytical procedures

The methods used for finished product testing are either compendial test methods or are identical to the methods used for active substance testing, with the exception of several methods. The test methods are sufficiently described.

Analytical procedures utilised in the specification tests of the finished product of BAT2506 included both compendial and non-compendial methods which are described, discussed and assessed both in the active substance and finished product sections.

Compendial methods are based on respective Ph. Eur. monographs.

Non-compendial analytical methods for the finished product are mainly same than those used for active substance.

Batch analyses

Batch release data are provided for BAT2506 finished product manufactured with the commercial manufacturing process at Bio-Thera Solutions, Ltd, China. All test results are within specifications.

Characterisation of Impurities

Concerning potential finished product impurities reference is in general made to corresponding active substance section, which is considered adequate as no new impurities are expected. All impurities were discussed in a tabular format in this section and the data evaluated during development and PPQ batch data were mentioned. The overall control of impurities is considered acceptable.

A risk assessment concerning nitrosamines in line with the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products 03 August 2020 EMA/409815/2020 has been provided. No risk has been identified, which is endorsed.

A risk assessment of elemental impurities of BAT2506 finished product was conducted. The levels of all elements complied with the recommendations from ICH Q3D (30% of PDE), hence they did not possess any safety risk. This is endorsed.

Reference standard and materials

For information on reference standards reference is made to corresponding active substance section, which is considered adequate, as the same materials are used for active substance and finished product. The information provided is considered sufficient.

Container closure system

The BAT2506 finished product CCS consists of a Type I glass barrel with staked needle where the stainless steel 27 Gauge, ½ inch needle is fixed to the syringe barrel with an adhesive, a rubber plunger stopper, and a rigid needle shield (RNS) composed of elastomer that functions as sterility barrier and an outer rigid shield that enhances the removal of the needle-shield. The glass barrel and stopper are in immediate contact with the finished product and comply with applicable compendial requirements. The quality control testing is sufficiently described. Certificates of analysis have been provided for the PFS with needle and needle cover as well as the rubber stoppers used. The technique used for sterilisation have been stated. Sterility assurance levels (SAL) of 10-6 are stated. Residual EO, ethylene chlorohydrin (ECH) and ethylene bromohydrin (EBH) are tested according to ISO 10993-7:2008 and below acceptance levels.

Overall, 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.

3.3.4. Stability of the product

The Applicant claimed a 2-year shelf-life for the finished product when stored at 2°C-8°C.

In line with ICH Q5C the batches were tested under long-term (5±3℃), accelerated (25 ± 2°C) and stress (40±2°C) conditions. For products with proposed shelf-life of greater than 1 year, the studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter. The batches were tested in the identical container closure system used for commercial product as described in section P.7. Furthermore, a photostability study and mechanical shaking (200 rpm) study were performed. Data were provided for the BAT2506 50mg (100mg) finished product batches. The analytical methods used are considered sufficiently sensitive and able to detect the main degradation pathways of BAT2506 finished product.

A shelf life of 24 months, protected from light, is proposed for the finished product at long-term conditions.

The results of the photostability study showed that the BTA2506 finished product in the PFS is photosensitive. The packaging material of the marketing pack is expected to offer sufficient protection against light stress.

The mechanical stress study showed that shaking does not affect the quality of the finished product.

The provided post-approval stability protocol is considered sufficient.

Gotenfia may be stored at temperatures up to a maximum of 25°C for a single period of up to 15 days, but not exceeding the original expiry date printed on the carton. Once Gotenfia has been stored at room temperature, it should not be returned to refrigerated storage. Gotenfia must be discarded if not used within the 15 days of room temperature storage.

3.3.5. Post-approval change management protocol

The Applicant provided a post-approval change management protocol (PACMP) aiming to introduce a 50 and 100 mg prefilled pen presentation.

The PACMP is considered acceptable.

3.3.6. Biosimilarity

The biosimilarity exercise for BAT2506 followed the recommendations as laid down in EMA/CHMP/BWP/247713/2012.

The main analytical comparability (biosimilarity) study is described in sufficient detail. A risk assessment identified a comprehensive quality attribute list tested during the study. A tiered approach (Tier 1-3) has been used for the comparison of quality attributes.

Primary structure

To investigate the analytical similarity of the primary structures of BAT2506 and Golimumab, several complementary characterisation methods were used, employing state-of-the-art analytical tools, such as high precision and accuracy mass spectrometry for protein sequence, and high-resolution chromatography.

Higher order structure

Higher-order-structure was analysed by Fourier transform infrared (FT-IR), near and far UV circular dichroism (CD). In summary no significant differences between BAT2506 batches and EU- and US-Simponi batches were reported.

Purity

Particles and aggregates were compared using dynamic light scattering (DLS), SEC-MALS, and sedimentation velocity analytical ultracentrifugation (SV-AUC).

Protein concentration

The protein concentration of the BAT2506 batches lies within the QR of EU-Simponi. However, there is a clear higher population seen. The protein concentration is controlled at release and the acceptance criteria are considered to sufficiently guarantee that there will be no difference in efficacy or safety between both products.

Biological & Functional Activities

The Fab-mediated activities of golimumab were investigated using several binding and cell-based potency assays. Binding to soluble and membrane bound TNFa was shown by ELISA and SPR techniques. Furthermore, the inhibition of IL-8 secretion or apoptosis in HUVEC and U937 cells, respectively, were compared.

Comparative Stability Study Data

The degradation profiles of BAT2506 and EU-Simponi were compared using accelerated and forced temperature, as well as stress (photostability, low, pH, high pH and oxidation) studies.

Considering the totality of the data summarised in Tables 4 and 5, biosimilarity with Simponi (EMEA/H/C/992) is considered demonstrated from a quality point of view. Differences identified during the biosmilarity exercise were adequately justified and do not impact the biosimilarity conclusion.

Table 4: – Summary of results of biosimilarity assessment (structure, purity, and general properties)

Category	Attribute /Analysis parameter		Conclusion
Primary structure	Mass(LC-MS)	Intact masses (-Lys*2, G0F/G0F,Da)	Similar
		Intact masses (-Lys*2, G0F/G1F,Da)	Similar
		Intact masses (-Lys*2, G1F/G1F,Da)	Similar
		Intact deglycosylated masses(-Lys*2,Da)	Similar
		Reduced light chain(Da)	Similar
		Reduced heavy chain(-Lys, G0F, Da)	Similar
		Reduced heavy chain(-Lys, G1F,Da)	Similar
		Deglycosylated heavy chain(-Lys, Da)	Similar
	Peptide Mapping (LC-MS/MS)	Reduced peptide mapping	Similar
		Primary amino acid sequence coverage, peptide assignment, N/C-terminal sequencing	Similar
		Pyroglutamic Acid E N-TERM(%)	Similar
		Pyroglutamic Acid Q N-TERM (%)	Similar
		C-terminal Lysine truncation	Similar
		Oxidation HC M34 (%)	Similar

Category	Attribute /Analysis parameter		Conclusion
		Oxidation HC M113(%)	Difference
		Oxidation HC M261(%)	Difference
		Oxidation HC M437(%)	Difference
		Deamidation Succinimide N LC N93(%)	Difference
		Deamidation Succinimide N HC N43(%)	Difference
		Deamidation Succinimide N HC N324(%)	Similar
		Deamidation Succinimide N HC N393(%)	Similar
		Deamidation LC N93(%)	Difference
		Deamidation LC N138(%)	Similar
		Deamidation HC N43(%)	Difference
		Deamidation HC N324(%)	Similar
		Deamidation HC N393 or N398(%)	Similar
		Deamidation HC N443(%)	Similar
		Glycosylation N HC N306(%)	Similar
		Specific sites Deamidation Content LC N93 Deamidation (%)	Difference
		Specific sites Deamidation Content HC N43 Deamidation (%)	Difference
		Specific sites Deamidation Content HC N43 isoAPS (%)	Difference
		Non-reduced peptide mapping and disulfide bonds	Similar
	DTNB-Ellman	Free thiol content (mol/mol)	Similar
	Glycosylation Heterogeneity (HILIC-HPLC)(LC-MS/MS)	Glycosylation site	Similar
		%Galactosylation	Similar
		%High mannose	Difference
		%Afucosylation	Similar
		%Sialylation	Difference
	Free sialic acid by DMB-RP-UPLC	Sialic Acid-NGNA content (mol/mol)	Difference
		Sialic Acid-NANA content (mol/mol)	Difference
	Glycation by LC-MS	%Glycation	Difference
	Isoelectric point(cIEF)	Isoelectric profile	Similar
		pI of main peak	Similar
Higher Order Structure	Secondary Structure: FTIR	FTIR profile	Similar
	Secondary Structure:CD	Far UV CD profile	Similar
		Helix (%)	Similar
		Antiparallel (%)	Similar
		Parallel (%)	Similar
		Beta-Turn (%)	Similar
		Random Coil (%)	Similar

Category	Attribute /Analysis parameter		Conclusion
	Tertiary structure:CD	Near UV CD profile	Similar
	DSC	DSC profile	Similar
		T_{m1} (°C)	Similar
		T_{m2}(°C)	Similar
		T_{m3}(°C)	Similar
	DLS	Diameter (nm)	Similar
	SEC-MALS	Profile	Similar
		Molar mass of main (kDa)	Similar
		Molar mass of aggregate(kDa)	Similar
	SV-AUC	Average of sedimentation coefficient(c(s)(AU/S))	Similar
		Average of monomer percentage (%)	Similar
Product-related substances	SEC-HPLC	%HMW	Difference
		%Main peak	Similar
		%LMW	Similar
		Profile	Similar
	nrCE-SDS	%Pre peaks	Difference
		%Main peak	Difference
		Profile	Similar
	rCE-SDS	%NGHC	Difference
		%LC+HC	Difference
		Profile	Similar
	IEC-HPLC	%Acidic region	Difference
		%Main peak	Difference
		%Basic region	Similar
		Profile	Similar
	IEC-HPLC-CpB	%Acidic region	Difference
		%Main peak	Difference
		%Basic region	Difference
		Profile	Difference
General Properties	Protein concentration (mg/mL)		Similar

Table 5: – Summary of results of biosimilarity assessment (biological and functional activities)

Category	Quality Attribute/Parameter		Conclusion
Fab-mediated Activities	Binding to sTNFα (ELISA)	Relative binding activity (EC_{50}) (%)	Similar
	Neutralizing activity against sTNFα	Relative activity (EC_{50}) (%)	Similar
	Binding activity to tmTNFα (cell-based ELISA)	Relative binding activity (EC_{50}) (%)	Similar
	Inhibition of sTNFα-induced apoptosis in U937 cells	Relative activity (EC_{50}) (%)	Similar
	Binding kinetics to sTNFα (SPR)	On rates Ka(1/Ms) Off rates Kd (1/s) Equilibrium Constant K_D (M)	Similar
	Inhibition of sTNFα-induced the secretion of IL-8 in HUVEC	Relative activity (EC_{50}) (%)	Similar
Fc Binding Affinity	FcRn binding (BLI)	Relative Affinity (K_D) (%)	Similar
	FcγRIa binding (SPR)	Affinity (K_D)	Similar
	FcγRIIa(131H) binding (BLI)	Affinity (K_D)	Similar
	FcγRIIa(131R) binding (BLI)	Affinity (K_D)	Similar
	FcγRIIb binding (BLI)	Affinity (K_D)	Similar
	FcγRIIIa(158V) binding (BLI)	Relative Affinity (K_D) (%)	Similar
	FcγRIIIa(158F) binding (BLI)	Relative Affinity (K_D) (%)	Similar
	FcγRIIIb binding (BLI)	Affinity (K_D)	Similar
	C1q binding (BLI)	Relative Affinity (K_D) (%)	Similar
Fab and Fc-mediated Characterization	ADCC activity (Using tmTNFα-overexpressing CHO as Target cells)		Difference
	ADCC activity (Using LPS- stimulated PBMCs from healthy donors as Target cells)		Similar
	CDC activity (Cytotoxicity assay)		Similar

3.3.7. Adventitious agents

TSE compliance

The MCB of BAT2506 is free from TSE-risk substances and the active substance is produced in a serum-free culture medium. In addition, all materials used are obtained from approved vendors. In summary, compliance with the TSE Guideline is sufficiently demonstrated.

Virus safety

The fermentation process of BAT2506 is in a serum-free medium. This minimises a possible contamination of adventitious viruses. The cells used for production of BAT2506 have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB, with the exception of intracellular A-type retroviral particles. However, this is acceptable since there is sufficient capacity within the manufacturing process of BAT2506 for reduction of this type of viral particles. The purification process of BAT2506 includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated. During the manufacture of BAT2506 active substance, column chromatography resins are used during purification and reuse has been investigated. Model viruses used in the virus clearance study are mentioned in Table 6. In summary, virus safety of BAT2506 is sufficiently demonstrated.

Table 6: – Model viruses used in the virus clearance study

Virus	Virus Family	Envelope	Genome	Size (nm)	Shape
MVM (Minute Virus of Mice)	Parvoviridae	No	DNA	18–22	Icosahedral
X-MuLV (Xenotropic Murine Leukaemia Virus)	Retroviridae	Yes	RNA	80–130	Spherical
PrV (PseudoRabies Virus)	Herpesviridae	Yes	DNA	150–200	Spherical
Reo-3 (Reovirus type 3)	Reoviridae	No	RNA	60–80	Icosahedral

Overall, adventitious agents safety is considered sufficiently demonstrated.

3.4. Discussion and conclusion on chemical, pharmaceutical and biological aspects

Module 3 provided in support of the MAA for Gotenfia is in general considered adequate. Relevant information is included into the specific sections.

The manufacturing process for active substance and finished product has been adequately described and validated.

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the active substance and finished product.

The control strategy for active substance and finished product is appropriate. A NBOp was provided for the PFS confirming full compliance with the relevant GSPRs. The finished product shelf life of 24 months (2°C-8°C), protected from light, is acceptable.

The analytical comparability study is considered sufficient and confirms biosimilarity with Simponi (EMA/H/C/00992).

Recommendations not impacting the benefit/risk of Gotenfia have been agreed by the Applicant (see below).

Overall, the quality of this product is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Gotenfia is considered approvable from the quality point of view.

3.5. Recommendation(s) for future quality development

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

4. Non-clinical aspects

4.1. Introduction

Gotenfia (company code: BAT2506) is a recombinant human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human tumor necrosis factor alpha (TNF-α). This interaction prevents the binding of TNF-α to its receptors, thereby inhibiting the biological activity of TNF-α (a cytokine protein).

Only *in vitro* studies were provided which do not need to be conducted under GLP.

4.2. Analytical methods

The *in vitro* test methods used encompass ELISA, SPR, and several cell-based assays.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

In vitro primary pharmacodynamic studies comparing binding and functional activity were conducted as part of a comparative analytical assessment. The *in vitro* pharmacodynamic study data were included in the quality part of the dossier and evaluated in the quality assessment report (see section 4.).

In vivo primary pharmacodynamics studies have been conducted for the comparability assessment to meet regulatory requirements outside of the EU and submitted upon request to CHMP during the assessment. The efficacy of BAT2506 was assessed in Tg197 transgenic mouse model of arthritis. The study showed that the intraperitoneal administration of both BAT2506 and EU-Simponi reduced the symptoms of arthritis. The effects observed included body weight increase, reduction of *in vivo* and histopathological arthritis pathology. It was concluded that similar therapeutic efficacy between BAT2506 and EU-Simponi were shown in this study.

4.3.1.2. Secondary pharmacodynamics

No secondary pharmacodynamics studies were conducted and are not required.

4.3.1.3. Safety pharmacology

Cardiovascular function was assessed as part of a 4-week repeat dose toxicity study in cynomolgus monkeys subcutaneously administered BAT2506 (3, 10, 50 mg/kg) or EU-Simponi (10 mg/kg). No adverse effects of either test article were observed in safety pharmacology evaluations for electrocardiogram, body temperature and blood pressure.

4.3.1.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted and are not required.

4.3.2. Pharmacokinetics

A single-dose pharmacokinetic study was conducted in cynomolgus monkeys to compare the PK profile of BAT2506 and Simponi after a single subcutaneous dose of 3 mg/kg or 10 mg/kg. PK parameters evaluated included $t_{½}$, C_{max}, $AUC_{(0–216\ h)}$, $AUC_{(0–t)}$, AUC_{inf}, T_{max}, volume of distribution (V), clearance (Cl), and mean residence time (MRT). Plasma concentration data demonstrated that systemic exposure increased in an approximately dose-proportional manner for both BAT2506 and Simponi. Similarity assessment was based on C_{max} and $AUC_{(0–t)}$. The calculated BAT2506/Simponi ratios for mean C_{max} and $AUC_{(0–t)}$ within the same dose groups (BAT2506 vs EU-authorised Simponi or US-authorised Simponi) indicated comparable drug exposure. Overall, the PK profile of BAT2506 was similar to that of Simponi.

4.4. Toxicology

4.4.1. Single-dose toxicity

No single dose toxicity was conducted.

4.4.2. Repeat-dose toxicity

A repeat-dose toxicity was conducted in cynomolgus monkeys to compare the toxicity profile of BAT2506 and EU-Simponi. This was a 4-week subcutaneous injection toxicity study with a 6-week recovery period in cynomolgus monkeys.

Five groups of cynomolgus monkeys (n = 5/sex/group) received subcutaneous injections of BAT2506 at 3, 10, or 50 mg/kg, EU-authorised Simponi at 10 mg/kg, or saline (control), administered twice weekly for 4 weeks (9 doses total), followed by a 6-week recovery period. Toxicokinetic analysis showed that mean C_{max} and $AUC_{(0–t)}$ increased with dose for BAT2506, with no sex-related differences. Comparison of the 10 mg/kg BAT2506 group with the 10 mg/kg EU-authorised Simponi group indicated similar exposures (C_{max} and $AUC_{(0–t)}$).

No mortality or moribundity occurred and no treatment-related effects were observed on food consumption, blood oxygen saturation, ophthalmology, urinalysis, cytokines, serum immunoglobulins, or serum complement. For other parameters, some statistically significant differences versus controls were noted, but changes were minimal and within normal ranges. Histopathology revealed no BAT2506 or Simponi-related macroscopic or microscopic findings, and no changes in organ weights, at either the end of dosing or after recovery period. No treatment-related effects were observed in electrocardiogram (ECG), body temperature, blood pressure, or at injection sites.

4.4.3. Genotoxicity

No genotoxicity studies were conducted and are not required for biosimilars.

4.4.4. Carcinogenicity

No carcinogenicity studies were conducted and are not required for biosimilars.

4.4.5. Developmental and reproductive toxicity

No developmental and reproductive toxicity studies were conducted and are not required for biosimilars.

4.4.6. Toxicokinetics and exposure margins

The toxicokinetic profile of BAT2506 and Simponi was also compared in a repeat-dose toxicity study where BAT2506 and Simponi were subcutaneously administered to cynomolgus monkeys twice a week for 4 consecutive weeks, followed by a 6-week recovery period (see section 5.4.2.).

4.4.7. Local tolerance

The local tolerance of BAT2506 was evaluated as part of the 4-week repeat dose toxicity study. No abnormal injection site reactions including swelling, fever, oedema, erythema, or ulcers were observed in any group.

4.4.8. Other toxicity studies

The immunogenicity of BAT2506 was evaluated as part of the 4-week repeat dose toxicity study. No anti-drug antibodies (ADAs) were detected prior to dosing and in the BAT2506 high-dose group. However, confirmed positive ADAs were observed in the BAT2506 low- and mid-dose groups and in the Simponi group. Repeated administration of BAT2506 at lower doses appeared to induce ADA formation, with incidence and titers increasing with repeated dosing. At the end of the recovery period, ADAs remained detectable in the Simponi group and in BAT2506 low- and mid-dose groups, with no significant decrease in incidence or titer. The highest ADA incidence and titers occurred in the BAT2506 low-dose group, possibly due to drug-induced immunosuppression at higher doses or interference with ADA detection by high circulating drug concentrations. ADA incidence and titers were comparable between the BAT2506 mid-dose and Simponi groups (both 10 mg/kg).

4.4.9. Ecotoxicity/environmental risk assessment

The applicant provided a justification for not providing an environmental risk assessment (ERA) for golimumab:

Golimumab is a monoclonal antibody and is classified as a protein, an ERA is not required for this medicinal product in accordance with Art 8(3) of Directive 2001/83/EC and the corresponding guideline (EMEA/CHMP/SWP/447/00 Rev.1).

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

To demonstrate biosimilarity between Gotenfia (BAT2506) and EU-Simponi a comprehensive panel of *in vitro* binding and functional assays were conducted. The *in vitro* pharmacodynamics study data were included in Module 3 of the dossier and evaluated in the quality assessment report (see section 4.).

Secondary pharmacodynamics and pharmacodynamic drug interaction studies were not conducted.

This is acceptable as such studies are not required under EU guideline for biosimilar development (EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1; 2014); the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev 1)).

In vivo primary pharmacodynamics, pharmacokinetics/toxicokinetics and toxicology studies were conducted to meet regulatory requirements outside the EU. While such studies are not required under EU guidelines for biosimilar development, the applicant has provided, upon request, the relevant study reports along with a discussion of their relevance to the safety evaluation of BAT2506. The Tg197 transgenic mouse study supported similarity in biological activity and efficacy between BAT2506 and EU-Simponi. Two cynomolgus monkey studies assessed pharmacokinetics and toxicity comparability. Overall, no major pharmacokinetic, immunogenic, or toxicological differences were identified between BAT2506 and EU-Simponi. The studies did not reveal any safety concerns that would require attention or affect the conclusions of the assessment. These data are consistent with the conclusion of biosimilarity between BAT2506 and EU-Simponi from a non-clinical aspect.

In vitro assays are considered paramount for the non-clinical biosimilar comparability exercise since they are more specific and sensitive in detecting differences between the biosimilar and the reference medicinal product. The functionality *in-vitro* assays covered the relevant modes of action claimed in the indications and used representative materials from both BAT2506 and Simponi. The detected differences during the assessment did not warrant resolution through additional non-clinical *in vivo* data. Therefore, no additional non-clinical *in vivo* data - whether PD, PK or toxicology - were deemed necessary. This is also in line with the EMA Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

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, it is agreed that golimumab is not expected to pose a risk to the environment and that ERA studies are not considered needed in line with the EMA guideline (EMEA/CHMP/SWP/4447/00 Rev 1- Corr. *).

4.5.2. Conclusions

The non-clinical package is considered in line with the EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1; 2014) and the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev 1). The similarity between products is discussed in the Quality assessment report (see section 4). No concerns were raised from the non-clinical perspective.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product EU-Simponi.

5. Clinical aspects

5.1. Introduction

5.1.1. GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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.

Based on the review of clinical data CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 3.4.3.).

5.1.2. Tabular overview of clinical trials

Table 3: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 1					
BAT-2506-001-CR (pivotal)	RD, DB, Single-dose, Parallel Two-arm study	Single SC administration of 50 mg BAT2506 or EU- Simponi	Healthy male Chinese volunteers	Primary: To compare the pharmacokinetic (PK) similarity between BAT2506 and Simponi after a single subcutaneous injection in healthy Chinese male subjects. Secondary: To evaluate the safety and immunogenicity of BAT2506 and Simponi in healthy Chinese male subjects.	182 randomised and treated BAT2506: 91/87 EU-Simponi: 91/89
BAT-2506-003-CR (supportive)	RD, DB, Single-dose, Parallel Three-arm study	Single SC administration of 50 mg BAT2506, US-Simponi or EU- Simponi	Healthy male Chinese volunteers	Primary: To compare the similarity of pharmacokinetics (PK) between BAT2506 Injection and Simponi (EU-approved and US-licensed) after a single subcutaneous injection in healthy Chinese male subjects Secondary: To evaluate the safety, tolerability and immunogenicity of BAT2506 Injection with EU approved Simponi and US-licensed Simponi in healthy Chinese male subjects	369 randomised and treated BAT2506: 124/113 EU-Simponi: 127/116 US-Simponi: 124/116
Phase 3 Therapeutic confirmatory					
BAT-2506-002-CR (pivotal)	A Multicenter, DB, RD, Parallel-group Study for 52 weeks	50 mg Q4W SC BAT2506 or EU-Simponi or Simponi→BAT2506 (24weeks Simponi followed by BAT2506 for 24 weeks)	Subjects with active PsA	Primary: To demonstrate the equivalence of BAT2506 and Simponi on American College of Rheumatology (ACR) 20 response in subjects with active PsA Secondary: To compare the efficacy of BAT2506 with Simponi on additional efficacy parameters in subjects with active PsA • To compare the PK of BAT2506 with Simponi in subjects with active PsA • To compare PD parameter of BAT2506 with Simponi in subjects with active PsA • To compare the safety of BAT2506 with Simponi in subjects with active PsA • To compare the immunogenicity of BAT2506 with Simponi in subjects with active PsA • To assess safety and immunogenicity following transition from Simponi to BAT2506	704 randomised and treated BAT2506: 351/347 (TP1) EU-Simponi: 179/174 Simponi→BAT2506: 174/167

RD = randomised; DB = double blind; SC = sub-cutaneous; Q4W = every 4 weeks

5.2. Clinical pharmacology

5.2.1. Methods

ELISA Assay for the Quantitation of BAT2506 and Simponi in Human Serum

The method used by the applicant was validated. hTNFα-His was coated and bound on the solid phase 96-well plate and incubated overnight. Serum samples containing BAT2506 and Simponi were added on the second day after blocking. BAT2506 and Simponi in the serum sample specifically bound to the coated antigen, and then human anti- Simponi Horseradish Peroxidase (HRP) was added for detection, and finally, a solid phase carrier-BAT2506 and Simponi-enzyme complex was formed on the final plate, and then the corresponding substrate TMB (3,3′,5,5′-Tetramethylbenzidine) of HRP enzyme added. The colour intensity was positively correlated with the content of BAT2506 and Simponi by measuring the OD 450nm/620nm value with a microplate reader.

A full method validation was conducted.

ECL method using the Mesoscale Discovery (MSD) Platform for the Screening, Confirmatory, and Titration of anti-drug antibodies (ADA) against Simponi and BAT2506 in human serum

The detection of anti-Simponi/BAT2506 antibodies in human serum in the clinical studies BAT- 2506-001, BAT-2506-002 and BAT-2506-003 was achieved using an ADA assay. The assay used an affinity capture elution ECL immunoassay implemented using the Meso Scale Discovery (MSD) detection platform.

All samples underwent screening analysis. Samples with initial screening values ≥ the PSCP (cut point) were considered potential positive samples. Confirmation Assay was performed to assess the specificity of the positive screen samples and ensure accurate identification of true positive cases. For the confirmed positive samples, the titration assay was conducted to estimate the level of antibodies present.

The samples were subjected to acid treatment and buffer was added to neutralise them. Then, the neutralisation samples were added to a diluent plate and Sulfo-tag-BAT2506 added. After incubation the samples were then transferred to pre-blocked MSD plate. The ADA complexes were captured and fixed on the plate. After incubation, the plate was washed, and MSD read buffer was added to each well. The plate was read on a plate reader. The signal produced was proportional to the amount of anti-BAT2506/Simponi antibody present in the serum.

A full method validation was conducted.

ECL-based assay for the Detection of Neutralising Anti-BAT2506 and Anti- Simponi Antibodies in Human Serum using the Mesoscale Discovery (MSD) Platform

The detection of neutralising antibodies against BAT2506/Simponi in human serum in the clinical studies BAT-2506-001, BAT-2506-002 and BAT-2506-003 was achieved using a validated method.

Samples were subjected to acid treatment and captured by Sulfo-tag-BAT2506/ Simponi, forming the complexes. After incubation, the antibody complex was added to the TNF-α coated MSD plate. TNF-α protein, already pre-coated onto the plate, bound to Sulfo-tag labelled BAT2506/ Simponi, generating the ECL response. The plate was washed to remove any non-specific bound complexes and read buffer was added to each well of the plate. Subsequently, the plate was read on plate readerBinding of free Sulfo-tag BAT2506 to the TNF-α protein generated a luminescent signal, and the presence of NAb reduced the signal.

A full method validation was conducted.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The clinical development program for of BAT2506 consisted of two PK studies to compare the PK of BAT2506 with Simponi in healthy subjects (one is a supportive PK study in healthy volunteers as required by the US FDA) and one pivotal phase 3 efficacy study in subjects with psoriatic arthritis (PsA). Clinical PK and immunogenicity were investigated in all 3 studies. A population PK analysis was conducted with the pooled PK sampling data from 3 clinical trials of BAT2506 to further illustrate the PK comparability between BAT2506 and Simponi. An additional pharmacodynamic endpoint (CRP) was investigated in the phase 3 study only.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

A population PK analysis using a non-linear mixed effect modelling approach was conducted with the pooled PK sampling data from the 3 clinical trials BAT 2506-001-CR, BAT-2506-002-CR, and BAT-2506-003-CR. Modelling was done using NONMEM, version 7.5.0. Calculations and further statistics as well as exposure simulations were done using the software R. The model analysed typical PK parameters and inter-individual variabilities of BAT2506 and Simponi. Furthermore, it evaluated potentially relevant covariates and compared the magnitudes of these factors as well as simulated exposures between these products. The model compared AUC_{ss}, AUC_1, $C_{max,ss}$, $C_{min,ss}$, $C_{max,1}$, $C_{min,1}$ as relevant exposure metrics between BAT2506 and Simponi.
The following covariates were analysed for inclusion in the model:

Age, sex, body weight, body mass index, body surface area, race, albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, creatinine, creatinine clearance, glomerular filtration rate, white blood cell count, c reactive protein, health status (healthy vs. patient), smoke history, drinking, drug, anti-drug antibody (ADA, positive vs negative), combination with methotrexate.

The final model utilised to describe the data was a one compartment model with first order absorption and elimination from the central compartment. The main parameters describing the model where the volume of the central compartment (Vc) and the absorption rate constant (Ka). The first-order conditional estimation with interaction (FOCEI) has been chosen and the covariates were selected using a forward-inclusion-backward-elimination approach. For this the significance levels of $p < 0.01$

and p < 0.001 where used, respectively.

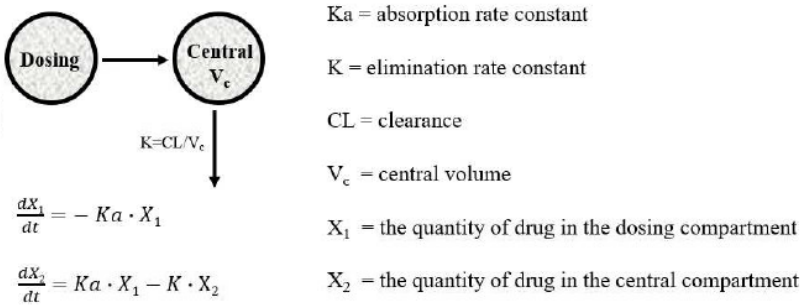
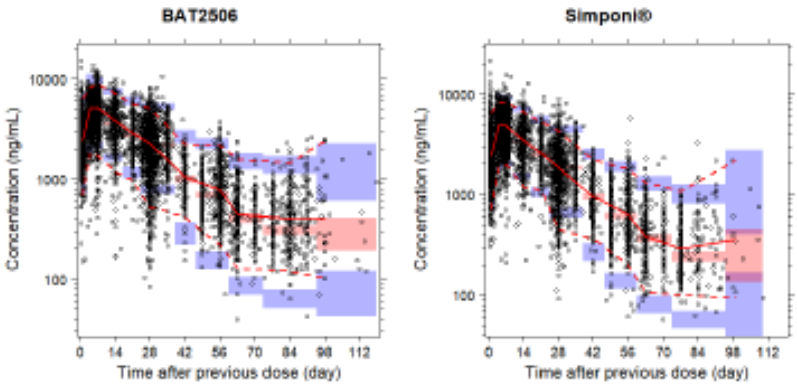


Figure *1*: Population PK model structure

The model was evaluated via of goodness of fit plots for the population as a whole as well as for each individual, pcVPC, NPC, Bootstrap, and shrinkage.
Body weight, health status, anti-drug antibodies, creatine clearance, white blood cell count and C reactive protein were identified as significant covariates on clearance, while body weight and health status were shown to be a significant influence on central volume.
A summary of the parameters of the final population PK model can be found below:

Table 4: Summary of final population PK parameters

Parameter	Parameter Description	Population Estimate (RSE%)	Inter-Individual Variability (RSE%)
$exp(\theta_1)$	Clearance of BAT2506, CL/F(L/day)	0.328 (2.06%)	37.1 (2.26%)
$exp(\theta_2)$	Clearance of Simponi®, CL/F (L/day)	0.345 (2.12%)	
$exp(\theta_3)$	Central volume of BAT2506, V_c/F (L)	9.15 (1.81%)	34.2 (2.94%)
$exp(\theta_4)$	Central volume of Simponi®, V_c/F (L)	9.86 (1.87%)	
$exp(\theta_5)$	Absorption rate of BAT2506, Ka (1/day)	0.501 (3.04%)	47.0 (4.47%)
$exp(\theta_6)$	Absorption rate of Simponi®, Ka, (1/day)	0.525 (2.56%)	
θ_7	Influence of WT on CL	0.882 (8.18%)	—
$exp(\theta_9)$	Influence of ADA on CL	1.3 (1.95%)	—
θ_{10}	Influence of WBC on CL	0.16 (19.2%)	—
$exp(\theta_{12})$	Influence of PAT on CL	1.17 (2.57%)	—
θ_{13}	Influence of CRP on CL	0.0324 (27.6%)	—
θ_{14}	Influence of CRCL on CL	0.147 (28.9%)	—
θ_8	Influence of WT on V_c	0.902 (6.84%)	—
$exp(\theta_{11})$	Influence of PAT on V_c	0.897 (2.31%)	—
$\omega^2_{CL/F,Vc/F}$	Covariance (CL/F, V_c/F)	0.0926 (6.08%)	—
σ_1	Proportion residual error (%)	17.5 (2.46%)	—
σ_2	Additive residual error (ng/mL)	30.3 (23.1%)	—



Points are observed concentrations, solid red line represents the median observed value, and dashed red lines represent 2.5%ile and 97.5%iles of the observed values. Pink shaded area represents the spread of the median predicted values (2.5th to 97.5th %ile), and purple shaded areas represent the spread (2.5%ile and 97.5%ile) of the 2.5th and 97.5th predicted percentile concentrations.

Figure *2*: pcVPC of BAT2506 and Simponi serum concentration time profiles

The model was then used to compare simulated exposures between BAT2506 and Simponi stratified by relevant covariates.
In case the model describes both the data for Simponi and BAT2506 well, one would expect to find similar central tendencies, for exposure metrics between the two products and similarly comparable variabilities for the analysed subgroups and PK parameters.

5.2.2.3. Bioequivalence in study BAT-2506-001

Study design

This study was a randomised, double-blind, parallel-controlled, single-dose phase 1 clinical study to compare the pharmacokinetic similarity between BAT2506 and Simponi, and also to assess the safety and immunogenicity of BAT2506 and Simponi.

The study planned to enrol 182 healthy male subjects who would be randomly assigned to the BAT2506 group or the Simponi group in a 1:1 ratio to receive a single subcutaneous injection of 50 mg BAT2506 or Simponi. All subjects were randomised by body weight-based stratification factors (weight ≥ 50 kg and < 65 kg and weight ≥65 kg and ≤ 80 kg).

The PK blood samples were collected before administration (within 1 hour pre-dose) (Day 1), and 12 hours (Day 1), 24 hours (Day 2), 48 hours (Day 3), 72 hours (Day 4), 96 hours (Day 5), 120 hours (Day 6), 144 hours (Day 7), 168 hours (Day 8), 192 hours (Day 9), 336 hours (Day 15), 504 hours (Day 22), 672 hours (Day 29), 840 hours (Day 36), 1008 hours (Day 43), 1176 hours (Day 50), 1344 hours (Day 57), and 1680 hours (Day 71) post-dose.

Treatments

Test drug: BAT2506
Reference drug: Golimumab (EU-Simponi)
Method of administration for the test and reference drug: Single dose of 50 mg, subcutaneous injection at the lower part of the abdomen below the navel

Study population

Key inclusion criteria

• Gender: Male

- Age: 18 to 50 years
- Weight: 50 to 80 kg (including the boundary values)
- Body mass index (BMI): 18 to 28 kg/m^2
- No clinically relevant deviations as judged by the Investigator in physical examination, vital sign measurements, abdominal colour Doppler ultrasound, and laboratory tests.
- Effective contraceptive measures from screening to within 6 months after dosing

Exclusion criteria

Exclusion criteria totally excluded prior use of golimumab and other biologics; Subjects positive for golimumab anti-drug antibody at screening were to be excluded as well.

Objectives and endpoints

Primary Study Objective

To compare the PK similarity between BAT2506 and Simponi after a single subcutaneous injection in healthy Chinese male subjects.

Secondary Study Objective

To evaluate the safety and immunogenicity of BAT2506 and Simponi in healthy Chinese male subjects.

Primary PK parameters:

- Area under the drug concentration-time curve from 0 to the sample collection time t (AUC_{0-t})
- Area under the drug concentration-time curve from 0 to infinity ($AUC_{0-\infty}$)
- Maximum drug concentration (C_{max})

Secondary PK parameters:

- Area under the drug concentration-time curve from 0 to 672 h (AUC_{0-672h})
- Time to maximum drug concentration (T_{max})
- Total clearance (CL/F)
- Elimination half-life ($t_{1/2}$)
- Apparent distribution volume (Vd)
- Terminal phase elimination rate constant (λz)

PK parameters were calculated by WinNonlin (Pharsight Corporation, 7.0) using the actual administered dose, actual sampling time and non-compartmental model.

Randomisation and blinding

Subjects were randomised to either BAT2506 group or the Golimumab group in a 1:1 ratio. All subjects were randomised by body weight-based stratification factors (weight ≥ 50 kg and < 65 kg and weight ≥ 65 kg and ≤ 80 kg).

The study was participant- and investigator-blinded. The process of blinding was adequately described. Data was unblinded only after data-base lock.

Sample size

Based on the PK data from clinical studies of Simponi, the CV among subjects was assumed to be 0.37. If it was predicted that the GMR was 0.95, two one-sided α = 0.05, power of test 1-β = 0.9, CV = 0.37, and the equivalent boundary for 90% CI of AUC_{0-t} and C_{max} was 0.80-1.25, then 152 evaluable subjects needed to be enrolled in the two groups. Given a dropout rate of 20%, at least 182 healthy male subjects should be enrolled, with 91 subjects each in the BAT2506 group and the Golimumab group.

As the actual CV of this study was uncertain, in order to control the sample size within the actually needed range as much as possible, it was scheduled that after 50% of the subjects (91 subjects) had completed the study, a blind assessment would be conducted for a full and accurate calculation of CV for the actually enrolled population. If CV was ≤ 0.37, subject recruitment would continue as originally planned; if CV was > 0.37, the sponsor would discuss with the investigator to determine whether to increase subject recruitment based on the actual CV.

PK results of a total of 94 subjects were included in the interim analysis. The calculated CV values of PK parameters $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were 38.30%, 37.45%, and 36.14%, respectively. And the CV values of $AUC_{0-\infty}$ and AUC_{0-t} were >0.37. Based on the estimated sample size required for different CV values, an evaluable sample size of 168 subjects was required when the CV value was 0.39. Considering that 176 subjects completed the study at present, the investigator and the sponsor decided not to increase the sample size.

Planned analysis of PK parameters

Each PK parameter was analysed by descriptive statistics. For the primary PK parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) and secondary PK parameter (AUC_{0-672h}), the number of subjects, mean, standard deviation, median, maximum, minimum, geometric mean, CV and geometric coefficient of variation was calculated. For secondary PK parameters (T_{max}, $t_{1/2}$, λz, CL/F, and Vd), the number of subjects, mean, standard deviation, median, maximum, minimum and CV was calculated.

