19 November 2015
EMA/CHMP/819219/2015
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Benepali

International non-proprietary name: etanercept

Procedure No. EMEA/H/C/004007/0000

## Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# Table of contents

# List of abbreviations

| | |
|---|---|
| $\lambda_z$ Lambda_z, | Terminal rate constant |
| ACR | American College of Rheumatology |
| ACR20 | 20% improvement according to the ACR criteria |
| ACR50 | 50% improvement according to the ACR criteria |
| ACR70 | 70% improvement according to the ACR criteria |
| ADCC | Antibody-dependent cell-mediated cytotoxicity |
| ANCOVA | Analysis of covariance |
| AS | Ankylosing spondylitis |
| AUC | Area under the concentration-time curve |
| $AUC_T$ | Area under the concentration-time curve over the dosing interval |
| AZA | Azathioprine |
| biw | Twice a week |
| BLA | Biologic License Application |
| BMWP | Biosimilar Medicinal Products Working Party |
| bw | Body weight |
| CDAI | Clinical disease activity index |
| CDC | Complement-dependent cytotoxicity |
| cfu | Colony forming unit |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| CL | Total body clearance |
| $C_{max}$ | Maximum serum concentration |
| $C_{max,ss}$ | Maximum serum concentration at steady state |
| CPMP | Committee for Proprietary Medicinal Products |
| CRP | C-reactive protein |
| CSR | Clinical study report |
| DAS | Disease activity score |
| db | Double-blind |
| DMARD | Disease-modifying anti-rheumatic drugs |
| EGA | Evaluator's global assessment |
| EM(E)A | European medicines Agency |
| enr | Enrolled |
| eow | Every other week |
| ESR | Erythrocyte sedimentation rate |
| EU | European Union |
| EULAR | The European League Against Rheumatism |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GH | General health |
| h | Hour(s) |
| HAQ | Health assessment questionnaire |
| HMW | High molecular weight |
| i.v. | Intravenous |
| ICH | International Conference on Harmonisation |
| IgG1 | Immunoglobulin G, subtype 1 |

| | |
|---|---|
| JIA | Juvenile idiopathic arthritis |
| kg | Kilogram |
| L | Litre |
| LMW | Low molecular weight |
| LRV | $Log_{10}$ reduction value |
| mAb | Monoclonal antibody |
| max | maximum |
| mc | Multicentre |
| mg | Milligram |
| min | minimum |
| mL | Millilitre |
| MTX | Methotrexate |
| N, n | Number |
| n.r. | Not reported |
| N/A | Not applicable |
| ND | No data available |
| NSAID | Non-steroid anti-inflammatory drugs |
| PD | Pharmacodynamic(s) |
| PGA | Patient's global assessment |
| PI | Product information |
| PK | Pharmacokinetic(s) |
| PP | Per-protocol |
| Ps | Psoriasis |
| PsA | Psoriatic arthritis |
| PUVA | Psoralen combined with ultraviolet A (UVA) |
| q4 | Every 4 weeks |
| q8 | Every 8 weeks |
| q6 | Every 6 weeks |
| QoL | Quality of life |
| qw | Every week |
| ra | Randomised |
| RA | Rheumatoid arthritis |
| RF | Rheumatoid factor |
| Rt | Retention time |
| s.c. | Subcutaneous |
| SD | Standard deviation |
| SDAI | Simplified disease activity index |
| SE | Standard error |
| SF-36 | Medical outcomes study short-form health survey |
| SJC | Swollen joint count |
| SmPC | Summary of product characteristics |
| SOC | System organ class |
| STD | Study |
| sTNF | Soluble tumour-necrosis factor alpha |
| $T_{½}$ | Terminal elimination half life |
| TB | Tuberculosis |
| TJC | Tender joint count |
| tm | Transmembrane |

| | |
|---|---|
| tmTNF | Membrane bound tumour necrosis factor |
| TNF | Tumour necrosis factor |
| TNFR | Tumour-necrosis factor receptor |
| TNFß | Tumour-necrosis factor beta |
| TNF α | Tumour-necrosis factor alpha |
| USA | United States of America |
| VAS | Visual analogue scale |
| $V_c$ | Volume of distribution in the central compartment |
| $V_p$ | Volume of distribution in the peripheral compartment |
| $V_{ss}$ | Volume of distribution at steady state |
| WGET | Wegener's Granulomatosis Etanercept Trial |
| Wk(s) | Week(s) |
| y | Year(s) |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Samsung Bioepis UK Limited (SBUK) submitted on 3 December 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Benepali, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004 .The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2014.

The applicant applied for the following indication:

Rheumatoid arthritis

Benepali in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Benepali can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Benepali is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

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

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis

Treatment of adults with severe 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 nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA).

**The legal basis for this application refers to:**

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

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

***Information on Paediatric requirements***

Not applicable

***Information relating to orphan market exclusivity***

***Similarity***

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

***Scientific Advice***

The applicant received Scientific Advice from the CHMP on 19 January 2012, 19 July 2012 and 19 December 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

***Licensing status***

The product was not licensed in any country at the time of submission of the application.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Andrea Laslop Co-Rapporteur: Outi Mäki-Ikola

- The application was received by the EMA on 3 December 2014.
- The procedure started on 24 December 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2015.
- The first PRAC Rapporteur Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 10 April 2015.
- During the meeting on 23 April 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 April 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2015.
- GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 August 2015.
- The second PRAC Rapporteur Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 10 September 2015.

- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 29 October 2015.
- The third and final PRAC Rapporteur Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 6 November 2015.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 16 November 2015.
- During the meeting on 19 November 2015, 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 Benepali.

# 2. Scientific discussion

## *2.1. Introduction*

**Problem statement**

This centralised marketing authorisation application concerns the Biotech medicinal product Benepali 50 mg, solution for injection, Article 3 (1) of Regulation EC No 726/2004, annex (1).

The application is submitted under Article 10(4) ('similar biological application) of Directive 2001/83/EC, as amended.

The reference medicinal product is Enbrel, 25 mg Powder and solvent for solution for injection, Pfizer Limited, originally authorised in the community on 03rd February 2000. The active substance is the tumour necrosis factor-α (TNF-α) inhibitor etanercept.

Benepali is presented in single-use pre-filled syringes and pre-filled pens containing 50 mg etanercept per mL to be administered via subcutaneous (SC) injection. As only a pharmaceutical form containing 50 mg etanercept per dose applies for MA, the applicant does not intend to claim the approved paediatric indications of Enbrel (paediatric plaque psoriasis, juvenile idiopathic arthritis).

**About the product**

Benepali is presented in single-use pre-filled syringes and pre-filled pens, in each case containing 50 mg etanercept per mL to be administered via subcutaneous (SC) injection. Benepali has been developed as a proposed similar biological medicinal product (biosimilar) to the reference medicinal product Enbrel having the tumour necrosis factor-α (TNF-α) inhibitor etanercept as the active substance.

The active substance of Benepali (etanercept; 50 mg/mL) is a clear to opalescent, colourless to pale yellow solution for injection. Benepali is presented in single-use pre-filled syringes and pre-filled pens containing 50 mg etanercept per mL to be administered via subcutaneous (SC) injection.

Etanercept (Enbrel) was first approved in 1998 by the US Food and Drug Administration (FDA) and in 2000 by the European Commission.

**Pharmacological Class**

Benepali is a homodimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human TNFR2/p75 to the Fc domain of human IgG1. The Fc component comprises the hinge, CH2 and CH3 regions, but the CH1 region is excluded. Benepali is produced by Chinese hamster ovary (CHO) cell expression system as a dimeric, secreted, soluble protein. The Fc region is dimerised via 3 disulphide bonds. Benepali consists of 934 amino acids (467 for the single chain) and has a molecular weight (MW) of approximately 130 kDa.

**Mechanism of Action**

Benepali is a recombinant human tumour necrosis factor receptor p75Fc fusion protein. It interferes with the soluble TNF-α by mimicking the inhibitory effects of naturally occurring soluble TNF receptors that deactivate TNF-α and therefore down-regulate immune responses. Benepali acts as a decoy receptor for TNF-α, reducing TNF-α effects and hence represents a competitive TNF-α inhibitor.

Etanercept belongs to the class of immunosuppressants (ATC code: L04AB01)

**Type of Application and aspects on development**

The application is submitted in accordance with Article 3(1) Indent 1 -Biotech medicinal product of Regulation (EC) No 726/2004. Eligibility for submission of an application for an EU Marketing Authorisation was confirmed on 25 April 2014 (ref. EMA/260956/2014).
The proposed legal basis for this Marketing Authorisation Application (MAA) is a similar biological application under Article 10(4) of Directive 2001/83/EC as amended. Similarity is claimed to Enbrel® (etanercept) as the reference medicinal product, which was first authorised in the EU for 25 mg Powder and solvent for solution for injection on 03 Feb 2000 (EU/1/99/126/001) thus having been marketed in the European Union for just over 15 years (MA number: EU/1/99/126/001; MA holder: Pfizer Ltd.).

To demonstrate that the similar biological and reference products already authorised in the community have similar profiles in terms of quality, safety and efficacy an extensive comparability exercise is required. The clinical development programme of Benepali has specifically considered the EU guidelines for similar biological medicinal products and bioequivalence:

| Guideline | Document Reference |
|---|---|
| Guideline on Similar Biological Medicinal Products. CHMP, 2005 | CHMP/437/04 |
| Draft Guideline on Similar Biological Medicinal Products. CHMP, 2013 | CHMP/437/04 Rev. 01 |
| Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues. EMEA, 2006 | EMEA/CHMP/BWP/49348/2005 |
| Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues. EMEA, 2006 | EMEA/CHMP/BMWP/42832/2005 |
| Guideline on similar biological medicinal products containing monoclonal antibodies | EMA/CHMP/BMWP/403543/2010 |
| Guideline on the investigation of bioequivalence. EMEA, 2010 | CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** |
| Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins, 2007 | EMEA/CHMP/BMWP/14327/2006 |

| Guideline | Document Reference |
|---|---|
| Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins. EMEA, 2007 | CHMP/EWP/89249/2004 |

Furthermore, during the development of Benepali the applicant sought scientific and procedural advice at the European Medicines Agency (EMA). The scientific advice procedures covered questions on the pharmaceutical quality, the nonclinical and clinical programme.

## *2.2. Quality aspects*

### 2.2.1. Introduction

Benepali has been developed as a proposed similar biological medicinal product (biosimilar) to the reference medicinal product Enbrel having the tumour necrosis factor-α (TNF-α) inhibitor etanercept as the active substance. Benepali active substance (etanercept; 50 mg/mL) is a clear to opalescent, colourless to pale yellow solution for injection. Benepali is presented in single-use pre-filled syringes and pre-filled pens containing 50 mg etanercept per mL to be administered via subcutaneous (SC) injection.

### 2.2.2. Active Substance

***General information***

Benepali is a homodimer of a chimeric protein, which consists of 934 amino acids, 467 amino acids for each chain. The homodimer has a molecular weight of approximately 130 kDa. Each etanercept single chain contains a total of 29 Cystein (Cys) residues. These Cys residues are linked by multiple intra-chain and inter-chain disulphide bonds. Benepali is a highly glycosylated fusion protein with each monomer containing 3 N-linked glycosylation sites and 13 potential O-linked glycosylation sites.