The ANCOVA method was used to evaluate the PK similarity between groups in log-transformed primary PK parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) and secondary PK parameters (AUC_{0-672h}). The group was included in the model as the fixed effect, and body weight stratum (weight ≥ 50 kg to < 65 kg and weight ≥ 65 kg to ≤ 80 kg) was used as a covariate. Based on the model, the least squares mean difference between the test drug and the reference drug, and its 90% CI were obtained on a logarithmic scale, and the GMR of the PK parameters of the test drug and the reference drug and its 90% CI were obtained using back-transformation. BAT2506 would be similar to Golimumab (Simponi) in terms of PK if the 90% CI of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} GMR (test/reference) was between 0.80 and 1.25.

Participant flow, important protocol deviations and numbers analysed

Table 5: Subject's Completion of the Study BAT-2506-001

	BAT2506 n (%)	Golimumab n (%)	Total n (%)
Number of subjects screened			576
Number of screening failures			394
Reasons for screening failure			
Failure to meet the eligibility criteria			392
Others			2
Number of subjects enrolled	91	91	182
Full Analysis Set (FAS)	90 (98.9)	90 (98.9)	180 (98.9)
Safety Analysis Set (SS)	90 (98.9)	90 (98.9)	180 (98.9)
Pharmacokinetic Parameter Set (PKPS)	90 (98.9)	90 (98.9)	180 (98.9)
Anti-Drug Antibody Analysis Set (ADA-AS)	90 (98.9)	90 (98.9)	180 (98.9)
Number of subjects who completed the study	87 (95.6)	89 (97.8)	176 (96.7)
Number of early withdrawals	4 (4.4)	2 (2.2)	6 (3.3)
Reasons for subject's early withdrawal from the study			
Occurrence of SAEs when the test dose was given or AEs necessitating withdrawal from the study, as judged by the investigator	1 (1.1)	0	1 (0.5)
Voluntary withdrawal decided by the subject	2 (2.2)	2 (2.2)	4 (2.2)
Other reasons	1 (1.1)	0	1 (0.5)

Notes: Percentages (%) were calculated using the number of subjects enrolled in each group as the denominator.
Data source: Table 14.1.1 and Listing 16.2.1.

All PK samples were collected in time and processed without deviation. One (1) subject missed a single visit at day 36; other protocol deviations included strenuous physical activity, non-fasting and temperature excursion of ADA samples.

Baseline data

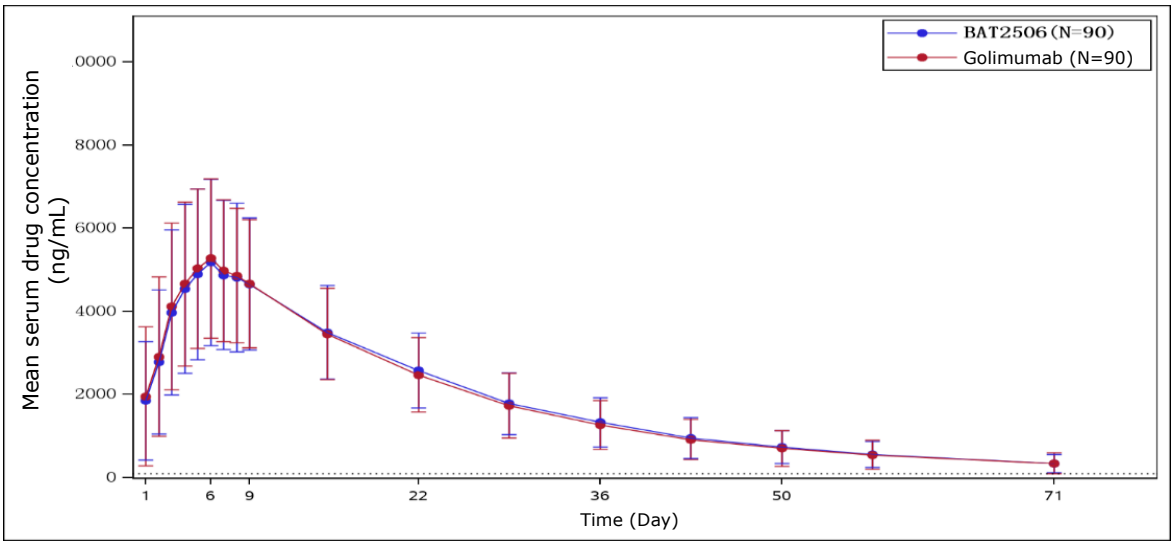
Table 6: Demographics and Other Baseline Characteristics (Full Analysis Set) in study BAT-2506-001

	BAT2506 (N=90)	**EU-Simponi (N=90)**	**Total (N=180)**
Age (years)			
Mean (SD)	35.0 (8.18)	35.6 (8.10)	35.3 (8.12)
Gender [n (%)]			
Male	90 (100)	90 (100)	180 (100)
Ethnicity [n (%)]			
Han ethnicity	84 (93.3)	87 (96.7)	171 (95.0)
Others	6 (6.7)	3 (3.3)	9 (5.0)
Height (cm)			
Mean (SD)	169.50 (5.741)	167.82 (5.058)	168.66 (5.460)
Weight (kg)			
Mean (SD)	66.39 (7.541)	65.20 (7.691)	65.80 (7.619)
Weight stratum [n(%)]			
≥ 50 kg to < 65 kg	44 (48.9)	43 (47.8)	87 (48.3)
≥ 65 kg to ≤ 80 kg	46 (51.1)	47 (52.2)	93 (51.7)
Body mass index (kg/m²)			
Mean (SD)	23.10 (2.332)	23.14 (2.496)	23.12 (2.409)

PK outcomes

Golimumab serum concentration time curves

Figure *3*: Mean Serum Drug Concentration Over Time (± Standard Deviation) - Linear Scale – PK Parameter Set – Study BAT-2506-001



Note: the dashed line in the figure is the lower limit of quantitation of the drug concentration in serum and the value is 100 ng/mL

Source: CSR-2506-001 Figure 1

PK parameters

Table 7: Summary of PK Parameters - Study BAT-2506-001

PK parameter (unit)	**Arithmetic mean ± SD (%CV) (N=180)**	
	BAT2506 (N=90)	**EU-Simponi (N=90)**
$AUC_{0-\infty}$ (h*ng/mL)	3272192.4055 ± 1274487.5673 (38.9490)	3219435.6094 ± 1353678.9980 (42.0471)
AUC_{0-t} (h*ng/mL)	3075690.6845 ± 1155199.0303 (37.5590)	3022590.6087 ± 1155958.5104 (38.2440)
AUC_{0-672h} (h*ng/mL)	2257181.3858 ± 791220.7685 (35.0535)	2248104.0985 ± 776700.9339 (34.5492)
C_{max} (ng/mL)	5384.8 ± 2048.42 (38.04)	5462.6 ± 1988.45 (36.40)
T_{max} (h)*	120.000 (48.00, 336.00)	120.000 (48.00, 192.00)
λ_z (L/h)	0.0020 ± 0.0007 (33.9285)	0.0022 ± 0.0011 (48.5289)
$t_{1/2}$ (h)	374.3706 (121.3334, 732.7402)	351.1410 (104.7712, 951.9990)
CL/F (l/h)	0.0181 ± 0.0089 (48.9151)	0.0180 ± 0.0071 (39.2170)
V_d/F (L)	9.4583 ± 4.3053 (45.5189)	8.7480 ± 3.5793 (40.9162)

Abbreviations: AUC0-∞=Area under the drug concentration-time curve from 0 to infinity (∞); AUC0-t =Area under the drug concentration-time curve from 0 to the sample collection time t; AUC0-672h =Area under the drug concentration-time curve from 0 to 672 h; Cmax =Maximum drug concentration; Tmax =Time to maximum drug concentration; λz =Elimination rate constant; t1/2 = Elimination half-life; CL/F =Total apparent clearance; CV =Coefficient of variation; Vd =Apparent distribution volume; SD = Standard deviation.

Note: *Tmax and t1/2 were expressed as median (min, max).
Data source: CSR BAT-2506-001 Table 17

PK Similarity Analysis

Table 8: Results of PK Similarity Analysis - Study BAT-2506-001

PK parameter (unit)	Geometric mean and ratio (N = 180)			Geometric coefficient of variation (%)	90% CI (%)
	BAT2506 (N=90)	EU-Simponi (N=90)	BAT2506/ EU-Simponi (%)		
$AUC_{0-\infty}$ (h*ng/mL)	3036429.8823	3008856.9529	100.92	41.5087	92.30-110.34
AUC_{0-t} (h*ng/mL)	2860775.2067	2846656.1755	100.50	40.4479	92.12-109.64
C_{max} (ng/mL)	4968.0	5159.3	96.29	42.24	87.93-105.45
AUC_{0-672h} (h*ng/mL)	2110448.4835	2139950.3202	98.62	38.4873	90.83-107.08

Abbreviations: AUC0-∞=Area under the drug concentration-time curve from 0 to infinity (∞); AUC0-t =Area under the drug concentration-time curve from 0 to the sample collection time t; AUC0-672h =Area under the drug concentration-time curve from 0 to 672 h; Cmax =Maximum drug concentration.

Non-parametric analysis was performed for the untransformed T_{max} and $t_{1/2}$ of BAT2506 and EU-Simponi using Hodges-Lehmann test. The median and 90% CI of the difference (BAT2506 - EU-Simponi) were 0.00 (0.00, 0.00) and 24.42 (-0.55, 48.04), respectively. Both 90% CI's contained zero indicating that T_{max} and $t_{1/2}$ of BAT2506 and Golimumab are similar.

Four (4) **sensitivity analyses** were performed:

Sensitivity Analysis-1: The stratification factor of body weight was not considered, one Analysis of variance (ANOVA) model with the group as the fixed effect was separately fitted to the log-transformed PK parameters. The results showed that the PK parameters of $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, and AUC_{0-672h} for both BAT2506 and EU-Simponi fell within the specified equivalence range of 80% - 125%. This indicates that the PK characteristics of both drugs remained similar even without considering body weight as a stratification factor.

Sensitivity Analysis-2: Four subjects (3 in BAT2506 group and 1 in EU- Simponi group) with incomplete sample collection were excluded from the analysis. After excluding the incomplete data, the PK parameters for $AUC_{0-\infty}$ and AUC_{0-t} of BAT2506 and EU- Simponi remained similar, as their least-squares GMR (90% CI) also fell within the equivalence range. The exclusion of the incomplete data had no effect on C_{max}, further supporting the similarity of PK characteristics.

Sensitivity Analysis-3: Thirteen subjects (4 in BAT2506 group and 9 in EU- Simponi group) who tested positive for ADA at the D71 visit were excluded. The analysis showed that excluding these subjects did not affect the similarity of PK parameters. The least-squares GMR (90% CI) of the PK parameters for BAT2506 and EU- Simponi all fell within the specified equivalence range.

Sensitivity Analysis-4: Fourteen subjects (4 in BAT2506 group and 10 in EU- Simponi group) who tested positive for ADA after drug administration were excluded. Similar to the previous analysis, the exclusion of these subjects did not impact the PK similarity between BAT2506 and EU- Simponi. The least-squares GMR (90% CI) of the PK parameters remained within the equivalence range.

Table 9: Summary of Sensitivity Analyses Performed for Study BAT-2506-001

Sensitivity Analysis	Geometric mean ratio (GMR)	PK Parameter $AUC_{0-\infty}$ (h*ng/mL)	AUC_{0-t} (h*ng/mL)	C_{max} (ng/mL)	AUC_{0-672h} (h*ng/mL)
1	BAT2506/ EU-Simponi (%) (n=90/90)	101.30	100.87	96.66	98.99
	90% CI (%)	91.79-111.79	91.62-111.06	87.46-106.83	90.30-108.51
2	BAT2506/ EU-Simponi (%) (n=87/90)	101.77	101.54	-	-
	90% CI (%)	92.99-111.37	93.03-110.83	-	-
3	BAT2506/ EU-Simponi (%) (n=86/81)	101.21	101.08	99.41	100.65
	90% CI (%)	92.48-110.76	92.56-110.38	90.49-109.21	92.46-109.57
4	BAT2506/ EU-Simponi (%) (n=86/80)	101.07	100.97	99.36	100.57
	90% CI (%)	92.30-110.67	92.42-110.32	90.39-109.22	92.34-109.54

Abbreviations: AUC0-∞=Area under the drug concentration-time curve from 0 to infinity (∞); AUC0-t =Area under the drug concentration-time curve from 0 to the sample collection time t; AUC0-672h =Area under the drug concentration-time curve from 0 to 672 h; Cmax =Maximum drug concentration.

As a blinded sample size reassessment was conducted that could lead to an inflation in type I error rate above the nominal level of 0.05, the applicant presented additional analyses with adjusted significance level upon request.

Table 10: Results of PK Similarity Analysis - Study BAT-2506-001: 91% CI and 95%CI for the geometric mean ratio of PK parameters

	Arithmetic		Geometry						
Pharmacokinetic parameters (N=180)	Mean (SD)	CV (%)	Mean (SD)	Geometric CV(%)	LS Mean	Geometric mean ratio (BAT2506/ Golimumab)	Geometric mean ratio 90%CI	Geometric mean ratio 91%CI	Geometric mean ratio 95%CI
AUC0□∞ (h*ng/mL) BAT2506(N=90)	3272192.4055 (1274487.5673)	38.949	3024921.4669 (1.5123)	43.1977	3036429.882	100.92	(92.30, 110.34)	(92.05,110.64)	(90.74,112.24)
Golimumab(N=90)	3219435.6094 (1353678.9980)	42.0471	2986092.3533 (1.4702)	40.017	3008856.953				
Total(N=180)	3245814.0074 (1311269.0923)	40.3988	3005444.2037 (1.4899)	41.5087					
AUC0□t (h*ng/mL) BAT2506(N=90)	3075690.6845 (1155199.0303)	37.559	2850155.1092 (1.5066)	42.7651	2860775.207	100.5	(92.12, 109.64)	(91.88,109.93)	(90.6,111.48)
Golimumab(N=90)	3022590.6087 (1155958.5104)	38.244	2825560.0397 (1.4474)	38.2809	2846656.176				
Total(N=180)	3049140.6466 (1152653.9619)	37.8026	2837830.9294 (1.4759)	40.4479					
AUC0□672h (h*ng/mL) BAT2506(N=90)	2257181.3858 (791220.7685)	35.0535	2102651.8466 (1.4956)	41.9368	2110448.484	98.62	(90.83, 107.08)	(90.6,107.35)	(89.41,108.78)
Golimumab(N=90)	2248104.0985 (776700.9339)	34.5492	2124168.2745 (1.4053)	35.0317	2139950.32				
Total(N=180)	2252642.7421 (781814.7178)	34.7066	2113382.6783 (1.4501)	38.4873					
Cmax (ng/mL) BAT2506(N=90)	5384.8 (2048.42)	38.04	4949.1 (1.56)	46.48	4968	96.29	(87.93, 105.45)	(87.68,105.75)	(86.41,107.3)
Golimumab(N=90)	5462.6 (1988.45)	36.4	5120.1 (1.44)	37.87	5159.3				
Total(N=180)	5423.7 (2013.39)	37.12	5033.9 (1.50)	42.24					

5.2.2.3.1. Supportive data on bioequivalence from study BAT-2506-003

Study BAT-2506-003 was a randomised, double-blind, single dose, parallel three-arm comparative study on PK and safety of BAT2506 injection versus the EU-Simponi and US-licensed Simponi in healthy Chinese male subjects. The use of the US-Simponi as reference product in study BAT-2506-003 was based on the US-FDA's advice to establish an acceptable scientific bridge to US-Simponi that includes three way, pairwise analytical and PK comparisons between BAT2506, US-Simponi and EU-Simponi.

A total of 375 healthy Chinese male subjects were enrolled in the study after eligibility confirmation. The enrolled subjects were randomly assigned to the BAT2506 Injection group, EU-Simponi group, or US-Simponi group in a 1:1:1 ratio on D-1 using the Interactive Web Response System (IWRS) assignment. The stratification factor in this study was weight, with categories of ≥50 kg and <65 kg, and ≥65 kg and ≤80 kg.

Based on the PK clinical study of Simponi, the study aimed to enrol a total of 336 evaluable subjects divided into 3 groups. This enrolment number considered a coefficient of variation of 43%, an expected GMR of 0.95, a 2-sided significance level of α = 0.05, power P = 0.928, and 90% confidence interval. To account for a 10% dropout rate, at least 375 subjects were to be enrolled, with 125 subjects in each group.

BAT2506 Injection, EU-Simponi, and US-Simponi were administered at a dosage of 50 mg in this clinical study.

The key inclusion criteria included healthy male subjects aged 18 to 55 years, with a BMI ranging from 18 to 28 kg/m2 and a body weight of 50 to 80 kg. Subjects were required to have normal or non-clinically significant abnormalities in physical examination and vital signs, abdominal colour Doppler ultrasound, laboratory tests, and other examination results.

PK sampling timepoints:

PK blood sample collection time points included (within 1 hour before administration) (D 1), and 12 hours (D 1), 24 hours (D 2), 48 hours (D 3), 72 hours (D 4), 96 hours (D 5), 120 hours (D 6), 144 hours (D 7), 168 hours (D 8), 192 hours (D 9), 336 hours (D 15), 504 hours (D 22), 672 hours (D 29), 840 hours (D 36), 1008 hours (D 43), 1176 hours (D 50), 1344 hours (D 57), 1512 hours (D 64), and 1848 hours (D 78), totaling 19 time points.

Primary PK parameters: $AUC_{0\text{-}inf}$ and C_{max}

Secondary PK endpoints: $AUC_{0\text{-}t}$, T_{max}, CL/F, $T_{1/2}$, Vd/F, Lambdaz

ANOVA methods were used to evaluate PK similarity between groups for PK parameter (C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$). The independent variables in the model included treatment and weight (50 kg ≤ weight < 65 kg and 65 kg ≤ weight ≤ 80 kg). If the 90% CI of GMR of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ fell within the equivalent interval of (0.8, 1.25), it could be proved that the PK between each two of test groups was biologically similar.

Table 11: Subject Enrolment and Disposition and Analysis Sets in Study BAT-2506-003

	BAT2506 n (%)	**EU-Simponi (Golimumab) n (%)**	**US-Simponi (Golimumab) n (%)**	**Total n (%)**
Number of subjects screened	-	-	-	766
Number of screening failures	-	-	-	391
Number of subjects enrolled	124	127	124	375
Full Analysis Set (FAS)	123 (99.2)	125 (98.4)	121 (97.6)	369 (98.4)
Safety Analysis Set (SS)	123 (99.2)	125 (98.4)	121 (97.6)	369 (98.4)
Pharmacokinetic Parameter Set (PKPS)	123 (99.2)	125 (98.4)	121 (97.6)	369 (98.4)
Anti-Drug Antibody Analysis Set (ADA-AS)	122 (98.4)	123 (96.9)	119 (96.0)	364 (97.1)
Number of subjects who completed the trial	113 (91.1)	116 (91.3)	116 (93.5)	345 (92.0)
Number of subjects withdrawn from the study	11 (8.9)	11 (8.7)	8 (6.5)	30 (8.0)
Primary reason for discontinuation				
Lost to follow-up	6 (4.8)	7 (5.5)	3 (2.4)	16 (4.3)
Voluntary withdrawal decided by the subject	5 (4.0)	3 (2.4)	4 (3.2)	12 (3.2)
Other reasons	0	1 (0.8)	1 (0.8)	2 (0.5)

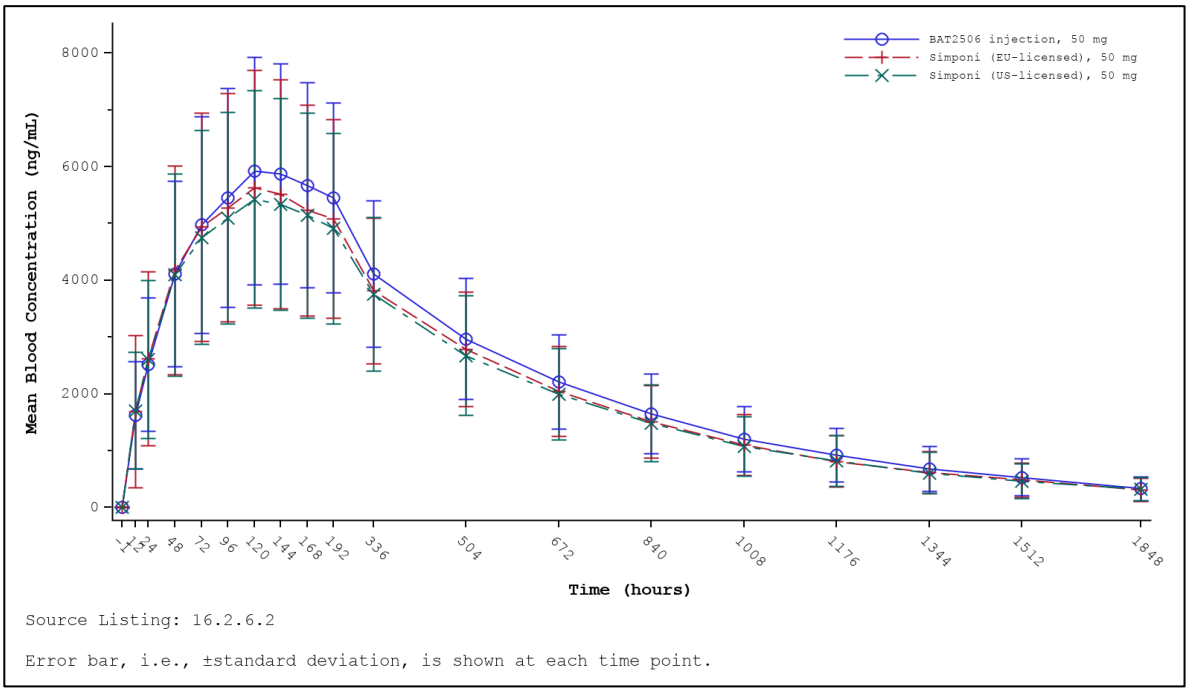
Abbreviations: FAS = Full analysis set; SS = Safety analysis set; PKPS = Pharmacokinetic parameter set

Notes: Percentages (%) were calculated using the number of subjects enrolled in each group as the denominator.

During the study, 17 subjects (4.5% of total) had major protocol deviations (PD). Out of these, 5 subjects (4.0%) were in the BAT2506 group, 5 subjects (3.9%) were in the EU Simponi group, and 7 subjects (5.6%) were in the US-Simponi group. Among the PD cases, 14 (3.7%) were due to visit compliance, 2 (0.5%) were violations of inclusion/exclusion criteria (one subject had diagnosed with diabetes and second had history of intermittent seizures), and 1 (0.3%) was related to visit compliance without safety concerns.

Table 12: Demographics and Other Baseline Characteristics (FAS) in Study BAT-2506-003

	BAT2506 n (%) (n=123)	**EU-Simponi (Golimumab) n (%) (n=125)**	**US-Simponi (Golimumab) n (%) (n=121)**	**Total n (%) (N=369)**
Age (years)				
Mean (SD)	35.2 (10.4)	34.8 (10.0)	35.1 (10.4)	35.0 (10.2)
Ethnicity [n (%)]				
Han ethnicity	113 (91.9)	117 (93.6)	110 (90.9)	340 (92.1)
Others	10 (8.1)	8 (6.4)	11 (9.1)	29 (7.9)
Height (cm)				
Mean (SD)	168.89 (5.92)	168.31 (5.57)	168.80 (6.24)	168.67 (5.90)
Weight (kg)				
Mean (SD)	65.76 (7.90)	66.13 (7.84)	66.23 (8.17)	66.04 (7.95)
Body mass index (kg/m^2)				
Mean (SD)	23.06 (2.64)	23.35 (2.62)	23.22 (2.39)	23.21 (2.55)



Data source: CSR BAT-2506-003, Figure 2

Figure *4*: Mean Blood Study Drug Concentration - Time (Linear) (PKCS) in Study BAT-2506-003

Table 13: Summary of PK Parameters in Study BAT-2506-003 for BAT2506 and EU Simponi

Parameter (unit)	Arithmetic mean ± SD (%CV)	
	BAT2506 (N=123)	**EU-Simponi (N=125)**
$AUC_{0-\infty}$ (h*ng/mL)	n=120	n=121
	3860000 ± 1430000 (37.0)	3590000 ± 1380000 (38.4)
AUC_{0-t} (h*ng/mL)	n=123	n=125
	3610000 ± 1360000 (37.7)	3340000 ± 1330000 (39.9)
C_{max} (ng/mL)	n=123	n=125
	6140 ± 2010 (32.8)	5870 ± 2190 (37.4)
T_{max} (h)	n=123	n=125
	134 ± 34 (25.4)	131 ± 33.6 (25.7)
λ_z (L/h)	n=120	n=121
	0.00206 ± 0.000737 (35.8)	0.00223 ± 0.000873 (39.2)
$t_{1/2}$ (h)	n=120	n=121
	370 ± 104 (28.2)	351 ± 116 (32.9)
$t_{1/2}$ (h)*	n=120	n=121
	368 (138-605)	351 (130-823)
CL/F (l/h)	120	n=121
	0.0152 ± 0.00772 (50.9)	0.0165 ± 0.00754 (45.8)
V_d/F (L)	n=120	n=121
	7.650 ± 3.290 (42.9)	7.970 ± 4.160 (52.2)
T_{max} (h)*	n=123	n=125
	121 (12.0, 193)	120 (12.0-192)

Abbreviations: AUC0-∞=Area under the drug concentration-time curve from 0 to infinity (∞); AUC0-t =Area under the drug concentration-time curve from 0 to the sample collection time t; Cmax =Maximum drug concentration; Tmax =Time to maximum drug concentration; λz =Elimination rate constant; t1/2 = Elimination half-life; CL/F =Total apparent clearance; CV =Coefficient of variation; Vd =Apparent distribution volume; SD = Standard deviation.

Note: *T1/2 and Tmax was also expressed as median (min, max).

Data source: CSR BAT-2506-003-CR, Table 11

Table 14: Results of PK Similarity Analysis of Study BAT-2506-003; Comparison BAT2506 vs EU Simponi

PK parameter (unit)	Groups	GM	GMR(T/R) (%)	GMR 90%CI	GMR 91% CI
C_{max} (ng/mL)	BAT2506 (n=117)	5995.22	1.07	(0.99, 1.15)	(0.99, 1.15)
	EU-Simponi (n=118)	5627.19			
$AUC_{0-\infty}$ (h*ng/mL)	BAT2506 (n=117)	3729091.21	1.09	(1.01, 1.17)	(1.01, 1.18)
	EU-Simponi (n=118)	3425197.61			
AUC_{0-t} (h*ng/mL)	BAT2506 (n=117)	3561184.38	1.09	(1.01, 1.17)	(1.01, 1.17)
	EU-Simponi (n=118)	3282071.54			

Abbreviations: AUC0-∞=Area under the drug concentration-time curve from 0 to infinity (∞); AUC0-t =Area under the drug concentration-time curve from 0 to the sample collection time t; Cmax =Maximum drug concentration; GM= geometric mean; GMR= geometric mean ratio; CI= confidence interval, T = BAT2506, R = EU-Simponi
Source: CSR BAT-2506-003 Table 14
Note: The general linear model (GLM) with the log-transformed PK parameter as the response, group and weight (50 ≤ weight < 65kg and 65 ≤ weight ≤ 80kg) as predictor.

Since a part of subjects underwent interim analysis in blind, in order to adjust the type I error, the GMR between groups and their 91% CI of PK parameter (C_{max}, $AUC_{0-\infty}$, and AUC_{0-t}) were calculated (see table above).

5.2.2.4. Pharmacokinetics in the target population – study BAT-2506-002

Study design

This was a multicenter, double-blind, randomised, parallel-group study to compare the efficacy, pharmacodynamics (PD), pharmacokinetics (PK), safety, and immunogenicity of BAT2506 versus EU Simponi in subjects with active psoriatic arthritis (PsA).

For details on study design see section 6.3 of this overview.

Test and reference products, doses and mode of administration, concomitant and rescue medication

• Test: BAT2506, 50 mg once every 4 weeks, SC injection

• Reference: EU Simponi, 50 mg once every 4 weeks, SC injection

In total, 13 scheduled doses were planned to be administered to subjects over the course of the entire Treatment Period, including 6 scheduled doses during TP1, and 7 scheduled doses during TP2.

The dose and dosing regimen were identical to the label instructions of the reference product (Simponi) in the treatment of PsA.

A transition of 50% of Simponi patients to BAT2506 at Week 24 was planned for the study in order to investigate the impact of transition particularly in terms of assessment of safety and immunogenicity, and to meet the requirements of some regulatory agencies, in particular the FDA.

In this study, the use of MTX was allowed but with a cap for 50% and the use of MTX (yes/no) was included as a stratification factor to ensure that the different treatment groups had similar baseline cohorts. MTX routes of administration and doses (not to exceed 25 mg/week) were required to be stable for at least 4 weeks prior to the first administration of the study drug and throughout the study. A stable dose for at least 2 weeks was required prior to the first administration of the study drug in case of NSAIS or corticosteroid use.

NSAIDs and other short course analgesics (excluding high potency opioids) were possible rescue medication.

PK objectives and endpoints

Secondary PK objective: To compare the PK of BAT2506 with EU Simponi in subjects with active PsA

Blood samples were collected for measurement of serum concentrations of Golimumab on Week 0, 1, 2, 4, 8, 12, 13, 14, 24, 36, 48, 52, 56, and 60. Descriptive statistics were presented by timepoint and treatment. Trough samples were collected prior to administration of study drug on the day of the scheduled visit. Three (3) additional PK timepoints (Week 1, Week 2, and Week 13) were added during global protocol Version 2.0 and one additional timepoint (SFU2) was added per the suggestion from EMA. Thus, these later added PK samples were only collected among partial subjects after protocol confirmed effective in the related sites.

PK parameters were determined using a population PK modeling approach, including AUC_{0-t} (truncated AUC after first administration until second administration), $AUC_{0-\tau}$ (AUC over dosage interval at steady state), C_{max} (maximum concentration at steady state), C_{trough} (trough concentration before next dosing of study drug at steady state).

Analysis Sets and Study Subjects

Per PK Analysis Set for TP1 (PKS1): The PKS1 consisted of all subjects in the Safety Analysis Set who had at least one quantifiable PK concentration during TP1 (from Week 0 to Week 24), excluding observations after relevant intercurrent events that might impact PK evaluations. Subjects in the PKS1 were analysed under the treatment as actually received. The PKS1 was used for analyses of PK during TP1.

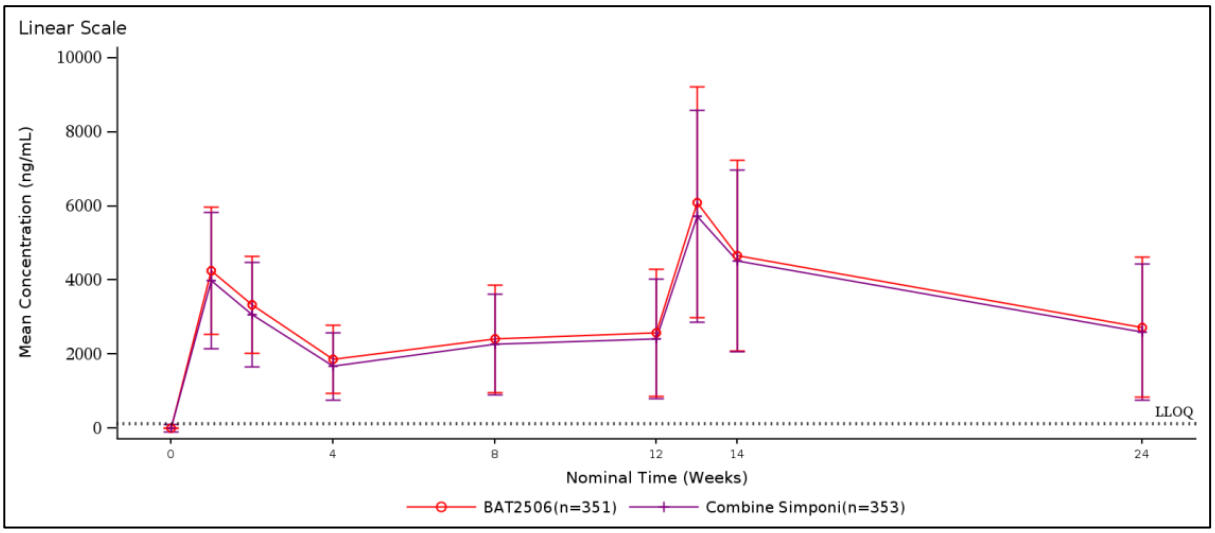
Per PK Analysis Set for TP2 (PKS2): The PKS2 consisted of all subjects in the Safety Analysis Set who had at least one quantifiable PK concentration during TP2 (from Week 24 to Week 52), excluding observations after relevant events after Week 24 that may impact PK evaluations. Subjects in the PKS2 was analysed under the treatment as actually received. The PKS2 was used for analyses of PK during TP2.

In the PK Analysis Set 1 (PKS1), a total of 704 subjects (100.0%) were included. In the PKS2, a total of 667 subjects (94.7%) were included, with 336 subjects (95.7%) in the BAT2506 group, 168 subjects (93.9%) in the EU Simponi group, and 163 subjects (93.7%) in the Simponi→BAT2506 group.

For details on study population see section 6.3 of this overview.

PK results

Figure *5*: Mean (± SD) Serum Concentration Versus Nominal Time Weeks (Linear and Semi logarithmic Scale) (PK Analysis Set 1) - Study BAT-2506-002



Source: BAT-2506-002-CR, Figure 11-10

Table 15: Summary of Serum Concentration Over Time (PK Analysis Set 1) - Study BAT-2506-002

Nominal Time Point	Statistics	BAT2506 (N =351) (ng/mL)	Simponi (N = 179) (ng/mL)	Simponi→BAT2506 (N = 174) (ng/mL)	Combine Simponi (N = 353) (ng/mL)
Week 1	BLQ	1	2	0	2
	n	338	172	164	336
	Geometric Mean	3917	3377	3793	3575
	Geometric CV%	45.9	60.1	49.3	55.3
	Mean (SD)	4258 (1715)	3782 (1780)	4201 (1879)	3986 (1838)
	CV%	40.3	47.1	44.7	46.1
	Median	4160	3570	4135	3695
	Min, Max	0.000, 10600	0.000, 9420	947.0, 12100	0.000, 12100
Week 8	BLQ	8	5	2	7
	n	332	165	166	331
	Geometric Mean	2055	1836	1975	1905
	Geometric CV%	75.5	82.8	72.3	77.5
	Mean (SD)	2416 (1448)	2201 (1402)	2322 (1326)	2262 (1364)
	CV%	60	63.7	57.1	60.3
	Median	2225	2090	2120	2120
	Min, Max	0.000, 10100	0.000, 7220	0.000, 8850	0.000, 8850
Week14	BLQ	5	5	1	6
	n	317	156	155	311

Nominal Time Point	Statistics	BAT2506 (N =351) (ng/mL)	Simponi (N = 179) (ng/mL)	Simponi→BAT2506 (N = 174) (ng/mL)	Combine Simponi (N = 353) (ng/mL)
	Geometric Mean	3897	3826	4013	3919
	Geometric CV%	86.3	62.4	77.6	70.1
	Mean (SD)	4663 (2568)	4291 (2425)	4749 (2469)	4519 (2454)
	CV%	55.1	56.5	52	54.3
	Median	4430	3900	4440	4230
	Min, Max	0.000, 18400	0.000, 13000	0.000, 13400	0.000, 13400
Week 24	BLQ	20	9	11	20
	n	303	147	149	296
	Geometric Mean	2350	2084	2313	2195
	Geometric CV%	82.6	96.8	84.6	90.8
	Mean (SD)	2730 (1887)	2536 (1828)	2667 (1865)	2602 (1845)
	CV%	69.1	72.1	69.9	70.9
	Median	2480	2520	2380	2405
	Min, Max	0.000, 10100	0.000, 8920	0.000, 10200	0.000, 10200

Abbreviations: SD = Standard Deviation, CV = Coefficient of Variation, Geo = Geometric, Max = maximum, Min = minimum, NC = Not Calculated. N = number of subjects who received treatment, n = number of subjects with non-missing values. BLQ=number of subjects below the limit of quantification.
Source: BAT-2506-002-CR, Table 11-64 and Table 14.2.2.1.18.1

As per the agency's request, comparison of C_{trough} at both week 8 and week 12 (at expected steady state) from study BAT-2506-002-CR between BAT2506 and Combine Simponi (i.e. Simponi and Simponi/BAT2506) were provided by presentation of geometric mean ratio with point estimates and 95% confidence intervals.

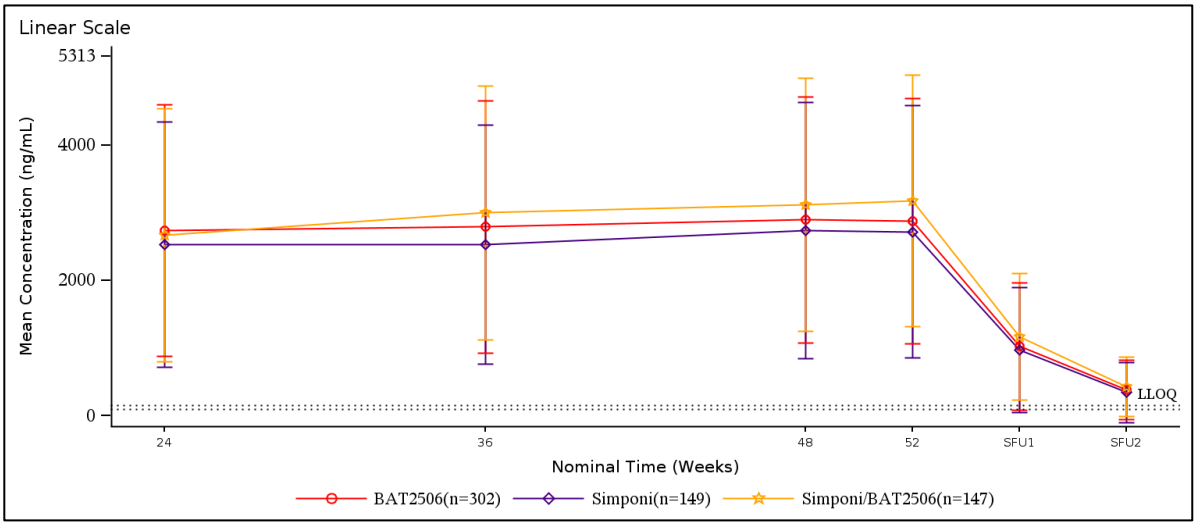
Table 16: Comparison of C_{trough} at week 8 and week 12 - Study BAT-2506-002

Nominal	Time Point	Statistics	BAT2506	Simponi	Simponi/BAT2506	Combine Simponi
			(N=351)	(N=179)	(N=174)	(N=353)
Week 8	pre-dose	BLQ(1)	8	5	2	7
		n	332	165	166	331
		Geometric Mean	2055	1836	1975	1905
		Geometric CV%	75.5	82.8	72.3	77.5
		Mean (SD)	2416 (1448)	2201 (1402)	2322 (1326)	2262 (1364)
		CV%	60	63.7	57.1	60.3
		Median	2225	2090	2120	2120
		Min, Max	0.000, 10100	0.000, 7220	0.000, 8850	0.000, 8850
	BAT2506 VS Combine Simponi	GMR	1.08			
		95%CI of GMR	(0.99,1.18)			

Week 12	pre-dose	BLQ (1)	18	11	6	17
		n	330	162	161	323
		Geometric Mean	2190	2016	2097	2057
		Geometric CV%	89.4	83.9	82.8	83.2
		Mean (SD)	2583 (1713)	2353 (1683)	2480 (1534)	2416 (1609)
		CV%	66.3	71.5	61.8	66.6
		Median	2445	2075	2320	2170
		Min, Max	0.000, 10800	0.000, 8590	0.000, 7120	0.000, 8590
	BAT2506 VS Combine Simponi	GMR	1.06			
		95%CI of GMR	(0.97,1.17)			

Abbreviations: Ctrough=trough concentration; BLQ=below the limit of quantification; CI=confidence interval; CV=coefficient of variation; GMR=geometric mean ratio; Max=maximum; Min=minimum; N=number; SD=standard deviation.

Source: Gotenfia – Responses to D120 questions - clinical



Source: BAT-2506-002-CR, Figure 11-11

Figure *6*: Mean (± SD) Serum Concentration Versus Nominal Time Weeks (Linear and Semi Logarithmic Scale) (PK Analysis Set 2) - Study BAT-2506-002

Table 17: Summary of Serum Concentration Over Time (PK Analysis Set 2) – Study BAT-2506-002

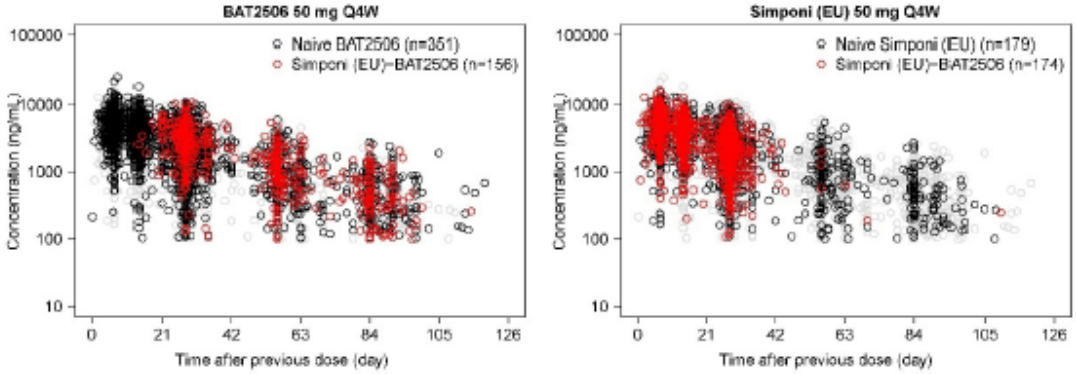
Nominal Time Point	Statistics	BAT2506 (N =336)	Simponi (N = 168)	Simponi→BAT2506 (N = 163)	Combine Simponi (N = 331)
Week 52	BLQ	9	3	4	7
	n	285	138	141	279
	Geometric Mean	2418	2146	2690	2405
	Geometric CV%	80.9	97	84.6	91.9
	Mean (SD)	2878 (1817)	2720 (1861)	3179 (1855)	2952 (1869)
	CV%	63.1	68.4	58.4	63.3
	Median	2630	2390	3060	2770
	Min, Max	0.000, 9790	0.000, 9390	0.000, 10700	0.000, 10700

Abbreviations: SD = Standard Deviation, CV = Coefficient of Variation, Geo = Geometric, Max = maximum, Min = minimum, NC = Not Calculated. N = number of subjects who received treatment, n=number of subjects with non-missing values. BLQ=number of subjects below the limit of quantification.
Source: CSR_BAT-2506-002-CR, Table 11-65

Assessment of similarity by simulation from population PK model

The serum concentrations of BAT2506 and EU/US sourced Simponi were simulated using the Bayesian *post-hoc* PK parameters following 50 mg Q4W of BAT2506 or Simponi doses for 13 times, the PK parameters predicted by Bayesian *post-hoc* method were used to simulate the PK curve. Samples were collected over a 4-week period during the 1st and 13th cycles, with measurements taken every 2 hours in the first two weeks and every 6 hr in the subsequent two weeks. The PK exposures of BAT2506 and EU/US sourced Simponi (area under the curve at steady state [AUC_{ss}], area under the curve after first dose [AUC_1], maximum concentration at steady state [$C_{max,ss}$], maximum concentration after first dose [C_{max1}], minimum concentration at steady state [$C_{min,ss}$], and minimum concentration after first dose [C_{min1}]) in subjects were summarised, and PK similarity was compared. The subjects (N=156) who transitioned from Simponi to BAT2506 used the Simponi PK parameter.

Furthermore, a total of 1000 patients were simulated using the final popPK model parameter estimates and estimated subject-specific random effects. Two scenarios were compared: one where Simponi is given continuously for 28 weeks, and another where Simponi is given continuously for 24 weeks, followed by BAT2506 starting at week 24. The exposure difference between the two scenarios during the interval from week 24 to 28 was compared (Table 27).



Black circles: the naive BAT2506 observed concentration. Red circles: the EU sourced Simponi® observed concentration. Light grey circles: collected drug concentration for all samples (3 groups) in BAT-2506-002-CR.

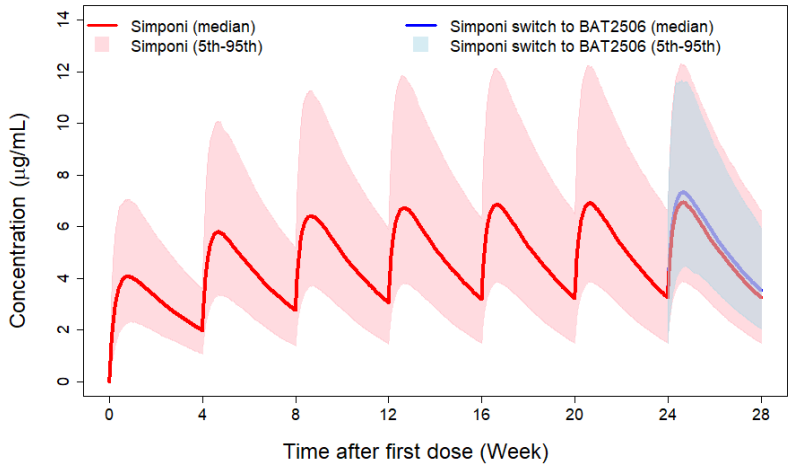
Figure *7*: BAT2506 and Simponi observed concentration versus time in BAT-2506-002

Table 18: PK Parameters Comparation in BAT2506 and Simponi by popPK model

Exposures		**BAT2506 (N=564)**	**Simponi (N=689)**
AUC_1(μg*hr/mL)	Mean (SD)	2168.52 (781.76)	2109.17 (807.12)
	Mean (CV%)	2168.52 (36.1%)	2109.17 (38.3%)
	Median [Min, Max]	2136.27 [450.34, 5444.29]	2001.86 [420.39, 5206.61]
	Median [Q05, Q95]	2136.27 [1060.69, 3538.28]	2001.86 [924.19, 3505.14]
	Geo. mean (Geo. CV%)	2025.78 (39.5%)	1949.64 (43.1%)
C_{max1} (μg/mL)	Mean (SD)	4.61 (1.64)	4.55 (1.77)
	Mean (CV%)	4.61 (35.6%)	4.55 (38.9%)
	Median [Min, Max]	4.46 [0.825, 11.6]	4.35 [0.816, 11.4]
	Median [Q05, Q95]	4.46 [2.25, 7.71]	4.35 [1.98, 7.70]
	Geo. mean (Geo. CV%)	4.32 (39.1%)	4.19 (43.8%)
C_{min1} (μg/mL)	Mean (SD)	1.93 (0.844)	1.84 (0.819)
	Mean (CV%)	1.93 (43.8%)	1.84 (44.6%)
	Median [Min, Max]	1.86 [0.302, 6.04]	1.74 [0.120, 5.18]
	Median [Q05, Q95]	1.86 [0.733, 3.48]	1.74 [0.625, 3.33]
	Geo. mean (Geo. CV%)	1.74 (50.5%)	1.65 (52.7%)
AUC_{ss}(μg*hr/mL)	Mean (SD)	3364.97 (1426.39)	3238.51 (1389.84)
	Mean (CV%)	3364.97 (42.4%)	3238.51 (42.9%)
	Median [Min, Max]	3229.00 [752.644, 10728.3]	3037.09 [447.613, 8821.64]
	Median [Q05, Q95]	3229.00 [1467.45, 5930.34]	3037.09 [1301.88, 5824.17]
	Geo. mean (Geo. CV%)	3073.81 (45.8%)	2944.07 (47.7%)
$C_{max,ss}$ (μg/mL)	Mean (SD)	7.00 (2.69)	6.82 (2.72)
	Mean (CV%)	7.00 (38.4%)	6.82 (39.9%)
	Median [Min, Max]	6.75 [1.53, 19.9]	6.39 [1.42, 18.6]

	Median [Q05, Q95]	6.75 [3.37, 11.6]	6.39 [2.98, 11.7]
	Geo. mean (Geo. CV%)	6.49 (41.6%)	6.27 (44.3%)
$C_{min,ss}$ (µg/mL)	Mean (SD)	2.93 (1.58)	2.78 (1.50)
	Mean (CV%)	2.93 (54.0%)	2.78 (53.9%)
	Median [Min, Max]	2.66 [0.319, 11.3]	2.55 [0.126, 9.53]
	Median [Q05, Q95]	2.66 [0.918, 5.87]	2.55 [0.771, 5.69]
	Geo. mean (Geo. CV%)	2.52 (62.5%)	2.38 (63.9%)

Abbreviations: AUC1=area under the curve after first dose; Cmax1=maximum concentration after first dose; Cmax,ss= maximum concentration at steady state; Cmin1=minimum concentration after first dose; Cmin,ss= minimum concentration at steady state; CV=coefficient of variation; Geo.=geometric; Max=maximum; Min=minimum; N=number; Q05=5% quantile; Q95=95% quantile; SD=standard deviation.
Source: Gotenfia – Responses to D120 questions - clinical



Source: Gotenfia – Responses to D120 questions – clinical

Figure *8*: Simulated Concentration Versus Time Plot of Simponi Switch to BAT2506 (1000 virtual patients)

Table 19: Exposures Summary of BAT2506 and Simponi at Week 24 – Week 28 (after IMP switch) – 1000 virtual patients

	Exposure	**BAT2506 (N=1000)**	**Simponi (N=1000)**
AUC_{ss} (µg*hr/mL)	Mean (SD)	3865.43 (1157.25)	3745.48 (1415.62)
	Mean (CV%)	3865.43 (29.9%)	3745.48 (37.8%)
	Median [Min, Max]	3700.20 [1439.24, 8582.17]	3506.95 [877.526, 10472.8]
	Median [Q05, Q95]	3700.20 [2302.17, 5948.88]	3506.95 [1878.24, 6300.53]
	Geo. mean (Geo. CV%)	3699.79 (30.4%)	3498.59 (38.4%)
$C_{max, ss}$ (µg/mL)	Mean (SD)	7.66 (2.28)	7.42 (2.60)
	Mean (CV%)	7.66 (29.8%)	7.42 (35.1%)
	Median [Min, Max]	7.43 [3.12, 17.4]	7.01 [1.55, 18.4]
	Median [Q05, Q95]	7.43 [4.54, 11.9]	7.01 [3.98, 12.4]
	Geo. mean (Geo. CV%)	7.33 (30.3%)	6.99 (35.7%)

$C_{min, ss}$ (µg/mL)	Mean (SD)	3.71 (1.26)	3.59 (1.66)
	Mean (CV%)	3.71 (33.9%)	3.59 (46.1%)
	Median [Min, Max]	3.55 [0.802, 9.37]	3.27 [0.604, 12.3]
	Median [Q05, Q95]	3.55 [2.07, 5.96]	3.27 [1.51, 6.63]
	Geo. mean (Geo. CV%)	3.51 (34.7%)	3.25 (48.0%)

Abbreviations: AUCss=area under the curve at steady state; Cmax,ss= maximum concentration at steady state; Cmin,ss= minimum concentration at steady state; CV=coefficient of variation; Geo.=geometric; Max=maximum; Min=minimum; N=number; Q05=5% quantile; Q95=95% quantile; SD=standard deviation.
Source: Gotenfia – Responses to D120 questions - clinical

5.2.2.5. Special populations

Relevant co-variates including sex, race, weight, and age were investigated in the presented population PK model. There was moderate inter-individual variability which was similar between BAT2506 and EU Simponi. The population PK model also provided simulations of exposure stratified by different covariates. The impact of co-variates on golimumab PK was overall comparable between BAT2506 and EU Simponi.

Paediatric population

The applicant is seeking approval of the adult formulation (50 mg and 100 mg pre-filled syringe) only. The adult formulation is suitable for paediatric patients with a body weight of at least 40 kg. There is no dosage form for Gotenfia that allows for a 45 mg/0.45 mL dose available for administration to children with polyarticular juvenile idiopathic arthritis weighing less than 40 kg. Thus, it is not possible to administer Gotenfia to patients that require a 45 mg/0.45 mL dose. If a 45 mg/0.45 mL dose is required, another golimumab product should be used instead.

5.2.3. Pharmacodynamics

The pharmacodynamics of golimumab was investigated in the phase 3 study BAT-2506-002 contributing to the present submission.

For information on overall study design and population of phase 3 study, see section 6.3 and 6.4 of this report.

5.2.3.1. Mechanism of action

Golimumab is a fully human anti-TNF-α monoclonal antibody that binds to both the soluble and transmembrane bioactive form of TNF-α, blocks TNF-α from binding to its receptor, and inhibits TNF-α -mediated signaling, thereby suppressing abnormal immunisation reaction and inflammation mediated by TNF receptors.

5.2.3.2. Primary and secondary pharmacology

Primary pharmacology in study BAT-2506-002

Secondary PD objective: To compare PD parameter of BAT2506 with EU Simponi in subjects with active PsA.

Secondary PD endpoints: Change from Baseline in C reactive protein (CRP) overtime. Impact of CRP changes on efficacy and safety.

Blood samples were collected for evaluation of CRP during screening period (up to 4 weeks), Week 0, 4, 8, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. The CRP related PD analysis was performed, as CRP is one component of ACR 20/50/70.

Table 20: Summary of CRP Over Time: TP1 and TP2 – Study BAT-2506-002

Treatment Period 1 (FAS 1)	**BAT2506 (N=351)**	**Simponi (N=179)**	**Simponi→BAT2506 (N=174)**	**Combine Simponi(N=353)**
	mean (SD)	**mean (SD)**	**mean (SD)**	**mean (SD)**
n	**344**	**172**	**171**	**343**
Week 8	2.817 (6.523)	3.547 (12.614)	2.546 (4.046)	3.048 (9.378)
Week 8 Change from Baseline	-4.509 (9.064)	-3.627 (14.473)	-4.453 (12.185)	-4.039 (13.368)
Week 8 Percent Change from Baseline	-21.0646 (156.8140)	-24.3486 (80.1659)	-18.2578 (134.6432)	-21.3121 (110.6073)
n	**334**	**173**	**167**	**340**
Week 14	2.705 (5.577)	2.283 (3.509)	2.132 (3.201)	2.209 (3.357)
Week 14 Change from Baseline	-4.801 (11.796)	-4.832 (10.461)	-5.053 (13.187)	-4.941 (11.861)
Week 14 Percent Change from Baseline	-9.7005 (354.6351)	-38.7381 (55.2003)	-25.7994 (93.5922)	-32.3829 (76.6634)
n	**336**	**172**	**163**	**335**
Week 24	2.968 (6.808)	2.591 (4.098)	2.652 (4.522)	2.621 (4.303)
Week 24 Change from Baseline	-3.862 (9.909)	-4.506 (11.417)	-5.001 (14.097)	-4.747 (12.774)
Week 24 Percent Change from Baseline	-8.4823 (206.9530)	-22.8707 (102.9748)	-18.4511 (139.0908)	-20.7203 (121.7263)
Treatment Period 2 (FAS 2)	**BAT2506 (N=341)**	**Simponi (N=172)**	**Simponi→BAT2506 (N=166)**	
n	**320**	**163**	**155**	
Week 52	2.486 (3.848)	2.263 (3.592)	2.219 (3.218)	
Week 52 Change from Baseline	-4.452 (9.588)	-4.494 (10.169)	-5.637 (14.493)	
Week 52 Percent Change from Baseline	-21.9899 (115.2749)	-21.5674 (246.3103)	-28.9147 (86.5310)	

Abbreviations: CRP = C reactive protein; SD = standard deviation, FAS = Full analysis set

Source: CSR BAT-2506-002-CR, Table 11-48 and Table 11- 49

In line with the EMA guideline "Guideline on similar biological medicinal products containing monoclonal antibodies: nonclinical and clinical issues" (EMA/CHMP/BMWP/403543/2010), secondary pharmacodynamics studies were not performed.

5.2.3.3. Immunological events

Results on immunogenicity from phase 1 studies

Study BAT-2506-001

ADA testing of golimumab was performed in the screening period. After randomisation, immunogenicity blood samples were collected from: before administration (within 1 hour pre-dose) (Day 1), and 672 hours (Day 29), 1176 hours (Day 50), and 1680 hours (Day 71) post-dose, a total of 4 time points, used for immunogenicity studies.

A total of 14 subjects were positive for ADA, of which 1 subject was positive for ADA for the first time on D29, 8 subjects were positive for ADA for the first time on D50, and 5 subjects were positive for ADA for the first time on D71. Most ADA positive subjects had neutralising antibodies (N=12).

Study BAT-2506-003

Time points of immunogenic blood samples after randomisation, include pre-dose (within 1 hour before administration) (D 1), and 336 hours after administration (D 15), 672 hours (D 29), 1176 hours (D 50), and 1848 hours (D 78), a total of 5 time points, which were to be used for immunogenicity studies. Samples from ADA-positive sampling point were to be further tested for neutralising antibodies (NAb).

A total of 46 (12.6%) subjects were with at least one positive ADA test during the study. The ADA incidence in BAT2506, EU-Simponi and US-Simponi group were 11 (9.0%), 19 (15.4%) and 16 (13.4%), respectively. There were 3 subjects in the BAT2506 group with ADA positive before baseline but negative after administration. The first time occurring positive ADA after administration was D15 observed in BAT2506 and US-Simponi groups.

A total of 40 (11.0%) subjects were with at least one positive NAb test during the study, and the NAb incidence in BAT2506, EU-Simponi and US-Simponi group were 8 (6.6%), 19 (15.4%) and 13 (10.9%), respectively, showing that the majority subject with ADA positive were also NAb positive.

Results on immunogenicity from phase 3 study BAT-2506-002

Blood samples for immunogenicity assessment were collected at Week 0, 2, 4, 8, 12, 14, 24, 36, 48, 52, 56, and 60 in study BAT-2506-002. When suspected immune response-related AE (eg, hypersensitivity, injection site reaction) happened, it was strongly recommended for additional ADA sample collection within 3 days of occurrence of the AE.

Study subjects were given 'positive' subject IM status if they had at least one confirmed positive sample at any time (including Baseline) during the treatment FU periods. Study subjects were given 'negative' subject IM status if all evaluated IM sample results during the treatment and FU period were negative, and they had at least one evaluable IM result post dose.

Table 21: Overview of ADA incidence for overall period (IAS 1) - Study BAT-2506-002

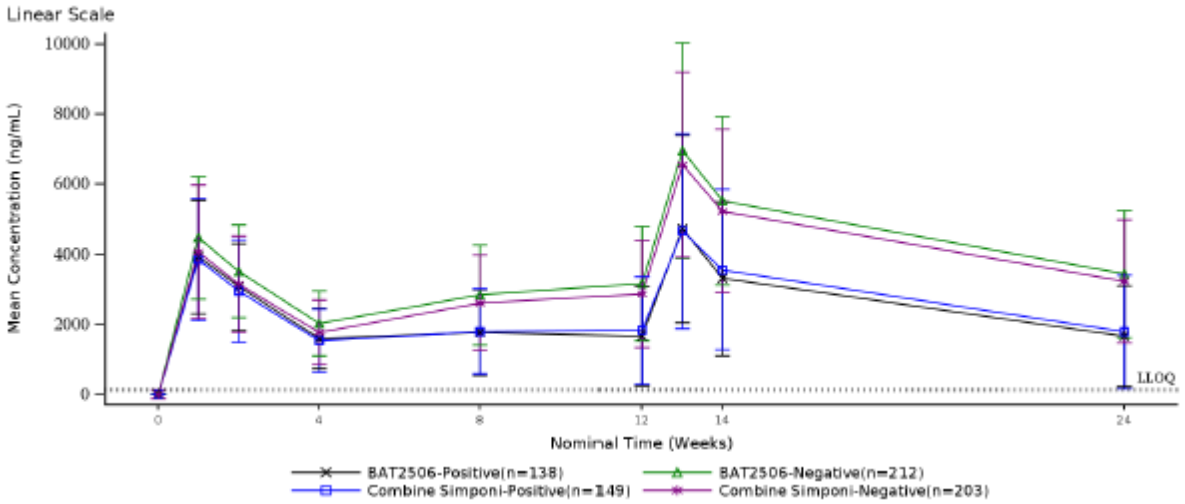
Visit ADA test	BAT2506 (N=351)	Simponi (N=187)	Simponi→BAT2506 (N=166)	Combine Simponi (N=353)	All Subjects (N=704)
Up to Week 8					
ADA Positive	45 (12.9)	24 (12.9)	10 (6.1)	34 (9.7)	79 (11.3)
NAb positive	41 (11.8)	18 (9.7)	7 (4.2)	25 (7.1)	66 (9.4)
Up to Week 14					
ADA Positive	94 (27.0)	64 (34.4)	44 (26.5)	108 (30.7)	202 (28.9)
NAb positive	92 (26.4)	59 (31.7)	42 (25.3)	101 (28.7)	193 (27.6)
Up to Week 24					
ADA Positive	138 (39.4)	81 (43.5)	68 (41.0)	149 (42.3)	287 (40.9)
NAb positive	135 (38.6)	76 (40.9)	67 (40.4)	143 (40.6)	278 (39.6)
Up to Week 52					
ADA Positive	153 (43.7)	85 (45.5)	76 (45.8)	-	314 (44.7)
NAb positive	150 (42.9)	81 (43.3)	73 (44.0)	-	304 (43.2)

Abbreviations: ADA= Anti-Drug antibody, NAb=neutralising antibodies, N=number of subjects in the analysis set, n=number of subjects in the specified category

Source: BAT-2506-002-CR, Table 11-68

The incidence of subjects with positive ADA and NAb were lower in the subgroup analysis of concomitant use of MTX compared to non-MTX user during the study. Overall, in the subgroup analysis of concomitant use of MTX, a total of 104 subjects (33.1%) were reported positive ADA, including 52 subjects (33.1%) in BAT2506 group, 29 subjects (34.9%) in Simponi group, and 23 subjects (31.1%) in Simponi→BAT2506 group; a total of 96 subjects (30.6%) were reported positive NAb, including 50 subjects (31.8%) in BAT2506 group, 26 subjects (31.3%) in Simponi group, and 20 subjects (27.0%) in Simponi→BAT2506 group. Overall, in the subgroup analysis of concomitant use of non-MTX, a total of 216 subjects (55.5%) were reported positive ADA, including 103 subjects (53.4%) in BAT2506 group, 58 subjects (55.8%) in Simponi group, and 55 subjects (59.8%) in Simponi→BAT2506 group; a total of 213 subjects (54.8%) were reported positive NAb, including 102 subjects (52.8%) in BAT2506 group, 56 subjects (53.8%) in Simponi group, and 55 subjects (59.8%) in Simponi→BAT2506 group. Overall, the results indicated that the use of MTX may inhibit the immunogenicity response either by BAT2506 or Simponi.

Impact of ADA status on PK

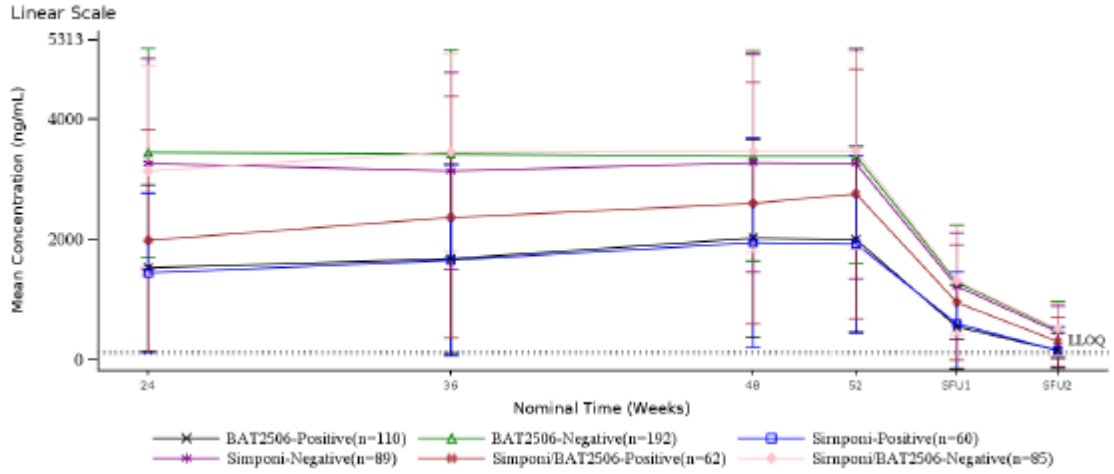


Abbreviations: ADA = Anti-Drug antibody, n = number of subjects with non-missing values, LLOQ = Lower Limit of Quantification.

Dotted line indicates LLOQ = 100 and 150 ng/mL.

Source: Figure 14.2.2.1.18.6.

Figure *9*: Mean (± SD) Serum Concentration Versus Nominal Time Weeks (Linear Scale) (PK Analysis Set 1) by ADA status



Abbreviations: ADA = Anti-Drug antibody, n = number of subjects with non-missing values, LLOQ = Lower Limit of Quantification; SFU = Safety Follow-Up.

Dotted line indicates LLOQ = 100 and 150 ng/mL.

Source: Figure 14.2.2.1.18.7.

Figure *10*: Mean (± SD) Serum Concentration Versus Nominal Time Weeks (Linear Scale) (PK Analysis Set 2) by ADA status

ADA was identified as a significant covariate in the PopPK analysis. Exposures in the ADA-negative group were higher than those in the ADA-positive group. Upon comparing exposure results, it was observed that the geometric mean ratio changes ranges of BAT2506 and Simponi positive subjects relative to their respective negative groups, were -38.2% to -17.4% and -33.4% to -12.5%, respectively.

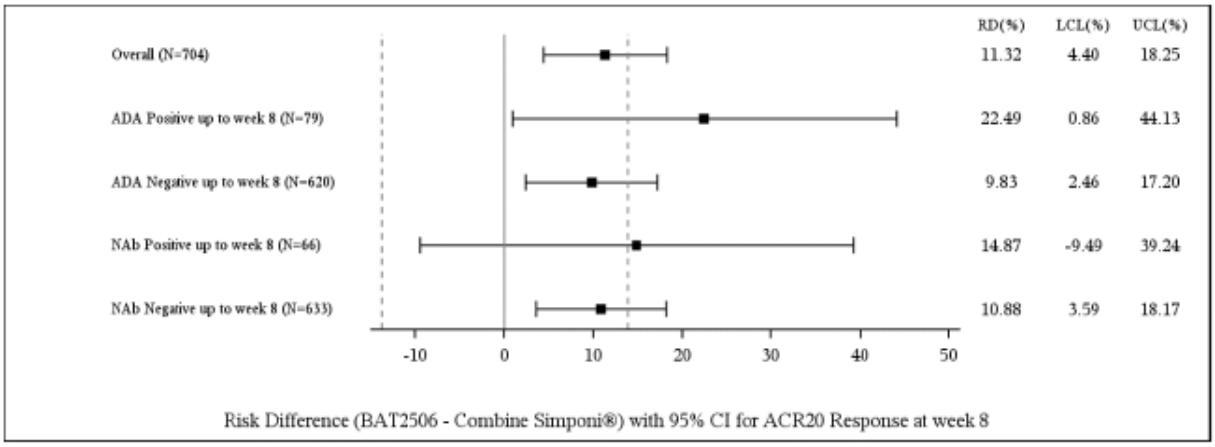
Table 22: Impact of ADA on geometric mean (%CV) estimated exposure of BAT2506 and Simponi from popPK model

Characteristics		BAT2506		Simponi®	
		ADA negative	ADA positive	ADA negative	ADA positive
No. of subjects (%)		397 (31.7)	167 (13.3)	480 (38.3)	209 (16.7)
AUC_1 (µg*hr/mL)	geomean (%CV)	2177.5 (33.8)	1706.1 (36.5)	2064.2 (36.5)	1710 (40.1)
	difference (%)[a]	—	-21.6	—	-17.2
C_{max1} (µg/mL)	geomean (%CV)	4.6 (34.1)	3.8 (36.1)	4.4 (37.9)	3.8 (40.1)
	difference (%)[a]	—	-17.4	—	-12.5
C_{min1} (µg/mL)	geomean (%CV)	2 (39.3)	1.3 (47.2)	1.8 (40.5)	1.3 (50.5)
	difference (%)[a]	—	-32.4	—	-28.2
AUC_{ss} (µg*hr/mL)	geomean (%CV)	3395.5 (39)	2426.2 (43.1)	3191.6 (40.1)	2445.8 (46.2)
	difference (%)[a]	—	-28.5	—	-23.4
$C_{max,ss}$ (µg/mL)	geomean (%CV)	7.1 (35.8)	5.3 (38.2)	6.7 (38.1)	5.4 (41.2)
	difference (%)[a]	—	-24.5	—	-18.9
$C_{min,ss}$ (µg/mL)	geomean (%CV)	2.9 (48.6)	1.8 (59)	2.7 (48.8)	1.8 (62.5)
	difference (%)[a]	—	-38.2	—	-33.4

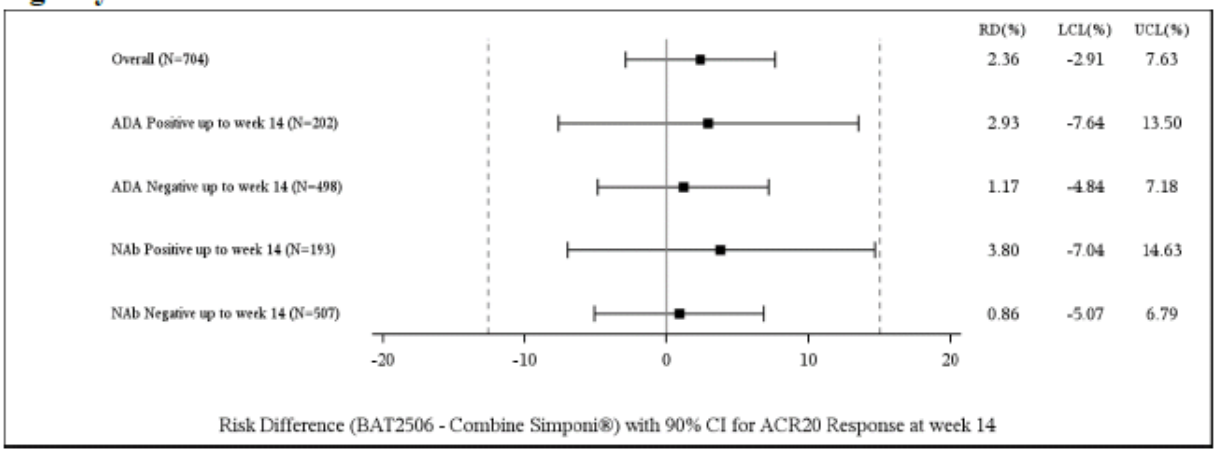
a %difference from the geometric mean simulated exposures of ADA negative subjects.

Impact of ADA status on Efficacy

Agency: EMA



Agency: FDA



Abbreviations: ACR = American college of rheumatology; ADA=Anti-Drug antibody; CI = confidence interval; NAb = neutralising antibodies; CI = confidence interval; EMA = European Medicines Agency; FDA = Food and Drug Administration; RD = Common Risk Difference; LCL = Lower confidence limit; MH = Mantel-Haenszel; MTX = methotrexate; NMPA = National Medical Products Administration; UCL = upper confidence limit.

90/95% CI is a Clopper Pearson 90/95% CI Wilson CI for binomial proportions.

The treatment group difference is analysed using Stratified MH test adjusted by the randomisation strata (region [Asia/Europe], concomitant use of MTX [yes/no], body weight [≤84 kg/>84 kg] and plaque psoriatic involvement [<12 mild, ≥12 moderate/severe]). 90/95% CI for the common risk difference is calculated based on the MH method and carried out 2-tailed on 5%/2.5% level of significance.

Source: Figure 14.3.7.10

Figure *11*: Forest Plot of Proportion of Subjects Achieving ACR 20 at Week 8 and Week 14 by ADA Status (Full Analysis Set 1) – Study BAT-2506-002

Table 23: Primary estimand, ACR20 response by ADA status subgroups at Week 24

	BAT2506 (N=351)	**Combine Simponi** (N=353)
OVERALL		
Number of subjects evaluable for ACR response at Week 24 - observed	336	334
ACR20 Response at Week 24 - EMA		
n/Nx [(1)]	284/351	272/353
Proportion of responders (%) (95% CI) [(2)]	84.44	81.49
	(80.51, 88.37)	(77.27, 85.71)
Common Risk Difference (%) (BAT2506 - Combine Simponi) [(3)]	3.17	
95% CI for Common Risk Difference (%) [(3)(4)]	(-2.60, 8.94)	
ADA Positive (up to week 24)		
Number of subjects evaluable for ACR response at Week 24 - observed	136	145
ACR20 Response at Week 24 - EMA		
n/Nx (1)	110/138	120/149
Proportion of responders (%) (95% CI) [(2)]	81.23	83.06
	(74.60, 87.87)	(76.89, 89.22)
Common Risk Difference (%) (BAT2506 - Combine Simponi) [(3)]	-1.29	
95% CI for Common Risk Difference (%) [(3)(4)]	(-10.52, 7.93)	
ADA Negative (up to week 24)		
Number of subjects evaluable for ACR response at Week 24 - observed	200	189
ACR20 Response at Week 24 - EMA		
n/Nx (1)	174/212	152/203
Proportion of responders (%) (95% CI) [(2)]	86.55	80.74
	(81.75, 91.36)	(75.02, 86.45)
Common Risk Difference (%) (BAT2506 - Combine Simponi) [(3)]	6.32	
95% CI for Common Risk Difference (%) [(3)(4)]	(-1.19, 13.84)	

Subjects with any intercurrent event or missing at Week 24 analysis window defined in SAP are imputed according to SAP section 4.2.1.2.

(1) n= number of responders observed; Nx= number of subjects with ACR response after imputation.

(2) Proportion and 95% CI is a Clopper Pearson 95% CI for binomial proportions after multiple imputation.

(3) The common risk difference between treatment groups is analysed using Mantel-Haenszel (MH) approach adjusted by
the randomisation strata (region (Asia/Europe), concomitant use of MTX (yes/no), body weight (≤84 kg/>84 kg) and plaque psoriatic involvement (<12 mild, ≥12 moderate/severe)) after multiple imputation.

(4) The 95% confidence interval for the common risk difference is calculated based on the Mantel-Haenszel Method at an overall significance level of 5% after multiple imputation.

Source: Gotenfia – Responses to D120 questions - clinical

5.2.4. Overall discussion and conclusions on clinical pharmacology

5.2.4.1. Discussion

Pharmacokinetics (PK)

Three (3) clinical studies were completed for Simponi (BAT2506) from which PK data was obtained from two phase 1 studies in healthy volunteers (one is a supportive PK study including US-Simponi as required by the US FDA) and a phase 3 study in subjects with PsA. Furthermore, a population PK

model was developed based on serum concentration data collected from the 3 clinical studies and aimed to further describe the PK of golimumab and to assess PK similarity of BAT2506 and Simponi in PsA patients. The resulting PK database is deemed sufficient for a biosimilar assessment.

Bioanalytical methods

An ELISA assay for the quantitation of BAT2506 and Simponi in human serum was developed and fully validated. EMA guideline EMA/CHMP/ICH/172948/2019 is not cited in validation reports, however, relevant acceptance criteria from guideline were applied throughout the method validation. Bioanalytical similarity of the biosimilar and originator has been successfully confirmed, thus use of BAT2596 only as reference standard is acceptable. The PK assay has been validated for selectivity in healthy serum; in-study selectivity for patient study BAT-2506-003 was confirmed by the use of pre-dose samples from 10 PsA patients. Interference with TNF- α (0.001 µg/mL, 0.01 µg/mL and 0.1µg/mL) was determined at LLOQ (0.1µg/ml) during validation. Based on literature references (Owczarek, 2012[1], Arican, 2005[2]), the levels of TNF- α in serum appear to range in the order of units to tens of pg/mL in patients and controls and do not reach levels of ≥ 1000 pg/mL (0.001µg/mL, lowest concentration tested). Thus, the issue was not further pursued.

A partial validation was conducted for addition of the new analyte US-Simponi. As the absolute bioanalytical bias difference between the two methods was measured to be ≤ 10%, the validation parameters, except for the stability of US-Simponi, were taken from full validation, which was acceptable.

In-study performance of the assays was demonstrated by back- calculated calibration standards, inter-batch precision and accuracy of QC samples and ISR. Study samples were analysed without exceeding the validated short-term, long-term or freeze-thaw stability periods. In the test for parallelism, there was no significant difference between spiked and real samples. Overall, method performance in clinical studies was deemed appropriate.

PK in healthy volunteers

Study BAT-2506-001-CR was a randomised, double-blind, two-arm, single-dose, parallel-group study in healthy adult volunteers. General design aspects were discussed in EMA Scientific Advice (EMEA/H/SA/4480/1/2020/III) after study start/during reporting phase and EMA guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010) was followed. Overall study design aspects are acceptable. The parallel group design is deemed appropriate considering the half-life and immunogenic potential of golimumab. The PK sampling times are considered sufficient to capture C_{max}. Considering all the data available, there is also no concern that $AUC_{0\text{-}inf}$ was not adequately covered. The study population of this phase 1 pivotal PK study was highly standardised by inclusion criteria with restriction in gender (male only), age (18-50 years), BMI (18-28 kg/m^2), and body weight (50-80kg) and 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.

EU-approved product was used as comparator. Both products were applied as pre-filled syringe (PFS). A single dose of BAT2506 or EU Simponi was administered subcutaneously at the lower part of the abdomen at day 1. The route of administration with application site restriction is agreed as it is sensitive to detect any potential PK differences during the absorption phase. The selected dose of 50 mg is the lowest therapeutic adult dose of Simponi. This is considered adequate for a single dose

[1] Owczarek D, Cibor D, Głowacki MK, Cieśla A, Mach P. TNF-α and soluble forms of TNF receptors 1 and 2 in the serum of patients with Crohn's disease and ulcerative colitis. Pol Arch Med Wewn. 2012;122(12):616-623.
[2] Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm. 2005;2005(5):273-279.

study in healthy volunteers. According to SmPC of Simponi, PK of golimumab should be within the linear range (linear between doses 50 - 400 mg). Protein content of the selected batches was tested almost identical between test and reference product BAT2506 (103.7mg/ml; EU Simponi 103 mg/ml) and thus, impact should be negligible.

For the pivotal PK study, statistical analysis as well as PK analysis set was pre-planned (before data base lock). For non-compartmental analysis, all BLQ values occurring after first quantifiable concentration were handled as missing in the non-compartmental analysis. This is potentially problematic as it may overestimate golimumab serum concentration. However, the applicant provided sensitivity analysis for AUC_{0-t} and AUC_{0-inf} with BLQ values after the first quantifiable concentration set to zero and with all BLQ values as observed/measured. The statistical analyses from sensitivity analyses show that primary PK parameters were still within the acceptance range of 80.00 to 125.00%, which is reassuring.