***Manufacture, characterisation and process controls***

***Description of manufacturing process and process controls***

The manufacturing process begins with thawing of a vial of the working cell bank (WCB), which is a Chinese Hamster Ovary (CHO) cell line transfected with Benepali expression vector. After thawing of the WCB vial, the culture is serially expanded in cell mass and volume for inoculation into the production bioreactor. The cell culture fluid is subsequently purified through a series of chromatographic steps, virus inactivation and filtration steps and ultrafiltration/diafiltration steps.

***Origin, source, and history of the cell line development***

The cell line for Benepali was established by transformation of Benepali expression vector into Chinese Hamster Ovary cells. Based on the established cell line, a two-tier cell bank system was generated and characterised in accordance with ICH Guideline Q5D. Extended end of production cell banks (EEPCBs) were generated to allow further testing of characterisation, genetic stability and viral safety of the cell banking system. The genetic stability of the Benepali cell substrate was confirmed by genetic and phenotypic analysis methods, in conformance with the ICH guideline Q5B.

***Process validation and/or evaluation***

Process consistency studies were conducted to assess the consistency of the process at the active substance manufacturing facility. The data presented in the validation reports demonstrate high batch to batch consistency both for the upstream cell culture process and for the downstream purification process.

All pre-defined acceptance criteria for process parameters and in-process controls were met, no manufacturing deviations were encountered during the validation runs. The clearance of process-related impurities was validated for the Benepali active substance manufacturing process. The results of the process-related impurities clearance studies demonstrate that the Benepali active substance process will provide appropriate reduction of process related impurities.

The stability of process intermediates associated with the Benepali active substance process was validated to demonstrate the consistency of the Benepali manufacturing processes in the active substance manufacturing facility. In general, the results of the hold time studies support the claimed maximum hold times.

Overall, the process controls implemented during the Benepali active substance manufacturing process will ensure that the process operates consistently and will also ensure the consistency and quality of the Benepali active substance.

***Manufacturing process development***

The manufacturing process and control strategy for Benepali was developed based on the initial process development studies, clinical manufacturing experience, process characterisation studies, and process and product risk assessments. Product risk assessments were carried out to identify CQAs. The results were used to classify the process parameters and define the process control strategy. The process scale-up was performed as a linear scale-up, and only minor changes were made to accommodate manufacturing equipment. Comparability assessment between the Benepali pilot and clinical and have been established based on experimental or historical data. The control strategy for Benepali active substance manufacturing with regard to the classification and control of input parameters is considered adequate.

***Characterisation***

Benepali has been characterised using appropriate techniques as described in the ICH guideline Q6B. The structural characterisation has included measurement of molecular weight by mass spectrometry, amino acid analysis by peptide mapping with 100% sequence coverage, N- and C-terminal sequence analysis by liquid chromatography electrospray ionization mass spectrometry/ mass spectrometry (LC-ESI-MS/MS) as well as determination of the C-terminal variants, peptide mapping, met oxidation and de-amidation by LC-MS, disulphide bond analysis and quantification of free sulfhydryl groups. An adequate description of the inter- and intra-chain disulphide bonds has been presented. The purity of monomer and size-dependent product-specific impurities (high and low molecular weight forms) has been addressed by size exclusion chromatography (SEC) and high pressure size-exclusion chromatography (HP-SEC) with multi-angle laser light scattering (MALLS) detection, hydrophobic interaction chromatography (HIC) as well as reducing & non-reducing capillary electrophoresis (CE-SDS) and analytical ultracentrifugation (AUC). For characterisation of the charged variant profile cation exchange chromatography (CEX) as well as imaged capillary isoelectric focusing (icIEF) has been used. In addition, different results generated by the two above mentioned, orthogonal methods for charged variants have been sufficiently justified.

The N-linked glycosylation sites have been determined using LC-ESI-MS/MS, the N-glycan structures were identified by LC-MS, the relative quantity of N-glycan species has been determined by hydrophilic interaction ultra-performance liquid chromatography. Also the Fc specific glycan profile has been elucidated. In addition, the O-glycan sites have been identified by LC-MS, the O-glycan profile has been elucidated by ß-elimination. Also the content of total sialic acid has been analysed using ion-exclusion chromatography.

Higher order structures have been addressed by hydrogen/deuterium exchange experiments, differential scanning calorimetry (DSC), micro flow imaging (MFI), dynamic light scattering (DLS), fluorescence spectroscopy (intrinsic and extrinsic), Fourier transform infrared spectroscopy (FITR) and far-UV CD spectroscopy.

The mode of action relevant biological activities have been characterised by binding assays to TNF-α and LTα3 (TNF-β) as well as by a cell-based TNF-α neutralisation assay. Fc-related binding assays have addressed binding to FcγRIa, FcγRIIa and FcγRIIb, FcγRIIIa (V158 and F158 allotype) and FcγRIIIb, and to FcRn. In addition, binding to TNF-α from different species, binding to C1q, ADCC and CDC activity, and apoptosis have been investigated as part of the biological characterisation program.

Impurities clearance validation has been conducted to support that the Benepali purification process is capable of significantly removing these impurities from the Benepali active substance.

***Specification***

The active substance specification includes test methods for identity, glycan content, biological activity, purity and impurities, endotoxin. Other general tests (appearance, pH, osmolality) are also included in the specification.

Complete method descriptions, as well as method validation data (summary and original reports) have been provided. A comprehensive discussion on the variability of N-glycans observed in one specific active substance batch and the corresponding finished product batch has been provided.

Batch analyses data derived from eight Benepali active substance batches indicate the manufacturing process can perform effectively and reproducibly to produce bulk active substance meeting its predetermined specifications and quality attributes.

***Reference standards***

The primary reference standard (PRS) was prepared from Benepali active substance. Qualification of PRS was performed against the Intermediate Reference Standard and involved quality control tests as well as characterisation tests on the primary structure, quantity, identity, purity, biological activity and process-related impurities. All test results met the specifications or acceptance criteria defined by the pre-approved qualification protocol. The results confirm that PRS is suitable for use as a reference standard in all analyses requiring a reference standard. The Applicant was encouraged to calibrate/qualify the primary reference standard against the WHO Etanercept standard once it becomes available.

The working reference standard will be established from a Benepali active substance batch manufactured using the proposed commercial process. The working reference standard will be used for batch release of commercial batches. As requested a protocol for qualification of new working reference standards has been submitted.

***Container closure system***

The container closure system proposed by the Applicant for the storage of the active substance is of acceptable quality.

***Stability***

The primary and supportive studies were performed according to the current ICH guidelines. The results from all these studies demonstrate that there are no significant changes in the quality of Benepali active substance under the long-term and intermediate storage conditions. Based on the data provided the proposed shelf-life was considered acceptable.

## 2.2.3. Finished Medicinal Product

### Description of the product and Pharmaceutical Development

#### *Description and composition of the finished product*

Benepali finished product (FP) is a clear to opalescent, colourless to pale yellow, sterile and preservative-free solution for injection. The active substance is etanercept and the active substance and finished product formulations are identical. The excipients contained in the active substance and finished product are sucrose, sodium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate and water for injections. All excipients comply with compendial monographs.

#### *Pharmaceutical Development*

The excipients and formulation of Benepali finished product are similar to the reference product Enbrel. Compatibility of the active substance and excipients has been studied in formulation development and formulation robustness studies. The studies performed resulted in establishment of the Benepali formulation. Considering that Benepali is developed as a biosimilar of Enbrel, the formulation would be expected to be very close to the originator formulation. This is the case, however some differences have been implemented as a result of the formulation development studies. These include the exclusion of L-arginine hydrochloride in the formulation. These differences do not affect the stability of the Benepali finished product in comparison with Enbrel. The difference should also have no clinical effects. The overall results of the formulation robustness study indicate that the formulation is sufficiently robust at the proposed storage conditions, and that the protein concentration and pH are important factors to ensure acceptable quality of the finished product throughout the shelf life.

### Manufacture of the product

#### *Description of manufacturing process*

The Benepali finished product manufacturing process involves manufacturing of the PFS and PFP presentations, the latter consisting of assembly of the PFS into a pen device. The manufacturing process of Benepali finished product PFSs consists of thawing of the active substance, homogenisation, sterile filtration, and aseptic filling. Information regarding leachables/extractables from the container which is used in the course of finished product manufacture has been submitted. There are no intermediates in the Benepali manufacturing process.

#### *Process validation*

The manufacturing of the full commercial scale process has been validated. Based on the provided data it can be concluded that the manufacturing process for Benepali is capable of consistent and homogenous performance.

### *Product specification*

The finished product specification includes test methods for identity, glycan content, biological activity, purity and impurities, endotoxin. Other general tests (appearance, pH, osmolality) are also included in the specification. The analytical procedures used for release and shelf life testing of Benepali and finished product have been appropriately described and validated.

### Container closure system

Benepali finished product is supplied in a pre-filled syringe (PFS) and a pre-filled pen (PFP). The PFS consists of a clear type I glass barrel with rubber plunger, stainless steel needle and rubber needle shield.

The immediate container in the PFP is the same PFS, and the PFP is the PFS assembled into a pen device. Compliance with Ph. Eur. has been confirmed with the container closure components as requested.

### *Stability of the product*

The studies were performed according to the current ICH guidelines. Temperature cycling studies have also been performed where the finished product was exposed to several cycles of low and elevated temperatures. The results show that Benepali finished product tolerates the applied excursions in temperature without significant degradation or other negative impact on quality attributes.

The results generated during the stability studies support the proposed shelf life of 30 months at 5°C ± 3°C. Of note, the Applicant referred to the Product Information (PI) of Enbrel® which states that "Enbrel may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks". Thus, a patient convenience stability study was performed to support the storage condition for Benepali of up to four weeks at a temperature of ≤ 25°C subsequent to long-term storage at 5 ± 3°C . Data available from one finished product batch at the end of shelf-life support this claim. Nevertheless, the Applicant is recommended to submit stability data (four weeks storage at 25°C) from two additional finished product batches to further support storage up to four weeks at ≤ 25°C subsequent to long-term storage at 5°C ± 3°C as soon as the data becomes available.

### *Adventitious agents*

The strategy used to ensure that the Benepali active substance and the resulting finished product are free of adventitious agents has been provided. The strategy is in compliance with the requirements in the ICH Guideline Q5A.

Animal derived raw materials were used to establish the Benepali cell line. The raw materials sourced from TSE relevant animals all originate from countries with the lowest possible BSE risk (negligible BSE risk; Category A) based on the World Organisation for Animal Health (OIE) classification. Certificates of Suitability and / or Certificates of Origin have been provided for all these raw materials. Mycoplasma testing for qualification of the MCB, WCB and EEPCB was performed in accordance with ICH guidelines (Q5D). Furthermore, during active substance manufacture, the unprocessed bulk is analysed for mycoplasma which is also based on Ph. Eur. 2.6.7. No mycoplasma has been detected in the unprocessed bulks.