Sample size calculation was based on available originator data. As CV was regarded as uncertain, a blinded PK interim analysis was conducted after 50% subjects had completed the study in order to re-assess sample size. A blinded sample size reassessment could lead to an inflation in type I error rate above the nominal level of 0.05. Based on the article literature "Blinded sample size re-estimation in crossover bioequivalence trials" (D. Golkowski et al, 2014[3]) the applicant argued, that the following conclusion can be drawn: "When conducting an interim analysis to estimate the CV value in a blinded manner upon collecting 50% of the data, and with the required sample size being 80 or greater, the actual type 1 error rate will not exceed 0.055. This represents an increase of no more than 10% relative to the nominal significance level (α= 0.05)." To correct the type I error, 91% CI and 95%CI for the geometric mean ratio of PK parameters (with pairwise comparisons among the three treatments groups) were calculated and presented by the applicant, which correspond to nominal levels of 0.045 and 0.025, and would hence allow for an alpha inflation of 10% resp. 50%, which seems to be conservative in light of the publication (D. Golkowski et al, 2014) and hence acceptable. The 91% CI and 95% CI for the GMR of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} all fell within the equivalence margin of (0.80,1.25), which is reassuring.

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

Demographic baseline data represent the highly standardised population. The male Chinese subjects had a mean age (SD) of 35.3 (8.12) years, a mean body weight (SD) of 65.80 (7.619) kg, a mean BMI (SD) of 23.12 (2.409) kg/m^2, and a mean height (SD) of 168.66 (5.460) cm; 171 subjects (95%) were Han ethnicity. Overall, the demographic baseline characteristics in BAT2506 group were comparable to those in EU Simponi group.

None of the subjects had pre-dose golimumab concentrations in the study. Arithmetic Mean (±SD) serum golimumab concentration versus time curves following single SC dose administration of BAT2506 and EU Simponi indicate similar course of golimumab concentrations over time of both products. Furthermore, descriptive statistics of golimumab concentration at different timepoints were presented. CV (%) ranged from 31.86 to 85.4% at timepoints p.a., thus, variability was rather high but comparable between treatment groups.

The 90% CIs for test to reference ratios of C_{max}, AUC_{0-t} and AUC_{0-inf} were contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for the pair-wise comparison among the 2 study drugs (C_{max}: 96.29% [87.93% - 105.45%] AUC_{0-t}: 100.50% [92.12% - 109.64%] AUC_{0-inf}: 100.92% [92.30% - 110.34%]). Thus, primary PK analysis supports the claim of similarity between biosimilar and originator. Furthermore, the means of the secondary PK parameters (i.e., $t_{1/2}$, Kel, Vd

[3] Golkowski D, Fried T, Kieser M. Blinded sample size re-estimation in crossover bioequivalence trials. Pharm Stat. 2014 May-Jun;13(3):157-62.

and CL/F) and median T_{max} were comparable between the study treatments and the 90% CIs of the GMRS for the secondary PK parameter AUC_{0-672h} were also within the equivalence margins of 80.00-125.00%.

Additionally, 4 sensitivity analyses were conducted. Sensitivity analysis 1 investigated robustness of the primary analysis by applying an ANOVA model instead of ANCOVA (with body weight as co-variate). Results indicate that even when body weight is not considered as stratification factor, all 3 primary PK parameters were contained within the pre-defined acceptance range of 80.00-125.00%. Sensitivity analysis 2 excluded 2 subjects with incomplete sampling potentially affecting analysis of AUC_{0-t} and AUC_{0-inf}. Results indicate that the 2 patients with incomplete sampling only marginally changed the outcome; AUC_{0-t} and AUC_{0-inf} were still contained within the pre-defined acceptance range. Furthermore, exclusion of the 13 subjects tested ADA positive at day 71 or of the 14 subjects tested ADA positive after drug administration, as done for sensitivity analysis 3 or 4, did not affect the similarity of PK parameters. Overall, sensitivity analyses presented support the claim of PK biosimilarity.

Study BAT-2506-003-CR was a randomised, double-blind, single dose, parallel three-arm comparative study on PK and safety of BAT2506 versus EU-Simponi and US-licensed Simponi in healthy Chinese male subjects. The study was conducted to meet FDA's requirements and is considered as supportive here.

The same dose was applied as compared to the pivotal PK study BAT-2506-001. Furthermore, population characteristics obtained by same key inclusion and exclusion criteria were comparable for both studies. PK sampling was prolonged, with latest sampling time point at D78 p.a. (study BAT-2506-001: D71 p.a.). Primary PK endpoints and applied acceptance limits were in line with EMA guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). An ANOVA method was applied; body weight (weight ≥ 50 kg to < 65 kg and weight ≥ 65 kg to ≤ 80 kg) was included as covariate.

The PKPS included 369 subjects and was identical to FAS. The demographic and baseline characteristics were comparable among the treatment groups. Arithmetic Mean (±SD) serum golimumab concentration versus time curves indicate overall similar course of golimumab concentrations over time of BAT-2506 and EU Simponi, with slightly higher exposure seen after BAT2506 application. This is also reflected by slightly higher numerical values of BAT2506 for AUC_{0-t}, AUC_{0-inf} and C_{max}. However, the 90% CIs for test to reference ratios of AUC_{0-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. Confidence intervals were rather narrow, but not evenly spread around 1 (100%), reflecting the somewhat higher exposure seen with BAT2506 in this study.

As a blinded interim analysis was conducted when 188 subjects (50%) had completed the study, the GMR between groups and their 91% CI of PK parameter (C_{max}, AUC_{0-inf}, and AUC_{0-t}) were also calculated, in order to adjust the type I error. They also fell within the pre-specified acceptance boundaries of 80.00% to 125.00%.

Reasons for subject exclusion from the bioequivalence analysis included missing samples, $AUC_{expol>20\%}$, first sample C_{max}, ADA/nAB positive prior dosing. Additional sensitivity analyses were performed that included those subjects – results fell within the acceptance range in all cases.

Overall, results from study BAT-2506-003 support the claim on PK similarity between BAT2506 and EU Simponi.

PK in target population

For the **phase 3 study BAT-2506-002-CR** in the PsA target population, a sparse sampling was conducted. The applicant provided concentration time profiles and summarising statistics of

golimumab serum concentrations. Golimumab was applied once every 4 weeks; IMP switch was conducted at week 24. In addition to trough values (prior dosing), additional samples were obtained after the first dose and the fourth dose, where steady state is expected to be reached. Indeed, the serum trough concentrations increased from baseline to week 8 with a slight increase from weeks 8 to 12 for both treatment groups. At each time point in TP1 (prior to IMP switch), variability was high with CV%>50. Golimumab concentration time profiles indicate comparable PK characteristics of both products in the patient population. In order to further support the claim on PK similarity of BAT2506 and EU Simponi under steady state against the background of failed primary efficacy endpoint, the applicant was asked to provide comparison of C_{trough} at both, week 8 and week 12 (at expected steady state). For both timepoints the GMR and corresponding 95% CI were fully within the equivalence margin of (0.80, 1.25) for PK comparison, which is reassuring.

In TP2 (after IMP switch), 6 additional samples were obtained. There were numerical differences in mean serum concentrations between the 3 groups under investigation, with concentration Simponi→ BAT2506 > BAT2506 > Simponi at each timepoint investigated. The impact of IMP switch from Simponi to BAT2506 on PK profile seems to be low. This is further supported by simulation based on population PK model.

Population PK analysis

In order to support results from patient study BAT-2506-002 with sparse sampling, a population PK model was developed by the applicant and was used in order to further support the statement on PK similarity, analyse potential variabilities and covariates. Interindividual variabilities where moderate and similar between BAT2506 and Simponi. While some minor biases like potential correlation between covariates such as CRP and health status could be observed, the model was able to describe the observed data well. Model simulations were also used to compare exposures between Simponi and BAT2506 stratified by different covariates. Overall, the exposures were comparable between the respective groups. Only age showed minor deviations, most likely due to limited sample size in patients older than 65. The model was applied to provide supportive evidence only; it was not applied to simulate exposure in unexplored dosing regimens or to otherwise generate pivotal PK data. PK parameters area under the curve at steady state [AUC_{ss}], area under the curve after first dose [AUC_1], maximum concentration at steady state [$C_{max,ss}$], maximum concentration after first dose [C_{max1}], minimum concentration at steady state [$C_{min,ss}$], and minimum concentration after first dose [C_{min1}]) were calculated and compared between treatment groups. Treatment groups showed comparable results for all parameters under investigation. Furthermore, the ratio of geometric mean and the 90% CIs of the geometric mean ratios fall within the range of 80 - 125%, indicating that exposure in the 2 treatment groups is similar.

The SmpC wording on special populations is in line with the originator.

Pharmacodynamics

The mode of action of golimumab is established and comparable across different indications. Validated PD markers do not exist for the efficacy of TNF- α inhibitors; Establishment of PD biosimilarity is not expected.

In patient study BAT-2506-002, C-reactive protein (CRP) was analysed as secondary PD endpoint and was component of the primary efficacy measurement American College of Rheumatology Responses 20. Upon request, relevant information on analysis of CRP within the clinical trial program has been provided by the applicant. CRP was quantified together with other clinical safety parameter. The method was an immunoturbidimetric assay where human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies and aggregates were determined turbidimetrically. Analysis was performed at 2 locations on an equivalent instrument platform supplied by the same manufacture,

and using the same technology, methodology, calibrators, controls, assay reagents and analyser settings. Method validation considered accuracy, precision and total allowable error, which is acceptable.

Mean CRP at baseline was 7.69 mg/l for BAT2506 and 7.35 mg/l for Simponi combined group. At week 8 (timepoint for analysis of primary efficacy endpoint), the CRP reduction was comparable in both treatment groups (-21% change from baseline).

Immunogenicity

Clinical immunogenicity was evaluated by monitoring the humoral immune response (anti-drug antibodies [ADA] and neutralising ADA [NAb]) reactive with BAT2506, EU Simponi and US Simponi, respectively. The immunogenic profile was investigated in all 3 clinical trials, furthermore, the impact on clinical parameters (PK and efficacy) was assessed in patient study BAT-2506-002. Based on data from originator, ADA positivity is expected to be associated with reduced golimumab exposure.

Bioanalytical methods

Immunogenicity testing of BAT2506 and Simponi in the 3 clinical studies utilised a 3-tiered approach comprising a screening assay followed by a confirmatory assay and the analysis of ADA titer and neutralising capacity. For the screening, confirmation, and titration of anti-BAT2506/ Simponi (EU&US) antibodies in human serum, a semi quantitative ECL assay in Meso Scale Discovery was developed and fully validated. The employed tiered strategy agrees with the Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010). ADA testing was conducted by using a single assay approach with BAT2506 (biosimilar) used as antigen. Surrogate positive control of animal origin (rabbit anti-BAT2506 polyclonal antibodies) was used for preparation of positive controls (LPC 40 ng/mL, HPC 2000 ng/mL). The test for antigenic equivalence (the ability of the biosimilar and the originator to bind in a similar manner) was performed: excess concentrations of both the biosimilar and the originator inhibited the assay signal of the positive control to a similar extent. Thus, the antigenic equivalence was proved justifying a single assay approach to detect ADAs against both the biosimilar and the originator.

The assay was able to measure ADAs in presence of the circulating drug, the drug tolerance was 10 µg/mL of a drug at LPC level of ADA (40 ng/mL) and 50 µg/mL of a drug at 1000 ng/mL level of ADA, that is acceptable because concentrations of the circulating drug were lower than 10 µg/mL in most of study samples. Assay selectivity and matrix effect (in normal, 2% haemolysed and lipemic matrix) were acceptable. Assay specificity to the drug target, TNF- α, was assessed with higher concentration of TNF- α (1000 pg/mL) than expected in the study samples based on literature. Target interference was not observed.

The assay cut points were established using approximately 50 treatment naïve samples from healthy subjects in the validation; no additional validation in patient serum was conducted. The same cut-points as in the validation were used in the clinical studies. The screening cut-point was determined non-parametrically as the 95th percentile of the normalised data set. By use of the screening assay in patient study BAT-25506-002, the false positive rate of the pre-dose samples was determined to be 6.6 %, thus, within the desirable range of 2.0% to 11%. Therefore, it can be agreed that there was no need to set a new study specific cut-point.

A non-cell based ECL competitive ligand binding assay (CLB) has been developed and fully validated for determination of neutralising anti-drug antibodies in the pivotal clinical trials. The method was using Sulfo-tag-BAT2506/ Simponi to form the complexes with antibodies present in the samples. After incubation, the antibody complex was added to the TNF- α coated MSD plate. TNF- α protein bound sulfo-tag labelled BAT2506/ Simponi generated the ECL response. Binding of free sulfo tag-

BAT2506 to the TNF- α protein generates a luminescent signal and the presence of NAb is reducing the intensity of signal.

Surrogate positive control (rabbit anti-BAT2506 polyclonal antibodies) was used for preparation of positive controls. A floating cut-point was applied. Sensitivity of the method was 45.5 ng/mL. Assay precision was acceptable. The assay was tolerant to a high level of circulating drug (PC at 250 ng/mL and above can tolerate 100 µg/mL of drug). The assay was demonstrated to be selective and specific (for TNF- α concentration up to 100 ng/mL at low PC). Antigenic equivalence was investigated during validation, however, both detection solutions (sulfo-TAG BAT2506 and sulfo-TAG Simponi) were used during study sample analysis.

Results on immunogenicity

In study **BAT-2506-001-CR,** sampling was sparse (4 samples), with earliest timepoint p.a. at day 29. However, as only 1 subject was ADA positive at day 29, no tendency for early ADA formation is indicated and thus, no issue is raised here. Afterwards, 8 subjects were positive for ADA for the first time on D50, and 5 subjects on D71. Most ADA positive subjects had neutralising antibodies. The overall incidence for ADA in 2 groups were: 4(4.4%) for BAT2506 compared to 10(11.1%) for EU-Simponi, and the overall incidence for NAb in 2 groups were: 4(4.4%) for BAT2506 compared to 8(8.9%) for EU-Simponi.

In study **BAT-2506-003CR,** an additional timepoint at day 15 was amended and the last sample timepoint was at day 78. Three (3) subjects in the BAT2506 group were ADA positive before dosing, with an overall incidence of 0.8%, thus below the 1% false positive rate. A total of 46 (12.6%) subjects were tested ADA positive during the study. The ADA incidence in BAT2506, EU-Simponi and US-Simponi group were 11 (9.0%), 19 (15.4%) and 16 (13.4%), respectively. Mean ADA titer was low throughout the study. The NAb incidence in BAT2506, EU-Simponi and US-Simponi group were 8 (6.6%), 19 (15.4%) and 13 (10.9%), respectively. In the EU Simponi group, with highest incidence of ADA/nAB positivity, there was also a noticeable difference in mean AUC0-inf of ADA positive vs ADA negative subgroups.

Overall, ADA incidence after a single golimumab dose in healthy subjects was rather low, with a tendency for lower immunogenic potential of BAT2506 compared to Simponi. The potential impact of ADA/nAB positivity on PK biosimilarity assumption was investigated and does not raise concern.

In study **BAT-2506-002-CR**, the overall ADA incidence was around 40%. Results were comparable between treatment groups: at week 24, 38.5% of subjects were ADA positive in the BAT2506 group, vs. 41.5% in the Simponi group. IMP switch after week 24 did not have a relevant impact on ADA incidence rates in TP2: 42.1% were ADA positive in the Simponi→BAT2506 group vs 37.2% in the BAT2506 group and 39.3% in the Simponi group. Most subjects tested ADA positive were also nAB positive. Also here, results were comparable between treatment groups: During TP1, 38.6% of subjects were nAB positive in the BAT2506 group vs. 40.6% in the Simponi combined group. IMP switch did not significantly change occurrence of nAbs: during TP2 39.0% were nAb positive in the Simponi→BAT2506 group vs 36.6% in the BAT2506 group and 37.5% in the Simponi group. The median ADA titers were similar between treatment groups and no increase was observed in the Simponi→BAT2506 group.

As previously seen with the originator, also here, the incidence of ADA and nAb positives was lower in the subgroup of patients with concomitant use of MTX compared to non-MTX user during the study.

The **impact of ADA on PK** was further investigated. Serum concentration vs time curves as well as descriptive statistics of serum concentrations by timepoint were presented by ADA and nAB status. During TP1, the ADA and nAb positivity showed an impact on the mean serum concentration profiles of both, BAT2506 and Simponi groups, from week 4 until week 24. At week 24 (prior to IMP switch)

geometric mean golimumab concentration was 2967ng/ml in the BAT2506 ADA negative group vs 1534ng/ml in the ADA positive group, as well as 2726ng/ml in the Simponi ADA negative group vs 1568ng/ml in the ADA positive group. After IMP switch, the impact of ADA on golimumab exposure remained until end of study for all 3 treatment groups. Overall, the magnitude of change in exposure due to ADA and nABs is deemed to be comparable between BAT2506 and Simponi based on data from study BAT-2506-002. This is further supported by popPK analysis where differences in estimated BAT2506 and Simponi PK parameters in ADA positive subjects vs ADA negative subjects were comparable.

As the majority of ADA positive subjects was also nAB positive, the impact on efficacy was further investigated and compared between originator and biosimilar. The applicant provided **subgroup analysis of the efficacy endpoints** "proportion of subjects achieving ACR 20 at week 8 and week 14" by ADA and nAB status. At week 8, the upper confidence limits of all subgroups (ADA/Nab positive/negative up to week 8) between the BAT2506 group and the combined Simponi group were higher than the predefined upper limit of 13.8%, which is in line with outcome of the primary analysis. For ADA and nAB positive subgroups with low number of subjects, even point estimate was above the upper confidence limits and confidence intervals were wide. At week 14, the ACR 20 response in all subgroups was overall similar to the overall response. To further exclude different impact of ADA and nABs on efficacy of originator and biosimilar, additional subgroup analyses were conducted at a later timepoint, were ADA positive rate was about 40%. Analysis of ACR20 and ACR50 at week 24 by ADA status (ADA positive and ADA negative subgroups) was presented. It is agreed that efficacy response in ACR20 and ACR50 was comparable between ADA positive and ADA negative patients in both treatment groups. Results confirm that formation of anti-golimumab antibodies had no apparent correlation with efficacy.

The impact of ADA on safety is discussed in the safety section 6.4.11.

According to Originator **SmPC**, across the phase 3 RA, PsA and AS studies through week 52, antibodies to golimumab were detected by an enzyme immunoassay (EIA) method in 5% (105/2 062) of golimumab treated patients. Also here, almost all ADA positive patients were nAB positive as well. The higher rates of ADAs and nABs compared to literature data seen here with another assay are not a concern *per se* for biosimilarity assessment, as rates were overall comparable between treatment groups. Formation of anti-golimumab antibodies may be associated with decreased systemic exposure to golimumab but no apparent correlation of antibody development with efficacy has been observed. The section 5.1 of the SmPC has been updated accordingly.

5.2.4.2. Conclusions

The presented clinical pharmacology data are deemed sufficient for a biosimilar development.

In the pivotal PK phase 1 clinical trial BAT-2506-001-CR, the 90% CIs for test to reference ratios of C_{max}, AUC_{0-t} and AUC_{0-inf} were contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for the pair-wise comparison among the biosimilar and originator. Results indicate PK biosimilarity of BAT-2506 and EU Simponi are further supported by results obtained in the additional phase 1 study as well as by sparse sampling and popPK analysis in the phase 3 PsA patient population.

Rather high ADA incidence rates (about 40%) were determined in the PsA patient population and associated with reduced golimumab exposure. As ADA incidence was comparable in both products, the high rates are not of concern *per se* and no apparent correlation of antibody development with efficacy has been observed. Section 5.1 of the SmPC wording was updated accordingly.

Overall, biosimilarity is supported from a clinical pharmacology perspective.

5.3. Clinical efficacy

5.3.1. Dose response studies

Not applicable.

5.3.2. Main study

5.3.2.1. Study BAT-2506-002-CR

5.3.2.1.1. Study design

Study Design

Study BAT-2506-002-CR was a phase 3, multicenter, randomised, double-blind, parallel-group study of BAT2506 in comparison with EU-approved Simponi in patients with active PsA. The study consisted of up to 4-week Screening Period, a 52-week Treatment Period (scheduled treatment duration), and an 8-week Safety Follow-up (SFU) Period.

The Treatment Period (TP) included 2 parts:

- Treatment Period 1 (TP1): Week 0 to week 24
- Treatment Period 2 (TP2): Week 24 to week 52

At week 0, subjects were randomised in a 1:2:1 ratio into 3 groups (Simponi, BAT2506, and Simponi→BAT2506 including a switch of treatment in TP (starting at week 24).

The primary endpoint (percentage of subjects achieving ACR 20 response) was evaluated at week 8 for the EMA analysis. Efficacy analysis for other regulatory agencies (FDA and NMPA) included evaluation of the primary endpoint at week 14.

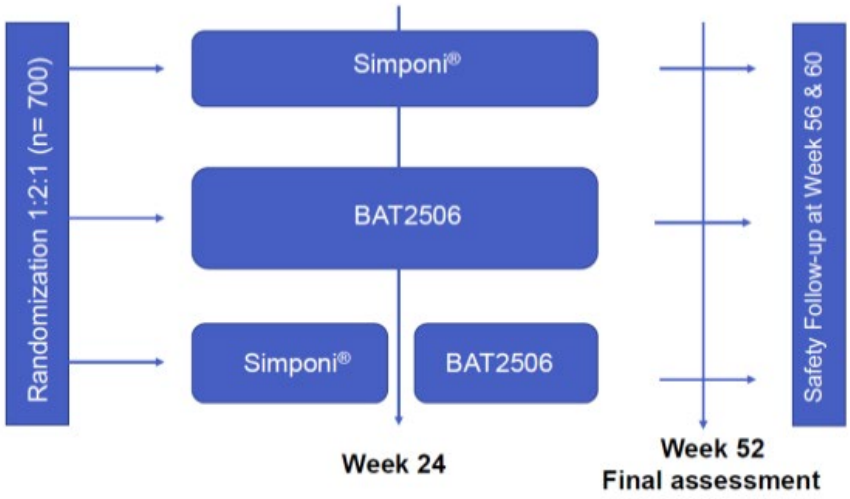


Figure *12*: Study schema

Treatment

Trial intervention

Study drugs (i.e. BAT2506 or Simponi) were administered subcutaneously at 50 mg once every 4 weeks using a single-dose pre-filled syringe.

In total, 13 scheduled doses were planned to be administered to subjects over the course of the entire TPs, including 6 scheduled doses during TP1 and 7 scheduled doses during TP2. The last administration was on Week 48.

Concomitant and rescue therapies

For participants who were using methotrexate, leflunomide, or sulfasalazine, hydroxychloroquine, NSAIDs or oral corticosteroids at Screening, continuation of these drugs was allowed per rules defined in the inclusion criteria. The number of randomised subjects with concomitant use of MTX was capped to 50 %.

Prohibited medications included Epidural, intra-articular, intramuscular, or intravenous corticosteroids, cytotoxic drugs (azathioprine, cyclosporine, cyclophosphamide) with required wash-outs as defined in the exclusion criteria.

Rescue Medication included NSAIDs (increasing stable dose or initiating new NSAIDS) up to the maximum recommended doses to treat a flare for up to 2 weeks during the study as well as short course analgesics other than NSAIDs for up to 7 days during the study. No use of Rescue Medication was reported during the study.

Randomisation

At Week 0, approximately 700 eligible participants were planned to be randomised in a 1:2:1 ratio into one of the 3 groups:

• Simponi 50 mg (Week 0 to week 48)

• BAT2506 50 mg (Week 0 to week 48)

• Simponi 50 mg (Week 0 to week 20) followed by BAT2506 50 mg (Week 24 to week 48)

All participants were planned to be centrally randomised using an Interactive Response Technology (IRT).

Randomisation was planned to be stratified by 1) region (Asia/Europe), 2) concomitant use of DMARDs and MTX (DMARDs+ MTX- / DMARDs+ MTX+ / DMARDs-), and 3) body weight (≤70 kg / > 70 kg to ≤ 84 kg / >84 kg to ≤96.8 kg / >96.8 kg).

Blinding

The trial was planned as a double-blind trial. The randomisation allocation was planned to not be revealed to study participants, investigators, and study site personnel. As BAT2506 and Simponi injections may not look fully similar in the package appearance, unblinded personnel appropriately delegated by the Principal Investigator were planned to be required to prepare and administer the study medication in order to maintain the blind.

Patient population

The study was conducted in Bulgaria, Czech Republic, Poland, Ukraine, and China.
Main inclusion criteria:

- Subject was a male or female, aged from 18 to 80 years at Screening.
- Subject had PsA for at least 6 months prior to the first administration of the study drug and meets CASPAR classification criteria for PsA at Screening.
- Subject had active PsA defined by the presence of ≥3 of 68 tender joint counts and ≥3 of 66 swollen joint counts at Screening and Randomisation.
- Subject had active PsA at Screening despite previous DMARD or NSAID therapy. DMARD therapy was defined as taking DMARD for at least 3 months, or evidence of DMARD intolerance. NSAID therapy was defined as taking an NSAID for at least 4 weeks (or had intolerance to or contraindication to NSAID therapy).
- Subject had at least one active psoriatic lesion with a qualifying lesion of at least 2 cm in diameter at Screening and Randomisation.
- Subject was negative for rheumatoid factor and anti-cyclic citrullinated peptide antibodies at Screening.
- If subject was using MTX, he/she was required to have started treatment at least 3 months prior to the first administration of the study drug and to have no serious toxic side effects attributable to MTX. MTX routes of administration and doses (not to exceed 25 mg/week) were required to be stable for at least 4 weeks prior to the first administration of the study drug and throughout the study.
- If subject was using NSAIDs, including selective cyclooxygenase (COX)-2 inhibitors, and other analgesics, he/she was required to be on a stable dose for at least 2 weeks prior to the first administration of the study drug. If subject was currently not using NSAIDs/COX-2 inhibitors/other analgesics, he/she was required not to have received NSAIDs/analgesics for at least 2 weeks prior to the first administration of the study drug.
- If subject was using oral corticosteroids, he/she was required to be on corticosteroids for at least 4 weeks prior to Screening with a stable dose equivalent to ≤10 mg of prednisone/day for at least 2 weeks prior to the first administration of the study drug.
- If subject was currently not using corticosteroids, he/she was required not to have received oral corticosteroids for at least 2 weeks prior to the first administration of the study drug.

Main exclusion criteria:

- Subject had a diagnosis of inflammatory conditions other than psoriasis or PsA including, but not limited to rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, reactive arthritis, and Lyme disease.
- Subject was currently receiving or had previously received any biological agent or targeted DMARDs for the treatment of PsA or psoriasis.
- Subject had previously received any other nonbiological DMARDs (apart from MTX), including sulfasalazine, hydroxychloroquine or apremilast within 8 weeks prior to the first administration of the study drug; or had previously received leflunomide within 12 weeks (except at least 4 weeks prior to the first administration of the study drug, the subject had documented completion of standard cholestyramine or activated charcoal washout procedure).
- Subject had received epidural, intra-articular, intramuscular, or intravenous (IV) corticosteroids during the 4 weeks prior to first administration of study drug.
- Subject had been treated with cytotoxic agents, (including but not limited to azathioprine, cyclosporine, cyclophosphamide), nitrogen mustard, chlorambucil, or other alkylating agents within 6 months prior to the first administration of the study drug.
- Subject had received psoralen with ultraviolet light A or systemic retinoids within 4 weeks prior to the first administration of the study drug.
- Subject had received topical treatments for psoriasis (e.g., corticosteroids, keratolytics, coal tar, anthralin, vitamin D3 analogs, or topical tacrolimus, and retinoids) within 2 weeks prior to the first administration of the study drug.
- Participant has received IV immunoglobulins or plasmapheresis within 6 months prior to the first administration of the study drug.
- Subject had any complementary therapies including ayurvedic medicine, traditional Chinese medication(s), acupuncture, or other unapproved medication for the treatment of PsA within 4 weeks prior to the first dose. For any locally-approved PsA treatments that were not listed in the inclusion/exclusion criteria (e.g., Cloud G in China), discussion regarding the washout period requirement with the Medical Monitor was advised.

5.3.2.1.2. Objectives and estimands

Primary objective

Primary objective of the trial was to demonstrate the equivalence of BAT2506 and Simponi on ACR 20 response in participants with active PsA based on the primary endpoint ACR20 response at week 8.

The null and alternative hypotheses for the primary endpoint (ACR20 at week 8) were planned to be the following (with the EMA similarity interval at week 8 given by [-13.8%, +13.8%]):

• H0: ($\pi_{BAT2506} - \pi_{Simponi} \leq -13.8\%$) or ($\pi_{BAT2506} - \pi_{Simponi} \geq +13.8\%$)

• H1: $-13.8\% < (\pi_{BAT2506} - \pi_{Simponi}) < +13.8\%$.

where $\pi_{BAT2506} - \pi_{Simponi}$ denotes the true common ACR20 response probability difference at week 8 between BAT2506 and Simponi, respectively (assumed to be common across the strata used in the stratified randomisation).

The derivation of the margin for the EMA was based on the ACR 20 response probability at week 8, assumed as 44% vs 8% (Simponi 50 mg vs placebo) with a treatment difference of 35.9% with 95%

CI = (26.4%, 45.3%), based on the results from the GO-REVEAL trial, due to the applicant. In order to preserve about 50% of the treatment effect vs placebo (using the lower bound of the 95% CI of 26.4%) the equivalence margin was justified as 13.8%.

Estimands for the primary objective

Table 24: Estimands for primary objective

Population	**Patients with active PSA.**
Treatment condition<s>	Assignment to BAT2506 or Simoni, in the hypothetical scenario of no discontinuation of study treatment (up to Week 4 dosing) due to other reason related to COVID-19 pandemic, no change in MTX prior to ACR assessment at Week 8 due to other reason related to COVID-19 pandemic, no missed study treatment injection up to Week 4 related to COVID-19 pandemic; regardless of discontinuation due to other reason not related to lack of efficacy and COVID-19 pandemic, change in MTX prior to ACR assessment at Week 8 due to other reason not related to lack of efficacy and COVID-19 pandemic, missed study treatment injection up to Week 4 not related to COVID-19 pandemic, rescue medication prior to ACR assessment up to Week 8.
Endpoint (variable)	ACR20 at Week 8
Population-level summary	Difference between treatments in proportion of subjects achieving ACR20 response at Week 8
Intercurrent events and strategy to handle them	
Death prior to assessment of ACR at Week 8	Composite strategy (nonresponse)
New PsA treatment prior to ACR assessment at Week 8	Composite strategy (nonresponse)
Discontinuation of study treatment (up to Week 4 dosing) *due to lack of efficacy*	Composite strategy (nonresponse)
Discontinuation of study treatment (up to Week 4 dosing) *due to other reason not related to lack of efficacy and COVID-19 pandemic*	Treatment policy strategy
Discontinuation of study treatment (up to Week 4 dosing) *due to other reason related to COVID-19 pandemic*	Hypothetical strategy
Change in MTX prior to ACR assessment at Week 8 *due to lack of efficacy*	Composite strategy (nonresponse)

Population	Patients with active PSA.
(increase or initiation)	
Change in MTX prior to ACR assessment at Week 8 *due to other reason not related to lack of efficacy and COVID-19 pandemic*	Treatment policy strategy
Change in MTX prior to ACR assessment at Week 8 *due to other reason related to COVID-19 pandemic*	Hypothetical strategy
Missed study treatment injection up to Week 4 *not related to COVID-19 pandemic*	Treatment policy strategy
Missed study treatment injection up to Week 4 *related to COVID-19 pandemic*	Hypothetical strategy
Rescue medication prior to ACR assessment up to Week 8	Treatment policy strategy

The clinical question of interest was to analyse whether BAT2506 and Simponi are equivalent, measured by the difference in the ACR20 proportions (counting "Death prior to assessment of ACR at Week 8", "New PsA treatment prior to ACR assessment at Week 8", "Discontinuation of study treatment (up to Week 4 dosing) due to lack of efficacy" and "Change in MTX prior to ACR assessment at Week 8 due to lack of efficacy (increase or initiation)" as non-response) **in the hypothetical scenario of** no discontinuation of study treatment (up to Week 4 dosing) due to other reason related to COVID-19 pandemic, no change in MTX prior to ACR assessment at Week 8 due to other reason related to COVID-19 pandemic, no missed study treatment injection up to Week 4 related to COVID-19 pandemic; **regardless of** discontinuation due to other reason not related to lack of efficacy and COVID 19 pandemic, change in MTX prior to ACR assessment at Week 8 due to other reason not related to lack of efficacy and COVID-19 pandemic, missed study treatment injection up to Week 4 not related to COVID-19 pandemic, rescue medication prior to ACR assessment up to Week 8.

The handling of ACR data missing after ICEs or of data observed after ICE's is described.

There was a further Secondary Estimand (Table 33) defined for the primary endpoint/objective. The only difference to the primary estimand is that the intercurrent events "Discontinuation of study treatment (up to Week 4 dosing) due to other reason not related to lack of efficacy and COVID-19 pandemic", "Change in MTX prior to ACR assessment at Week 8 due to other reason not related to lack of efficacy and COVID-19 pandemic" and "Missed study treatment injection up to Week 4 not related to COVID-19 pandemic" are also handled with a hypothetical strategy and only "Rescue medication prior to ACR assessment up to Week 8" is still handled with a treatment policy strategy.

Table 25: Secondary Estimand for primary objective

Population	**Patients with active PSA.**
Treatment condition<s>	Assignment to BAT2506 or Simoni, in the hypothetical scenario of no discontinuation of study treatment (up to Week 4 dosing) due to other reason related to COVID-19 pandemic or due to other reason not related to lack of efficacy and COVID-19 pandemic, no change in MTX prior to ACR assessment at Week 8 due to other reason related to COVID-19 pandemic or due to other reason not related to lack of efficacy and COVID-19 pandemic, no missed study treatment injection up to Week 4 related to COVID-19 or not related to COVID-19 pandemic; regardless of rescue medication prior to ACR assessment up to Week 8.
Endpoint (variable)	ACR20 at Week 8
Population-level summary	Difference between treatments in proportion of subjects achieving ACR20 response at Week 8
Intercurrent events and strategy to handle them	
Death prior to assessment of ACR at Week 8	Composite strategy (nonresponse)
New PsA treatment prior to ACR assessment at Week 8	Composite strategy (nonresponse)
Discontinuation of study treatment (up to Week 4 dosing) *due to lack of efficacy*	Composite strategy (nonresponse)
Discontinuation of study treatment (up to Week 4 dosing) *due to other reason not related to lack of efficacy and COVID-19 pandemic*	Hypothetical strategy
Discontinuation of study treatment (up to Week 4 dosing) *due to other reason related to COVID-19 pandemic*	Hypothetical strategy
Change in MTX prior to ACR assessment at Week 8 *due to lack of efficacy (increase or initiation)*	Composite strategy (nonresponse)
Change in MTX prior to ACR assessment at Week 8 *due to other reason not related to lack of efficacy and COVID-19 pandemic*	Hypothetical strategy
Change in MTX prior to ACR assessment at Week 8 *due to other reason related to COVID-19 pandemic*	Hypothetical strategy

Population	Patients with active PSA.
Missed study treatment injection up to Week 4 *not related to COVID-19 pandemic*	Hypothetical strategy
Missed study treatment injection up to Week 4 *related to COVID-19 pandemic*	Hypothetical strategy
Rescue medication prior to ACR assessment up to Week 8	Treatment policy strategy

Statistical methods for estimation and sensitivity analysis on primary estimand

Analysis sets

The Full Analysis Set (FAS) was planned to comprise all participants randomised to a study treatment arm. Treatment groups were planned to follow the randomised assignments.

The Per Protocol Set (PPS) was planned to comprise all participants randomised into the study, who received at least one dose of study drug, without any major protocol deviation that has a significant influence on the primary endpoint evaluation.

Analysis of Primary endpoint

The primary efficacy analysis was planned to aim to demonstrate equivalence in the ACR20 response probability between BAT2506 and Simponi. The FAS was planned to be the primary analysis set and the primary and secondary estimand were planned to be estimated using Mantel-Haenszel approach stratified by region (Asia/Europe), concomitant use of MTX (yes/no), body weight (≤84 kg/>84 kg), and plaque psoriatic involvement (<12 mild, ≥12 moderate/severe) for point estimation and 2-sided CI for the common difference in ACR20 response probabilities between the two treatments (BAT2506 versus Simponi).

Equivalence between the two treatments (BAT2506 versus Simponi) was planned to be declared if the 2-sided 95% CI for the common ACR20 response probability difference between the two treatments would be entirely contained within the similarity interval of [-13.8%, 13.8%] at week 8 for EMA.

Handling of missing data

Handling of missing ACR data in patients without ICEs:

- multiple imputation assuming missing at random (MAR).

Handling of ACR data missing after ICEs:

- single imputation (non-response) when applying composite variable strategy.
- multiple imputation with specific missing not at random (MNAR) algorithm based on data from patients not affected by the respective ICE for hypothetical strategy.
- multiple imputation assuming MAR when applying treatment policy strategy.

Handling of ACR data observed after ICEs:

- replaced by non-response (single imputation) in the analysis when applying composite variable strategy.

- replaced by multiple imputation algorithm based on data from patients not affected by the respective ICE when applying hypothetical strategy.
- kept in the analysis when applying treatment policy strategy.

Sensitivity analyses

The following sensitivity and supplementary analyses of the primary efficacy endpoint were conducted:

Table 26: Sensitivity analysis of the primary endpoint

Approach	Analysis Set	Modeling method	Estimand	ICE/ICE Strategy	Missing Data Strategy
Sensitivity analysis 1	FAS	Same with primary analysis	NA	NA	Same with primary analysis
Sensitivity analysis 2	FAS	Same with primary analysis	Primary estimand	Same with primary analysis	Observed
Sensitivity analysis 3	FAS	Same with primary analysis	NA	NA	Observed
Sensitivity analysis 4	FAS	Tipping point analysis	Primary estimand	Same with primary analysis	NA
Sensitivity analysis 5	FAS (patient used the true stratificati on results which was define as PD)	Same with primary analysis (Mantel-Haenszel approach with stratified factors)	Primary estimand	Same with primary analysis	Same with primary analysis
Sensitivity analysis 6	FAS	Same with primary analysis	Primary estimand	Same with primary analysis	Same with primary analysis, remote visit will impute as non-responder
Sensitivity analysis 7	FAS	Logistic Regression	Primary estimand	Same with primary analysis	Same with primary analysis

Secondary objectives

Secondary objective of the trial was to compare the efficacy of BAT2506 with Simponi on the following additional efficacy parameters in participants with active PsA:

- ACR 20/50/70 over time

- PASI 75/PASI 90/PASI 100 response over time (in a subset of participants with at least 3% body surface area psoriasis involvement at baseline)
- Change from baseline in DAS28-CRP over time
- DAS28-CRP response (good or moderate response) over time
- Change from baseline in HAQ-DI over time
- Change from baseline in NAPSI over time
- Change from baseline in ACR core components: swollen joint count, tender joint count, Patient's assessment of Arthritis Pain(VAS), Participant's Global Assessment of Disease Activity (VAS), Physician's Global Assessment of Disease Activity (VAS), HAQDI, and CRP over time
- Change from baseline in PASI over time.

The study also conducted an *ad hoc* analysis for DAS28-CRP and ACR components post database lock. Especially the equivalence of BAT2506 and Simponi on DAS28-CRP in subjects with active PsA was evaluated based on the Mean difference of DAS28-CRP at week 8 for EMA. Therefore, a t-test was conducted between the BAT2506 group and the combined group Simponi group to test if the 95% CI of difference was within the equivalence margin 0.6 (referring to DAS28 EULAR response criteria21) at week 8 for EMA, it could indicate similarity between the 2 groups. No imputation or estimand were applied to the analysis, only observed data was analysed.