Virus safety testing on the MCB and WCB were performed in accordance with ICH guidelines Q5A and Q5D. The MCB, WCB, and EEPCB were analysed and confirmed to be free of adventitious viruses.

The virus clearance capacity of the Benepali active substance purification process has been validated in accordance with the ICH Guideline Q5A (R1). Certain steps, which were considered as effective steps for viral clearance, were selected and their vial clearance capacity validated. Virus inactivation and chromatography steps were selected for validation. All purification processes mentioned above have orthogonal purification mechanisms, and thus there is no overestimation of viral clearance capacity by repetition of processes having similar mechanisms. Four relevant model viruses were selected for these studies. The adventitious agent safety evaluation presented was sufficient and adequate.

## Medical device

The Benepali Pre-filled Pen (PFP) is a single-use, disposable, spring-loaded injection device that is designed to assist with the delivery of a single dose of Benepali finished product from the Benepali pre-filled syringe. The PFP covers the pre-filled syringe (PFS) to form the PFP strength of 50 mg, which will be supplied as a stand-alone dosage form.

## Biosimilarity

A characterisation study (Characterisation study 2) has been performed to assess similarity of Benepali Process Validation Run (PVR) materials to Enbrel from European Union (EU), United States of America (US) and Korea (KR) markets, as well as to demonstrate comparability of the PVR to the clinical process. In this characterisation study, structural, physicochemical, and biological characterisation has been performed to compare multiple batches of clinical active substance, clinical finished product, PVR active substance, and PVR finished product with multiple batches of EU-sourced Enbrel (EU Enbrel), US-sourced Enbrel (US Enbrel), and Korea-sourced Enbrel (KR Enbrel).

The test items have been selected to demonstrate the similarity of Benepali to Enbrel with regards to the primary, secondary and tertiary structure, glycosylation, post-translational modifications (PTMs) and biological activities. Critical quality attributes (CQAs) for assessment of similarity have been defined based on the mode of action (MoA) of etanercept and results from structure-activity relationship (SAR) studies.

Prior to the head-to-head characterisation studies, extensive characterisation has been performed on representative batches of EU Enbrel. The analytical data from the characterisation studies have been used to establish the similarity ranges. To determine similarity of Benepali to Enbrel, the CQAs have been evaluated according to the similarity range, and non-CQAs have been assessed through head-to-head comparison of analytical data.

The similarity ranges for test items have been set by statistical analysis of multiple batches of EU Enbrel. The number of batches used to set the similarity range varied for each test item.

In addition, comparative stability studies have been conducted to compare the degradation profiles of Benepali active substance and finished product with Enbrel. The comparative stability studies have involved high temperatures (accelerated and stress conditions), forced degradation (freeze-thaw and oxidation) and photostability studies.

The molecular weight of Benepali has been determined using mass spectrometry. The results of testing demonstrated that the molecular weights (MWs) of Benepali and the reference products were similar.

The full amino acid sequence of Benepali finished product has been compared to the amino acid sequence encoded by the proposed DNA sequence. The results show that the amino acid sequence of Benepali is identical to that of EU Enbrel.

N-terminal sequencing has been performed by LC-ESI-MS/MS in order to determine the integrity of Benepali and EU Enbrel. Results from analysis show that the N-terminal peptide sequence of Benepali is identical to that of Enbrel. The C-terminal sequence of Benepali and Enbrel has been analysed by using LC-ESI-MS/MS Two forms of C-terminal peptides are found in both Benepali and EU Enbrel.

Peptide mapping has been performed using LC-ESI-MS/MS after subsequent digestion with different proteases. The resulting peptides have been analysed with respect to their post-translational modifications, sequence variants, and whole sequence. The chromatograms for Benepali and EU Enbrel show identical patterns between Benepali and EU Enbrel, irrespective of protease used.

The results for Met oxidation by LC-MS demonstrate that the relative content of the oxidised form are similar to that of EU Enbrel. The deamidation level of Asn has been quantified using LC-ESI-MS/MS. The relative deamidation levels of the possible Asn residues for Benepali and Enbrel have been assessed and only minor differences are observed. The results from the FcRn binding assay show that these minor differences have no effect on FcRn binding affinity and the minor difference between deamidation of Asn are not considered significant.

The disulphide bonds have been analysed using LC-ESI-MS/MS. The results are considered comparable.

Minor differences are seen in the molar concentration of free sulfhydryl content and the %free sulfhydryl between Benepali and EU Enbrel. However, the result suggests that essentially all 58 Cys residues (29 residues per monomer) are linked by disulphide bonds and there is practically no free Cys residue.

The relative level of the Lys variant in Benepali is lower than that in EU Enbrel indicating that most of the Lys on the C-terminus of Benepali has been found cleaved. The heterogeneity of C-terminal residues is a characteristic of therapeutic monoclonal antibodies and C-terminal Lys variation that is known not to impact PK profiles. Results from the TNF-α binding functional assay demonstrate that C-terminal Lys content has no impact on TNF-α binding activity.

Slight differences have been observed in the SEC chromatograms for Benepali with Enbrel. From the results of HP-SEC with MALLS analysis and SV-AUC analysis, the HMW in both Benepali and Enbrel have been identified mainly as dimers and therefore the difference in peak appearance is not considered significant.

Differences in the hydrophobic interaction chromatography (HIC) peaks have been characterised through the Structure-Activity Relationship (SAR) study. The results of the SAR study support that the difference in relative peak contents between Benepali and the reference product is not considered significant. Observed differences have been sufficiently justified.

The charge variant content by cation exchange high performance chromatography (CEX-HPLC) is different in Benepali compared to EU Enbrel. The level of %Main + %Acidic in Benepali is higher than that of Enbrel and the level of %Basic in Benepali is lower than the Enbrel. The difference in charge variant content between Benepali and EU Enbrel has been characterised through the SAR study. The results indicate that the difference in the content of the basic charge variant is mainly caused by the difference in the content of C-terminus with Lys, but there were no significant difference in TNF-α binding activities of the basic variants from Benepali and Enbrel.

Reducing and non-reducing CE-SDS shows a comparable peak profile.

Charge heterogeneities by icIEF indicate a higher content of acidic isoform and lower content of basic isoform of Benepali when compared with Enbrel. SAR studies have been performed using CEX-HPLC and it has been found that the charge variant content does not affect TNF-α binding activity. Concerning the detected different charged variant profile additional data to confirm the conclusions made by the applicant have been submitted.

In summary, the applicant has provided sufficient evidence that these differences as well as the differences in the glycosylation profile have no impact on the MoA relevant biological functions, thus these differences in the charged variant profile do not raise a concern to the biosimilarity claim.

The N-linked glycosylation sites of Benepali and Enbrel have been determined using LC-ESI-MS/MS. From the results, the N-linked glycosylation sites of Benepali are identified as identical to those of EU Enbrel. The N-glycan structures of Benepali and Enbrel have been identified using LC-ESI-MS/MS. The results demonstrate that the N-glycan profile of Benepali is similar to EU Enbrel. Hydrophilic interaction ultra-performance liquid chromatography (HILIC-UPLC) has been used to determine the relative quantity of N-glycan species. The results show that the N-glycan profiles of Benepali batches are different from those of EU Enbrel. The afucosylated glycan content in Benepali is higher than observed for EU Enbrel. The afucosylated glycan level in therapeutic proteins is associated with FcγRIIIa binding activity and ADCC. However, ADCC is not considered to be a mechanism of action of etanercept so these differences are not clinically meaningful. The results from ADCC analysis demonstrate similar low ADCC activity between Benepali and Enbrel. The neutral galactosylated glycan content in Benepali seems to be more variable

than observed for EU Enbrel. The content of neutral galactosylated glycan is generally associated with CDC activity for monoclonal antibodies. However, CDC is not known to be a mechanism of action of etanercept and, the results from analysis demonstrate similar CDC activity between Benepali and Enbrel.

O-linked glycosylated peptides have been analysed using reverse phase (RP)-UPLC coupled to ESI-MS/MS. All O-linked glycosylated sites identified in Benepali are identical to those found in EU Enbrel. The O-glycan profile by ß-elimination shows that Benepali and EU Enbrel are similar considering both O-glycan occupancy and contents. The sialic acid content of Benepali and Enbrel has been analysed using ion-exclusion chromatography. The total sialic acid (TSA), (N-glycolylneuraminic acid, NeuGc (NGNA), and N-acetylneuraminic acid, NeuAc (NANA)) contents of Benepali are considered similar to those of EU-Enbrel.

Results derived from hydrogen/deutererium exchange and from DSC indicate that Benepali is similar to EU Enbrel. MFI used for the quantification and visualisation of sub-visible particles in the µm-size range show that the particle concentrations for particles in all size ranges are lower in Benepali when compared to EU Enbrel. DLS used to analyse sub-visible aggregates in the nm-size range indicate that the main peak diameter is similar between Benepali and EU Enbrel and Benepali has been shown to be as mono-disperse as Enbrel. The results obtained from HP-SEC with MALLS detection indicate that chromatograms from UV detection and MW estimation of monomer peak are similar for Benepali and EU Enbrel. Fluorescence spectroscopy as well as FTIR and Far-UV CD show that overall the generated spectra for Benepali are within the range of the spectra for EU Enbrel.

Measurement of binding to TNF-α and LTα3 (TNF-ß) by the FRET assay shows that the ranges for the binding activity of Benepali and EU Enbrel relative to the bioassay standard are similar. The TNF-α neutralisation assay by reporter gene demonstrates that the potency of Benepali is within the similarity range defined for the similarity exercise.

Fc related biological assays including the FcγRIa binding assay, FcγRIIa binding assay, FcγRIIb binding assay, FcγRIIIa binding assay, and FcRn binding assay indicate slight differences in the FcγRIa binding, FcγRIIIa (both allotypes) binding, and in the FcγRIIIb binding between Benepali and Enbrel.

Binding affinities have been compared with more sophisticated methods such as surface plasmon resonance (SPR) and results (Kd, on-/off-rates) and support the similarity claim. Additional biological assays including TNF-α binding from different species, apoptosis, C1q binding, CDC, and ADCC assay demonstrate similarity.

Forced-degradation stability has been conducted on Benepali, and Enbrel to observe product degradation or aggregation. The results from both the freeze-thaw stability study and the oxidation study show that although degradation as observed for both products, the degradation profiles are comparable. Photostability studies demonstrate that Benepali and EU Enbrel should be stored in a carton protected from light. Confirmatory photostability study has been performed using Benepali PVR finished product as well as Enbrel in commercial packaging. Degradation has not been shown in the analysis results of the commercially packaged Benepali finished product or EU Enbrel.

### 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information about the active substance and finished product was of acceptable quality. Sufficient evidence regarding the manufacturing processes has been provided. Specification limits and analytical methods are suitable to control the quality of the active substance and the finished product. The finished product was well characterised. The stability program is considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC. Of note, the Applicant referred to the Product Information (PI) of Enbrel® which states that “Enbrel® may

be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks". Thus, a patient convenience stability study was performed to support the storage condition for Benepali of up to four weeks at a temperature of ≤ 25° C subsequent to long-term storage at 5 ± 3° C. Data available support this claim.

The Applicant has conducted a considerable amount of additional work to justify that observed differences in the biosimilarity assessment have no impact on the efficacy and safety when comparing Benepali with its reference product. From these aspects there is no issue which could question the biosimilarity claim of Benepali to Enbrel. Of note, the applicant has clarified that Benepali has been developed to the currently marketed quality profile of Enbrel: No Enbrel batches presenting the former quality profile have been included in the biosimilarity development.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance and the finished product have been appropriately characterised and in general satisfactory documentation has been provided. The results indicate that the active substance as well as the finished product can be reproducibly manufactured.

### 2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended an additional point for further investigation.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

The nonclinical programme for Benepali (also referred to as SB4 throughout this Report), included a series of in vitro studies including binding and cell based assays in order to demonstrate similarity between Benepali and Enbrel. In addition, an efficacy study in BALB/c mice, a PK study in SD rats and a repeated dose toxicity study in Cynomolgus monkeys including a toxicokinetic assessment and an evaluation of potential anti-drug antibody formation were performed to demonstrate similarity between Benepali and Enbrel.

In line with 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) and "Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues" (EMEA/CHMP/BMWP/403543/2010) further studies regarding pharmacology, pharmacokinetics, genotoxicity, reproduction toxicology and carcinogenicity have not been submitted.

### 2.3.2. Pharmacology

#### *Primary pharmacodynamic studies*

The primary pharmacodynamics study package consisted of in vitro studies related to the mechanism of action (MOA) of etanercept evaluating the relative binding activities of Benepali and Enbrel to TNF-α or LT-α3. The inhibitory activity of Benepali or Enbrel on the TNF-α signalling pathway was measured using a reporter gene assay. Although etanercept has low Fc-related binding activities compared to other TNF-α antagonists, Fc-related binding activities towards Fc gamma receptors, the FcRn receptor and C1q as well as Fc-related effector functions such as ADCC and CDC were determined for Benepali and Enbrel.

**Mechanism of Action Related Assays:**

The studies submitted which investigated Fab-related biological activities were (also referred to as "MOA-related biological assays") were: TNF-α, LT-α3 Binding Assays and a TNF-α Neutralisation Cell Based Assay.

To analyse the relative binding potency of SB4 or Enbrel to TNF-α or LT-α3, Fluorescence Resonance Energy Transfer (FRET)-based assays were developed and qualified. A TNF-α neutralisation assay was developed and qualified to measure the inhibitory activity of SB4 or Enbrel based on the activation of reporter gene in a cell system.

Data were analysed to calculate relative binding activity using US Enbrel as standard. Similarity ranges for all assays were calculated from different EU RMP batches and are shown with the results from these studies in **Table 1.**

**Table 1. Similarity assessment for SB4 and Enbrel: Mechanism of Action related bioassays**

| **Category** | | **MOA-Related Bioassays** | | |
|---|---|---|---|---|
| **Analytical Method** | | **TNF-α Binding Assay** | **LT-α3 Binding Assay** | **TNF-α Neutralisation Cell Based Assay** |
| | | % relative binding activity | | % relative potency |
| **Similarity range#** | | **91-112** | **87-116** | **81-133** |
| SB4 Clinical Batches | DS batch | 108 | 98 | 96 |
| | DP batch | 99-108 | 98-109 | 96-104 |
| SB4 PVR Material | DS batch | 104-107 | 100-107 | 94-107 |
| | DP batch | 106-112 | 100-115 | 90-98 |
| EU Enbrel® | | 102-110 | 96-111 | 78-114 |

# The similarity range was set by statistical analysis based on the tolerance interval with the given set of available data points.

*DS: drug substance, DP: drug product, PVR: Process validation run*

In addition, TNF-α binding affinity of Benepali (SB4) and EU Enbrel were compared using Surface Plasmon Resonance (SPR) as an orthogonal method to the FRET assay. The TNF-αand LTα3 binding – SPR based studies did not show a statistically significant difference between SB4 and Enbrel (data not shown).

**Non-Mechanism of Action Related Assays:**

As etanercept is known to have low Fc-related binding activities compared to other TNF-α antagonists, clinical outcomes of etanercept are not related to Fc-related binding activities. Therefore, Fc-related functions of etanercept are considered non-MOA related. The predominant function of the Fc region in etanercept is to prolong the half-life rather than to impart Fc-mediated efficacy. The panel of assays submitted included FcγRIa-, FcγRIIa-, FcγRIIb-, FcγRIIIa (V-type)-, and FcRn-binding and was considered appropriate. The tolerance interval generated a comparability range derived from an acceptable number of originator batches and was met with only a few exceptions for FcγRIa binding. The summary of these results are presented in **Table 2.**

**Table 2. Similarity Assessment: Non-Mode of Action Related Ligand Binding Assays**

| **Binding Assays** | **FcγRIa** | **FcγRIIa** | **FcγRIIb** | **FcγRIIIa (V-type)** | **FcRn** |
|---|---|---|---|---|---|
| | %Rel. binding activity | Binding affinity (KD) µM | | | |
| **Similarity range#** | **90-121** | **2.10-4.94** | **18.1-33.5** | **2.50-4.09** | **4.80–11.8** |

| | | | | | |
|---|---|---|---|---|---|
| SB4 Clinical Batches | | | | | |
| DS batch | 117 | 3.18 | 24.9 | 2.58 | 8.02 |
| DP batch | 116-122 | 2.69-3.80 | 20.0-26.7 | 2.59-2.75 | 7.80-9.49 |
| SB4 PVR Material | | | | | |
| DS batch | 95–117 | 2.93-3.47 | 21.3-27.1 | 2.61-2.72 | 7.81-10.5 |
| DP batch | 94-123 | 3.86-4.28 | 21.8-23.3 | 2.74-2.83 | 8.75-10.0 |
| EU Enbrel® | 104-112 | 2.83-4.20 | 22.8 - 30.9 | 3.30-3.56 | 7.25-8.42 |

# The similarity range was set by statistical analysis based on the tolerance interval with the given set of available data points.
*DS: drug substance, DP: drug product, PVR: Process validation run*

In contrast to the rest of the panel of assays using SPR – FcγRIa binding was measured by a competitive FRET assay. As the FcγRIa binding activity measured by FRET assay for the DP batches was marginally outside the similarity range, SPR based studies were submitted for the tested SB4 PVR DP batches and did not show any statistically significant differences (two sample t-test) to EU Enbrel batches.

**Additional functional assays:**

In addition to the MOA-related and non-MOA related biological assays, general antibody therapeutics-related characteristic functions or properties were submitted as additional functional assays to compare SB4 with EU Enbrel. These included TNF-α binding assays from different species, FcγRIIIa (F158 allotype), FcγRIIIb and C1q binding assays, a complement-dependent cytotoxicity (CDC) assay, an antibody dependent cell-mediated cytotoxicity (ADCC) assay, and an apoptosis activity assay (data not shown).

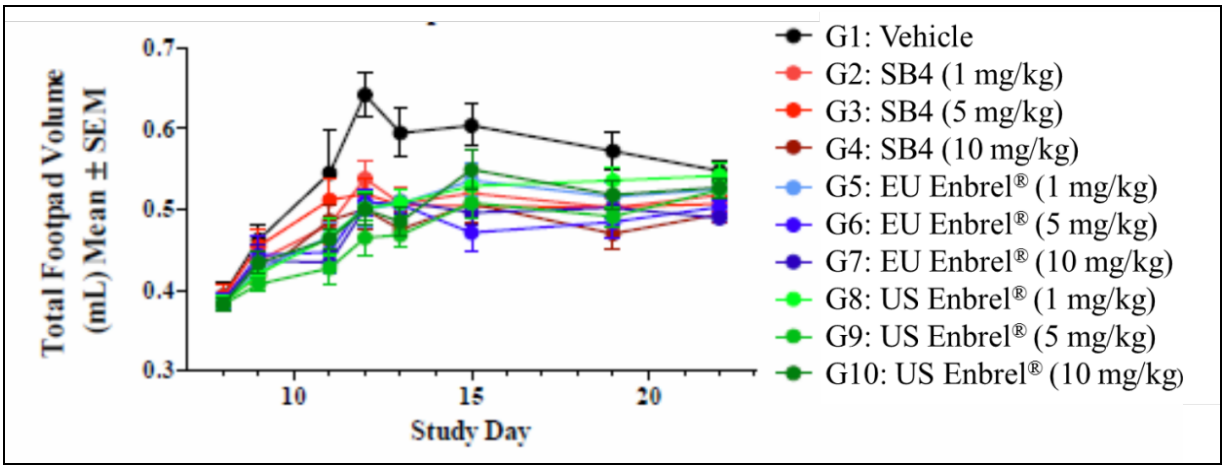
***In Vivo* Mouse Model of Collagen-Induced Arthritis:**

A study was conducted to demonstrate similar suppressive activity of SB4 and Enbrel on TNF-α mediated pathology in a mouse (BALB/c) model of collagen antibody-induced arthritis (CAIA). For Enbrel, EU sourced Enbrel (EU Enbrel) was used as the reference product and results from US sourced Enbrel (US Enbrel) were used as supportive data only.

In this study, SB4 and Enbrel suppressed the development of arthritis which was determined by footpad volume changes (mean disease burden AUC and disease suppression), clinical scores, and ankle histopathological evaluation. No significant differences were detected among treated groups in the majority of study endpoints.

Each test article showed statistically significant reductions of mean total footpad volumes on Day 12 and mean maximum footpad volumes at all dose levels (**Figure 1**). Furthermore, each test article showed statistically significant reductions in the mean disease burden AUC without indicating important differences between SB4 and Enbrel (data not shown).

**Figure 1. Comparative in vivo functionality of SB4 and Enbrel; the effects on total hind limb footpad volume changes in a mouse model of CAIA**




Each test article also showed statistically significant reductions of mean total clinical score at one or more dose levels. In addition, mice treated with any test article showed less destruction of joint architecture than those treated with the vehicle (data not shown).

Mice were euthanised on day 22 for histopathological evaluation of progression of arthritis. Anterior- and posterior-tibiotalus, dorso- and ventro-distal central tarsal and dorsal tarsal-metatarsal from each limb section were examined and signs of inflammation, pannus, cartilage damage, bone resorption, and periosteal change / exostosis were scored 0 - 5 (from normal to severe). Scores were summed for each animal and mean ± SEM histopathology scores on each analysed parameter were calculated. A maximum score was 25/animal. The number of animals within the determined range (sum of scores for 5 metrics of arthritis) is shown in **Table 3**.