For each component of the ACR, both continuous results and binary results were present for the BAT2506 group and the combined Simponi group, as observed by visits in TP1. No imputation and estimand was in this summary table, only observed data was analysed.

Estimands for the secondary objectives

No estimand framework was provided for the secondary objectives/endpoints. Data was analysed as observed.

Statistical methods for estimation and sensitivity analysis on the secondary endpoints

All secondary efficacy endpoints were planned to be summarised over time and compared between treatments and/or treatment groups.

Continuous efficacy variables (e.g., each component of the ACR20 criteria, DAS28 criteria) were planned to be summarised descriptively by treatments and/or treatment groups and visit using n, mean, standard deviation, median, minimum and maximum.

Categorical efficacy variables (eg, ACR20) were planned to be summarised descriptively by treatments and/or treatment groups and visit using counts and percentages. These were planned to be analysed similarly to that of the primary endpoint; 95% exact CI were planned to be provided within each treatment group; the Wald CI for the difference in percentages between the treatment groups at all time points.

No estimand framework was provided for the secondary endpoints and hence no intercurrent event handling was performed.

The same subgroup analyses as for the primary endpoint were conducted.

5.3.2.1.3. Results

Participant flow and numbers analysed

Recruitment

Date of First Observation: 05 May 2021
Date of Last Observation: 06 October 2023

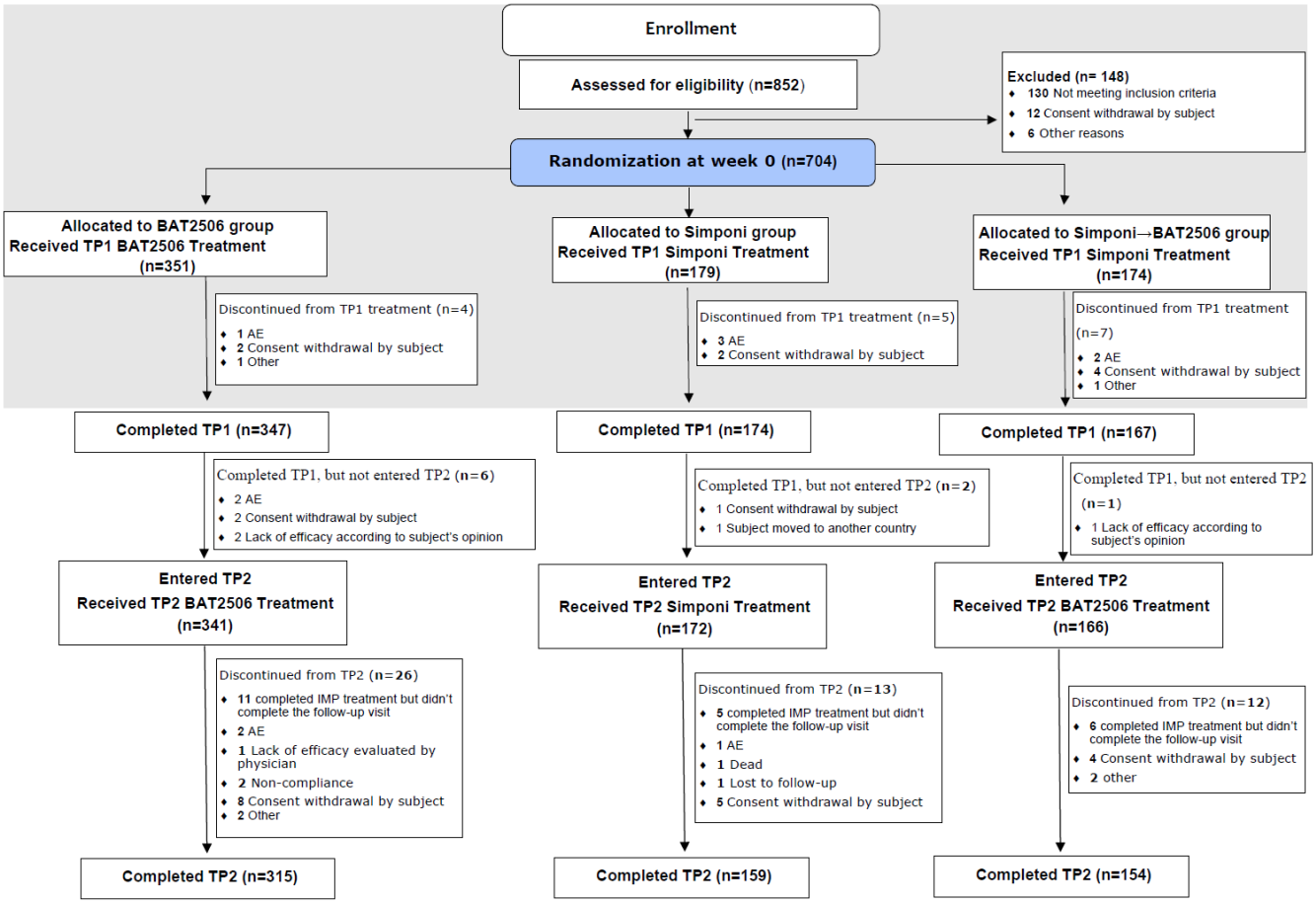


Figure *13*: Subject Disposition – Flow Chart

Numbers analysed

The Full Analysis Set for TP1 (FAS1) was the primary analysis set which comprised all subjects randomised to a study treatment arm (n=704; 100%).

The FAS for TP2 (FAS2) comprised all subjects randomised to a study treatment arm and have at least one visit at or after week 24 (n=679; 96.4 %).

A Per Protocol set at week 8 (PPS8) was used for supportive efficacy analysis which consisted of all subjects in the FAS set who received at least one administration of study drug during TP1, had at least one post-baseline ACR core components assessment during TP1, and additionally for whom there were no major protocol deviations affecting primary efficacy at week 8 (n=685; 97.3 %).

Deviations from study plan

Protocol amendments

The first version of protocol 1.0 (19 Aug 2020) underwent 2 amendments.

The protocol was updated to version 2.0 (10 Nov 2020) based on feedback from EMA. Modifications included among others the change of timepoint of the primary endpoint to week 8 for studies conducted under the EMA while analysis for other agencies was conducted at week 14; clarifications on the use of prohibited concomitant medication; addition of plaque psoriatic involvement as stratification factor; and an updated equivalence margin from 15% to 13.8%.

The protocol was updated to version 3.0 (15 Nov 2021) due to the statistical analysis requirement for estimand, and feedback received from EMA and FDA. Modifications included among others updates to the statistical analyses with estimand framework; increase of the sample size to 700 subjects; addition of an enrolment cap of 50% for participants using concomitant MTX.

Protocol deviations

A total of 117 subjects (16.6%) had at least one major protocol deviation during the study.

The most common frequently reported protocol deviation was related to the study drug admin/study treatment affecting 43 subjects (6.1%). Following closely behind were deviation in visit schedule, which affected in 39 subjects (5.5%). Among these major protocol deviations, 21 subjects (3.0%) were related with Coronavirus disease 2019 (COVID-19) and 13 (1.8%) cases with war, respectively.

Baseline data

Table 27: Demographic and Other Baseline Characteristics (Full Analysis Set 1)

Characteristic	BAT2506 (N=351)	Simponi (N=179)	Simponi→ BAT2506 (N=174)	Combined Simponi (N=353)	All Subjects (N=704)
Sex, n (%)					
Male	180 (51.3%)	97 (54.2%)	81 (46.6%)	178 (50.4%)	358 (50.9%)
Female	171 (48.7%)	82 (45.8%)	93 (53.4%)	1175 (49.6%)	346 (49.1%)
Region, n (%)					
Asia	44 (12.5%)	25 (14.0%)	23 (13.2%)	48 (13.6%)	92 (13.1%)
Europe	307 (87.5%)	154 (86.0%)	151 (86.8%)	305 (86.4%)	612 (86.9%)
Race					
Asian	44 (12.5%)	25 (14.0%)	24 (13.8%)	49 (13.9%)	93 (13.2%)
White	307 (87.5%)	154 (86.0%)	150 (86.2%)	304 (86.1%)	611 (86.8%)
Age (years)					
Mean (SD)	46.6 (11.8)	44.9 (12.1)	45.1 (12.7)	45.0 (12.4)	45.8 (12.1)
Median	47.0	45.0	46.0	45.0	46.0
Min, Max	18, 78	20, 74	19, 73	19, 74	18, 78
Body weight (kg)					
Mean (SD)	81.92 (17.01)	82.98 (19.03)	80.19 (19.04)	81.60 (19.06)	81.76 (18.05)
Height (cm)					
Mean (SD)	171.1 (9.8)	170.9 (9.5)	170.0 (8.6)	170.5 (9.0)	170.8 (9.4)

Characteristic	BAT2506 (N=351)	Simponi (N=179)	Simponi→ BAT2506 (N=174)	Combined Simponi (N=353)	All Subjects (N=704)
BMI (kg/m^2)					
Mean (SD)	27.88 (4.93)	28.38 (5.94)	27.60 (5.72)	27.99 (5.84)	27.94 (5.40)
Concomitant use of MTX					
Yes	155 (44.2%)	81 (45.3%)	75 (43.1%)	156 (44.2%)	311 (44.2%)
No	196 (55.8%)	98 (54.7%)	99 (56.9%)	197 (55.8%)	393 (55.8%)
Plaque Psoriatic Involvement					
Mild (<12)	287 (81.8%)	151 (84.4%)	145 (83.3%)	296 (83.9%)	583 (82.8%)
Moderate and Severe (≥12)	64 (18.2%)	28 (15.6%)	29 (16.7%)	57 (16.1%)	121 (17.2%)

Abbreviations: BMI = Body Mass Index; Max = maximum; Min = minimum; MTX = Methotrexate; N=number of subjects in the analysis set. SD = Standard deviation.
Note: Baseline is defined as the last assessment prior to first dosing.
Source: CSR Study BAT-2506-002-CR, Table 14.1.4.1.1.

Baseline disease characteristics

The majority of subjects (523 subjects, 74.3%) had taken DMARD(s) before Screening. The mean (SD) tender joint count was 15.6 (11.3); the mean (SD) swollen joint count was 9.2 (6.8); the mean (SD) Patient's assessment of Arthritis Pain (VAS) was 58.4 (22.3); the mean (SD) Participant's Global Assessment of Disease Activity (VAS) was 63.3 (20.3); the mean (SD) Physician's Global Assessment of Disease Activity (VAS) was 65.0 (14.7); the mean (SD) HAQ-DI was 1.12 (0.59); the mean (SD) PASI was 6.47 (7.36); the mean (SD) NAPSI was 25.1 (32.0); the mean (SD) CRP was 7.52 mg/L (13.38); and the mean (SD) DAS28 was 4.4533 (0.9846). The subjects' disease characteristics at Baseline were comparable among the 3 treatment groups, BAT2506, Simponi, and Simponi→BAT2506.

Table 28: Baseline Disease Characteristics (Full Analysis Set 1)

Demographic Variable	BAT2506 (N=351)	Simponi® (N=179)	Simponi®/BAT2506 (N=174)	Combine Simponi® (N=353)	All Subjects (N=704)
Tender joint count					
n	351	179	174	353	704
Mean (SD)	15.7 (11.2)	14.8 (11.9)	16.2 (11.0)	15.5 (11.5)	15.6 (11.3)
Median	12.0	11.0	13.0	12.0	12.0
Min, Max	3, 64	3, 66	3, 66	3, 66	3, 66
Swollen joint count					
n	351	179	174	353	704
Mean (SD)	9.1 (6.7)	9.3 (7.3)	9.4 (6.5)	9.3 (6.9)	9.2 (6.8)
Median	7.0	7.0	7.0	7.0	7.0
Min, Max	2, 44	3, 41	3, 50	3, 50	2, 50
Patient's assessment of Arthritis Pain (VAS)					
n	351	177	174	351	702
Mean (SD)	58.7 (22.3)	56.1 (22.2)	60.1 (22.1)	58.1 (22.2)	58.4 (22.3)
Median	61.0	60.0	63.0	60.0	61.0
Min, Max	0, 100	0, 100	0, 100	0, 100	0, 100
Participant's Global Assessment of Disease Activity (VAS)					
n	351	176	174	350	701
Mean (SD)	64.3 (20.1)	61.2 (20.8)	63.3 (20.2)	62.2 (20.5)	63.3 (20.3)
Median	69.0	62.0	62.5	62.0	65.0
Min, Max	0, 100	6, 100	7, 100	6, 100	0, 100

Physician's Global Assessment of Disease Activity (VAS)					
n	351	176	174	350	701
Mean (SD)	65.5 (15.1)	65.1 (14.4)	64.0 (14.3)	64.5 (14.4)	65.0 (14.7)
Median	67.0	65.0	65.0	65.0	66.0
Min, Max	15, 97	28, 98	26, 93	26, 98	15, 98
Health Assessment Questionnaire Disability Index (HAQ-DI)					
n	350	176	173	349	699
Mean (SD)	1.12 (0.60)	1.11 (0.59)	1.14 (0.59)	1.12 (0.59)	1.12 (0.59)
Median	1.10	1.10	1.10	1.10	1.10
Min, Max	0, 2.5	0, 2.6	0, 2.8	0, 2.8	0, 2.8
Psoriasis Area and Severity Index (PASI)					
n	351	178	174	352	703
Mean (SD)	6.72 (7.32)	6.35 (7.27)	6.11 (7.53)	6.23 (7.39)	6.47 (7.36)
Median	3.90	3.60	3.05	3.45	3.60
Min, Max	0.1, 41.6	0.3, 45	0.2, 43	0.2, 45	0.1, 45
Nail Psoriasis Severity Index (NAPSI)					
n	351	177	173	350	701
Mean (SD)	23.1 (29.1)	28.9 (36.0)	25.1 (33.4)	27.0 (34.7)	25.1 (32.0)
Median	12.0	15.0	12.0	14.0	12.0
Min, Max	0, 160	0, 160	0, 138	0, 160	0, 160
C-reactive protein (mg/L)					
n	351	179	174	353	704
Mean (SD)	7.69 (13.67)	7.30 (11.72)	7.40 (14.42)	7.35 (13.10)	7.52 (13.38)
Median	3.00	3.00	2.90	3.00	3.00
Min, Max	0.6, 138.4	0.6, 79.3	0.6, 95.1	0.6, 95.1	0.6, 138.4
Disease Activity Score 28					
n	351	177	174	351	702
Mean (SD)	4.4702 (0.9878)	4.3628 (1.0168)	4.5112 (0.9432)	4.4364 (0.9824)	4.4533 (0.9846)
Median	4.4288	4.3430	4.5471	4.4487	4.4311
Min, Max	1.3739, 7.1385	1.4232, 7.1787	1.7659, 6.9603	1.4232, 7.1787	1.3739, 7.1787

Note: Baseline is defined as the last assessment prior to first dosing.
Source: CSR Study BAT-2506-002-CR, Table 14.1.4.2.1.

Outcomes and estimation

Primary Endpoint

Percentage of subjects achieving ACR 20 response at Week 8

The primary efficacy analyses were performed on the FAS for the proportion of subjects achieving ACR 20 response at week 8 with pre-defined equivalence margins for estimated difference in ACR 20 response probability of [-13.8%, +13.8%], based on 95% CI.

The common risk difference in ACR20 response rates between the BAT2506 group and the combined Simponi group was 11.32% with a 95% CI of (4.40, 18.25) at week 8. Thus, the upper bound fell outside the predefined equivalence margin of 13.8% while the lower bound was contained within the margin.

Table 29: Proportion of Subjects Achieving ACR20 Response at Week 8 (Study BAT-2506-002-CR, FAS)

Statistic	BAT2506 N=351 (1)	Combine Simponi N=353 (1)
Primary Estimand		
n/Nx (1)	257/351	217/353
Proportion of responders (%) (95% CI) (2)	74.53 (69.94, 79.12)	63.41 (58.30, 68.52)
Common Risk Difference (%) (BAT2506 - Combined Simponi) (3)	11.32	
95% CI for Common Risk Difference (%) (3) (4)	(4.40, 18.25)	
Secondary Estimand EMA[c]		
n/Nx (1)	257/351	217/353
Proportion of responders (%) (95% CI) (2)	74.62 (69.98, 79.25)	63.42 (58.28, 68.56)
Common Risk Difference (%) (BAT2506 - Combined Simponi) (3)	11.41	
95% CI for Common Risk Difference (%) (3) (4)	(4.42, 18.40)	

Abbreviations: ACR = American college of rheumatology; CI = confidence interval; EMA = European Medicines Agency;; n= number of responders observed;
(1) n=number of responders observed; N=number of subjects in the analysis set; Nx= number of subjects with ACR 20 response after imputation.
(2) Proportion and 90/95% CI was a Clopper Pearson 90/95% CI for binomial proportions after multiple imputation
(3) The Common Risk Difference was analysed using Mantel-Haenszel (MH) approach adjusted by the randomisation strata (region [Asia/Europe], concomitant use of MTX [yes/no], body weight [≤84kg/>84kg] and plaque psoriatic involvement [<12 mild, ≥12 moderate/severe]) after multiple imputation.
(4) 90/95% CI for the Common Risk Difference was calculated based on the Mantel-Haenszel method and carried out 2-tailed on 5%/2.5% level of significance after multiple imputation.
Source: CSR Study BAT-2506-002-CR, Table 14.2.1.1.1 and Table 14.2.1.1.3

Additional analysis

Percentage of subjects achieving ACR 20 response at week 14 (FDA analysis)

The primary efficacy analyses were performed on the FAS for FDA for the proportion of subjects achieving ACR 20 response at week 14. The common risk difference in ACR 20 response rates between the BAT2506 group and the combined Simponi group was 2.36%, with a 90% CI of (-2.91, 7.63). The CIs fully fell within the predefined equivalence margin set by the FDA [-12.6%, +15%].

Sensitivity analysis

The CI upper bounds in all sensitivity analyses exceeded the predefined equivalence upper margin set for of 13.8%. In all sensitivity analyses a positive common risk difference was observed in ACR20 response at week 8 between BAT2506 and Simponi.

Supplementary analyses

Supplementary analyses of primary estimand included analysis of missing data imputed by LOCF and analysis in Per Protocol Set at weeks 8 for ACR20 response. The CIs did not fully fall within the predefined equivalence margin set by EMA [13.8%, 13.8%].

Secondary Endpoints

Percentage of subjects achieving ACR 20/50/70 over time

The proportions of subjects achieving ACR50 and ACR70 response up to week 24 and ACR20 at week 24 are summarised in the table below.

Table 30: Summary of ACR20/ACR50/ACR70 Response Over Time – Treatment Period 1 (Full Analysis Set 1)

	BAT2506 (N=351)	Simponi (N=179)	Simponi →BAT2506 (N=174)	Combine Simponi (N=353)
ACR20				
Week24				
n/Nx (1)	284/351	139/179	133/174	272/353
Proportion of responder (%)	84.37	82.43	80.72	81.59
Common Risk Difference (%) (BAT2506 - Combine Simponi) (2)			3.17	
95% CI for Common Risk Difference (%) (2) (3)			(-2.60, 8.94)	
ACR50				
Week8				
n/Nx (1)	124/351	55/179	62/174	117/353
Proportion of responder (%)	36.03	32.12	36.03	34.05
Common Risk Difference (%) (BAT2506 - Combine Simponi) (2)			2.19	
95% CI for Common Risk Difference (%) (2) (3)			(-4.98, 9.35)	
Week14				
n/Nx (1)	168/351	83/179	86/174	169/353
Proportion of responder (%)	49.29	48.46	51.78	50.10
Common Risk Difference (%) (BAT2506 - Combine Simponi) (2)			-0.70	
95% CI for Common Risk Difference (%) (2) (3)			(-8.23, 6.84)	
Week24				
n/Nx (1)	193/351	99/179	92/174	191/353
Proportion of responder (%)	57.41	58.52	55.98	57.27
Common Risk Difference (%) (BAT2506 - Combine Simponi) (2)			0.40	
95% CI for Common Risk Difference (%) (2) (3)			(-7.08, 7.89)	
ACR70				
Week8				
n/Nx (1)	56/351	25/179	26/174	51/353
Proportion of responder (%)	16.21	14.16	15.20	14.67
Common Risk Difference (%) (BAT2506 - Combine Simponi) (2)			1.76	

95% CI for Common Risk Difference (%) (2) (3)			(-3.61, 7.13)	
Week14				
n/Nx (1)	100/351	35/179	45/174	80/353
Proportion of responder (%)	29.06	20.00	26.35	23.13
Common Risk Difference (%) (BAT2506 - Combine Simponi) (2)			6.08	
95% CI for Common Risk Difference (%) (2) (3)			(-0.48, 12.64)	
Week24				
n/Nx (1)	123/351	67/179	60/174	127/353
Proportion of responder (%)	36.13	39.13	35.52	37.35
Common Risk Difference (%) (BAT2506 - Combine Simponi) (2)			-1.19	
95% CI for Common Risk Difference (%) (2) (3)			(-8.39, 6.02)	

(1) n= number of responders observed; N=number of subjects in the analysis set; Nx= number of subjects with ACR 50 response after imputation.

(2) The common risk difference between treatment group was analysed using MH approach adjusted by the randomisation strata (region [Asia/Europe], concomitant use of MTX [yes/no], body weight [≤84 kg/>84 kg] and plaque psoriatic involvement [<12 mild, ≥12 moderate/severe]) after multiple imputation.

(3) 95% CI for the common risk difference was calculated based on the MH method and carried out 2-tailed on 5%/2.5% level of significance after multiple imputation.

Source: Extract from Table 14.2.2.1.2.1.

Table 31: Summary of ACR20, ACR50 and ACR70 Response Over Time – Treatment Period 2 (Full Analysis Set 2)

		ACR20			ACR50		
Visit	**Statistic**	**BAT2506 (N=351 [1])**	**Simponi (N=179)**	**Simponi→BAT2506 (N=174)**	**BAT2506 (N=351)**	**Simponi (N=179)**	**Simponi →BAT2506 (N=174)**
Week 52	n/Nx [1]	290/341	141/172	133/166	224/341	115/172	105/166
	Proportion of responder (%) 95% CI [2]	89.81 (86.51, 93.10)	88.31 (83.41, 93.22)	85.12 (79.62, 90.62)	69.72 (64.73, 74.71)	71.74 (64.79, 78.70)	66.99 (59.66, 74.32)
		ACR70					
	n/Nx [1]	164/341	82/172	71/166			
	Proportion of responder (%) 95% CI [2]	50.35 (44.91, 55.79)	50.64 (42.98, 58.30)	44.91 (37.19, 52.63)			

Abbreviations: ACR = American college of rheumatology; CI = confidence interval; EMA = European Medicines Agency;
(1) n= number of responders observed; N=number of subjects in the analysis set; Nx= number of subjects with ACR 20 response after imputation.
(2) 90/95% CI was a Clopper Pearson 90/95% CI for binomial proportions after multiple imputation

Source: CSR Study BAT-2506-002-CR, Table 14.2.2.1.1.2, Table 14.2.2.1.2.2 and Table 14.2.2.1.3.2.

The figure below shows the ACR20 response over time up to week 52.

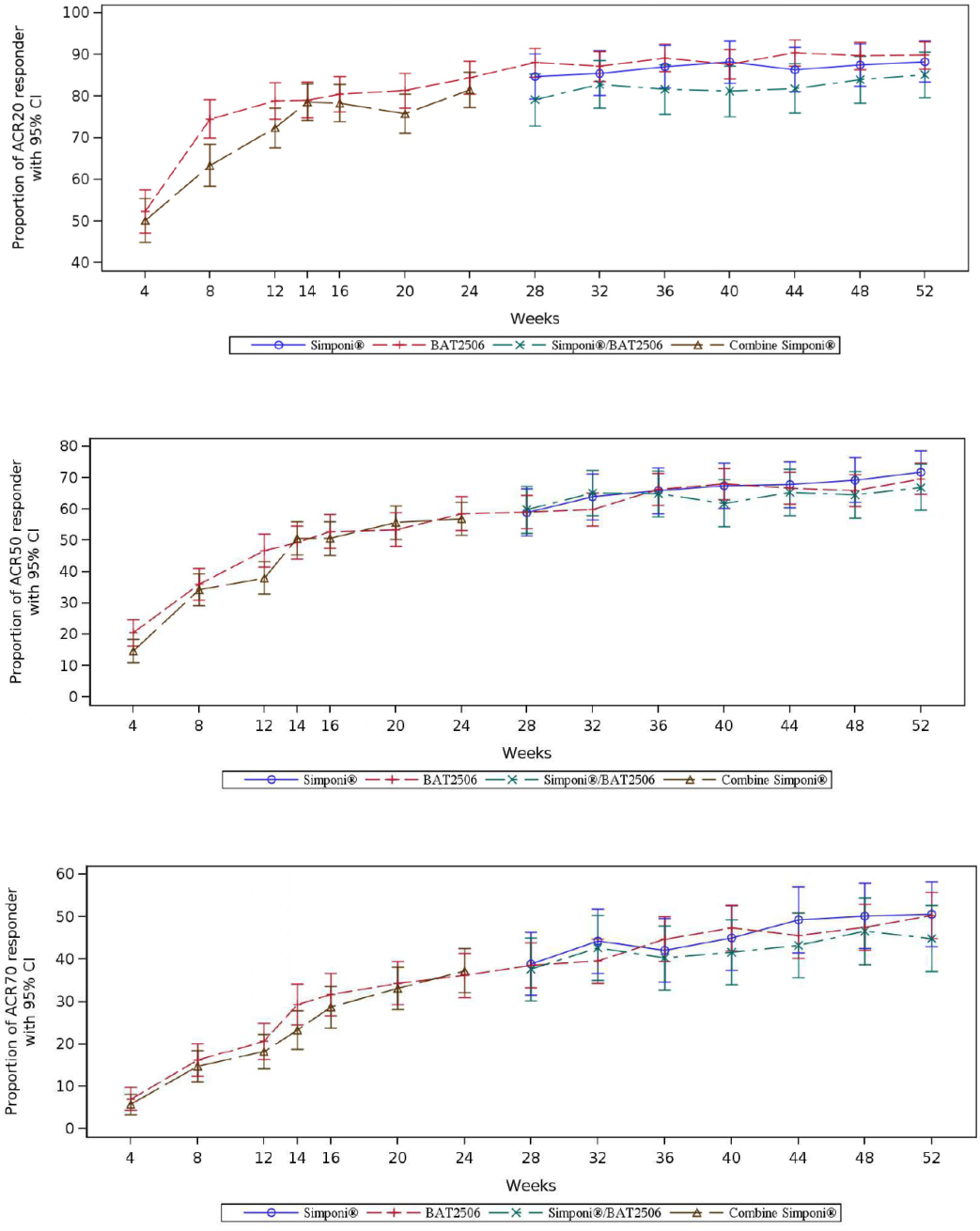


Figure *14*: Summary of ACR20, ACR50, and ACR70 Response Over Time (FAS)

Change from Baseline in ACR Core Components

Table 32: ACR Core Components at Week 8

ACR Components	Mean (SD)							
	BAT2506				Combined Simponi			
	Baseline	Week 8	Change from baseline	Percent Change from baseline	Baseline	Week 8	Change from baseline	Percent Change from baseline
Swollen Joint Count[1]	9.1490 (6.7197)	2.5770 (3.9172)	-6.5833 (6.0531)	-71.51% (33.69)	9.3253 (6.8839)	3.0453 (4.8759)	-6.2691 (5.4754)	-68.65% (34.20)
Tender Joint Count[1]	15.6697 (11.2095)	6.2823 (7.6618)	-9.4309 (9.4957)	-60.04% (39.37)	15.5091 (11.4784)	7.0645 (9.4843)	-8.4448 (8.7270)	-56.39% (37.36)
Patient's Assessment of Arthritis Pain (VAS)[1]	58.7 (22.3)	34.8 (23.8)	-23.8 (23.2)	38.73% (44.71])	58.1 (22.2)	36.5 (24.3)	-21.4 (25.2)	32.09% (67.61)
Participant's Global Assessment of Disease Activity (VAS)[1]	64.3 (20.1)	38.4 (22.5)	-25.8 (24.1)	37.35% (42.30)	62.2 (20.5)	38.0 (22.7)	-24.2 (23.7)	-35.40% (45.45])
Physician's Global Assessment of Disease Activity (VAS)[1]	65.5 (15.1)	27.6 (17.6)	-38.0 (19.4)	57.37% (26.40)	64.5 (14.4)	29.8 (18.9)	-34.6 (21.1)	52.73% (30.61)
C-Reactive Protein[1]	7.689 (13.674)	2.817 (6.523)	-4.509 (9.064)	-21.06% (156.81)	7.349 (13.103)	3.048 (9.378)	-4.039 (13.368)	21.31% (110.61)
HAQ-DI[1]	1.12 (0.60)	0.73 (0.59)	-0.39 (0.46)	-37.67% (43.31)	1.12 (0.59)	0.77 (0.62)	-0.35 (0.47)	-34.46% (43.31)

Abbreviations: ACR = American College of Rheumatology; HAQ-DI = Health Assessment Questionnaire Disability Index; SD = Standard deviation; VAS = Visual analog scale

[1]Data presented as Mean (SD)

Source: CSR Study BAT-2506-002-CR, Table 14.2.2.1.12.1, 14.2.2.1.12.2, 14.2.2.1.10.1

Change from Baseline in DAS28-CRP over time

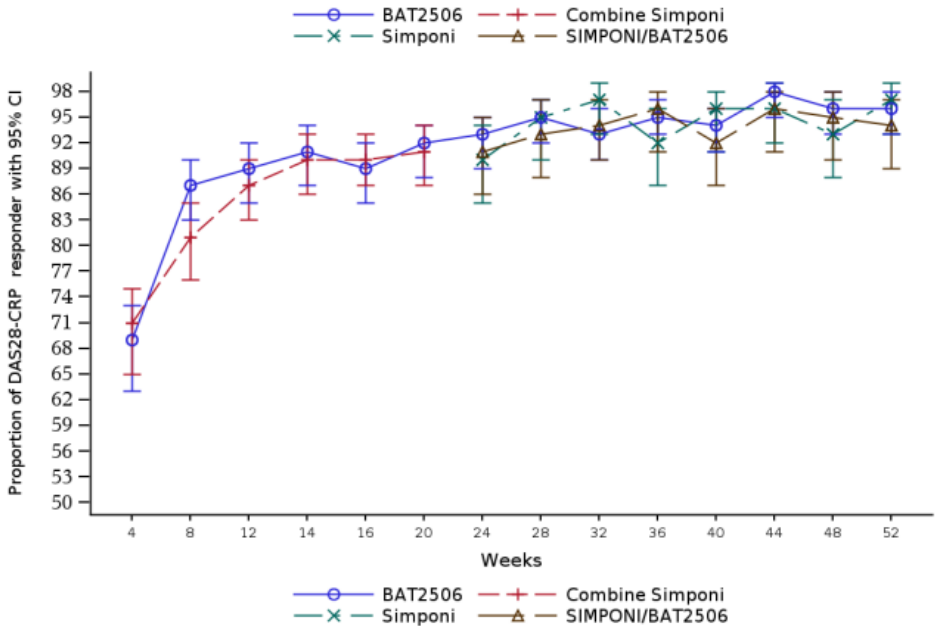
Table 33: Summary of DAS28-CRP Score Over Time – Treatment Period 1 (Full Analysis Set 1)

Visit	Statistic	BAT2506 (N=351)	Simponi (N=179)	Simponi →BAT2506 (N=174)	Combined Simponi (N=353)
Week 8	n	343	172	171	343
	Mean (SD)	2.9131 (1.0521)	2.8727 (1.1412)	3.0154 (1.1197)	2.9439 (1.1311)
	Median	2.8714	2.7561	3.0142	2.8894
	Min, Max	1.1292, 7.1372	1.1712, 6.7897	1.2375, 5.8721	1.1712, 6.7897
Week 8 Change from Baseline	n	343	170	171	341
	Mean (SD)	-1.6315 (1.0107)	-1.5568 (1.1344)	-1.5303 (1.0290)	-1.5435 (1.0813)
	Median	-1.5374	-1.3134	-1.4423	-1.3976
	Min, Max	-5.0689, 1.1480	-4.9373, 0.6667	-4.5304, 1.0484	-4.9373, 1.0484
Week 14	n	333	172	166	338
	Mean (SD)	2.5926 (1.0258)	2.5443 (1.0723)	2.5718 (0.9524)	2.5578 (1.0138)
	Median	2.5092	2.3574	2.5894	2.4652
	Min, Max	1.1292, 6.3230	1.1432, 6.0269	1.1292, 5.2055	1.1292, 6.0269
Week 14 Change from Baseline	n	333	170	166	336
	Mean (SD)	-1.9674 (1.0520)	-1.8849 (1.1444)	-1.9687 (1.0455)	-1.9263 (1.0958)
	Median	-1.8968	-1.7897	-1.8766	-1.8519
	Min, Max	-5.6046, 0.4583	-5.5071, 0.4139	-4.6822, 0.6129	-5.5071, 0.6129
Week 24	n	335	172	163	335
	Mean (SD)	2.3487 (0.9616)	2.3005 (1.0010)	2.3355 (0.9303)	2.3176 (0.9660)
	Median	2.1576	2.1165	2.2152	2.1651
	Min, Max	1.1292, 6.5579	1.1292, 6.0296	1.1292, 5.5834	1.1292, 6.0296
Week 24 Change from Baseline	n	335	170	163	333
	Mean (SD)	-2.1766 (1.0970)	-2.1305 (1.1882)	-2.2178 (1.0780)	-2.1732 (1.1347)
	Median	-2.1577	-2.0179	-2.2259	-2.1180
	Min, Max	-5.5766, 1.0879	-5.5874, 0.9619	-4.7791, 1.2580	-5.5874, 1.2580

Abbreviations: DAS28 = disease activity score 28; CRP = C-reactive protein; Max = maximum; Min = minimum; n= number of responders observed; N=number of subjects in the analysis set; SD = Standard deviation; DAS28-CRP = [0.56√(TJC28) + 0.28√(SJC28) + 0.36*ln(CRP+1)] +0.014*GH + 0.96
Source CSR Study BAT-2506-002-CR, Table 14.2.2.1.8.1.

DAS28 CRP Response (Good or Moderate Response) Over Time

Figure *15*: Summary of DAS28-CRP Response (Good or Moderate) Over Time (Full Analysis Set)

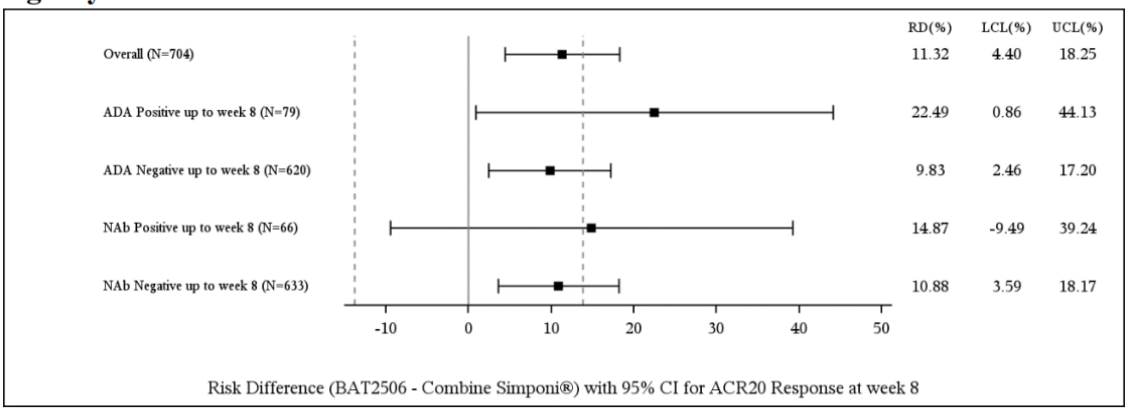


Abbreviations: CI = confidence interval; DAS28-CRP = Disease Activity Score 28 – C-reactive protein. DAS28-CRP responder: subjects' DAS28-CRP with good and moderate category. 90/95% CI was a Clopper Pearson 90/95% CI for binomial proportions. FAS1 was applied for TP1, FAS2 was applied for TP2.
Source CSR Study BAT-2506-002-CR, Figure 14.2.2.1.9.3.

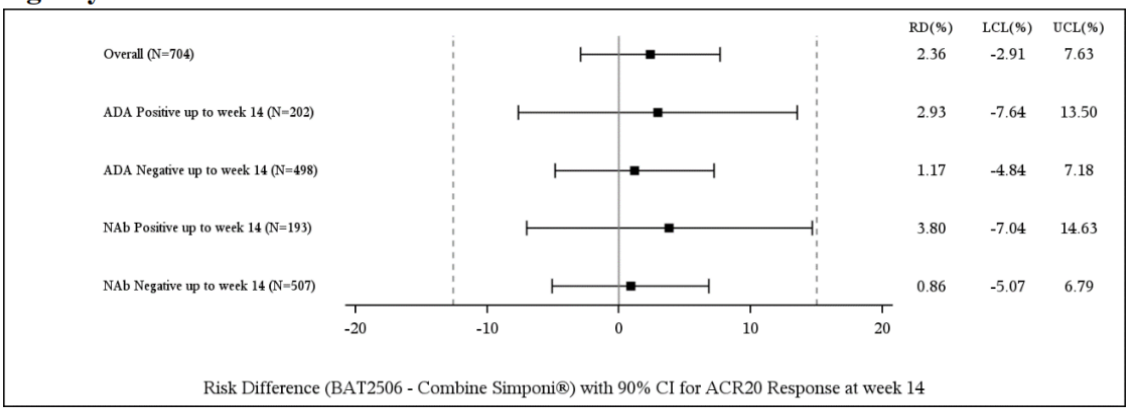
Immunogenicity

Figure *16*: Forest Plot of Proportion of Subjects Achieving ACR 20 at Week 8 and Week 14 by ADA Status (Full Analysis Set 1)

Agency: EMA



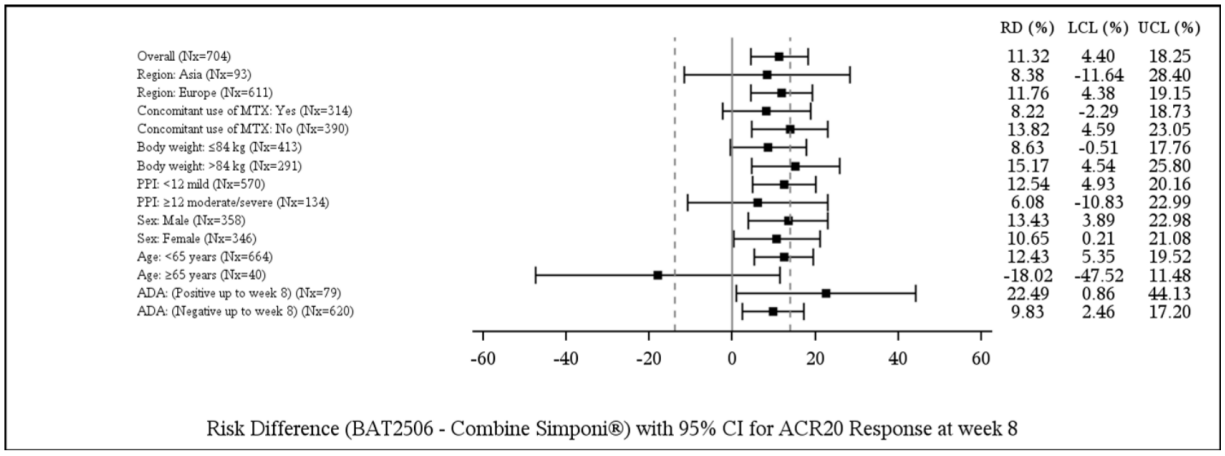
Agency: FDA

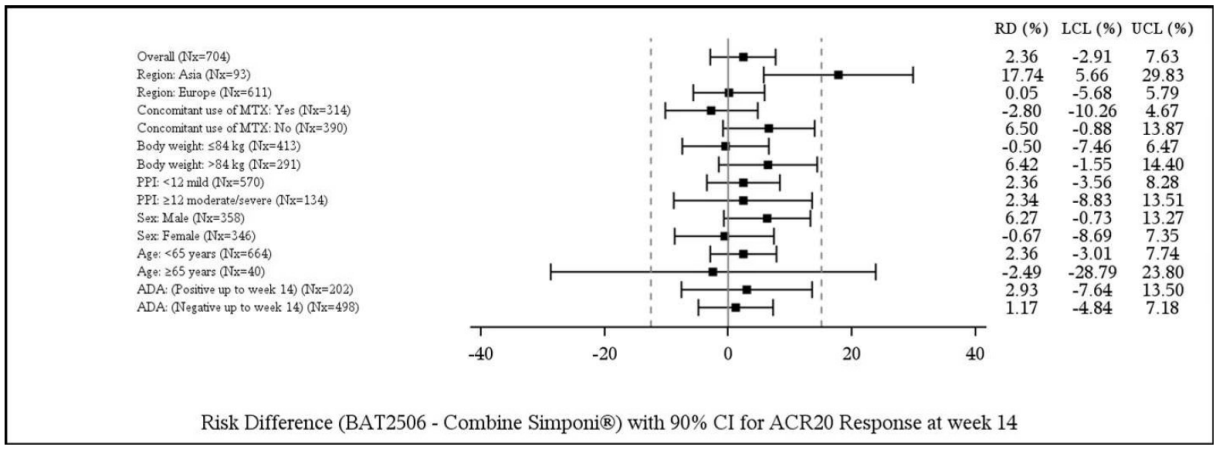


Abbreviations: ACR = American college of rheumatology; ADA=Anti-Drug antibody; CI = confidence interval; NAb = neutralising antibodies; CI = confidence interval; EMA = European Medicines Agency; FDA = Food and Drug Administration; RD = Common Risk Difference; LCL = Lower confidence limit; UCL = upper confidence limit
Source: CSR Study BAT-2506-002-CR, Figure 14.3.7.10.