**Table 3. Comparative *in vivo* functionality of SB4 and Enbrel; the effects on histopathology scores on arthritis in a mouse model of CAIA**

| Composite Histopathology Score[a] | Number of Animals within the Indicated Range | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | SB4 (mg/kg) | | | EU Enbrel (mg/kg) | | | US Enbrel (mg/kg) | | |
| | 0 | 1 | 5 | 10 | 1 | 5 | 10 | 1 | 5 | 10 |
| 0 | 0 | 2 | 2 | 1 | 4 | 6 | 4 | 7 | 6 | 1 |
| 1 - 5 | 2 | 3 | 5 | 5 | 5 | 2 | 3 | 1 | 3 | 4 |
| 6 - 10 | 5 | 3 | 1 | 3 | 1 | 2 | 3 | 0 | 1 | 5 |
| 11 - 15 | 3 | 2 | 2 | 1 | 0 | 0 | 0 | 2 | 0 | 0 |
| 16 - 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 21 - 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

[a]*Composite Histopathology Score = sum of the scores for 5 metrics of arthritis (inflammation, pannus, cartilage damage, bone resorption, and periosteal changes / exostosis) based on histopathological evaluation of left hind limb ankle regions, with 0-5 points for each metric: 0 - normal, 1 - minimal, 2 - mild, 3 - moderate, 4 - marked, 5 - severe. Maximum score:25/animal.*

***Secondary pharmacodynamic studies***

No secondary pharmacodynamic studies have been submitted in line with relevant guidelines including the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

***Safety pharmacology programme***

No safety pharmacology studies were submitted in line with CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

***Pharmacodynamic drug interactions***

No comparative studies assessing PD drug interactions were submitted in line with relevant guidelines including the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

## 2.3.3. Pharmacokinetics

The pharmacokinetic section comprised a single dose study in SD rats, supported by validation studies to detect and quantify SB4 and Enbrel. Additional pharmacokinetic data were collected as part of a repeat-dose toxicity/toxicokinetic study (Study 2064-004, see Sections Repeat dose toxicity and Toxicokinetic data of this Report).

### Absorption

**RD-00407: Pharmacokinetics study of SB4 in Sprague-Dawley rats**

A total of 10 male Sprague-Dawley rats (SD) received a single subcutaneous administration of 1 mg/kg SB4 or Enbrel (5 rats/group). Serum samples were collected 2, 6, 12, 24, 36, 48, 72, 96 and 120 hours after dosing from jugular vein and etanercept levels were quantified with a ELISA kit. The $AUC_0$ to $AUC_{last}$ was calculated using linear-logarithmic trapezoidal rule by non-compartmental analysis. The $C_{max}$ and $T_{max}$ were obtained directly from the concentration-time data, and the $t_{1/2}$ was calculated for each individual.

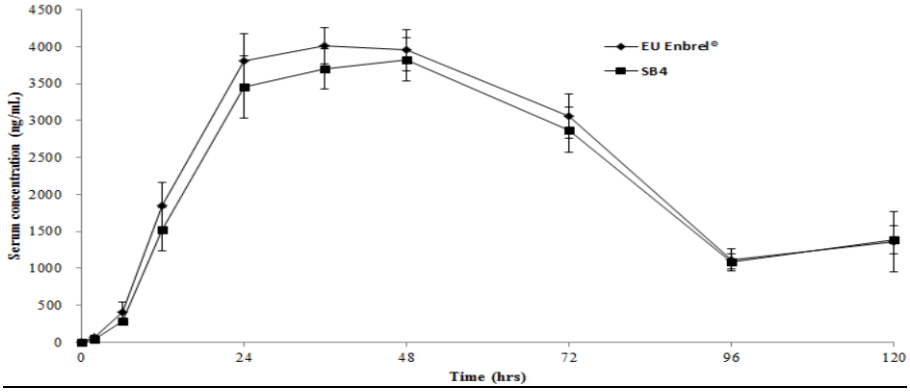
The mean serum concentrations in **Table 4** after a single dose subcutaneous administration of SB4 or Enbrel. The mean $AUC_{0\text{-}120h}$ ranged from 243106 to 309168 ng·hr/mL for SB4 and from 273133 to 328929 ng·hr/mL for Enbrel. The mean $C_{max}$ was 3854 ± 294 ng/mL for SB4 and 4052 ± 235 ng/mL for

Enbrel. These serum concentration-time profiles were similar according to the data analysis using unpaired t-test.

**Table 4. PK comparability of SB4 over Enbrel after single subcutaneous administration in rats**

| Test Article | Dose (mg/kg) | - | $AUC_{last}$ (ng*hr/mL) | | Cmax (ng/mL) | | Tmax (hr) | $T_{1/2}$ (hr) |
|---|---|---|---|---|---|---|---|---|
| SB4 | 1 | Mean | 281760 | $p$ = 0.2674 | 3854 | $p$ = 0.2730 | 46.0 | 45.6 |
| | | StDev | 24230 | | 294 | | 5.4 | 5.9 |
| EU Enbrel | 1 | Mean | 300097 | | 4052 | | 38.0 | 41.4 |
| | | StDev | 24415 | | 235 | | 10.0 | 7.5 |

**Figure 2. Mean serum concentration of etanercept after single subcutaneous administration in rats of SB4 and Enbrel (1 mg/kg)**




## Distribution

No distribution studies were submitted in line with the CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

## Metabolism and excretion

No metabolism studies were submitted in line with the CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

## PK drug interaction

No studies assessing pharmacokinetic drug interactions were submitted in line with the CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

## 2.3.4. Toxicology

***Single dose toxicity***

No comparative single-dose toxicity study was submitted in line with the guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

***Repeat dose toxicity***

**2064-004: A 4-week repeat dose toxicity study of SB4 in Cynomolgus monkeys**

A GLP compliant 4 week repeat dose toxicity and toxicokinetic study was conducted in Cynomolgus monkeys to evaluate the potential subchronic toxicity, toxicokinetic and immunogenicity profiles of SB4 and Enbrel. The study was conducted as a three-arm study with SB4, EU Enbrel and US Enbrel. Cynomolgus monkeys (n=3/gender/group) received 1 mg/kg (low dose, representing the human clinical dose) or 15 mg/kg (high dose) of SB4 or EU Enbrel (or US Enbrel) in prefilled syringes, administered via bolus injection subcutaneously twice weekly on Days 1, 4, 8, 11, 15, 18, 22, and 25.

Mortality, clinical signs, body weights and food consumption were recorded and ophthalmoscopic and electrocardiographic examinations were conducted. At study termination, necropsy examinations were performed, organ weights were recorded, and tissues were microscopically examined. Blood samples were collected for clinical pathology evaluations prior dosing and prior termination, for determination of serum concentrations and toxicokinetic evaluation on prior dosing (on Day 1, Day 25) and at 2, 6, 12, 24, 48 and 72 hours post-dosing and for immunogenicity analysis prior dosing (on Day 1, Day 22) and at termination.

Benepali and Enbrel were well tolerated up to 15 mg/kg/dose with no reference or test article related effects on mean body weight, ECG, clinical pathology parameters and ophthalmic findings. There was no toxicity noted on body weight, body weight changes or in food consumption (data not shown).

All serum samples from animals treated with low dose (1 mg/kg) SB4 and Enbrel were positive for anti-etanercept antibodies at Day 22 and at study termination. The ADA response was less prevalent in high dose (15 mg/kg) group, which could be related to the drug tolerance.

The incidence of perivascular lymphoid infiltrates in the brain was increased in test article-treated groups, but was considered being a common background finding in Cynomolgus monkeys. No other test article-related microscopic observations were noted at the end of dosing phase. The microscopical evaluation of the liver tissues revealed no differences between the SB4 and Enbrel groups. There were no differences in the injection site reactions between the SB4 and Enbrel treated groups.

Mild elevations in globulins relative to pre-test values were observed in all treatment groups (including the vehicle control group). The increase was up to 1.3-fold in the SB4 group and US Enbrel group and up to 1.5-fold in the EU Enbrel group.

***Genotoxicity***

No genotoxicity studies were submitted in line with the CHMP guidance on similar biological medicinal products (EMEA/CHMP/BMWP/42832/2005) which states that other routine toxicological studies such as mutagenicity (genotoxicity) are not required for similar biological medicinal products, unless indicated by results of repeat-dose studies. As data obtained from the repeat-dose toxicity studies did not indicate any cause for concern, it was considered that genotoxicity studies were not necessary for this product.

***Carcinogenicity***

Carcinogenicity studies were not submitted in line with the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010), and the CHMP guidance on similar biological medicinal products (EMEA/CHMP/BMWP/42832/2005).

***Reproduction Toxicity***

Reproductive and developmental toxicity studies were not submitted, in line with the CHMP Guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/ 403543/2010), and the CHMP guidance on biosimilar medicinal products (EMEA/CHMP/BMWP/42832/2005).

***Toxicokinetic data***

**2064-004: Toxicokinetics in part of a 4-week repeat dose toxicity study of SB4 in Cynomolgus monkeys**

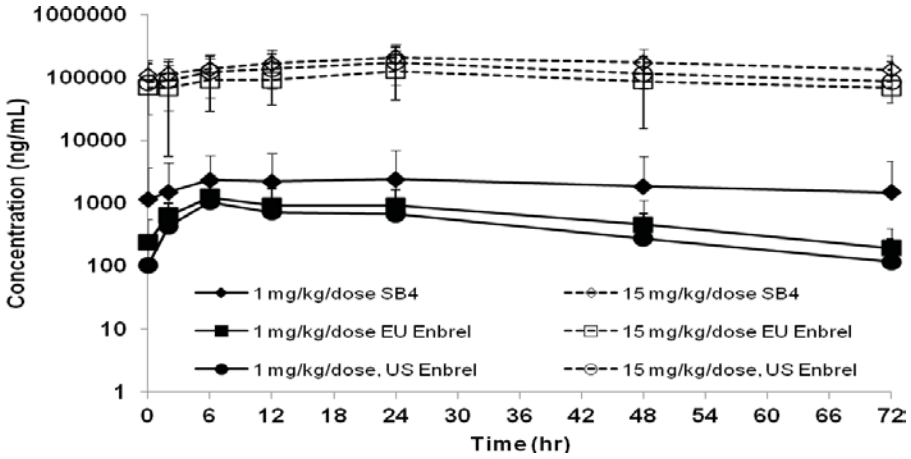
No marked differences were between male and female kinetic parameters between SB4 and Enbrel groups, but the kinetic parameters varied between the male and female animals at 1 mg/kg/dose on Day 25. Toxicokinetic parameters are summarised in the **Table 5,** and mean serum concentrations at day 25 are presented in **Figure 3.**

**Table 5. Comparative toxicokinetic data and systemic exposure to SB4 and Enbrel in Cynomolgus monkeys (Mean values)**

| Daily Doses mg/kg | Test Article | $C_{max}$ (µg/mL) | | | | $AUC_{(0\text{-}last)}$ (µg·hr/mL) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 25 | | Day 1 | | Day 25 | |
| | | Male | Female | Male | Female | Male | Female | Male | Female |
| 1 | SB4 | 12.7 | 11.0 | 5.07 | 0.662 | 755 | 6206 | 271 | 17.5 |
| | EU Enbrel | 11.7 | 50.1<br>13.0[b] | 2.49 | 0.303 | 639 | 1420<br>719[b] | 83.6 | 10.7 |
| | US Enbrel | 11.1 | 12.3 | 2.0[c] | 0.494 | 649 | 739 | 61.2[c] | 14.6 |
| 15 | SB4 | 173 | 148 | 229 | 192 | 10200 | 9080 | 13400 | 11100 |
| | EU Enbrel | 145<br>125[a] | 152 | 213 | 44.6 | 7180<br>7170[a] | 9570 | 11700 | 1940 |
| | US Enbrel | 179 | 148 | 232 | 122 | 11300 | 8780 | 12500 | 6020 |

*[a] Value excluding data for animal 415; [b] Value excluding data for animal 412; [c] Value excluding data for animal 439, which was euthanized in extremis on Day 17*

**Figure 3. Mean (±SD) Serum Concentrations of etanercept in Monkeys (Sexes Combined) given Twice- Weekly Subcutaneous Injections of SB4, EU Enbrel or US Enbrel (Day 25)**




***Local Tolerance***

No separate local tolerance studies were submitted. Histopathological assessments of local (injection site) tolerance were carried out in the 4-week repeat-dose toxicity study in Cynomolgus monkeys. Microscopic findings confined to the epidermis (chronic/active inflammation, exudate on epidermal surface) were likely the result of self-induced trauma at the injection site and not directly related to the test articles. The injection site reactions between the SB4 and Enbrel treated groups were considered similar.

***Other toxicity studies***

Immunogenicity assessment of SB4 in comparison with Enbrel was included into the repeat-dose toxicity study in Cynomolgus monkeys (2064-004).

All animals treated with the low dose of SB4 or Enbrel (1 mg/kg/dose) had detectable levels of anti-etanercept antibodies at the Day 22 predose and/or terminal collection intervals, although one SB4 animal was only marginally positive.

Formation of anti-etanercept antibodies in the high dose (15 mg/kg) groups were detected in 1 out of 6 monkeys that received SB4 and in 3 out of 6 monkeys that received Enbrel.

## 2.3.5. Ecotoxicity / environmental risk assessment

The Applicant provided a justification for not submitting any environmental risk assessment studies based on the fact that Benepali is a protein and therefore unlikely to pose a significant risk to the environment which is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

## 2.3.6. Discussion on non-clinical aspects

The applicant performed a set of assays testing pharmacologic properties of the biosimilar candidate Benepali in comparison with EU sourced RMP Enbrel, which was generally considered in line with current European guidance on development of biosimilars.

The comparability exercise focused on the evaluation of primary pharmacology by in vitro ligand binding studies and bioassays. These in vitro tests were divided in MOA-related assays (Fab-related biological activities), non-MOA related assays (selected Fc-related binding assays) and "additional assays".

Studies with Fab-related biological activities represent those with the highest relevance in demonstrating biosimilarity. For these assays, similarity between Benepali (SB4) with EU RMP was shown.

Although some minor differences in non-MOA related assays were observed, such as FcγRIIIa binding affinity, FcγRIIIb binding affinity, and ADCC activity, those are not expected to translate into clinically relevant differences. Additional functional assays provided further supportive evidence of the similarity between SB4 and Enbrel.

A mouse model of collagen antibody-induced arthritis (CAIA) examined pharmacology of Benepali (SB4) and Enbrel in a comparative manner. Differences in this study were noted only in the histopathological evaluation of the ankle, indicating less efficiency of Benepali (SB4) as compared to the Enbrel in the suppression of arthritis signs. However, the different results of the histopathological scores between Benepali and EU Enbrel suggested by the CAIA mouse study do not indicate significant differences for the treatment responses between the Benepali (SB4) and the EU-Enbrel (and US-Enbrel), and are thus unlikely to be of clinical significance. This was further corroborated by the results submitted from the clinical efficacy and safety study of Benepali and EU Enbrel (see section Clinical efficacy of this Report) which demonstrated comparability between the two products with respect to various efficacy endpoints, including a modified Total Sharp Score (mTSS) determined at Week 52 via radiography in RA patients. These clinical findings were considered more relevant than this isolated animal finding.

The pharmacokinetic profile of Benepali was evaluated in comparison with Enbrel following a single subcutaneous injection of 1 mg/kg in rats. The translational value of the in vivo pharmacokinetic study is limited as the rat is a non-relevant species... Additional pharmacokinetic data was collected as part of a repeat-dose toxicity/toxicokinetic study in cynomolgus monkeys, following subcutaneous injections twice weekly doses of 1 mg/kg and 15 mg/kg. No significant differences were observed in mean serum concentrations, $C_{max}$ and AUC on Day 1 between Benepali and Enbrel in Cynomolgus monkeys. On Day 25 the $C_{max}$ and $AUC_{(0\text{-last})}$ for lower dose (1 mg/kg) Benepali were slightly higher than those of Enbrel, but there was considerable variability in the results within the group. Due to the small scale of the study this result could fall within the intrinsic variability or be affected by the anti-drug antibodies. It is concluded that within the limitations of the assays, the pharmacokinetics of Benepali after subcutaneous administration (at a dose of 1 mg/kg and 15 mg/kg) are similar to those of Enbrel.

The absence of studies into distribution, metabolism, excretion and drug-drug interactions was consistent with CHMP guidance (EMA/CHMP/BMWP/403543/2010 Guideline on similar biological medicinal products containing monoclonal antibodies).

A GLP compliant 4 week repeat dose toxicity study in Cynomolgus monkeys was conducted to evaluate the potential subchronic toxicity of Benepali in comparison to the reference products EU Enbrel and US Enbrel, respectively. Despite the low number of animals used per group and the inter-individual variations between the animals which was reported the results showed that toxicity, toxicokinetic, and immunogenicity profiles of Benepali showed a similar trend to those of Enbrel.

Studies regarding reproduction toxicology are not required for non-clinical testing of biosimilars. The nature of the product and the type of application justifies the absence of developmental and reproductive toxicity (DART) studies.

The applicant did not submit any ERA studies with the appropriate justification in line to Corr. 2 of the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

Taken together, the submitted non-clinical data support the biosimilarity of Benepali (SB4) and Enbrel.

### 2.3.7. Conclusion on the non-clinical aspects

Comparative pharmacodynamics, pharmacokinetic and toxicology data demonstrated biosimilarity between Benepali and the reference product Enbrel. The provided non-clinical comparability exercise testing strategy was considered as appropriate. Relevant regulatory guidelines were taken into consideration.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

***GCP***

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.

A request for a routine GCP inspection was adopted by the CHMP for the following clinical study: SB4-G31-RA, in accordance with Article 57 of Council Regulation (EC) No. 726/2004 and article 15 of Directive 2001/20/EC.

The findings noted during the inspections were considered unlikely to have a significant impact on the quality of the data and therefore were used for the evaluation and assessment of the application.

The clinical development programme to demonstrate biosimilarity between SB04 and Enbrel is based on the trials listed in **Table 6**.

**Table 6. Tabular overview of clinical studies**

| Study No (Country) | Study Objectives | Design / Duration | Study Treatment | Study Subjects |
|---|---|---|---|---|
| **Healthy Subjects – Single-Dose** | | | | |
| SB4-G11-NHV<br>**Phase I**<br>(Germany) | Primary objective: PK equivalence ($AUC_{inf}$, $C_{max}$);<br>Secondary objectives: Safety / tolerability / immunogenicity | Controlled, randomised, single-blind, three-part, two-period, two-sequence, single-dose, cross-over /<br>Period 1: 21 days,<br>Period 2: 21 days<br>Washout: 7 days | Part A: SB4 vs. EU Enbrel®,<br>Part B: SB4 vs. US Enbrel®,<br>Part C: EU Enbrel® vs. US Enbrel®;<br>Single dose of 50 mg etanercept; SC injection (pre-filled syringe) | Healthy male subjects;<br>Part A: N=46 (n=23 per arm)<br>Part B: N=46 (n=23 per arm)<br>Part C: N=46 (n=23 per arm) |
| **Patient Population – Long-Term** | | | | |
| SB4-G31-RA<br>**Phase III**<br>(Bulgaria, Czech Republic, Hungary, Lithuania, Poland, Ukraine, United Kingdom, South Korea, Mexico, Colombia) | Primary objective: Comparative efficacy /equivalence (ACR20 response rate);<br>Secondary objectives: Safety / tolerability; immunogenicity; steady-state PK | Controlled, randomised (1:1), double-blind, parallel group, multicentre / 24 weeks and 52 weeks | SB4 vs. EU Enbrel®; 50 mg etanercept once weekly, SC injection (pre-filled syringe, self-administration) | RA patients with inadequate response to MTX;<br>N=596; (SB4, 299; EU Enbrel®, 297) |

ACR20: American College of Rheumatology 20% response criteria; $AUC_{inf}$: area under concentration-time curve from time zero to infinity; BA: bioavailability; $C_{max}$: maximum concentration; MTX: methotrexate; PK: pharmacokinetics; RA: rheumatoid arthritis; SC: subcutaneous

## 2.4.2. Pharmacokinetics

The clinical program to demonstrate similarity in pharmacokinetics and immunogenicity between Benepali (SB4) and Enbrel consisted of two clinical studies:

- SB4-G11-NHV: single dose PK, safety and immunogenicity study in healthy volunteers (n=138).
- SB4-G31-RA: efficacy, steady-state PK explorative subset, long-term safety and immunogenicity study in RA patients (n=79) as supportive.

**SB4-G11-NHV**

This was a single-centre, randomised, single blind, three-part, two period, two-sequence, single-dose, crossover study to compare the PK, safety, tolerability and immunogenicity of three formulations of etanercept.

The primary objective was to investigate and compare the PK profiles of etanercept between SB4 and Enbrel (EU and US sourced).

This randomised, single-blind, 2-period, 2-sequence, single-dose, cross-over, clinical study included the following 3 different parts:

- Part A: 46 subjects were randomised to receive a single-dose of SB4 or EU sourced Enbrel in period 1 followed by the cross-over treatment in period 2.
- Part B: 46 subjects were randomised to receive a single-dose of SB4 or US sourced Enbrel in period followed by the cross-over treatment in period 2.
- Part C: 46 subjects were randomised to receive a single-dose of EU sourced Enbrel or US sourced Enbrel in period 1 followed by the cross-over treatment in period 2.

**Treatment**

Each enrolled subject received two different single doses of etanercept 50 mg in the form of either the test formulation (SB4) or reference formulations (EU sourced Enbrel or US sourced Enbrel. These investigational products were administered as two subcutaneous injections separated by a washout period of 28 days. The total administered dose for each study subject was therefore 100 mg of etanercept.

**Secondary pK endpoints**

$AUC_{last}$, $T_{max}$, $V_z/F$ (apparent volume of distribution during the terminal phase), $\lambda_z$ (terminal rate constant), $\ln(2)/\lambda_z(t_{½})$ (=terminal half-life), CL/F (apparent total clearance), % $AUC_{extrap}$ (area under the concentration-time curve extrapolated from time t to infinity as a percentage of total AUC).

The trial was conducted in a sequential manner to minimise safety risks of the first use in humans.

The demographic characteristics were balanced between the sequences in each part (data not shown).