Pre-defined and post-hoc subgroup analyses

Figure *17*: Forest Plot of Proportion of Subjects Achieving ACR 20 at Week 8 and Week 14 (Full Analysis Set 1)





Abbreviations: ADA = anti-drug antibody; CI = confidence interval; LCL=Lower confidence limit; MH = Mantel-Haenszel; MTX = methotrexate; Nx= number of subjects with ACR 20 response after imputation; PPI=plaque psoriatic involvement; RD=Common Risk Difference; UCL=upper confidence limit.

(1) 90/95% CI was a Clopper Pearson 90/95% CI for binomial proportions after multiple imputation.
(2) The common risk difference between treatment group was analysed using Mantel-Haenszel (MH) test adjusted by the randomisation strata (region [Asia/Europe], concomitant use of MTX [yes/no], body weight [≤84 kg/>84 kg] and plaque psoriatic involvement [<12 mild, ≥12 moderate/severe]) after multiple imputation.
(3) 90/95% CI for the common risk difference was calculated based on the MH method and carried out 2-tailed on 5%/2.5% level of significance after multiple imputation.
Source: CSR Study BAT-2506-002-CR, Figure 14.2.1.1.2

Pre-defined and post-hoc sensitivity analyses

Table 34: Results for primary and secondary estimand, sensitivity and supplemental analysis

Analysis	**ACR 20 at Week 8**
Primary Estimand	11.32% (95% CI: 4.40,18.25)
Secondary Estimand	11.41% (95% CI: 4.42, 18.40)
Sensitivity Analysis 1	11.43% (95% CI: 4.53, 18.33)
Sensitivity Analysis 2	11.21% (95% CI: 4.23%, 18.19)
Sensitivity Analysis 3	11.21% (95% CI: 4.25, 18.16)
Sensitivity Analysis 4 (Tipping Point)	Margin never met
Sensitivity Analysis 5	11.25% (95% CI: 4.32, 18.19)
Sensitivity Analysis 6	11.37% (95% CI: 4.41, 18.32)
Sensitivity Analysis 7	11.16% (95% CI: 4.33, 17.99)
Supplementary Analysis 1	10.56% (95% CI: 3.64, 17.48)
Supplementary Analysis 2	11.56% (95% CI: 4.57, 18.56)

Ancillary analyses

Ad hoc Analyses in DAS28-CRP

Ad hoc analyses of DAS28-CRP to evaluate the efficacy comparison between the 2 treatment groups in TP1, including week 8 and week 14 are provided below.

Table 35: Summary of Treatment Difference of DAS28-CRP Change from Baseline Over Time (Week4 - Week14)

	BAT2506 Mean (N=351)	Simponi Mean (N=353)	Mean Difference (BAT2506 - Combine Simponi)	95% CI for Mean Difference
Week 4	-1.2158	-1.1676	-0.0482	(-0.1907,0.0943)
Week 8	-1.6315	-1.5435	-0.0880	(-0.2451, 0.0691)
Week 12	-1.8257	-1.7727	-0.0530	(-0.2123, 0.1063)
Week 14	-1.9674	-1.9263	-0.0411	(-0.2042, 0.1220)

CI = Confidence Interval;
95% CI for within-group and between-group differences were calculated using t-distribution based methods.
Note 1: Baseline is defined as the last assessment prior to first dosing.

Figure *18*: DAS28-CRP (mean change from baseline) over time

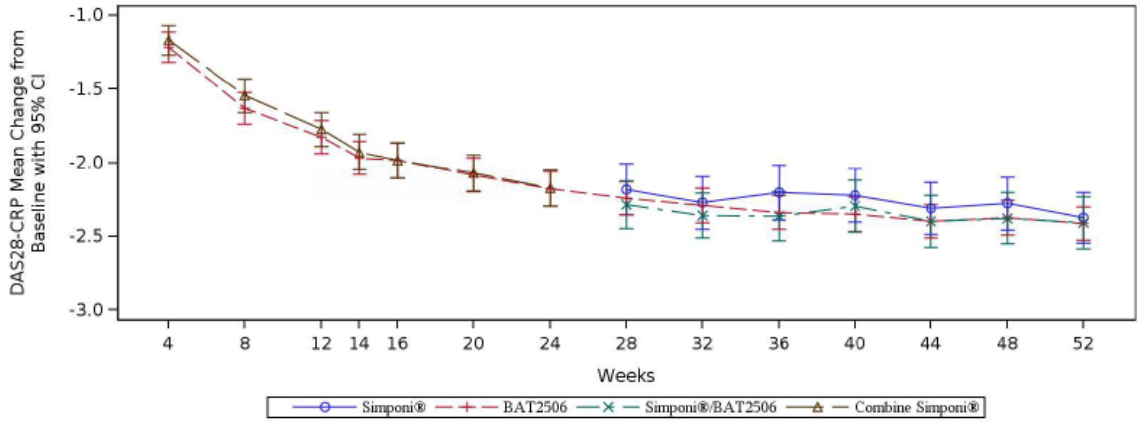


Table 36: Summary of Treatment Difference of DAS28-CRP Score-Over Time - Treatment Period 1 (Overall)

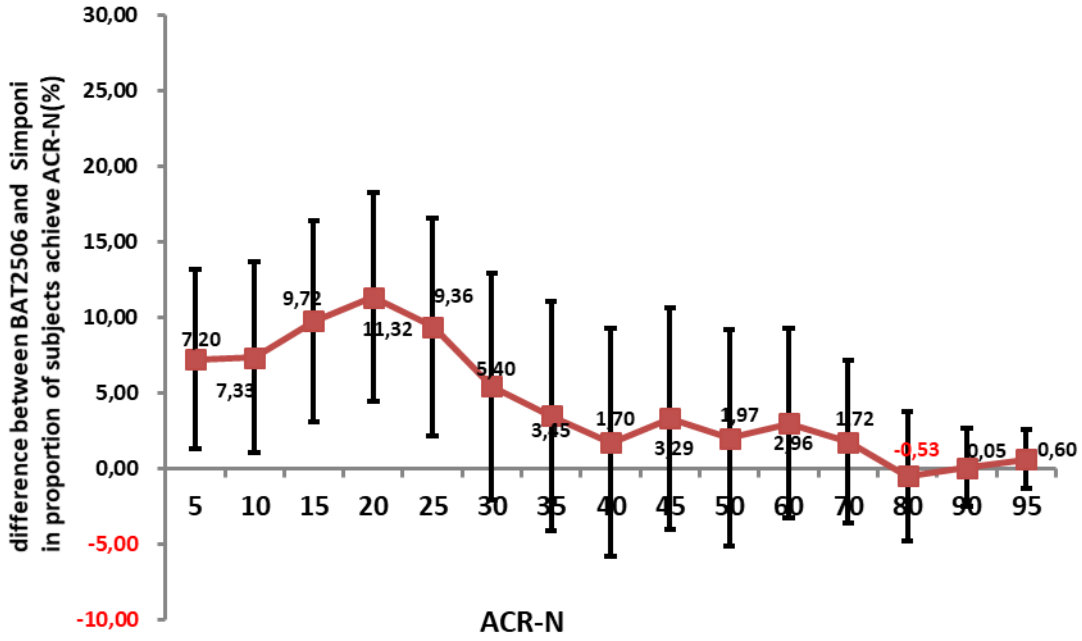
	Statistic	BAT2506 (N=351)	Combined Simponi (N=353)
Baseline	N	351	351
	Mean (95% CI)	4.5485	4.4951
	95% CI for Mean	(4.4467, 4.6502)	(4.3939, 4.5962)
	Mean Difference (BAT2506 – Combined Simponi)	0.0534	
	95% CI for Mean Difference	(-0.0898, 0.1966)	
Week 8	N	343	343
	Mean (95% CI)	2.9131	2.9439
	95% CI for Mean	(2.8014, 3.0248)	(2.8237, 3.0640)
	Mean Difference (BAT2506 – Combined Simponi)	-0.0308	
	95% CI for Mean Difference	(-0.1945, 0.1330)	
Week 14	N	333	338
	Mean (95% CI)	2.5926	2.5578
	95% CI for Mean	(2.4820, 2.7032)	(2.4493, 2.6663)
	Mean Difference (BAT2506 – Combined Simponi)	0.0348	
	95% CI for Mean Difference	(-0.1198, 0.1894)	

Abbreviations: CI = confidence interval; CRP = C-reactive protein; DAS28 = disease activity score 28; n = number of responders observed; N=number of subjects in the analysis set; SD = Standard deviation
Source: CSR Study BAT-2506-002-CR, Table 14.2.2.1.8.1.

Ad hoc analysis in ACR-N

An ad hoc analysis in ACR-N were also conducted post the CSR finalisation, to further compare the efficacy between treatment arms in different level of disease improvement at week 8, N represents the percentage of improvement in ACR criteria.

Figure *19*: Difference between BAT2506 and Simponi in proportion of subjects achieving ACR response (FAS)



ACR-N: the N percentage of improvement in ACR criteria
Source: Data form Table 14.2.1.1.1.adhoc1 of BAT-2506-002-CR

5.3.3. Clinical studies in special populations

Not applicable

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

Not applicable

5.3.5. Overall discussion and conclusions on clinical efficacy

5.3.5.1. Discussion

The clinical development program for BAT2506 comprised a single randomised, double-blind, comparative phase 3 study BAT-2506-002-CR to compare the efficacy and safety of BAT2506 and EU-Simponi. This study also included PK assessments and evaluation of immunogenicity.

Study Design

Study BAT-2506-002-CR was conducted in patients with psoriatic arthritis (PsA) that had an active disease despite previous csDMARD or NSAID therapy. All patients had skin involvement. Concomitant treatment with immunosuppressants was allowed. Enrolment of patients with use of MTX was capped to 50%.

The choice of PsA as the study population is considered appropriate. Extrapolation of efficacy to other indications where neutralisation of soluble TNF-α is the primary mode of action (i.e. rheumatoid, juvenile idiopathic arthritis and axial spondyloarthritis) is also supported. Furthermore, extrapolation to the ulcerative colitis indication, where additional mechanism such as binding and effector functions involving membrane-bound TNF-α are relevant, has also been substantiated through additional experimental evidence submitted during the assessment.

The study included active-controlled treatment for 52 weeks and was subdivided in two treatment periods (TP1: week 0 to week 24; and TP2: week 24 to week 52) with the three treatment groups Simponi, BAT2506, and Simponi→BAT2506, the later including a switch of from Simponi to BAT2506 starting after week 24. BAT2506 and Simponi were administered subcutaneously (SC) once every 4 weeks according to Simponi labelling. The selected dose 50 mg is the standard dose in adults in PsA and is acceptable.

The primary efficacy endpoint was the proportion of subjects achieving an ACR20 response at week 8. The use of the ACR20 response criteria for the comparative efficacy analysis was appropriate for the chosen study population. This was in line with Scientific Advice given. Secondary endpoints included the evaluation of ACR50 and ACR70 responses, change in the ACR core components, change in DAS28, change in PASI, change in NAPSI, and change in HAQ-DI. The choice of secondary endpoints was also adequate for the disease.

Of note, the timepoint of the primary endpoint was changed from week 14 to week 8 based on CHMP advice (EMA/CHMP/SAWP/316562/2020) as this time point which is in a steeper part of the ACR20 response curve is more sensitive to detect differences between the product and the originator. This is of particular relevance as the primary endpoint was not met in the study.

The Full Analysis Set 1 (FAS1) was the primary analysis set and the primary estimand was estimated using Mantel-Haenszel approach stratified by region (Asia/Europe), concomitant use of MTX (yes/no), body weight (≤84 kg/>84 kg), and plaque psoriatic involvement (<12 mild, ≥12 moderate/severe) for point estimation along with 2-sided confidence intervals (CI) for the common difference in ACR 20 response proportions between the treatments. The primary estimand pursued a treatment policy strategy for ICEs which are not related to lack of efficacy, a composite strategy for ICEs related to lack of efficacy (counted as non-responders) and a hypothetical strategy for ICEs related to COVID-19. A secondary estimand was defined, for which ICEs not related to lack of efficacy have also get handled with a hypothetical strategy. The predefined estimands are endorsed. The primary and secondary estimand together with the large number of pre-planned sensitivity analyses are considered sufficient to allow a comprehensive assessment.

The predefined equivalence margin was [-13.8%, 13.8%]. The choice of the equivalence margin should always be based on a combination of statistical reasoning and clinical judgement. A thorough clinical justification (which preferably should have been delivered a priori) why the equivalence margin could be judged as being clinically acceptable and not as being clinically relevant was missing. It should be noted that these issues were already flagged in the Scientific advice procedure (EMA/SA/0000050874, 25 March 2021) and were not implemented as recommended. The chosen margin was not sufficiently justified. However, CHMP considered that even if a tighter margin would have been applied this would have only resulted in the confidence interval being even further above the upper boundary, and the principal issue of a missed primary endpoint (as discussed further below) would still remain. The issue relating to the margin generation was therefore not further pursued.

A minimum of 700 participants (350 participants per group) was planned to provide at least 87.3% power for an equivalence test with a margin of 13.8%, a true difference of 2% and two one-sided tests with type 1 error of 2.5% for EMA. Based on the assumptions used by the applicant for the

justification of the margin (see issues above) the sample size calculation was reproducible, and the sample size was considered adequate.

Study population

The study enrolled patients with active PsA despite previous DMARD or NSAID therapies (ie. taking DMARD for at least 3 months, or evidence of DMARD intolerance, or taking an NSAID for at least 4 weeks, or with intolerance/contraindication to NSAID therapy). Patients had to present with psoriatic skin involvement with at least one active qualifying psoriatic lesion. Concomitant use of MTX was allowed if MTX was initiated at least 3 months before with no serious side effects and with a stable dose (max. 25 mg/week) for ≥4 weeks. Concomitant use of NSAIDs and oral corticosteroids (max dose: 10 mg/day) was also allowed. Concomitant use of DMARDs and MTX was used as stratification factor. Patients who had received any biological agent or targeted DMARDs for the treatment of PsA or psoriasis were excluded. Enrollment in case other non-biological treatments had been received was only possible after protocol-defined wash-out periods which were adequately defined. The chosen study population was considered relevant and with sufficient sensitivity for the biosimilarity assessment. Eligibility criteria were appropriate to select the adequately homogeneous patient population.

Study Conduct

The first patient was enrolled on 05 May 2021. The protocol underwent 2 amendments mainly to incorporate agency feedback. The first amendment was introduced before first enrolment. Both amendments were considered to not have significantly influenced the conduct of the study. There was a quite high number of patients with major protocol deviations (16.6%) which was in part driven by incorrect stratification factor entries (category: Ip Admin/Study Treat; 6.1%). Wrong data entries were corrected. Other frequent major protocol deviations included the category of visit schedule (5.5%) and procedures/tests (3.7%) and to COVID-19 (3.0%) or war (1.8%). No substantial imbalances between the groups were observed. Patients with events significantly impacting the efficacy analysis were low.

Disposition

This study was initiated at 63 sites, and there were 60 sites which screened subjects. A total of 704 patients were randomised into TP1 and received either BAT2506 (n=351) or Simponi (n=353). These patients were included in the FAS which was used for the primary analysis. The per-protocol set mainly included the same patients as for the FAS, except for 19 patients that were excluded. Nearly all patients completed TP1 (n= 688; 97.7%). A total of 4 patients (1.1%) in the BAT2506 group and a slightly higher number in the Simponi group (n=12; 3.4%) discontinued treatment in TP1. Main reasons for discontinuation were adverse event or consent withdrawal. The majority of patients completing TP1 also entered TP2 (n=679; 96.4%) with a total of 628 patients (89.2%) completing TP2 (ie. treatment until week 52). Subject disposition was overall comparable between treatment groups throughout the study.

Baseline data

The recruited study population was considered representative of the targeted population of PsA. Baseline disease characteristics were overall balanced between the groups and overall reflect the anticipated study population of patients with active PsA.

The mean age was 45.8 years; 50.9 % of patients were males. Most of the patients were recruited in Europe (86.9%), other patients were recruited in China (13.1%). A total of 44.2% patients had concomitant use of MTX during the study. A total 98.6% of patients had at least one concomitant

medication; the most frequently used prior concomitant therapies were folic acid (44.3%), MTX (34.2%) and colecalciferol (19.9%). Use of concomitant medication was overall balanced between treatment arms.

Patients presented with active PsA disease as reflected by increased mean tender joint and swollen joint counts of (15.6 and 9.2, respectively) as well as increases measures for arthritis pain, disability, and global assessment of disease activity. The mean CRP was 7.52 mg/L. All patients had psoriatic skin involvement with the majority (82.8%) presenting with mild plaque psoriatic involvement (<12) as expected for the disease. Consequently, the mean PASI score was 6.47.

Efficacy data

The predefined equivalence margin for EMA was ±13.8% for the 95% CI. The Full Analysis Set 1 (FAS1) was used for the primary analyses of efficacy. This analysis set consisted of all patients who were randomised to treatment (n=704).

Percentage of subjects achieving ACR 20 response at Week 8 (Primary endpoint)

The study did not meet its primary endpoint. The overall numbers and proportions of subjects who achieved an ACR 20 response at week 8 were 257 (74.53%) in the BAT2506 group and 217 (63.41%) in the combined Simponi group. The common risk difference was 11.32% with a 95% CI of (4.40, 18.25) at week 8. The upper bound fell outside the predefined equivalence margin of 13.8%. Sensitivity and tipping point analysis as well as supplemental analysis (including the PPS analysis) overall yielded very similar point estimates with CIs falling outside the upper bound in all analysis.

The observed difference did not seem to be caused by bias introduced due to imbalances within the study population as baseline demographics and disease characteristics as well as concomitant immunosuppressive use was balanced. There was an overall low number of intercurrent events leading to similar findings in the PPS-Analysis. No indications that the observed difference was caused by substantial imbalances within the study population or bias introduced during study conduct have been identified. Thus, as the observed difference seems real and not due to errors in study design, population differences, or unexpected events during the trial the observed difference may be attributable to random variation and therefore should be interpreted with caution.

Overall, these results point towards a better response of BAT2506 (ie. a higher proportion of patients reaching the symptom improvement by at least 20% in ACR) at an early time after initiation of treatment (i.e. week 8). At later timepoints (ie. week 14, week 24 and week 52) ACR20 response rates became similar with all risk differences being contained within the margin. In this regard, the applicant referred to the comparison of ACR20 responses at week 14 used as primary endpoint for FDA, which showed similar results (risk difference: 2.36%; 90%CI: -2.91, 7.63) with CIs falling within the FDA margin as an argument for equivalence demonstration.

Secondary Endpoints

In contrast to ACR20 responses, the proportion of patients achieving ACR50 or ACR70 at week 8 was similar with a common risk difference of 2.19 (95% CI: -4.98, 9.35) and 1.76 (95% CI: -3.61, 7.13), respectively. ACR50 and ACR70 response rates at later timepoints were also similar. Notably, ACR70 response rates at week 14 pointed towards a difference of (risk difference: 6.08) with a 95 % CI (-0.48 12.64). The applicant also conducted a *post-hoc* analysis, to further compare the efficacy throughout different ACR response levels (5%, 10%, 15%, …, 95% improvement) at week 8. Except from ACR20, other ACR response criteria for higher improvement levels showed more comparable results which supports the applicant's argument that the observed difference at week 8 is more an isolated finding. This is acknowledged but it must also be noted that for nearly all symptom improvement levels, higher response rates were seen for BAT2506 at week 8.

The difference observed in ACR20 response rates at week 8 was not mainly driven by a particular ACR core component. Results for the ACR components appear similar at week 8. ACR component improvements started to become more and more similar at week 14, week 24, and week 52 reflecting the results seen for ACR20 responses over time. Notably, changes from baseline were numerically slightly larger for the BAT2506 group at this timepoint. Higher numerical core component levels were particularly seen in patients pain assessment and in physician's global disease activity assessment for the BAT2506.

Change from baseline values in DAS28-CRP over time appear overall similar. Of note, as also seen for ACR components slightly higher changes from baseline can also be noted at week 8 while values became more and more similar at later time points. There was no substantial difference in change from baseline values at week 52 in the patients switching from Simponi to BAT2506. To account for the difference seen in ACR20 response rates at week 8 (ie. the missed primary endpoint), the applicant performed an *ad-hoc* analysis for change from baseline in DAS28-CRP at week 8. The mean difference between BAT2506 and Simponi was -0.0880 with a 95% CI of (-0.2451, 0.0691). Keeping the limitations of such an *ad-hoc* analysis in mind, the results for DAS28-CRP suggested that when using a continuous efficacy measure instead of the categorial ACR response criteria more similar symptom improvements were observed. The missed primary endpoint can thus potentially be explained by the characteristics of the ACR score. In this regard, it may be noted that components not included in the DAS28-CRP score (e.g. Physician's Global Assessment, Pain Assessment) were among those components with the largest differences seen for ACR components at week 8. It remains unclear why a difference may manifest only in such particular score components of the ACR score. This does however not impact the conclusion on biosimilarity.

The proportion of DAS28-CRP responders (good or moderate response) over time overall showed a similar progression as to what was observed for ACR responders. There was also a notable higher number of responders at week 8 in the BAT2506 group (86.8% vs. 80.94%) which appears mostly driven by patients with a moderate DAS28 CRP response, again pointing towards a higher number of patients with lower symptom improvements at an early stage of treatment. DAS28-CRP responders started to become similar at later timepoints up to week 52.

Changes from baseline in HAQ-DI and NAPSI are overall in line to what has already been observed for ACR and DAS28-CRP. While values were overall similar, numerical higher improvements were seen for BAT2506 early after treatment while values appear to become more and more similar at later timepoints. The proportion of subjects who achieved PASI 75, PASI 90 or PASI 100 response was similar, but response rates were again numerically higher in the BAT2506 at most of the timepoints tested. At week 8, the mean change from baseline in PASI was -56.52% in BAT2506 group vs. -42.40% in the combined Simponi group. More similar changes were seen at week 14 (-69.84 vs. 67.26), Week 24 (-77.40% vs. -70.84% and later on.

Subgroup analysis

Subgroup analyses for the primary efficacy endpoint were conducted for gender, age group, region, concomitant use of MTX (Yes/No), body weight, plaque psoriatic involvement (PPI; <12 mild, ≥12 moderate/ severe), ADA status, and nAbs status. At week 8, risk differences for subgroups tended to be in favour for BAT2506 with point estimates largely being closely within or outside the equivalence margin consistent with results seen for ACR20 response rates at week 8. Of note, risk differences did not largely differ in patients with or without concomitant MTX use. Given the low number of ADA positive patients at week 8, the effect of ADAs on the efficacy could not be clearly evaluated. Additional analyses of ACR20 and ACR50 at week 24 by ADA status (ADA positive and ADA negative subgroups) did not show any apparent correlation of anti-golimumab antibodies and efficacy outcomes (see section 6.2).

5.3.5.2. Conclusions on the clinical efficacy

The efficacy analysis conducted in study BAT-2506-002-CR in its totality supports clinical comparability between BAT2506 and Simponi. While the primary endpoint (proportion of ACR20 responses at week 8) was not met, symptom improvements were similar at later timepoints (week 14) and throughout the study (week 52) as seen for ACR response rates but also for the continuous DAS28-CRP scores. Overall, results for the secondary endpoints do support the claim for biosimilarity.

Overall, based on the totality of data provided biosimilarity in efficacy can be considered demonstrated.

5.4. Clinical safety

Safety data for BAT2506 is available from the three studies (BAT-2506-001-CR, BAT-2506-003-CR and BAT-2506-002-CR), where safety was assessed as part of the secondary study objectives.

Please refer to the table of studies in section 6.3.2.

5.4.1. Safety data collection

Adverse events were coded using either Medical Dictionary for Regulatory Activities (MedDRA) versions 23.0 (Study BAT-2506-001-CR), 26.0 (Study BAT-2506-003-CR) or 26.1 (Study BAT-2506-002-CR).

In all three studies, the safety assessments included were vital signs, symptoms and physical examination, injection site reactions, 12-lead ECGs, Laboratory tests (haematology, blood biochemistry, urinalysis, coagulation routine), immunogenicity and AEs.

The safety profile of Simponi is well established (Simponi SmPC).

Safety data are reported separately for each study, since the pivotal studies were conducted in different populations and different dosing settings.

5.4.2. Patient exposure

In healthy subjects (**Study BAT-2506-001-CR**), all individuals in the SS received a single, full dose of BAT2506 (n=90) or EU-Simponi (n=90) as a SC injection of 50 mg.

In healthy subjects (**Study BAT-2506-003-CR**), all individuals in the SS received a single, full dose of BAT2506 (n=123), EU-approved Simponi (n=125) or US-licensed Simponi (n=121) as an SC injection of 50 mg.

In subjects with PsA (**Study BAT-2506-002-CR**), in the SS all individuals received at least one dose of study drug, including 351 subjects received BAT2506 only, 187 subjects received EU Simponi only and 166 subjects received EU-Simponi followed by BAT2506. The mean (Standard Deviation [SD]) actual total dose administered was 12.3 (1.9) injections with a range from 1 to 13 injections. Extent of exposure and treatment compliance is summarised in Table 45.

Table 37: Extent of Exposure and Treatment Compliance (Study BAT-2506-002-CR)

	BAT2506 (N=351) n (%)	Simponi (N=187) n (%)	Simponi→ BAT2506 (N=166) n (%)	All subjects (N=704) n (%)
Treatment duration (Weeks) [1]				
Mean (SD)	50.5 (6.2)	48.1 (11.3)	51.5 (2.8)	50.1 (7.5)
Median	52.0	52.0	52.0	52.0
Actual dose administered (injections) overall				
Mean (SD)	12.4 (1.6)	11.8 (2.8)	12.7 (0.9)	12.3 (1.9)
Median	13.0	13.0	13.0	13.0
Min, Max	1, 13	1, 13	7, 13	1, 13
Actual dose administered (injections) in TP1				
n	351	187	166	704
Mean (SD)	5.9 (0.5)	5.7 (1.0)	5.9 (0.3)	5.8 (0.7)
Median	6.0	6.0	6.0	6.0
Min, Max	1, 6	1,6	3, 6	1, 6
Actual dose administered (injections) in TP2				
n	341	172	166	679
Mean (SD)	6.7 (0.8)	6.7 (1.0)	6.8 (0.9)	6.7 (0.9)
Median	7.0	7.0	7.0	7.0
Min, Max	2, 7	1, 7	1, 7	1, 7

[1] Treatment Duration =last administration visit/weeks + 4 weeks

5.4.3. Adverse events

Study BAT-2506-001-CR (Phase 1, Healthy Subjects)

Table 38: Summary Table of Adverse Events (SS, Study BAT-2506-001-CR)

	BAT2506 (N=90)			Golimumab (N=90)			Total (N=180)		
	Number of events	Number of subjects	Incidence (%)	Number of events	Number of subjects	Incidence (%)	Number of events	Number of subjects	Incidence (%)
All AEs	103	51	56.7	124	55	61.1	227	106	58.9
SAEs	2	1	1.1	0	0	0	2	1	0.6
TEAEs	103	51	56.7	124	55	61.1	227	106	58.9
TESAEs	2	1	1.1	0	0	0	2	1	0.6
TEAEs related to study drug	85	46	51.1	95	49	54.4	180	95	52.8
TESAEs related to study drug	2	1	1.1	0	0	0	2	1	0.6
TEAEs leading to early withdrawal	2	1	1.1	0	0	0	2	1	0.6
TESAEs leading to early withdrawal	2	1	1.1	0	0	0	2	1	0.6
TEAEs leading to death	0	0	0	0	0	0	0	0	0
Grade ≥ 3 TEAEs	7	4	4.4	6	4	4.4	13	8	4.4

Data source: Table 14.3.3.1

Table 39: Frequently reported TEAEs (≥4% of Subjects) In Healthy Subjects (Study BAT-2506-001-CR)

SOC PT	Number of subjects, n (%)		
	BAT2506 (N=90)	EU-Simponi (N=90)	Total (N=180)
Total	**51 (56.7)**	**55 (61.1)**	**106 (58.9)**
Investigations	**24 (26.7)**	**29 (32.2)**	**53 (29.4)**
Alanine aminotransferase increased	6 (6.7)	8 (8.9)	14 (7.8)
Blood bilirubin increased	7 (7.8)	3 (3.3)	10 (5.6)
Blood creatine phosphokinase increased	3 (3.3)	4 (4.4)	7 (3.9)
Aspartate aminotransferase increased	3 (3.3)	4 (4.4)	7 (3.9)
Neutrophil count decreased	4 (4.4)	2 (2.2)	6 (3.3)
White blood cell count increased	0 (0)	4 (4.4)	4 (2.2)
Metabolism and nutrition disorders	**16 (17.8)**	**20 (22.2)**	**36 (20)**
Hypertriglyceridemia	6 (6.7)	12 (13.3)	18 (10)
Hyperuricemia	9 (10.0)	6 (6.7)	15 (8.3)
Respiratory, thoracic and mediastinal disorders	**9 (10.0)**	**4 (4.4)**	**13 (7.2)**
Cough	4 (4.4)	1 (1.1)	5 (2.8)
Gastrointestinal disorders	**7 (7.8)**	**6 (6.7)**	**13 (7.2)**
Diarrhea	2 (2.2)	4 (4.4)	6 (3.3)
Cardiac disorders	**6 (6.7)**	**6 (6.7)**	**12 (6.7)**
Arrhythmia supraventricular	4 (4.4)	3 (3.3)	7 (3.9)
Infections and infestations	**4 (4.4)**	**4 (4.4)**	**8 (4.4)**
Upper respiratory tract infection	3 (3.3)	4 (4.4)	7 (3.9)

Source: CSR Study BAT-2506-001-CR, Table 14.3.3.2.1.

Study BAT-2506-002-CR (Phase 3, PsA Subjects)

Table 40: Overview of TEAEs During Treatment Period 1 (Safety Analysis Set 1)

	BAT2506 (N=351) n (%) [#]	Simponi (N=179) n (%) [#]	Simponi→ BAT2506 (N=174) n (%) [#]	Combine Simponi (N=353) n (%) [#]	All subjects (N=704) n (%) [#]
Any TEAEs	232 (66.1) [577]	108 (60.3) [239]	105 (60.3) [258]	213 (60.3) [497]	445 (63.2) [1074]
Serious AEs	10 (2.8) [10]	3 (1.7) [3]	1 (0.6) [1]	4 (1.1) [4]	14 (2.0) [14]
TEAEs leading to study drug interruption	17 (4.8) [21]	10 (5.6) [12]	10 (5.7) [18]	20 (5.7) [30]	37 (5.3) [51]
TEAEs leading to study drug withdrawal	3 (0.9) [3]	3 (1.7) [3]	2 (1.1) [2]	5 (1.4) [5]	8 (1.1) [8]
TEAEs related to study drug	72 (20.5) [156]	39 (21.8) [61]	35 (20.1) [72]	74 (21.0) [133]	146 (20.7) [289]
TEAEs with severe intensity	5 (1.4) [6]	2 (1.1) [2]	2 (1.1) [3]	4 (1.1) [5]	9 (1.3) [11]
TEAEs leading to death	0	0	0	0	0

n = number of subjects reporting at least one TEAE in that category.
# = number of individual occurrences of the TEAE in that category.
TEAEs with a start date after or on first dosing of TP1 and before or on first dosing of TP2 are included. In addition, if the AE start date on the same day of Week 24 with site injection reaction were counted on TP2.
Source: Table 14.3.1.1.1.

Table 41: Overview of TEAEs During Treatment Period 2 (Safety Analysis Set 2)

	BAT2506 (N=341) n (%) [#]	Simponi (N=172) n (%) [#]	Simponi→ BAT2506 (N=166) n (%) [#]	All subjects (N=679) n (%) [#]
Any TEAEs	226 (66.3) [561]	107 (62.2) [234]	111 (66.9) [280]	444 (65.4) [1075]
Serious AEs	9 (2.6) [9]	5 (2.9) [5]	4 (2.4) [4]	18 (2.7) [18]
TEAEs leading to study drug interruption	10 (2.9) [13]	7 (4.1) [7]	10 (6.0) [13]	27 (4.0) [33]
TEAEs leading to early withdrawal	2 (0.6) [2]	1 (0.6) [1]	0	3 (0.4) [3]
TEAEs related to study drug	67 (19.6) [116]	30 (17.4) [49]	24 (14.5) [42]	121 (17.8) [207]
TEAEs with severe intensity	5 (1.5) [6]	1 (0.6) [1]	1 (0.6) [2]	7 (1.0) [9]
TEAEs leading to death	0	1 (0.6) [1]	0	1 (0.1) [1]

n = number of subjects reporting at least one TEAE in that category.
# = number of individual occurrences of the TEAE in that category.
TEAEs with a start date after first dosing of TP2 and before or on the end of FU period date are included. In addition, if the AE start date on the same day of Week 24 with site injection reaction were counted on TP2.
Source: Table 14.3.1.1.2.

The most common TEAEs reported by PT in all subjects were upper respiratory tract infection (31 subjects [8.8%] in BAT2506 group, 18 subjects [10.1%] in Simponi group, 15 subjects [8.6%] in Simponi→BAT2506 group and 33 subjects [9.3%] in combined Simponi group during TP1, 38 subjects [11.1%] in BAT2506 group, 14 subjects [8.1%] in Simponi group and 30 subjects [18.1%] in Simponi→BAT2506 group during TP2) and nasopharyngitis (27 subjects [7.7%] in BAT2506 group, 14 subjects [7.8%] in Simponi group, 16 subjects [9.2%] in Simponi→BAT2506 group and 30 subjects [8.5%] in combined Simponi group during TP1, 34 subjects [10.0%] in BAT2506 group, 19 subjects [11.0%] in Simponi group and 12 subjects (7.2%) in Simponi→BAT2506 group during TP2). No notable differences were observed between the treatment groups in TP1 and TP2 (Table 50).

Table 42: Frequently reported TEAEs (≥4% of Subjects) In PsA Subjects (Study BAT-2506-002-CR)

SOC PT	Number of subjects, n (%)						
	TP1				TP2		
	BAT2506 (N=351)	Simponi (N=179)	Simponi→ BAT2506 (N=174)	Combined Simponi (N=353)	BAT2506 (N=341)	Simponi (N=172)	Simponi→ BAT2506 (N=166)
Total	**232 (66.1)**	**108 (60.3)**	**105 (60.3)**	**213 (60.3)**	**226 (66.3)**	**107 (62.2)**	**111 (66.9)**
Infections and infestations	**127 (36.2)**	**58 (32.4)**	**57 (32.8)**	**115 (32.6)**	**147 (43.1)**	**72 (41.9)**	**69 (41.6)**
Upper respiratory tract infection	31 (8.8)	18 (10.1)	15 (8.6)	33 (9.3)	38 (11.1)	14 (8.1)	30 (18.1)
Nasopharyngitis	27 (7.7)	14 (7.8)	16 (9.2)	30 (8.5)	34 (10.0)	19 (11.0)	12 (7.2)
COVID-19	24 (6.8)	9 (5.0)	10 (5.7)	19 (5.4)	27 (7.9)	7 (4.1)	9 (5.4)
Urinary Tract infection	11 (3.1)	6 (3.4)	8 (4.6)	14 (4.0)	6 (1.8)	5 (2.9)	4 (2.4)
Sinusitis	6 (1.7)	0 (0)	2 (1.1)	2 (0.6)	7 (2.1)	7 (4.1)	1 (0.6)
Investigations	**51 (14.5)**	**19 (10.6)**	**28 (16.1)**	**47 (13.3)**	**46 (13.5)**	**21 (12.2)**	**23 (13.9)**
Alanine aminotransferase increased	15 (4.3)	6 (3.4)	7 (4.0)	13 (3.7)	20 (5.9)	7 (4.1)	6 (3.6)
Low density lipoprotein increased	8 (2.3)	2 (1.1)	7 (4.0)	9 (2.5)	5 (1.5)	1 (0.6)	5 (3.0)
Aspartate aminotransferase increased	7 (2.0)	2 (1.1)	5 (2.9)	7 (2.0)	11 (3.2)	2 (1.2)	8 (4.8)
Metabolism and nutrition disorders	**42 (12.0)**	**18 (10.1)**	**16 (9.2)**	**34 (9.6)**	**29 (8.5)**	**14 (8.1)**	**16 (9.6)**
Hypercholesterolemia	15 (4.3)	7 (3.9)	8 (4.6)	15 (4.2)	8 (2.3)	1 (0.6)	7 (4.2)
Hypertriglyceridemia	11 (3.1)	3 (1.7)	7 (4.0)	10 (2.8)	9 (2.6)	3 (1.7)	6 (3.6)
Nervous system disorders	**20 (5.7)**	**15 (8.4)**	**6 (3.4)**	**21 (5.9)**	**11 (3.2)**	**4 (2.3)**	**8 (4.8)**
Headache	12 (3.4)	8 (4.5)	5 (2.9)	13 (3.7)	4 (1.2)	3 (1.7)	4 (2.4)

SOC PT	Number of subjects, n (%)						
	TP1				TP2		
	BAT2506 (N=351)	Simponi (N=179)	Simponi→ BAT2506 (N=174)	Combined Simponi (N=353)	BAT2506 (N=341)	Simponi (N=172)	Simponi→ BAT2506 (N=166)
Gastrointestinal disorders	**28 (8.0)**	**13 (7.3)**	**12 (6.9)**	**25 (7.1)**	**19 (5.6)**	**12 (7.0)**	**10 (6.0)**
Diarrhea	10 (2.8)	4 (2.2)	5 (2.9)	9 (2.5)	7 (2.1)	7 (4.1)	6 (3.6)
Musculoskeletal and connective tissue disorders	**32 (9.1)**	**10 (5.6)**	**7 (4.0)**	**17 (4.8)**	**38 (11.1)**	**10 (5.8)**	**18 (10.8)**
Psoriatic arthropathy	12 (3.4)	2 (1.1)	2 (1.1)	4 (1.1)	21 (6.2)	4 (2.3)	6 (3.6)

TEAEs with a start date after or on first dosing of TP1 and before or on first dosing of TP2 were included. In addition, if the AE start date on the same day of Week 24 with injection site reaction were counted on TP2.
TEAEs by SOC in TP1 ordered in decreasing frequency
Source: Study BAT-2506-002-CR Table 14.3.1.2.1 and 14.3.1.2.2.