**Results**

**Table 7. Disposition of subjects (SB4-G11-NHV)**

| | Part A | | | Part B | | | Part C | | |
|---|---|---|---|---|---|---|---|---|---|
| **Sequence** | **AB** | **BA** | **Total** | **AB** | **BA** | **Total** | **AB** | **BA** | **Total** |
| **Number (%) of Subjects** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Randomised | 23 | 23 | 46 | 23 | 23 | 46 | 23 | 23 | 46 |
| Completed Period 1 and Period 2 | | | | | | | | | |
| | 22 (95.7) | 23 (100.0) | 45 (97.8) | 23 (100.0) | 22 (95.7) | 45 (97.8) | 20 (87.0) | 22 (95.7) | 42 (91.3) |
| Discontinued from Period 1 | | | | | | | | | |
| | 1 (4.3) | 0 (0.0) | 1 (2.2) | 0 (0.0) | 1 (4.3) | 1 (2.2) | 3 (13.0) | 1 (4.3) | 4 (8.7) |
| Reason for discontinuation | | | | | | | | | |
| Adverse event | 1 (4.3) | 0 | 1 (2.2) | 0 | 1 (4.3) | 1 (2.2) | 1 (4.3) | 1 (4.3) | 2 (4.3) |
| Pathological lab | 0 | 0 | 0 | 0 | 0 | 0 | 1 (4.3) | 0 | 1 (2.2) |
| Others | 0 | 0 | 0 | 0 | 0 | 0 | 1 (4.3) | 0 | 1 (2.2) |
| Discontinued from Period 2 | | | | | | | | | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

AB and BA represent the sequence of treatments in each part.
- A: SB4, B: EU sourced Enbrel® in Part A
- A: SB4, B: US sourced Enbrel® in Part B
- A: EU sourced Enbrel®, B: US sourced Enbrel® in Part C

Percentages are based on the number of randomised subjects.
Subjects who discontinued during washout period are counted in the category of "Discontinued from Period 1".

Three subjects in part A were had non-zero baseline concentration of greater than 5% of $C_{max}$ in period 2. This was defined as a “carry-over effect” and these subjects’ PK parameters were excluded from the summary statistics and analysis of variance (ANOVA).

Primary PK analysis

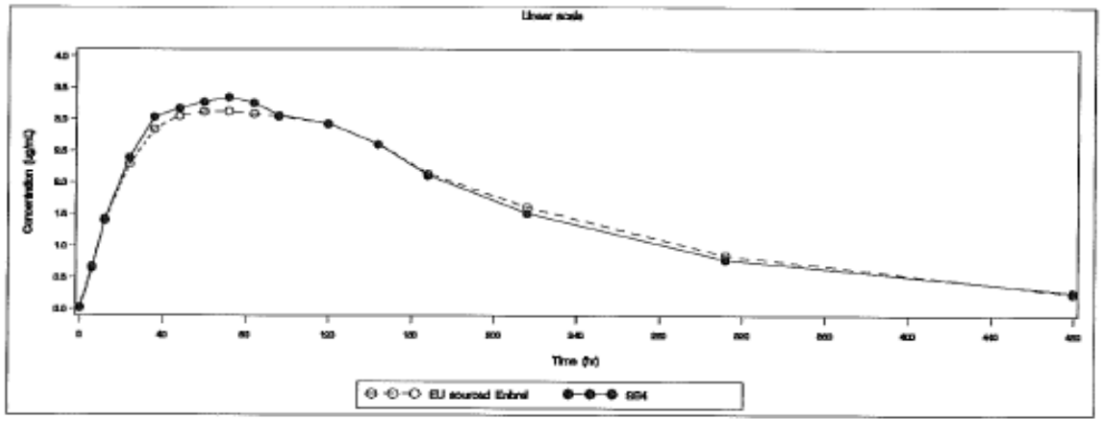
The mean (SD) PK parameters of the investigated products in part A of the study are shown in **Table 8**. The mean serum concentration versus nominal time curves on linear scale for Part A of SB4-G11-NHV are shown in **Figure 4**.

**Table 8. PK parameters of the investigated products after a single-dose of 50 mg s.c.**

| Parameter | Statistics | Part A | |
|---|---|---|---|
| | | SB4 | EU sourced Enbrel® |
| | | N = 45 | N = 45 |
| $AUC_{inf}$ | n | 42 | 42 |
| (µg·h/mL) | Mean | 769.069 | 771.680 |
| | SD | 243.9039 | 226.2874 |
| | Median | 772.425 | 790.480 |
| | Min | 331.650 | 339.815 |
| | Max | 1278.994 | 1167.015 |
| $C_{max}$ | n | 42 | 42 |
| (µg/mL) | Mean | 3.607 | 3.435 |
| | SD | 1.4298 | 1.2390 |
| | Median | 3.337 | 3.483 |
| | Min | 1.235 | 1.294 |
| | Max | 6.686 | 5.998 |
| $AUC_{last}$ | n | 42 | 42 |
| (µg·h/mL) | Mean | 728.169 | 734.015 |
| | SD | 234.7621 | 220.2722 |
| | Median | 723.986 | 743.629 |
| | Min | 306.598 | 308.166 |
| | Max | 1210.968 | 1100.399 |
| $T_{max}$ | n | 42 | 42 |
| (h) | Mean | 75.198 | 71.711 |
| | SD | 29.1358 | 24.7538 |
| | Median | 72.025 | 71.992 |
| | Min | 35.933 | 35.983 |
| | Max | 145.817 | 143.583 |
| $t_{1/2}$ | n | 42 | 42 |
| (h) | Mean | 105.782 | 100.340 |
| | SD | 11.6924 | 16.1335 |
| | Median | 103.714 | 102.395 |
| | Min | 84.428 | 68.637 |
| | Max | 137.443 | 135.816 |

*N is the number of subjects in PK population. The number of subjects who contributed to summary statistics was in part A: n = 42, Three subjects in part A and one subject in part B were excluded due to the carry-over effect.*

**Figure 4. The mean serum concentration versus nominal time curves on linear scale for Part A of SB4-G11-NHV**




Secondary PK analysis

The mean apparent volume of the distribution ($V_z$/F) for SB4 during the terminal phase in healthy males was 11.2 l (PK population Part A, N=42), compared to 10.5 for Enbrel (N=42) and the mean terminal $t_{1/2}$ for SB4 was 106 h (SD=11.7) compared to 100.3 (SD=16.1) for Enbrel.

The mean apparent total clearance (CL/F) for SB4 was 72.9 ml/h (SD=27.5) compared to 71.5 ml/h (SD=24.8) for Enbrel. The mean (SD) terminal rate constant ($\lambda_z$) was 0.007 (0.0007) and 0.007 (0.0012) for SB4 and Enbrel, respectively.

**SB4-G31-RA**

This was a randomised, double-blind, parallel group, multicentre, clinical study consisted of 52 weeks of active treatment (SB4 +MTX or Enbrel + MTX) and 4 weeks safety follow-up. The dose of etanercept administered was 50 mg s.c. injection once weekly. The MTX dose was 10-25 mg/week orally or parenterally. Details about the study methods are described under Clinical Efficacy.

The PK evaluation of SB4 compared to Enbrel was one of the secondary objectives of the study. PK analyses were performed in a subset of 79 (13.3%) patients, comprising the PK population (SB4: n=41 [13.7%]; EU Enbrel: n=38 [12.8%]). Six (6) subjects were excluded from the PK summaries, 2 in the SB4 group and 4 in the Enbrel group, due to data quality issues at one site (source data for the results of erythrocyte sedimentation rate tests performed at screening and randomization visits was not available).

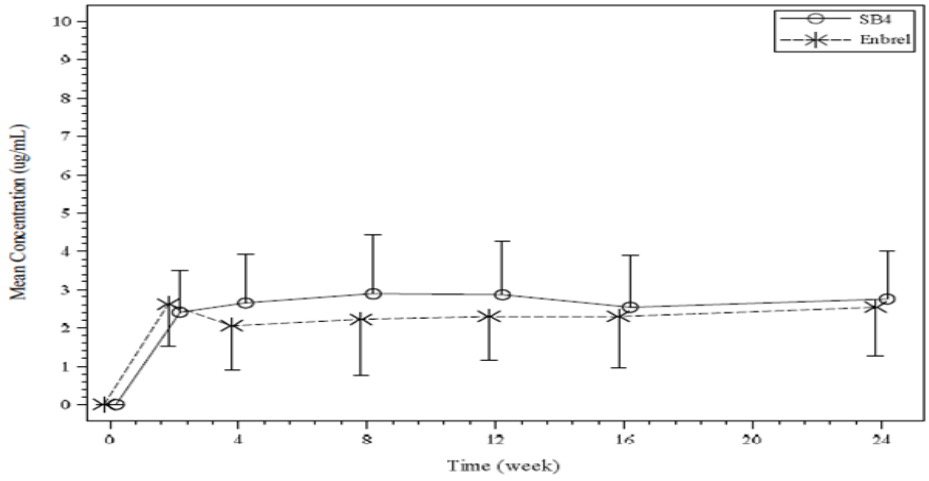
Serum concentrations were calculated at baseline and prior to dosing at Weeks 2, 4, 8, 12, 16, and 24 (trough concentration [$C_{trough}$]).

The following PK parameters were calculated at Week 8:Area under the concentration-time curve during the dosing interval ($AUC_T$), $C_{max}$, $C_{min}$, peak-trough concentration ratio, average serum concentration ($C_{av}$) during the dosing interval, degree of fluctuation, swing, $T_{max}$, CL/F, and $t_{½}$ at Week 8. As the PK analysis was exploratory, equivalence criteria were not used to compare the PK parameters between Benepali (SB4) and EU Enbrel. Sampling time points for PK parameters in week 8: 0, 24, 48, 72, 96, 120, 144, 186 h post dose.

**Pharmacokinetic results**

Ctrough from week 0 to week 24 is presented in **Figure 5**.

**Figure 5. Mean serum trough (predose) concentration-time profiles from week 0 to week 24**




*Error bars indicate standard deviation*

**PK Results at week 8**

**Table 9. Summary of key pharmacokinetic parameters for SB4 and EU Enbrel at week 8 in Study SB4-G31-RA**

| Parameter (Unit) | Statistics | SB4 50 mg N=41 | EU Enbrel® 50 mg N=38 |
|---|---|---|---|
| $AUC_T$ (µg·h/mL) | n | 36 | 34 |
| | Mean (SD) | 676.378 (255.065) | 520.899 (261.008) |
| | CV% | 37.7 | 50.1 |
| | Min, Max | 121.683, 1142.107 | 98.092, 1145.019 |
| $C_{max}$ (µg/mL) | n | 36 | 35 |
| | Mean (SD) | 5.140 (1.805) | 4.084 (2.133) |
| | CV% | 35.1 | 52.2 |
| | Min, Max | 0.892, 7.758 | 0.900, 9.644 |
| $T_{max}$ (h) | n | 36 | 35 |
| | Median | 47.84 | 47.75 |
| | CV% | 62.6 | 54.7 |
| | Min, Max | 0.00, 169.05 | 0.00, 167.55 |
| $C_{min}$ (µg/mL) | n | 36 | 35 |
| | Mean (SD) | 2.599 (1.383) | 1.826 (1.087) |
| | CV% | 53.2 | 59.5 |
| | Min, Max | 0.000, 5.231 | 0.000, 5.244 |
| CL/F (L/h) | n | 36 | 34 |
| | Mean (SD) | 0.093 (0.067) | 0.126 (0.084) |
| | CV% | 71.5 | 67.0 |
| | Min, Max | 0.044, 0.411 | 0.044, 0.510 |
| Fluctuation (%) | n | 36 | 34 |
| | Mean (SD) | 65.851 (27.151) | 72.681 (22.530) |
| | CV% | 41.2 | 31.0 |
| | Min, Max | 25.546, 136.377 | 33.792, 124.448 |

$AUC_T$:area under the concentration-time curve over the dosing interval; CL/F: apparent total clearance; $C_{max}$: maximum serum concentration; $C_{min}$: minimum serum concentration; CV%: coefficient of variation; Fluctuation = $100*(C_{max} - C_{min})/ C_{av}$; Max: maximum; Min: minimum; SD: standard deviation; $T_{max}$: time to $C_{max}$; $T_{max}$ is presented as median (max, min).