Study BAT-2506-003-CR (Phase 1, healthy subjects)

Table 43: Overall Summary of TEAE in Study BAT-2506-003-CR

	BAT2506 (N=123) n (%) m	EU-Simponi (N=125) n (%) m	US-Simponi (N=121) n (%) m	Overall (N=369) n (%) m
TEAE	103 (83.7) 287	102 (81.6) 270	98 (81.0) 242	303 (82.1) 799
Treatment-related TEAE	91 (74.0) 176	87 (69.6) 160	83 (68.6) 143	261 (70.7) 479
Grade 3 or higher TEAE	5 (4.1) 6	5 (4.0) 5	9 (7.4) 9	19 (5.1) 20
Treatment-related grade 3 or higher TEAE	3 (2.4) 4	1 (0.8) 1	2 (1.7) 2	6 (1.6) 7
Local injection site reaction	0	0	0	0
Leading to study withdrawn TEAE	0	0	0	0
Leading to death TEAE	0	0	0	0
SAE	0	0	0	0

Source: Study BAT-2506-003-CR Table 14.3.1.1

In general, the incidence of TEAEs was similar among the BAT2506 (83.7%), Simponi-EU (81.6%), and Simponi-US (81.0%) groups. The most frequently reported TEAEs across treatment groups by PT were blood triglycerides increased (22 subjects [17.9%] in BAT2506, 26 subjects [20.8%] in EU-Simponi, and 28 subjects [23.1%] in US-Simponi groups) and blood bilirubin increased (27 subjects [22.0%] in BAT2506, 16 subjects [12.8%] in EU-Simponi, and 21 subjects [17.4%] in US-Simponi groups).

Table 44: Frequently reported TEAEs (≥4% of Subjects) In Healthy Subjects (Study BAT-2506-003-CR)

SOC PT	Number of subjects, n (%)			
	BAT2506 (N = 123)	**EU-approved Simponi (N=125)**	**US-licensed Simponi (N=121)**	**Total (N=369)**
Total	**103 (83.7)**	**102 (81.6)**	**98 (81.0)**	**303 (82.1)**
Investigations	**88 (71.5)**	**80 (64.0)**	**75 (62.0)**	**243 (65.9)**
Blood triglycerides increased	22 (17.9)	26 (20.8)	28 (23.1)	76 (20.6)
Blood bilirubin increased	27 (22.0)	16 (12.8)	21 (17.4)	64 (17.3)
Alanine aminotransferase increased	16 (13.0)	16 (12.8)	12 (9.9)	44 (11.9)
Neutrophil count decreased	18 (14.6)	10 (8.0)	14 (11.6)	42 (11.4)
Aspartate aminotransferase increased	8 (6.5)	9 (7.2)	5 (4.1)	22 (6.0)
White blood cell count increased	10 (8.1)	1 (0.8)	9 (7.4)	20 (5.4)
Blood creatine phosphokinase increased	9 (7.3)	6 (4.8)	5 (4.1)	20 (5.4)
Bile acids increased	5 (4.1)	9 (7.2)	1 (0.8)	15 (4.1)
Blood creatinine increased	3 (2.4)	4 (3.2)	5 (4.1)	12 (3.3)
Blood phosphorus decreased	6 (4.9)	3 (2.4)	2 (1.7)	11 (3.0)
Neutrophil count increased	6 (4.9)	4 (3.2)	1 (0.8)	11 (3.0)
Red blood cells urine positive	5 (4.1)	4 (3.2)	2 (1.7)	11 (3.0)
White blood cell count increased	6 (4.9)	4 (3.2)	1 (0.8)	11 (3.0)
Infections and infestations	**33 (26.8)**	**40 (32.0)**	**36 (29.8)**	**109 (29.5)**
COVID-19	18 (14.6)	18 (14.4)	19 (15.7)	55 (14.9)
Upper respiratory tract infection	11 (8.9)	19 (15.2)	14 (11.6)	44 (11.9)
Metabolism and nutrition disorders	**17 (13.8)**	**26 (20.8)**	**24 (19.8)**	**67 (18.2)**
Hypertriglyceridemia	15 (12.2)	23 (18.4)	17 (14.0)	55 (14.9)
Hyperuricemia	1 (0.8)	5 (4.0)	11 (9.1)	17 (4.6)

Source: CSR Study BAT-2506-003-CR, Table 14.3.1.2.

5.4.3.1. Adverse drug reactions

Study BAT-2506-001-CR (Phase 1, Healthy Subjects)

Table 45: Summary of Study Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (SS, Study BAT-2506-001-CR, Healthy Subjects)

SOC PT	BAT2506 (N=90)			EU-Simponi (N=90)			Total (N=180)		
	Number of events	Number of subjects	Incidence (%)	Number of events	Number of subjects	Incidence (%)	Number of events	Number of subjects	Incidence (%)
Total	**85**	**46**	**51.1**	**95**	**49**	**54.4**	**180**	**95**	**52.8**
Investigations	**36**	**22**	**24.4**	**48**	**25**	**27.8**	**84**	**47**	**26.1**
Alanine aminotransferase increased	7	6	6.7	10	8	8.9	17	14	7.8
Blood bilirubin increased	10	7	7.8	6	3	3.3	16	10	5.6
Neutrophil count decreased	7	4	4.4	2	2	2.2	9	6	3.3
Aspartate aminotransferase increased	2	2	2.2	6	3	3.3	8	5	2.8
White blood cell count decreased	5	3	3.3	1	1	1.1	6	4	2.2
White blood cell count increased	0	0	0	5	4	4.4	5	4	2.2
Lymphocyte count increased	2	2	2.2	2	1	1.1	4	3	1.7
Blood creatine phosphokinase increased	1	1	1.1	3	2	2.2	4	3	1.7
Neutrophil count increased	0	0	0	4	3	3.3	4	3	1.7
Blood creatinine increased	1	1	1.1	2	2	2.2	3	3	1.7
Lipase increased	1	1	1.1	2	2	2.2	3	3	1.7
Amylase increased	0	0	0	1	1	1.1	1	1	0.6
White blood cells urine positive	0	0	0	1	1	1.1	1	1	0.6
Blood glucose increased	0	0	0	1	1	1.1	1	1	0.6
Platelet count decreased	0	0	0	1	1	1.1	1	1	0.6
Total bile acids increased	0	0	0	1	1	1.1	1	1	0.6
Metabolism and nutrition disorders	**15**	**14**	**15.6**	**17**	**15**	**16.7**	**32**	**29**	**16.1**
Hypertriglyceridemia	5	5	5.6	9	8	8.9	14	13	7.2
Hyperuricemia	9	9	10.0	5	5	5.6	14	14	7.8
Hyperglycemia	1	1	1.1	3	2	2.2	4	3	1.7
Respiratory, thoracic and mediastinal disorders	**13**	**9**	**10.0**	**4**	**4**	**4.4**	**17**	**13**	**7.2**
Cough	4	4	4.4	1	1	1.1	5	5	2.8
Oropharyngeal pain	1	1	1.1	3	3	3.3	4	4	2.2
Productive cough	3	3	3.3	0	0	0	3	3	1.7
Rhinorrhea	3	3	3.3	0	0	0	3	3	1.7
Nasal obstruction	1	1	1.1	0	0	0	1	1	0.6
Pleural effusion	1	1	1.1	0	0	0	1	1	0.6
Gastrointestinal disorders	**6**	**6**	**6.7**	**6**	**5**	**5.6**	**12**	**11**	**6.1**

SOC PT	BAT2506 (N=90)			EU-Simponi (N=90)			Total (N=180)		
	Number of events	Number of subjects	Incidence (%)	Number of events	Number of subjects	Incidence (%)	Number of events	Number of subjects	Incidence (%)
Diarrhea	2	2	2.2	5	4	4.4	7	6	3.3
Toothache	3	3	3.3	1	1	1.1	4	4	2.2
Abdominal pain	1	1	1.1	0	0	0	1	1	0.6
Cardiac disorders	**6**	**4**	**4.4**	**6**	**6**	**6.7**	**12**	**10**	**5.6**
Arrhythmia supraventricular	5	3	3.3	3	3	3.3	8	6	3.3
Supraventricular extrasystoles	1	1	1.1	1	1	1.1	2	2	1.1
Nodal rhythm	0	0	0	1	1	1.1	1	1	0.6
Ventricular extrasystoles	0	0	0	1	1	1.1	1	1	0.6
Infections and infestations	**6**	**4**	**4.4**	**4**	**4**	**4.4**	**10**	**8**	**4.4**
Upper respiratory tract infection	4	3	3.3	4	4	4.4	8	7	3.9
Pulmonary tuberculosis	1	1	1.1	0	0	0	1	1	0.6
Tuberculous pleurisy	1	1	1.1	0	0	0	1	1	0.6
General disorders and administration site conditions	**1**	**1**	**1.1**	**4**	**3**	**3.3**	**5**	**4**	**2.2**
Pyrexia	1	1	1.1	3	2	2.2	4	3	1.7
Asthenia	0	0	0	1	1	1.1	1	1	0.6
Renal and urinary disorders	**2**	**2**	**2.2**	**2**	**2**	**2.2**	**4**	**4**	**2.2**
Hematuria	2	2	2.2	2	2	2.2	4	4	2.2
Vascular disorders	**0**	**0**	**0**	**2**	**1**	**1.1**	**2**	**1**	**0.6**
Hypertension	0	0	0	2	1	1.1	2	1	0.6
Nervous system disorders	**0**	**0**	**0**	**1**	**1**	**1.1**	**1**	**1**	**0.6**
Headache	0	0	0	1	1	1.1	1	1	0.6
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**1**	**1**	**1.1**	**1**	**1**	**0.6**
Myalgia	0	0	0	1	1	1.1	1	1	0.6

Source: CSR Study BAT-2506-001-CR, Table 14.3.3.2.2.

Study BAT-2506-002-CR

During the study (TP1+TP2), most TEAEs were not considered to be related to treatment by the Investigator. Overall, the frequency of drug-related TEAEs were low and similar across treatment groups. The most common treatment-related TEAEs reported by PT were upper respiratory tract infection (10 subjects [2.8%] in BAT2506 group, 7 subjects [3.9%] in Simponi group, 3 subjects [1.8%] in Simponi→BAT2506 group and 10 subjects [2.8%] in combined Simponi group during TP1, 11 subjects [3.2%] in BAT2506 group, 2 subjects [1.2%] in Simponi group and 5 subjects (3.0%) in Simponi→BAT2506 group during TP2, and nasopharyngitis (6 subjects [1.7%] in BAT2506 group, 4

subjects [2.2%] in Simponi group, 1 subject [0.6%] in Simponi→BAT2506 group and 5 subjects [1.4%] in combined Simponi group during TP1, 10 subjects [2.9%] in BAT2506 group, 6 subjects [3.5%] in Simponi group and 2 subjects (1.2%) in combined Simponi group during TP2. The incidence of study drug-related TEAEs was similar in the two groups. Also, after switch in TP2, no noticeable changes in safety were observed in the Simponi→BAT2506 group.

Table 46: Summary of Common Treatment-Related TEAEs (≥ 1%) by SOC and Preferred Term During Treatment Period 1 and 2 (Study BAT-2506-002-CR, SAF1)

SOC PT	Number of subjects, n (%)						
	TP1				TP2		
	BAT2506 (N=351)	Simponi (N=179)	Simponi →BAT2506 (N=174)	Combined Simponi (N=353)	BAT2506 (N=341)	Simponi (N=172)	Simponi →BAT2506 (N=166)
Total	**72 (20.5)**	**39 (21.8)**	**35 (20.1)**	**74 (21.0)**	**67 (19.6)**	**30 (17.4)**	**24 (14.5)**
Infections and infestations	**31 (8.8)**	**18 (10.1)**	**9 (5.2)**	**27 (7.6)**	**41 (12.0)**	**16 (9.3)**	**12 (7.2)**
Upper respiratory tract infection	10 (2.8)	7 (3.9)	3 (1.7)	10 (2.8)	11 (3.2)	2 (1.2)	5 (3.0)
Nasopharyngitis	6 (1.7)	4 (2.2)	1 (0.6)	5 (1.4)	10 (2.9)	6 (3.5)	2 (1.2)
Pharyngitis	2 (0.6)	2 (1.1)	1 (0.6)	3 (0.8)	3 (0.9)	4 (2.3)	1 (0.6)
Urinary tract infection	5 (1.4)	2 (1.1)	1 (0.6)	3 (0.8)	2 (0.6)	1 (0.6)	1 (0.6)
Sinusitis	1 (0.3)	0 (0)	1 (0.6)	1 (0.3)	4 (1.2)	1 (0.6)	0 (0)
Investigations	**21 (6.0)**	**8 (4.5)**	**12 (6.9)**	**20 (5.7)**	**13 (3.8)**	**6 (3.5)**	**5 (3.0)**
Alanine aminotransferase increased	7 (2.0)	5 (2.8)	3 (1.7)	8 (2.3)	5 (1.5)	4 (2.3)	2 (1.2)
Aspartate aminotransferase increased	3 (0.9)	2 (1.1)	2 (1.1)	4 (1.1)	3 (0.9)	0 (0)	3 (1.8)
Low density lipoprotein increased	2 (0.6)	0 (0)	4 (2.3)	4 (1.1)	1 (0.3)	0 (0)	1 (0.6)
Neutrophil count decreased	2 (0.6)	1 (0.6)	1 (0.6)	2 (0.6)	1 (0.3)	0 (0)	2 (1.2)
Metabolism and nutrition disorders	**15 (4.3)**	**5 (2.8)**	**7 (4.0)**	**12 (3.4)**	**5 (1.5)**	**3 (1.7)**	**2 (1.2)**
Hypertriglyceridemia	8 (2.3)	0 (0)	2 (1.1)	2 (0.6)	3 (0.9)	1 (0.6)	0 (0)
Hypercholesterolemia	7 (2.0)	2 (1.1)	5 (2.9)	7 (2.0)	2 (0.6)	0 (0)	2 (1.2)
Hyperlipidemia	0 (0)	3 (1.7)	1 (0.6)	4 (1.1)	1 (0.3)	2 (1.2)	0 (0)
Nervous system disorders	**3 (0.9)**	**3 (1.7)**	**2 (1.1)**	**5 (1.4)**	**1 (0.3)**	**1 (0.6)**	**0 (0)**
Headache	2 (0.6)	1 (0.6)	2 (1.1)	3 (0.8)	0 (0)	1 (0.6)	0 (0)
Blood and lymphatic system disorders	**3 (0.9)**	**2 (1.1)**	**3 (1.7)**	**5 (1.4)**	**3 (0.9)**	**2 (1.2)**	**4 (2.4)**
Leukopenia	2 (0.6)	1 (0.6)	1 (0.6)	2 (0.6)	1 (0.3)	0 (0)	3 (1.8)
Gastrointestinal disorders	**3 (0.9)**	**0 (0)**	**2 (1.1)**	**2 (0.6)**	**1 (0.3)**	**3 (1.7)**	**2 (1.2)**
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.2)	2 (1.2)
Respiratory, thoracic and mediastinal disorders	**5 (1.4)**	**1 (0.6)**	**3 (1.7)**	**4 (1.1)**	**6 (1.8)**	**3 (1.7)**	**4 (2.4)**
Rhinorrhea	1 (0.3)	0 (0)	1 (0.6)	1 (0.3)	2 (0.6)	1 (0.6)	2 (1.2)

A subject reporting more than one TEAE were counted only once using the maximum relationship reported. TEAEs with a start date after or on first dosing of TP1 and before or on first dosing of TP2 were included. In addition, if the AE start date on the same day of Week 24 with injection site reaction were counted on TP2.
Source: CSR Study BAT-2506-002-CR, Table 14.3.1.4.1 and Table 14.3.1.4.2

Study BAT-2506-003-CR (Phase 1, Healthy Subjects)

Table 47: Summary of Common Treatment-Related TEAEs (≥ 4%) by SOC and Preferred Term (Study BAT-2506-003-CR, SS)

SOC PT	Number of subjects, n (%)			
	BAT2506 (N = 123)	**EU-approved Simponi® (N=125)**	**US-licensed Simponi® (N=121)**	**Total (N=369)**
Total	**91 (74.0)**	**87 (69.6)**	**83 (68.6)**	**261 (70.7)**
Investigations	**74 (60.2)**	**65 (52.0)**	**63 (52.1)**	**202 (54.7)**
Blood triglycerides increased	16 (13.0)	24 (19.2)	23 (19.0)	63 (17.1)
Blood bilirubin increased	23 (18.7)	12 (9.6)	20 (16.5)	55 (14.9)
Neutrophil count decreased	18 (14.6)	10 (8.0)	13 (10.7)	41 (11.1)
Alanine aminotransferase increased	10 (8.1)	14 (11.2)	9 (7.4)	33 (8.9)
White blood cell count decreased*	10 (8.1)	1 (0.8)	8 (6.6)	19 (5.1)
Infections and infestations	**13 (10.6)**	**22 (17.6)**	**14 (11.6)**	**49 (13.3)**
Upper respiratory tract infection	8 (6.5)	16 (12.8)	10 (8.3)	34 (9.2)
Metabolism and nutrition disorders	**13 (10.6)**	**16 (12.8)**	**15 (12.4)**	**44 (11.9)**
Hypertriglyceridemia	12 (9.8)	15 (12.0)	12 (9.9)	39 (10.6)

Source: CSR Study BAT-2506-003-CR, Table 14.3.1.3.
*Assessor's comment: There was a mistake in this table provided in the Clinical Summary of Safety and CSR (White blood cell count increased was listed twice), however it was correct in table 14.3.1.3. Therefore, the table above was corrected.

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Study BAT-2506-001-CR (Phase 1, healthy subjects)

AESIs

Table 48: Summary of AESIs Incidence, severity, and relationship to drug by PT (BAT-2506-001-CR)

AESIs **Preferred Term (PT)** Severity Relationship	**BAT2506 (N=90) n (%) m**	**Simponi (EU) (N=90) n (%) m**	**Overall (N=180) n (%) m**
Infections	**3 (3.3) 4**	**4 (4.4) 4**	**7 (3.9) 8**
Upper respiratory tract infection	**3 (3.3) 4**	**4 (4.4) 4**	**7 (3.9) 8**
Grade 1	1 (1.1) 2	3 (3.3) 3	4 (2.2) 5
Grade 2	2 (2.2) 2	1 (1.1) 1	3 (1.7) 3
Possibly related	3 (3.3) 4	4 (4.4) 4	7 (3.9) 8
Tuberculosis	**1 (1.1) 2**	**0**	**1 (0.6) 2**
Pulmonary tuberculosis	**1 (1.1) 1**	**0**	**1 (0.6) 1**
Grade 3	1 (1.1) 1	0	1 (0.6) 1
Possibly related	1 (1.1) 1	0	1 (0.6) 1
Tuberculous pleurisy	**1 (1.1) 1**	**0**	**1 (0.6) 1**
Grade 3	1 (1.1) 1	0	1 (0.6) 1
Possibly related	1 (1.1) 1	0	1 (0.6) 1
Hypersensitivity and allergic reactions	**0**	**0**	**0**
HBV reactivation	**0**	**0**	**0**

Malignancies	**0**	**0**	**0**

Note:
a) n: Number of subjects; m: Number of events.
b) The severity of AESIs were determined based on the CTCAE V5.0 (Grade 1 ~ Grade 5).
c) Criteria for the relationship of AESIs to the investigational drug includes: Definitely related, Probably related, Possibly related, Possibly unrelated, and Definitely unrelated.
Data source: BAT-2506-001-CR CSR Table 14.3.3.2.1, Table 14.3.3.3.1, and Table 14.3.3.4.

Serious adverse events

During the study period, only one subject in the BAT2506 group experienced 2 SAEs (PT: tuberculous pleurisy, pulmonary tuberculosis), while none subjects in the Golimumab group experienced SAEs. These 2 SAEs were possibly related to the study drug and led to the subject's early withdrawal from the trial.

Deaths

No deaths occurred during the study.

Study BAT-2506-002-CR (Phase 3, PsA Subjects)

AESIs

Table 49: Summary of AESIs Incidence, severity, and relationship to drug by PT (BAT-2506-002-CR During Overall Period)

AESIs **Preferred Term (PT)** Severity Relationship	**BAT2506 (N=351) n (%) m**	**Simponi (N=187) n (%) m**	**Simponi/BAT2506 (N=166) n (%) m**	**All Subjects (N=704) n (%) m**
Infections*	**214(61.0) 377**	**103 (55.1) 188**	**99 (59.6) 169**	**416 (59.1) 734**
Upper respiratory tract infection	**61 (17.4) 78**	**29 (15.5) 40**	**43 (25.9) 52**	**133 (18.9) 170**
Mild	27 (7.7) 32	14 (7.5) 20	23 (13.9) 27	64 (9.1) 79
Moderate	34 (9.7) 46	15 (8.0) 20	20 (12.0) 25	69 (9.8) 91
Related	18 (5.1) 24	8 (4.3) 12	8 (4.8) 9	34 (4.8) 45
Not related	43 (12.3) 54	21 (11.2) 28	35 (21.1) 43	99(14.1) 125
Nasopharyngitis	**56 (16.0) 71**	**27 (14.4) 37**	**25 (15.1) 32**	**108 (15.3) 140**
Mild	46 (13.1) 61	21 (11.2) 30	17 (10.2) 24	84(11.9) 115
Moderate	10 (2.8) 10	6 (3.2) 7	8 (4.8) 8	24 (3.4) 25
Related	14 (4.0) 19	8 (4.3) 13	3 (1.8) 4	25 (3.6) 36
Not related	42 (12.0) 52	19 (10.2) 24	22 (13.3) 28	83(11.8) 104
COVID-19	**49 (14.0) 51**	**16 (8.6) 16**	**19 (11.4) 20**	**84 (11.9) 87**
Mild	24 (6.8) 25	9 (4.8) 9	14 (8.4) 14	47 (6.7) 48
Moderate	25 (7.1) 26	7 (3.7) 7	5 (3.0) 6	37 (5.3) 39
Related	0	1 (0.5) 1	0	1 (0.1) 1
Not related	49 (14.0) 51	15 (8.0) 15	19 (11.4) 20	83 (11.8) 86
Tonsillitis	**18 (5.1) 19**	**5 (2.7) 5**	**6 (3.6) 6**	**29 (4.1) 30**
Mild	4 (1.1) 4	1 (0.5) 1	1 (0.6) 1	6 (0.9) 6
Moderate	14 (4.0) 15	4 (2.1) 4	5 (3.0) 5	23 (3.3) 24
Related	4 (1.1) 4	1 (0.5) 1	2 (1.2) 2	7 (1.0) 7
Not related	14 (4.0) 15	4 (2.1) 4	4 (2.4) 4	22 (3.1) 23
Pharyngitis	**17 (4.8) 18**	**7 (3.7) 9**	**7 (4.2) 7**	**31 (4.4) 34**
Mild	9 (2.6) 9	5 (2.7) 7	3 (1.8) 3	17 (2.4) 19
Moderate	8 (2.3) 9	2 (1.1) 2	4 (2.4) 4	14 (2.0) 15
Related	5 (1.4) 5	5 (2.7) 7	2 (1.2) 2	12 (1.7) 14
Not related	12 (3.4) 13	2 (1.1) 2	5 (3.0) 5	19 (2.7) 20
Urinary tract infection	**16 (4.6) 19**	**12 (6.4) 13**	**8 (4.8) 11**	**36 (5.1) 43**
Mild	9 (2.6) 12	8 (4.3) 8	4 (2.4) 7	21 (3.0) 27
Moderate	7 (2.0) 7	4 (2.1) 5	4 (2.4) 4	15 (2.1) 16
Related	7 (2.0) 8	3 (1.6) 3	1 (0.6) 3	11 (1.6) 14

Not related	9 (2.6) 11	9 (4.8) 10	7 (4.2) 8	25 (3.6) 29
Sinusitis	**11 (3.1) 14**	**7 (3.7) 8**	**3 (1.8) 3**	**21 (3.0) 25**
Mild	3 (0.9) 5	3 (1.6) 3	0	6 (0.9) 8
Moderate	8 (2.3) 9	4 (2.1) 5	3 (1.8) 3	15 (2.1) 17
Related	4 (1.1) 5	1 (0.5) 1	1 (0.6) 1	6 (0.9) 7
Not related	7 (2.0) 9	6 (3.2) 7	2 (1.2) 2	15 (2.1) 18
Bronchitis	**9 (2.6) 10**	**4 (2.1) 4**	**5 (3.0) 7**	**18 (2.6) 21**
Mild	2 (0.6) 2	1 (0.5) 1	0 (0) 1□	3 (0.4) 4
Moderate	7 (2.0) 8	3 (1.6) 3	5 (3.0) 6	15 (2.1) 17
Related	2 (0.6) 2	1 (0.5) 1	1 (0.6) 1	4 (0.6) 4
Not related	7 (2.0) 8	3 (1.6) 3	4 (2.4) 6	14 (2.0) 17
Oral herpes	**8 (2.3) 11**	**4 (2.1) 4**	**5 (3.0) 5**	**17 (2.4) 20**
Mild	6 (1.7) 7	3 (1.6) 3	2 (1.2) 2	11 (1.6) 12
Moderate	2 (0.6) 4	1 (0.5) 1	3 (1.8) 3	6 (0.9) 8
Related	2 (0.6) 2	2 (1.1) 2	2 (1.2) 2	6 (0.9) 6
Not related	6 (1.7) 9	2 (1.1) 2	3 (1.8) 3	11 (1.6) 14
Respiratory tract infection	**8 (2.3) 10**	**5 (2.7) 5**	**7 (4.2) 7**	**20 (2.8) 22**
Mild	3 (0.9) 5	2 (1.1) 2	1 (0.6) 1	6 (0.9) 8
Moderate	5 (1.4) 5	3 (1.6) 3	5 (3.0) 5	13 (1.8) 13
Severe	0	0	1 (0.6) 1	1 (0.1) 1
Related	1 (0.3) 1	2 (1.1) 2	0	3 (0.4) 3
Not related	7 (2.0) 9	3 (1.6) 3	7 (4.2) 7	17 (2.4) 19
Gastroenteritis	**7 (2.0) 7**	**7 (3.7) 7**	**1 (0.6) 1**	**15 (2.1) 15**
Mild	3 (0.9) 3	4 (2.1) 4	1 (0.6) 1	8 (1.1) 8
Moderate	3 (0.9) 3	3 (1.6) 3	0	6 (0.9) 6
Severe	1 (0.3) 1	0	0	1 (0.1) 1
Not related	7 (2.0) 7	7 (3.7) 7	1 (0.6) 1	15 (2.1) 15
Rhinitis	**6 (1.7) 10**	**6 (3.2) 6**	**2 (1.2) 2**	**14 (2.0) 18**
Mild	6 (1.7) 10	6 (3.2) 6	2 (1.2) 2	14 (2.0) 18
Related	3 (0.9) 4	2 (1.1) 2	0	5 (0.7) 6
Not related	3 (0.9) 6	4 (2.1) 4	2 (1.2) 2	9 (1.3) 12
Laryngitis	**4 (1.1) 4**	**0**	**2 (1.2) 2**	**6 (0.9) 6**
Mild	1 (0.3) 1	0	1 (0.6) 1	2 (0.3) 2
Moderate	3 (0.9) 3	0	1 (0.6) 1	4 (0.6) 4
Related	1 (0.3) 1	0	0	1 (0.1) 1
Not related	3 (0.9) 3	0	2 (1.2) 2	5 (0.7) 5
Acute sinusitis	**3 (0.9) 3**	**4 (2.1) 4**	**0**	**7 (1.0) 7**
Mild	1 (0.3) 1	0	0	1 (0.1) 1
Moderate	2 (0.6) 2	4 (2.1) 4	0	6 (0.9) 6
Related	1 (0.3) 1	0	0	1 (0.1) 1
Not related	2 (0.6) 2	4 (2.1) 4	0	6 (0.9) 6
Herpes zoster	**2 (0.6) 2**	**2 (1.1) 2**	**2 (1.2) 2**	**6 (0.9) 6**
Mild	0	0	1 (0.6) 1	1 (0.1) 1
Moderate	2 (0.6) 2	2 (1.1) 2	1 (0.6) 1	5 (0.7) 5
Related	1 (0.3) 1	0	1 (0.6) 1	2 (0.3) 2
Not related	1 (0.3) 1	2 (1.1) 2	1 (0.6) 1	4 (0.6) 4
Influenza	**2 (0.6) 2**	**2 (1.1) 2**	**0**	**4 (0.6) 4**
Mild	0	2 (1.1) 2	0	2 (0.3) 2
Moderate	2 (0.6) 2	0	0	2 (0.3) 2
Related	1 (0.3) 1	0	0	1 (0.1) 1
Not related	1 (0.3) 1	2 (1.1) 2	0	3 (0.4) 3
Suspected COVID-19	**2 (0.6) 2**	**3 (1.6) 3**	**1 (0.6) 1**	**6 (0.9) 6**
Mild	2 (0.6) 2	2 (1.1) 2	1 (0.6) 1	5 (0.7) 5
Moderate	0	1 (0.5) 1	0	1 (0.1) 1
Not related	2 (0.6) 2	3 (1.6) 3	1 (0.6) 1	6 (0.9) 6
Viral upper respiratory tract infection	**2 (0.6) 4**	**3 (1.6) 4**	**2 (1.2) 2**	**7 (1.0) 10**
Mild	2 (0.6) 4	2 (1.1) 3	2 (1.2) 2	6 (0.9) 9
Moderate	0	1 (0.5) 1	0	1 (0.1) 1
Not related	2 (0.6) 4	3 (1.6) 4	2 (1.2) 2	7 (1.0) 10
Herpes simplex	**0**	**2 (1.1) 4**	**0**	**2 (0.3) 4**
Mild	0	1 (0.5) 3	0	1 (0.1) 3
Moderate	0	1 (0.5) 1	0	1 (0.1) 1
Not related	0	2 (1.1) 4	0	2 (0.3) 4
Hypersensitivity and allergic reactions	**3 (0.9) 4**	**2 (1.1) 2**	**2 (1.2) 2**	**7 (1.0) 8**
Injection site erythema	**3 (0.9) 3**	**0**	**1 (0.6) 1**	**4 (0.6) 4**
Mild	3 (0.9) 3	0	1 (0.6) 1	4 (0.6) 4
Related	3 (0.9) 3	0	1 (0.6) 1	4 (0.6) 4
Administration site erythema	**1 (0.3) 1**	**0**	**0**	**1 (0.1) 1**
Mild	1 (0.3) 1	0	0	1 (0.1) 1
Related	1 (0.3) 1	0	0	1 (0.1) 1

Injection site inflammation	**0**	**1 (0.5) 1**	**0**	**1 (0.1) 1**
Mild	0	1 (0.5) 1	0	1 (0.1) 1
Related	0	1 (0.5) 1	0	1 (0.1) 1
Injection site warmth	**0**	**1 (0.5) 1**	**0**	**1 (0.1) 1**
Mild	0	1 (0.5) 1	0	1 (0.1) 1
Related	0	1 (0.5) 1	0	1 (0.1) 1
Puncture site erythema	**0**	**0**	**1 (0.6) 1**	**1 (0.1) 1**
Mild	0	0	1 (0.6) 1	1 (0.1) 1
Related	0	0	1 (0.6) 1	1 (0.1) 1
Malignancies	**7 (2.0) 10**	**4 (2.1) 4**	**4 (2.4) 4**	**15 (2.1) 18**
Uterine leiomyoma	**2 (0.6) 3**	**1 (0.5) 1**	**1 (0.6) 1**	**4 (0.6) 5**
Mild	0	1 (0.5) 1	0	1 (0.1) 1
Moderate	2 (0.6) 3	0	1 (0.6) 1	3 (0.4) 4
Not related	2 (0.6) 3	1 (0.5) 1	1 (0.6) 1	4 (0.6) 5
Haemangioma of liver	**1 (0.3) 1**	**0**	**0**	**1 (0.1) 1**
Mild	1 (0.3) 1	0	0	1 (0.1) 1
Not related	1 (0.3) 1	0	0	1 (0.1) 1
Keratoacanthoma	**1 (0.3) 1**	**0**	**0**	**1 (0.1) 1**
Mild	1 (0.3) 1	0	0	1 (0.1) 1
Not related	1 (0.3) 1	0	0	1 (0.1) 1
Lipoma of breast	**1 (0.3) 1**	**0**	**0**	**1 (0.1) 1**
Mild	1 (0.3) 1	0	0	1 (0.1) 1
Not related	1 (0.3) 1	0	0	1 (0.1) 1
Neoplasm prostate	**1 (0.3) 2**	**0**	**0**	**1 (0.1) 2**
Mild	1 (0.3) 2	0	0	1 (0.1) 2
Not related	1 (0.3) 2	0	0	1 (0.1) 2
Pituitary tumour benign	**1 (0.3) 1**	**0**	**0**	**1 (0.1) 1**
Mild	1 (0.3) 1	0	0	1 (0.1) 1
Not related	1 (0.3) 1	0	0	1 (0.1) 1
Prostate cancer	**1 (0.3) 1**	**0**	**0**	**1 (0.1) 1**
Mild	1 (0.3) 1	0	0	1 (0.1) 1
Not related	1 (0.3) 1	0	0	1 (0.1) 1
Fibroadenoma of breast	**0**	**0**	**2 (1.2) 2**	**2 (0.3) 2**
Mild	0	0	1 (0.6) 1	1 (0.1) 1
Moderate	0	0	1 (0.6) 1	1 (0.1) 1
Not related	0	0	2 (1.2) 2	2 (0.3) 2
Haemangioma	**0**	**0**	**1 (0.6) 1**	**1 (0.1) 1**
Mild	0	0	1 (0.6) 1	1 (0.1) 1
Not related	0	0	1 (0.6) 1	1 (0.1) 1
Hepatic cancer	**0**	**1 (0.5) 1**	**0**	**1 (0.1) 1**
Severe	0	1 (0.5) 1	0	1 (0.1) 1
Not related	0	1 (0.5) 1	0	1 (0.1) 1
Intraductal proliferative breast lesion	**0**	**1 (0.5) 1**	**0**	**1 (0.1) 1**
Moderate	0	1 (0.5) 1	0	1 (0.1) 1
Related	0	1 (0.5) 1	0	1 (0.1) 1
Melanocytic naevus	**0**	**1 (0.5) 1**	**0**	**1 (0.1) 1**
Moderate	0	1 (0.5) 1	0	1 (0.1) 1
Not related	0	1 (0.5) 1	0	1 (0.1) 1
Tuberculosis	**0**	**0**	**0**	**0**
HBV reactivation	**0**	**0**	**0**	**0**

Note:
a) n: Number of subjects; m: Number of events.
b) The severity of AESIs includes: Mild, Moderate, and Severe. "A patient reporting more than one TEAE is counted only once using the maximum intensity reported; while events are overall counts calculated without considering maximum intensity.
c) Criteria for the relationship of AESIs to the investigational drug includes: Related (AE with causality of Certain, Probable/Likely, Possible and Missing) and Not related.
d) *For Infection related AESI, only PT terms with incidence ≥ 1% (i.e., representing at least "common" frequency for adverse reactions in the Simponi SmPC) in any treatment group are listed.
Data source: BAT-2506-002-CR CSR Table 14.3.1.2.3, Table 14.3.1.3.3, and Table 14.3.1.4.3.

Serious adverse events

During the study (TP1+TP2) the incidence of serious TEAEs reported was low and similar across all treatment groups: 19 subjects (5.4%) in BAT2506 group, 8 subjects (4.3%) in Simponi group, and 5

subjects (3.0%) in Simponi→BAT2506 group. The majority of serious TEAEs were considered as not related to the study drug. For drug-related serious TEAEs during TP1 and TP2 see Table 58.

Table 50: Incidence of Drug-Related Serious TEAEs by System Organ Class and Preferred Term During TP1 and TP2 (Study BAT-2506-002-CR)

SOC PT	Number of subjects, n (%)						
	TP1				TP2		
	BAT2506 (N=351)	Simponi (N=179)	Simponi→ BAT2506 (N=174)	Combined Simponi (N=353)	BAT2506 (N=341)	Simponi (N=172)	Simponi→ BAT2506 (N=1166)
Any Drug-Related Serious TEAEs	**1 (0.3)**	**0 (0)**	**1 (0.6)**	**1 (0.3)**	**0 (0)**	**2 (1.2)**	**0 (0)**
Blood and lymphatic system disorders	**0 (0)**	**0 (0)**	**1 (0.6)**	**1 (0.3)**	**0 (0)**	**0 (0)**	**0 (0)**
Anemia	0 (0)	0 (0)	1 (0.6)	1 (0.3)	0 (0)	0 (0)	0 (0)
Infections and infestations	**1 (0.3)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Pneumonia	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (0.6)**	**0 (0)**
Intraductal proliferative breast lesion	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)
Reproductive system and breast disorders	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (0.6)**	**0 (0)**
Endometrial hyperplasia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)

TEAE were counted only once using the maximum relationship reported. Related AEs defined as AE with causality of Certain, Probable/Likely, Possible and Missing. Events are overall counts calculated without considering maximum relationship.

Source: CSR Study BAT-2506-002-CR, Table 14.3.2.2.1 and Table 14.3.2.2.2.

Deaths

During the study, one TEAE (PT: sudden death) leading to death was reported during TP2 in the Simponi treatment group. According to the narrative, the subject died after being admitted to hospital with cough and body soreness. In hospital the patient suddenly suffered cardiac arrest and did not recover. Both investigator and sponsor assessed the event of sudden death as not related to the study intervention. Autopsy was not performed. The patient's relevant medical history included: hepatic function abnormal, hyperlipidaemia, hypertension, interstitial lung disease, lymphocyte count decreased and psoriasis. A long-term decrease in lymphocyte count suggests a deficiency in cellular immune function. An acute infection in a patient with immune deficiency and underlying cardiovascular conditions was a likely trigger for sudden deterioration, contributing to the fatal outcome.

Study BAT-2506-003-CR (Phase 1, healthy subjects)

AESIs

Events of "infections and infestations" were common TEAEs (≥4%) and were observed across all the treatment groups in healthy subjects (109/369 [29.5%] overall). During the study period of BAT2506-003-CR, the study site in China encountered a period of COVID-19 outbreak after release of strict COVID-19 related lock down policy (including transportation limitation and quarantine procedures), the incidence of infections and infestations increased largely in 3 study groups compared with study BAT-2506-001-CR, but was comparable among 3 arms.

Table 51: Summary of AESIs Incidence, severity, and relationship to drug by PT (BAT-2506-003-CR)

AESIs Preferred Term (PT) Severity Relationship	BAT2506 (N=123) n (%) m	Simponi (EU) (N=125) n (%) m	Simponi (US) (N=121) n (%) m	Overall (N=369) n (%) m
Infections	**33 (26.8) 34**	**40 (32.0) 44**	**36 (29.8) 37**	**109 (29.5) 115**
COVID-19	**18 (14.6) 18**	**18 (14.4) 18**	**19 (15.7) 19**	**55 (14.9) 55**
Grade 1	7 (5.7)	6 (4.8)	5 (4.1)	18 (4.9)
Grade 2	10 (8.1)	12 (9.6)	14 (11.6)	36 (9.8)
Grade 3	1 (0.8)	0	0	1 (0.3)
Possibly unrelated	18 (14.6)	18 (14.4)	19 (15.7)	55 (14.9)
Upper respiratory tract infection	**11 (8.9) 11**	**19 (15.2) 20**	**14 (11.6) 14**	**44 (11.9) 45**
Grade 1	4 (3.3)	7 (5.6)	7 (5.8)	18 (4.9)
Grade 2	7 (5.7)	12 (9.6)	7 (5.8)	26 (7.0)
Possibly related	8 (6.5)	16 (12.8)	10 (8.3)	34 (9.2)
Possibly unrelated	3 (2.4)	3 (2.4)	4 (3.3)	10 (2.7)
Respiratory tract infection	**3 (2.4) 3**	**1 (0.8) 1**	**1 (0.8) 1**	**5 (1.4) 5**
Grade 1	0	0	1 (0.8)	1 (0.3)
Grade 2	3 (2.4)	1 (0.8)	0	4 (1.1)
Possibly related	3 (2.4)	1 (0.8)	1 (0.8)	5 (1.4)
Influenza	**0**	**2 (1.6) 2**	**1 (0.8) 1**	**3 (0.8) 3**
Grade 2	0	2 (1.6)	1 (0.8)	3 (0.8)
Possibly related	0	2 (1.6)	1 (0.8)	3 (0.8)
Viral infection	**1 (0.8) 1**	**0**	**1 (0.8) 1**	**2 (0.5) 2**
Grade 2	1 (0.8)	0	1 (0.8)	2 (0.5)
Possibly related	1 (0.8)	0	1 (0.8)	2 (0.5)
Molluscum contagiosum	**0**	**1 (0.8) 1**	**0**	**1 (0.3) 1**
Grade 2	0	1 (0.8)	0	1 (0.3)
Possibly related	0	1 (0.8)	0	1 (0.3)
Oral herpes	**0**	**0**	**1 (0.8) 1**	**1 (0.3) 1**
Grade 1	0	0	1 (0.8)	1 (0.3)
Possibly related	0	0	1 (0.8)	1 (0.3)
Otitis media	**0**	**1 (0.8) 1**	**0**	**1 (0.3) 1**
Grade 2	0	1 (0.8)	0	1 (0.3)
Possibly related	0	1 (0.8)	0	1 (0.3)
Tinea cruris	**1 (0.8) 1**	**0**	**0**	**1 (0.3) 1**
Grade 2	1 (0.8)	0	0	1 (0.3)
Possibly related	1 (0.8)	0	0	1 (0.3)
Urinary tract infection	**0**	**1 (0.8) 1**	**0**	**1 (0.3) 1**
Grade 2	0	1 (0.8)	0	1 (0.3)
Possibly related	0	1 (0.8)	0	1 (0.3)
Hypersensitivity and allergic reactions	**0**	**0**	**0**	**0**
Tuberculosis	**0**	**0**	**0**	**0**
HBV reactivation	**0**	**0**	**0**	**0**
Malignancies	**0**	**0**	**0**	**0**

Note:
a) n: Number of subjects; m: Number of events.
b) The severity of AESIs were determined based on the CTCAE V5.0 (Grade 1 ~ Grade 5).
c) Criteria for the relationship of AESIs to the investigational drug includes: Definitely related, Probably related, Possibly related, Possibly unrelated, and Definitely unrelated.
Data source: BAT-2506-003-CR CSR Table 14.3.1.2, Table 14.3.1.14, and Table 14.3.1.16.

Serious adverse events

There were no SAEs reported during the study.

Deaths

There were no deaths reported for any subject.

5.4.5. Discontinuation due to adverse events

Study BAT-2506-001-CR (Phase 1, healthy subjects)

During study BAT-2506-001-CR, one subject in the BAT2506 experienced 2 SAEs (PT: tuberculous pleurisy, pulmonary tuberculosis), which were judged to be possibly related to the study drug and led to early withdrawal.

Study BAT-2506-002-CR (Phase 3, PsA Subjects)

TEAEs leading to study drug withdrawal

Table 52: Incidence of TEAEs Leading to Study Drug Withdrawal by System Organ Class and Preferred Term During Overall Period (Safety Analysis Set 1)

System Organ Class Preferred Term	BAT2506 (N=351) n (%) [#]	Simponi (N=187) n (%) [#]	Simponi/BAT 2506 (N=166) n (%) [#]	All Subjects (N=704) n (%) [#]
Any TEAEs Leading to Study Drug Withdrawal	**5 (1.4) [5]**	**6 (3.2) [6]**	**0**	**11 (1.6) [11]**
Gastrointestinal disorders	**0**	**1 (0.5) [1]**	**0**	**1 (0.1) [1]**
Diarrhoea	0	1 (0.5) [1]	0	1 (0.1) [1]
Injury, poisoning and procedural complications	**1 (0.3) [1]**	**0**	**0**	**1 (0.1) [1]**
Head injury	1 (0.3) [1]	0	0	1 (0.1) [1]
Investigations	**1 (0.3) [1]**	**0**	**0**	**1 (0.1) [1]**
Alanine aminotransferase increased	1 (0.3) [1]	0	0	1 (0.1) [1]
Musculoskeletal and connective tissue disorders	**0**	**1 (0.5) [1]**	**0**	**1 (0.1) [1]**
Psoriatic arthropathy	0	1 (0.5) [1]	0	1 (0.1) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.3) [1]**	**2 (1.1) [2]**	**0**	**3 (0.4) [3]**
Prostate cancer	1 (0.3) [1]	0	0	1 (0.1) [1]
Hepatic cancer	0	1 (0.5) [1]	0	1 (0.1) [1]
Intraductal proliferative breast lesion	0	1 (0.5) [1]	0	1 (0.1) [1]
Nervous system disorders	**1 (0.3) [1]**	**0**	**0**	**1 (0.1) [1]**
Epilepsy	1 (0.3) [1]	0	0	1 (0.1) [1]
Reproductive system and breast disorders	**0**	**1 (0.5) [1]**	**0**	**1 (0.1) [1]**
Heavy menstrual bleeding	0	1 (0.5) [1]	0	1 (0.1) [1]
Skin and subcutaneous tissue disorders	**1 (0.3) [1]**	**1 (0.5) [1]**	**0**	**2 (0.3) [2]**
Psoriasis	1 (0.3) [1]	0	0	1 (0.1) [1]
Angioedema	0	1 (0.5) [1]	0	1 (0.1) [1]

Source: Table 14.3.2.4.3
Note: Subjects in Simponi/BAT2506 group didn't enter to TP2 will be summarized in Simponi group.

TEAEs leading to study drug interruption

During the study (TP1+TP2), incidence of TEAE leading to study drug interruption was low and similar across treatment groups. TEAEs leading to study drug interruption were most commonly reported in the SOC of infections and infestations (43 subjects [6.1%]). Upper respiratory tract infection (10 subjects [1.4%]) and COVID-19 (8 subjects [1.1%]) was the two most commonly reported TEAEs leading to study drug interruption in all subjects by PT during the study.

During TP1, incidence of TEAE leading to study drug interruption was low and similar across treatment groups: 17 subjects (4.8%) in BAT2506 group, 10 subjects (5.6%) in Simponi group, 10 subjects (5.7%) in Simponi→BAT2506 group, and 20 subjects (5.7%) in combined Simponi group. TEAEs leading to study drug interruption were most commonly reported in the SOC of infections and infestations (26 subjects [3.7%]). The most common TEAEs leading to study drug interruption reported by PT in all subjects was COVID-19 (7 subjects [1.0%]).

During TP2, incidence of TEAE leading to study drug interruption was low and similar proportion of TEAE leading to study drug interruption across treatment groups: 10 subjects (2.9%) in BAT2506 group, 7 subjects (4.1%) in Simponi group and 10 subjects (6.0%) in Simponi→BAT2506 group. During TP2, TEAEs leading to study drug interruption were most commonly reported in the SOC of infections and infestations (17 subjects [2.5%]). The most common TEAE leading to study drug interruption reported by PT in all subjects was upper respiratory tract infection (6 subjects [0.9%], including 3 subjects [1.8%] in Simponi→BAT2506 group, 2 subjects [1.2%] in Simponi group, and 1 subject [0.3%] in BAT2506 group, respectively).

BAT-2506-003-CR (Phase 1, healthy subjects)

There were no AEs that lead to treatment or study discontinuation.

5.4.6. Safety in special populations

Not applicable.

5.4.7. Immunological events

Immunogenicity Effect on Safety

Possible immune response-related AE (eg, hypersensitivity, injection site reaction) were collected in the pivotal phase 3 study through EDC, with a question added following each AE's input to determine whether or not it was an injection site reaction.

For the immunogenicity-related safety observation, low immunogenicity related safety events happened in this study. During TP1, a total of 4 subjects (0.6%) were reported with the injection site reaction TEAEs, 2 subjects in the BAT2506 group and Simponi group each. During TP2, a total of 3 subjects (0.4%) were reported with the injection site reaction TEAEs, 1 subject in the BAT2506 group and 2 subjects in the Simponi→BAT2506 group. BAT2506 and Simponi had a similar immunogenicity-related safety profile, and no obvious safety changes were observed after switch.

The immunogenicity related safety analysis also revealed that immunogenicity did not influence the effect or safety of the study drug in the two phase 1 studies.

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

Not applicable.

5.4.9. Vital signs and laboratory findings

Study BAT-2506-001-CR (Phase 1, healthy subjects)

For the assessment of liver function, "Alanine aminotransferase increased" was reported in >6.7% of healthy subjects who received BAT2506, with no discernible differences between treatment groups. In SS (total subjects), abnormal laboratory findings with a high incidence (≥ 5%) by PT included hypertriglyceridemia [18 events (10.0%)], hyperuricemia [15 events (8.3%)], alanine aminotransferase increased [14 events (7.8%)], and blood bilirubin increased [10 events (5.6%)].

No abnormal and clinically significant coagulation findings were observed in the BAT2506 group or the EU-Simponi group.

In 6 subjects in the BAT2506 group, 12-lead ECG findings were normal/abnormal but clinically

insignificant at baseline and turned abnormal and clinically significant after administration. In 6 subjects in the EU-Simponi group, 12-lead ECG findings were normal/abnormal but clinically insignificant at baseline and turned abnormal and clinically significant after administration.

None of the subjects experienced abnormal injection site reactions.

Study BAT-2506-002-CR (Phase 3, PsA Subjects)

The haematology results were normal for most of subjects during the study in each treatment group. No clinically meaningful trends were observed in haematology variable shifts from baseline to post-baseline in any of the treatment groups.

The clinical chemistry results were normal for most of subjects during the study in each treatment group. No clinically meaningful trends were observed in clinical chemistry variable shifts from baseline to post-baseline in any of the treatment groups.

There were no clinically meaningful findings in the vital sign's measurements, physical examination assessments, and ECG, or other observations related to safety in this study. The assessments and observations were comparable across treatment groups.

Study BAT-2506-003-CR (Phase 1, healthy subjects)

There were 14 subjects with clinically significant abnormalities in ECG (3 in BAT2506, 8 in EU-Simponi and 3 in US-Simponi group). The clinically significant abnormalities values included: Sinus rhythm, abnormal ECG, Occasional Premature ventricular contractions, Sinus bradycardia with irregular abnormal electrocardiogram, Atrial rhythm, abnormal ECG, Occasional premature atrial contraction.

5.4.10. Post marketing experience

Not applicable.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

The safety database is informed by two phase 1 studies BAT-2506-001-CR (pivotal) and BAT-2506-003-CR (supportive) in healthy male volunteers and by the pivotal phase 3 study BAT-2506-002-CR in patients with active PsA. The safety database is comprised of 1253 subjects, of which 730 subjects received at least one full dose of BAT2506. In all presented studies, the safety and tolerability as well as immunogenicity data have been monitored as a secondary endpoint. Results were not pooled due to heterogeneity of the study populations (healthy participants vs participants with PsA) and the dosing period/exposure (single-dose vs. multiple-dose). The safety assessments were designed to capture the known safety issues listed in the Simponi product information and were considered appropriate. Drug exposure was similar between study arms in all three clinical studies.

Demographic and baseline characteristics were well balanced between the treatment groups.

The most frequently reported medical history by PT in the efficacy study were hypertension and obesity. The most frequently used prior medication was methotrexate. No clinically meaningful differences were observed between the treatment groups regarding medical history and prior medication.

The concomitant medications were administered due to the occurrence of AEs in the PK studies. In the efficacy study, the most frequently concomitant medications were folic acid, methotrexate and colecalciferol. No group-specific pattern was observed.

The length of safety follow-up was also adequate. Overall, the safety database is considered sufficiently large for evaluation of the safety profile of BAT2506 compared to Simponi.

Study BAT-2506-001-CR (Phase 1, healthy subjects)

The number of reported TEAEs were marginally higher in the golimumab (Simponi) arm than in the BAT2506 arm. Most TEAEs were mild to moderate in intensity. 4 subjects in each group experienced Grade ≥3 TEAEs. Only one subject in the BAT2506 experienced two SAEs (PT: tuberculous pleurisy, pulmonary tuberculosis) that were judged to be possibly related to the study drug and led to early withdrawal, whereas none of the subjects in the golimumab arm experienced SAEs or AEs leading to early withdrawal. No death was reported. No major differences between treatment groups in the reported TEAEs were identified.

Nevertheless, the number of drug-related TEAEs after single dosing is considered untypically high (180/227 events; 89.2%). Treatment-related TEAEs were most commonly reported under the SOCs of Investigations and Metabolism and nutrition disorders, with alanine aminotransferase increased, hypertriglyceridemia, and hyperuricemia being the most frequent drug-related TEAEs. While golimumab is known to affect liver function tests and white blood cell counts, the high frequency of abnormal other laboratory results considered drug-related, especially in the context of single dosing, is unexpected. These results could also potentially be attributed to undisclosed factors such as deviations from a non-fasting state, dietary habits, Gilbert syndrome, recent alcohol consumption or strenuous exercise prior to the study visit and/or underlying infections, rather than being a direct effect of the study treatment, particularly in the later follow-up stages. Specifically, the study protocol did not specify the duration of fasting or abstinence from strenuous exercise or alcohol before the study visits during the observation period. Overall, the relatedness of TEAEs seems to be overestimated by the investigator which led to the unexpectedly high number of reported drug-related TEAEs. As no significant differences were noted between the safety profiles of BAT2506 and Simponi, reassessment of the relatedness of TEAEs was not further pursued.

No AESIs have been pre-specified. In line with the known safety profile of golimumab, upper respiratory tract infections were reported in equal numbers in both treatment arms. Some minor numerical imbalances were noted in drug-related TEAEs in the SOC Respiratory, thoracic and mediastinal disorders. However, as they are driven by a few AEs, these differences are not considered clinically meaningful. As stated above, one subject had two events of tuberculosis (PT: tuberculous pleurisy, pulmonary tuberculosis). No malignancies or HBV reactivation was reported. No local infusion-related or hypersensitivity reactions were observed in this study. No immunogenicity-related safety TEAEs occurred during the study.

Study BAT-2506-002-CR (Phase 3, PsA Subjects)

Drug exposure was comparable across treatment arms over a median period of 52 weeks. 577 of 704 (82%) subjects experienced at least one TEAE during the overall study period.

During TP1, a slightly higher percentage of subjects experienced any TEAEs, severe TEAEs and serious TEAEs in the BAT2506 arm compared to the combined Simponi arm. The majority of TEAEs were mild or moderate. 3 subjects in the BAT2506 arm and 5 subjects in the combined Simponi arm had TEAEs leading to study drug withdrawal.

During TP2, the number of TEAEs and percentage of subjects experiencing TEAEs as well as serious AEs were overall comparable between the three treatment arms. Small proportion of participants

experienced TEAEs with severe intensity- 5 (1.5%) participants in the BAT2506 group and 1 (0.6%) participant each in the Simponi and Simponi/BAT2506 group. 2 subjects in the BAT2506 arm and one subject in the Simponi arm had TEAEs leading to study drug withdrawal, whereas none of the subjects in the Simponi→BAT2506 arm withdrew early due to TEAEs during TP2.

The most common reported TEAEs by SOC were Infections and infestations, followed by Investigations and Metabolism and nutrition disorders. The most common TEAEs by PT reported in all subjects were upper respiratory tract infection, nasopharyngitis, and COVID-19.

Drug-related TEAEs were reported in in 203 subjects (28.8%). Whereas the number of drug-related TEAEs were comparable between the treatment groups, numbers were slightly higher during TP1 than during TP2. Most common treatment-related TEAEs reported by PT were upper respiratory tract infection, nasopharyngitis and alanine aminotransferase increased which is in line with the known safety profile of Simponi. Overall, no issues arise from the reported ADRs.

Serious TEAEs were reported in 32 subjects throughout the overall period of the study. Numbers were overall balanced, with marginally higher numbers reported in the BAT2506 arm compared to the Simponi arms during TP1. 4 serious TEAEs were considered drug-related by the investigator - 1 participant in the BAT2506 group (pneumonia), 2 participants in the Simponi group (intraductal proliferative breast lesion and endometrial hyperplasia) and 1 participant in the Simponi/BAT2506 group (anaemia). Narratives for all SAEs were provided. Two additional serious events (pneumonia, anaemia) were re-classified as possibly related by the sponsor. No issues arise from the drug-related serious ADRs.

One subject in the Simponi group experienced a fatal event (sudden death) which was considered not drug-related. Infections are a known adverse effect of golimumab resulting from TNF-α inhibition. No new safety concern was identified.

Infections, hypersensitivity and allergic reactions, tuberculosis, hepatitis B virus reactivation and malignancies were considered AESI.

Infections were overall balanced between treatment groups. Though, higher number of infections were noted during TP2 compared to TP1. The high incidence of infections can be seen in the context of the post-COVID-19 pandemic period (study start 27 May 2021/ study end 06 Oct 2023) in which the release of COVID-19 related restrictions and reduced population immunity led to significant increases of respiratory infections globally. Nevertheless, no safety issues arise from these data. The number of injection-site reactions and hypersensitivity reactions were low and comparable between treatment arms. There were 15 events reported in the SOC Neoplasms, the overall incidence was comparable between treatment arms and most events were considered to be unrelated to study drug. No event of tuberculosis or HBV reactivation was reported.

A total of 11 subjects withdrew early due to AEs of which 8 subjects during TP1 and 3 subjects during TP2. The numbers were balanced between treatment arms, and most events were not considered related to the study drug. The discontinuations were well described; all narratives were found in the documentation and reasons for withdrawal from the study are considered acceptable. There were also some treatment interruptions, caused mostly by infections (upper respiratory tract infections, COVID-19), however the incidence of these interruptions was comparable between treatment groups and the reasons presented by the Applicant are acceptable.

In line with the known safety profile of Simponi, the most common reported laboratory AEs were ALT increased, LDL increased, and AST increased. These numbers were overall balanced between treatment groups during TP1 and TP2. No issues arise from laboratory assessments, vital signs or ECG parameters.

The effect of ADA/NAb on safety has been investigated with regard to injection site reactions. These numbers were low, and incidence was balanced between treatment groups.

Overall, no safety concerns have been identified that would indicate differences in the safety profile between BAT2506 and Simponi.

Study BAT-2506-003-CR (Phase 1, healthy subjects)

AEs were reported with similar frequencies between treatment groups: 83.7% of participants in the BAT2506 group, 81.6% of participants in the EU-Simponi group and 81.0% of participants in the US-Simponi group. Most of these were considered treatment related. The number of related grades ≥3 TEAEs were balanced between treatment arms. No subject experienced SAEs or TEAEs leading to early withdrawal, early discontinuation or death.

No major differences between treatment groups in the reported TEAEs were identified. Treatment-related TEAEs were most commonly reported under the SOC of investigations, infections and infestations and metabolism and nutrition disorders. As already noted for Study BAT-2506-001-CR, it appeared that the relatedness of several TEAEs with the study drug was overestimated by the investigator, especially with regard to single dosing.

Some numerical imbalances in the events under the SOC Investigations and Infections and Infestations between the three treatment arms were noted. For the SOC investigations, higher number of events were reported for BAT2506 compared to EU-and US-Simponi. For the SOC infections and infestations, the imbalance is mainly due to a slightly higher number of infections reported in the EU-Simponi arm compared to the BAT2506 and US-Simponi arms. Of note, a higher number of infections were reported during this study compared to the study BAT-2506-001-CR. As pointed out by the applicant, this should be seen in the context of the COVID-19 pandemic. No event of malignancies, injection site reactions, tuberculosis or HBV reactivation was reported. No immunogenicity-related safety TEAEs occurred during the study.

The list of safety concerns in the risk management plan (RMP) are in line with the ones of the reference medicinal product Simponi (see 7.1.1.).

5.4.11.1.2. Adverse drug reactions in the SmPC

The adverse drug reactions in the SmPC are line with the ones of the originator Simponi.

5.4.11.2. Conclusions on clinical safety

The submitted data from the two phase 1 PK biosimilarity studies and the phase 3 efficacy study indicated that BAT2506 and Simponi have similar safety profiles. No major imbalances or in the frequency of ADRs between treatment arms or safety concerns have been noted, even after switching from Simponi to BAT2506. The overall safety profile of BAT2406 appears to be in line with known safety profile of the reference product EU-Simponi.

Biosimilarity is supported from a safety perspective.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

Table 53: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	Serious infections Demyelinating disorders Malignancy
Important potential risks	Serious depression including suicidality Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero
Missing information	Long-term safety in paediatric patients

6.1.2. Discussion on proposed safety specification

The safety concerns are in line with the safety concerns of the reference product Simponi. The provided safety specification is considered acceptable.

The PRAC agrees with the conclusions of the CHMP, that the summary of safety concerns is aligned with the reference product for the relevant indications and is considered acceptable.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

- **Routine pharmacovigilance activities**

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are as follows:

Specific adverse reaction follow-up questionnaires for the safety concerns:

- **Serious infections**

- TOI TFUQ (Topic of Interest Targeted Follow-up Questionnaire) to collect information on serious infections and opportunistic infections
- TOI TFUQ to collect information on TB
- TOI TFUQ to collect information on progressive multifocal leukoencephalopathy/reversible posterior leukoencephalopathy syndrome

- **Malignancy**

- TOI TFUQ to collect information on malignancy events (including lymphoma, second and secondary malignancies). Particular attention is paid to subjects ≤30 years of age.

Other forms of routine pharmacovigilance activities

Not applicable

• **Additional pharmacovigilance activities**

The applicant did not propose any additional pharmacovigilance activities.

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

The proposed routine pharmacovigilance activities are aligned with the routine pharmacovigilance activities of the reference product and thus appropriate.

6.2.2.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned; this is acceptable.

6.3. Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies have been imposed or are planned; this is considered reasonable.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 54: Planned routine risk minimisation measures

Safety concern	**Routine risk minimisation activities**
Serious infections	**Routine risk communication:** SmPC sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), and 4.8 (Undesirable effects) Package Leaflet (PL) sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special warnings and precautions for use) • Guidance on evaluating patients for infections prior to treatment initiation, monitoring patients for infections during and after treatment, and managing patients who develop infections

	SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • Recommendations regarding the administration of live vaccines to patients receiving Gotenfia PL sections 2 and 4 • Patients are advised to notify their doctor if they have an infection before using Gotenfia or if they experience symptoms of an infection during Gotenfia treatment **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription
Demyelinating disorders	**Routine risk communication:** SmPC sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) PL sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special warnings and precautions for use) • Guidance to discontinue use of Gotenfia if demyelinating disorders develop PL sections 2 and 4 • Patients are advised to notify their doctor if they have been diagnosed with nervous system disease before using Gotenfia or if they experience any symptoms of nervous system disease **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription
Malignancy	**Routine risk communication:** SmPC sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) PL sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special warnings and precautions for use)

	• Recommendation to screen patients with UC who are at increased risk for or have a history of colon dysplasia or colon carcinoma for dysplasia before treatment initiation and throughout their disease course • Recommendation to perform periodic skin examination PL section 2 • Patients are advised to notify their doctor have been diagnosed with lymphoma or any other cancer before using Gotenfia or if they experience symptoms of lymphoma, skin cancer, or leukaemia; patient who may be at increased risk for cancer should discuss with their doctor whether treatment with a TNF blocker is appropriate PL section 4 • Patients are advised to notify their doctor if they experience symptoms of lymphoma, skin cancer, or leukaemia **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription
Serious depression including suicidality	**Routine risk communication:** SmPC section 4.8 (Undesirable effects) PL section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription
Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero	**Routine risk communication:** SmPC sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy, and lactation) PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.6 (Fertility, pregnancy, and lactation) • Recommendations regarding the administration of live vaccines to infants exposed to golimumab in utero PL section 2

	• Patients who take Gotenfia while pregnant are advised tell their baby's doctor and other HCPs about their use of Gotenfia before their baby receives any vaccine **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription
Long-term safety in pediatric patients	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription

In addition, the applicant has proposed the following additional risk minimisation measures:

Table 55: Additional risk minimisation measures

Patient Card Objectives: The goal of the Patient Card is to educate patients on important safety information that they need to be aware of before and during treatment with Gotenfia. The Patient Card addresses the following important risks: - Serious infections (including opportunistic infections, tuberculosis, hepatitis B virus reactivation) - Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero* Rationale for the additional risk minimisation activity: To enhance patient knowledge regarding the risk of infection associated with Gotenfia treatment and to remind patients who received Gotenfia during pregnancy to inform their infant's physician before the infant receives any live vaccine. Target audience and planned distribution path: The Patient Card is provided as part of the product packaging. Plans to evaluate the effectiveness of the interventions and criteria for success: The Marketing Authorisation Holder will evaluate the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation (routine pharmacovigilance).

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The routine risk minimisation measures are aligned with the reference product and considered sufficient.

6.4.2.2. Additional risk minimisation measures

The additional risk minimisation measures are aligned with the reference product and are considered acceptable and sufficient.

Section "V.2. Additional Risk Minimisation Measure" of the RMP includes a sentence that "The Marketing Authorisation Holder will evaluate the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation (routine pharmacovigilance)." This sentence is not included in the corresponding section of the reference product's RMP but considered acceptable.

6.5. RMP Summary and RMP Annexes overall conclusion

Annex 6 includes the following text, in line with the reference product:

Draft Key Messages of the Additional Risk Minimisation Measures

Patient Card

The educational program consists of a Patient Card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professionals (HCPs) treating the patient about ongoing treatment with the product.

The Patient Card shall contain the following key messages:

- A reminder to patients to show the Patient Card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using Gotenfia.
- A statement that the brand name and batch number should be recorded.
- Provision to record the type, date and result of TB screenings.
- That treatment with Gotenfia may increase the risks of serious infection, opportunistic infections, tuberculosis, hepatitis B reactivation, and breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero; and when to seek attention from a HCP.
- Contact details of the prescriber.

The language of the respective Patient Card can be found in the Gotenfia Product Information, Appendix IIIA.

The RMP Part VI and the RMP Annexes are acceptable.

6.6. PRAC Outcome at D166

PRAC endorsed the PRAC Rapporteur's assessment of the RMP and its conclusions, without further additions.

6.7. Overall conclusion on the Risk Management Plan

☒The CHMP and PRAC consider that the risk management plan version (RMP Version number: 0.2) is acceptable.

The Applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and

identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. 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.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

In this biosimilar application, the applicant is seeking all indications of the reference product Simponi. The SmPC is aligned with the SmPC of Simponi.

8.1.2. SmPC section 4.2 justification

The applicant only applied to the 50 mg and 100 mg dose strengths in pre-filled syringe, but not the 45 mg/0.45 mL dose strength. Thus, dosing in children with polyarticular Juvenile Idiopathic Arthritis and a body weight under 40 kg is not possible with Gotenfia. This is currently reflected in the SmPC section 4.2. If a 45 mg/0.45 mL dose is required, another golimumab product should be used instead.

8.2. Labelling

8.2.1. Package leaflet (PL)

The package leaflet is also in line with the originator.

8.2.2. 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 Simponi 50 mg solution for injection in pre-filled syringe. The bridging report submitted by the applicant has been found acceptable.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, golimumab is included in the additional monitoring list since it is a biological product that is not covered by the previous category and 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 will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Biosimilarity assessment

9.1. Comparability exercise and indications claimed

Gotenfia (BAT2506, golimumab) was developed as a biosimilar to the reference medicinal product Simponi (golimumab).

The applicant applied for all approved therapeutic indications of the reference product Simponi. These indications are:

Rheumatoid arthritis (RA)

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

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

Gotenfia, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Gotenfia in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

Psoriatic arthritis (PsA)

Gotenfia, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Gotenfia has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Gotenfia is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)

Gotenfia is indicated for the treatment of adults with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative colitis (UC)

Gotenfia is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

The product has been developed for subcutaneous administration. The applicant only applied for the 50 mg and 100 mg solution for injection in pre-filled syringe. The applicant did not apply for the paediatric strength, 45 mg/0.45 ml solution for injection, which is intended for the treatment of active polyarticular juvenile idiopathic arthritis for children with body weight of less than 40 kg.

Comparability exercise

Quality aspects

A comprehensive analytical biosimilarity exercise comparing BAT2506 with the reference medicinal products EU-Simponi has been performed. A large number of batches, which can be expected to sufficiently reflect product variability of both the proposed biosimilar and the reference medicinal product, was analysed. The BAT2506 batches have been manufactured according to the clinical and intended commercial process. A risk assessment identified a comprehensive quality attribute list tested during the study, which encompass primary and higher order structures, purity parameters, post-translational modifications, biological functions (including Fc-effector functions) and degradation profiles.

A tiered approach (Tier 1-3) has been used for the comparison of quality attributes. For tier 1 a statistical approach using a two-sided confidence interval of the mean of the proposed biosimilar product within ±δ has been applied for quality (biosimilarity) range definition. The δ is based on the standard deviation of all the RP lots tested and multiplied by 1.5. For tier 2 a statistical approach using sample means ± x-time standard deviation was used for quality (biosimilarity) range definition, where appropriate. The x was defined as 3. The approach is in general considered acceptable taking the high number of reference product batches into account. The Applicant considered biosimilarity as highly similar if 90% of BAT2506 batches fall into the quality range. Tier 3 acceptance criteria are qualitative comparisons of chromatograms, gels, etc, that are obtained side-by-side and for the expectation approach is applied to attributes that were not expected to vary, such as molecular weight.

Non-clinical aspects

To demonstrate biosimilarity between BAT2506 and EU-Simponi a comprehensive panel of *in vitro* binding and functional assays were conducted and evaluated as part of the quality part. *In vivo* studies were conducted to meet regulatory requirements outside the EU.

Clinical aspects

A comparability exercise for clinical data was carried out as part of the clinical development program for Gotenfia, which included two phase 1 studies in healthy male subjects (study BAT-2506-001-CR, BAT-2506-003-CR) and a phase 3 efficacy study in patients with active PsA (study BAT-2506-002-CR). The PK of BAT2506 and EU-Simponi were assessed in the pivotal phase 1 study (study BAT-2506-001-CR), with additional support from the phase 1 study BAT-2506-03-CR, which focused on

evaluating PK biosimilarity between BAT2506, US-Simponi and EU-Simponi. The primary evaluation of biosimilarity in terms of efficacy and safety was conducted in the phase 3 study (BAT-2506-002-CR). This approach is in line with biosimilar development programs. The applicant has mostly followed the recommendations made in the EMA Scientific Advice.

9.2. Results supporting biosimilarity

Quality aspects

As described in section 4.3.6. above in more detail the primary structure and post-translational modifications of BAT2506 show some differences in comparison to its reference medicinal product EU-Simponi. The differences can mainly be attributed to the difference in the expression cell lines (CHO vs. SP2/0). The provided data showed no impact especially on the potency of the product. In terms of purity comparable results were reported with differences in pre-peaks (nrCE-SDS) and charged variants (IEC-HPLC) which were also shown to not impact efficacy or safety. The stability profiles between BAT2506 and EU-Simponi were comparable.

Non-clinical aspects

Although *in vivo* studies are not required based on EU guideline, the results of the studies showed similarity between BAT2506 and EU-Simponi from a non-clinical aspect.

Clinical aspects

Pharmacokinetics

The pivotal data for demonstrating PK similarity with the EU reference product (Simponi) are obtained from a single-dose study in healthy volunteers (BAT-2506-001-CR). Pharmacokinetic comparability has been demonstrated for BAT2506 versus EU Simponi. The 90% CIs of the primary parameters ($AUC_{0\text{-}inf}$, C_{max} and $AUC_{0\text{-}t}$) were contained within the predefined 80.00% to 125.00% bioequivalence limits. An additional supportive phase 1 study (BAT-2506-003-CR) in a comparable population produced comparable results.

In the pivotal efficacy and safety study (BAT-2506-002-CR), PK trough concentration samples were collected from all study patients at scheduled visits. A population PK analysis did not indicate relevant differences in PK characteristics of both products.

Efficacy

Data from the phase 3 study BAT-2506-002-CR conducted in patients with PsA were provided to compare efficacy between BAT2506 and Simponi. The primary efficacy endpoint was the proportion of ACR20 responders at week 8 with the predefined equivalence margin [-13.8%, 13.8%], based on 95% CI. The common risk difference in ACR20 response rates between the BAT2506 group and the combined Simponi group was 11.32% with a 95% CI of (4.40, 18.25) at week 8. Thus, the upper bound fell outside the predefined equivalence margin of 13.8% while the lower bound was contained within the margin. However, in patients with PsA, similar treatment responses between BAT2506 and EU-Simponi were observed in ACR and DAS28-CRP response criteria and change in DAS28-CRP scores starting at week 14 which lasted until the end of treatment at week 52. Similar symptom improvements were seen for relevant disease domains such as psoriatic skin involvement, nail involvement and physical function starting at week 14.

Safety

The safety database was considered sufficiently large for the biosimilarity exercise. Based on the provided safety data of the three clinical studies, the observed safety findings are overall comparable

between Gotenfia and Simponi.

Immunogenicity

Rather high ADA incidence rates (about 40%) were determined in the PsA patient population and associated with reduced golimumab exposure. According to SmPC of Simponi, across the phase 3 RA, PsA and AS studies through week 52, antibodies to golimumab were detected by an enzyme immunoassay (EIA) method in 5% (105/2 062) of golimumab treated patients. Also here, almost all ADA positive patients were nAB positive as well. The higher rates of ADAs and nABs compared to literature data seen here with another assay are not a concern per se for biosimilarity assessment, as rates were overall comparable between treatment groups. No apparent correlation of antibody development with efficacy has been observed. The section 5.1 of the SmPC has been updated accordingly.

9.3. Uncertainties and limitations about biosimilarity

The phase 3 efficacy study (BAT-2506-002-CR) did not meet its primary endpoint, defined as the proportion of ACR20 responders at week 8. The results for this endpoint - including subgroup analyses by randomisation and sensitivity analyses - fell outside the predefined equivalence limits [-13.8%, 13.8%]. However, similar responses between BAT2506 and Simponi were seen at later timepoints (i.e. week 14 and to week 52). Additionally, results for other secondary endpoints provided supportive evidence for the claim of biosimilarity. Therefore, the efficacy analysis conducted in study BAT-2506-002-CR in its totality supports clinical comparability between BAT2506 and Simponi.

The protein content in BAT2506 is slightly higher in comparison to EU-Simponi. Given the different assays used to measure protein content at release vs analytical comparability exercise the difference is expected even higher. As a result, the upper limit for the acceptance criterion at release has been significantly lowered.

Overall, all uncertainties identified during the assessment have been appropriately addressed and no concerns remain for the demonstration of biosimilarity.

9.4. Discussion on biosimilarity

Quality

The analytical comparability exercise is in general considered well designed and the totality of data presented support biosimilarity.

Pharmacokinetics

The pivotal PK study (BAT-2506-001-CR) conducted in healthy male subjects demonstrated PK biosimilarity between BAT2506 and EU Simponi as the primary PK parameters $AUC_{0\text{-}inf}$, C_{max} and $AUC_{0\text{-}t}$ (also for the secondary PK parameters) fell within the acceptance range of 80.00% to 125.00%. An additional supportive phase 1 study in a comparable population produced comparable results. The PK clinical data support the claim on PK biosimilarity between BAT2506 and EU Simponi.

Efficacy

The efficacy analysis conducted in study BAT-2506-002-CR in its totality supports clinical comparability between BAT2506 and Simponi. While the primary endpoint (proportion of ACR20 responses at week 8) was not met symptom improvements were similar at later timepoints (week 14)

and throughout the study (week 52) as seen for ACR response rates but also DAS28-CRP scores. Overall, results for the secondary endpoints support the claim for biosimilarity.

Safety

The safety assessment conducted in the two phase 1 PK and the phase 3 efficacy study was appropriately performed, taking into account the established safety profile of Simponi. Overall, the submitted safety data support biosimilarity of Gotenfia to Simponi from a safety perspective.

Immunogenicity

ADA incidence rates were comparable between BAT2506 and EU Simponi in the PsA population under investigation. The magnitude of change in golimumab exposure due to ADA and nABs was comparable between BAT2506 and EU Simponi based on data from study BAT-2506-002-CR. The presence of ADAs did not influence the efficacy or safety of the study drug.

9.5. Extrapolation of safety and efficacy

Gotenfia was developed as a biosimilar to the reference medicinal product Simponi. The applicant is seeking approval for the same therapeutic indications as those currently authorised for Simponi, namely: rheumatoid arthritis, psoriatic arthritis, axial spondylarthritis, ulcerative arthritis and juvenile idiopathic arthritis.

Approval is being sought for the 50 mg and 100 mg solutions for subcutaneous injection in pre-filled syringes. The applicant has not applied for authorisation of the same strengths in pre-filled pens, nor for the paediatric strength of the 45 mg/ 0.45 ml.

The active substance, golimumab, is a fully human IgG1 monoclonal antibody that specifically binds to both soluble and membrane-bound TNFα, blocks TNFα binding to its receptor (TNFR), and inhibits TNFα-mediated signaling. Blocking of TNFα signalling has been shown to ameliorate symptoms of diseases characterised by inflammation due to autoimmune or hyper-immune reactions.

The choice of psoriatic arthritis as the study population is considered appropriate. Extrapolation of efficacy to other indications were neutralisation of soluble TNF-α is the primary mode of action - namely rheumatoid, juvenile arthritis, and axial spondyloarthritis - is also supported. The applicant has provided sufficient justification demonstrating that TNF-α plays a key role in the pathogenesis of these conditions.

Furthermore, extrapolation to the ulcerative colitis indication, where additional mechanism such as binding and effector functions involving membrane-bound TNF-α are relevant, has also been substantiated through additional experimental evidence submitted during the assessment.

The Simponi product information supports the conclusion that, aside from body weight, intrinsic and extrinsic factors do not significantly impact the pharmacokinetic, safety or effectiveness of golimumab in paediatric patients compared to adults. Measures to account for the impact of body weight (i.e, weight-based dosing) are appropriately addressed in the product labelling. Given that biosimilarity has been established, comparable efficacy between Gotenfia and Simponi is expected in the intended paediatric indication.

There is no dosage form for Gotenfia that allows for a 45 mg/0.45 mL dose available for administration to children with polyarticular juvenile idiopathic arthritis weighing less than 40 kg. Thus, it is not possible to administer Gotenfia to patients that require a 45 mg/0.45 mL dose. If a

45 mg/0.45 mL dose is required, another golimumab product should be used instead. This is adequately reflected in the section 4.2 of the SmPC.

The clinical evidence presented in this application is supportive of the conclusion that there are no clinically efficacy or safety meaningful differences between Gotenfia and EU-Simponi. The analytical biosimilarity at the quality level is also considered demonstrated between Gotenfia and EU-Simponi. Extrapolation of similarity to the adults and paediatric indications is supported.

9.6. Conclusions on biosimilarity and benefit risk balance

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