Mean exposure parameters were higher (+ 30% for $AUC_T$, 26% for $C_{max}$ and 42% for $C_{min}$) following Benepali (SB4) than with EU Enbrel. The median Tmax was comparable (approximately 48 hours) between Benepali (SB4) and EU Enbrel. The PK parameters showed considerable inter-subject variability (CV%), ranging from 35.1% to 71.5% following Benepali (SB4) and from 31.0% to 67.0% with EU Enbrel.

While mean exposure parameters were slightly higher for Benepali (SB4) with a large variability, the range (minimum, maximum) of all exposure parameters ($AUC_T$, $C_{max}$ and $C_{min}$) following Benepali (SB4) was comparable with those for EU Enbrel.

***Absorption***

No bioavailability studies were submitted for SB4.

***Distribution***

The mean apparent volume of the distribution ($V_z/F$) for the SB4 during the terminal phase in healthy males was in the range between 10.3 and 11.2 l (study SB4-G11-NHV).

***Elimination***

The mean terminal $t_{1/2}$ of SB4 in healthy males was calculated to be about 106 h ~ 4 days after s.c. administration study (SB4-G11-NHV).

***Dose proportionality and time dependencies***

Dose-proportionality was not evaluated. In the clinical studies, the study products were administered at the recommended therapeutic of Enbrel.

***Special populations***

No studies were performed in patients with hepatic impairment and in patients with renal impairment as these are not required for a similar biological medicinal product.

***Pharmacokinetic interaction studies***

No PK interaction studies were performed as these are not required for a similar biological medicinal product.

## 2.4.3. Pharmacodynamics

SB4 is a recombinant human tumour necrosis factor receptor p75Fc fusion protein. It interferes with the soluble TNF α by mimicking the inhibitory effects of naturally occurring soluble TNF receptors that deactivate TNF-α and therefore down-regulate immune responses. SB4 acts as a decoy receptor for TNF-α, reducing TNF-α effects and hence represents a competitive TNF-α inhibitor.

In accordance with EU guidance (EMEA/CHMP/BMWP/ 42832/2005; EMA/CHMP/BMWP/403543/2010), clinical evidence for comparability/similarity can be demonstrated by PD surrogate endpoints or clinical evidence. In case of SB4, clinical evidence for similarity was aimed to be demonstrated by clinical rather than PD endpoints. The Applicant did not submit further clinical studies on the PD of etanercept.

## 2.4.4. Discussion on clinical pharmacology

Study (SB4-G11-NHV) was considered pivotal for the comparative PK evaluation between SB4 and Enbrel.

Healthy subjects are considered the most homogenous population when performing a comparative PK study regarding this application. The design was in line with the recommendations of the Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

The results of the primary endpoints were well within the pre-defined acceptance range.

Three study subjects were excluded from the statistical analyses in the comparison between Benepali (SB4) and EU sourced Enbrel due to the carry-over effect. This approach was considered appropriate.

The secondary endpoints were presented as descriptive statistics, without defining an acceptance range, which is in accordance with relevant EU guidelines. Also the secondary PK parameters were comparable between investigated products. The intra-subject CV was low (12.221 for $AUC_{inf}$ and 14.205 for $C_{max}$).

Design, selected dose and sample size were considered adequate to evaluate PK- bioequivalence between SB4 and Enbrel.

Additional PK-data were gathered from the efficacy and safety study (SB4-G31-RA) from a subset of 79 subjects. The PK characteristics of etanercept from Benepali (SB4) were compared to Enbrel by determining the trough (pre-dose) concentrations from week 0 to week 24 and by calculating the steady-state PK parameters at week 8.

### 2.4.5. Conclusions on clinical pharmacology

Study SB4-G11-NHV was considered pivotal for the comparative PK evaluation, and according the results of this study Benepali (SB4) and Enbrel were considered bioequivalent.

## *2.5. Clinical efficacy*

### 2.5.1. Dose response studies

No dose-response studies were submitted. As this application relates to a biosimilar product, there is no requirement for dose-response studies. The proposed dosing regimens for SB4 are identical to those approved for Enbrel.

### 2.5.2. Main study

**Study SB4-G31-RA**

A randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of SB4 compared to Enbrel in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy.

***Methods***

***Study Participants***
Main Inclusion Criteria

- Male or female aged 18-75 years old at the time of signing of the consent form;
- Had been diagnosed as having RA according to the revised 1987 American College of Rheumatology (ACR) criteria for at least 6 months, but not exceeding 15 years prior to screening;
- Had moderate to severe active disease despite MTX therapy defined as:

a) More than or equal to six swollen joints and more than or equal to six tender joints (from the 66/68 joint count system) at Screening and Randomisation;
b) Either erythrocyte sedimentation rate (ESR; Westergren) ≥ 28 mm/h or serum C-reactive protein (CRP) ≥ 1.0 mg/dL at Screening;

- Had been treated with MTX for at least 6 months prior to Randomisation and be on a stable dose of MTX 10–25 mg/week given orally or parenterally for at least 4 weeks prior to screening.

Main exclusion Criteria

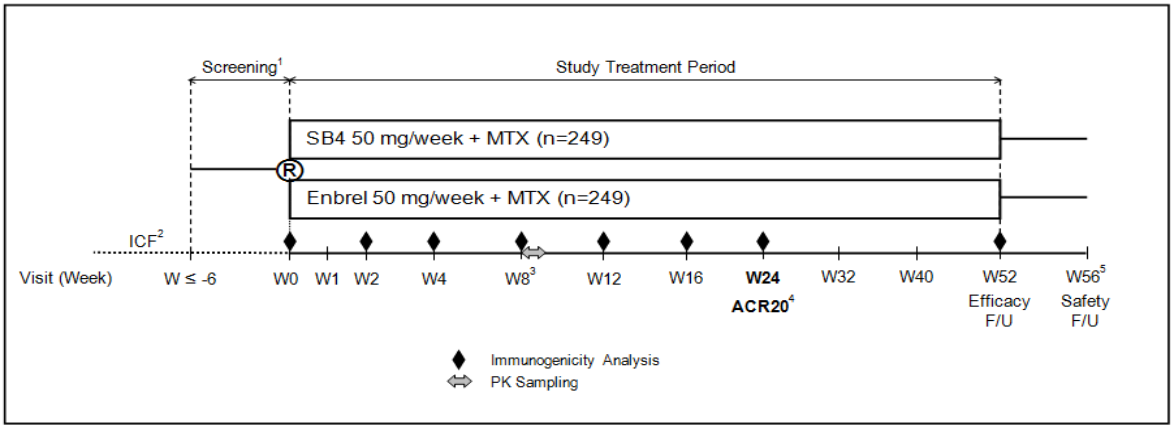
- Had been treated previously with any biological agents including any TNF-$\alpha$ inhibitor;
- Had been taking any of the following concomitant medications, within the timeframe specified:
  a. Corticosteroids above levels equivalent to 10 mg prednisolone daily within 4 weeks prior to Randomisation;
  b. Any disease-modifying anti-rheumatic drugs (DMARDs)/systemic immunosuppresssive agents, other than MTX, including hydroxy-chloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine or mycophenolate mofetil within 4 weeks prior to randomisation;
  c. Leflunomide within 12 weeks prior to randomisation or within 4 weeks prior to randomisation if the subject had washout with 8 g of cholestyramine three times daily for at least 11 days;
  d. Alkylating agents within 12 months prior to randomisation;
  e. Live/live-attenuated vaccine within 8 weeks prior to randomisation;
  f. Injectable corticosteroids within 4 weeks prior to randomisation;
  g. IP from another study within five half-lives of that product prior to randomisation or use of an investigational device at screening;
- Had a positive serological test for hepatitis B or hepatitis C or had a known history of infection;
- Had a current diagnosis of active tuberculosis (TB);
- Had any of the following conditions:
  - Other inflammatory or rheumatic diseases;
  - History of any malignancy within the previous 5 years prior to screening;
  - History of lymphoproliferative disease including lymphoma;
  - History of congestive heart failure (New York Heart Association Class III/IV) or unstable angina.

***Treatments***

The study design is presented in **Figure 6**.

A total of 498 subjects with moderate to severe RA despite MTX therapy were to be randomised in a 1:1 ratio to receive either SB4 50 mg (n=249) or Enbrel 50 mg (n=249) once-weekly for 52 weeks via subcutaneous injection. Subjects were followed in the study for up to 56 weeks after Randomisation, consisting of 52 weeks of active treatment and 4 weeks of safety follow-up.

**Figure 6. Graphical design of Study SB4-G31-RA**




*ACR20=American College of Rheumatology 20% response criteria; F/U=Follow-up; ICF=Informed consent form; MTX=methotrexate; R=Randomisation; W=Week. 1 Screening had to be done within 6 weeks prior to Randomisation. 2 Informed consent had to be obtained prior to any study related procedures. 3 Blood sampling at 24, 48, 72, 96 and 168 h after injection at Week 8 in the subgroup undergoing PK assessment. $C_{trough}$ was assessed in the PK population at Weeks 0, 2, 4, 8, 12, 16 and 24. 4 The primary endpoint (ACR20 response) was assessed at Week 24.*

***Objectives***

Primary objectives:

The primary objective of this study was to demonstrate the equivalence of SB4 to Enbrel at Week 24, in terms of American College of Rheumatology 20% response criteria (ACR20) response rate in subjects with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) therapy.

Secondary objectives:

The secondary objectives were:

- To evaluate efficacy of SB4 compared to Enbrel using relevant efficacy endpoints other than ACR20 at Week 24 in subjects with moderate to severe RA despite MTX therapy;
- To evaluate safety and tolerability of SB4 compared to Enbrel in subjects with moderate to severe RA despite MTX therapy;
- To evaluate pharmacokinetics (PK) of SB4 compared to Enbrel in subjects with moderate to severe RA despite MTX therapy;
- To evaluate immunogenicity of SB4 compared to Enbrel in subjects with moderate to severe RA despite MTX therapy.

***Outcomes/endpoints***

The primary efficacy endpoint was the ACR20 response rate at Week 24.

The secondary efficacy endpoints were:

- ACR50 and ACR70 response at Week 24
- ACR20, ACR50 and ACR70 at Week 52.
- The numeric index of the ACR response (ACR-N) at Week 24 and Week 52.
- AUC of ACR-N up to Week 24.
- The disease activity score based on a 28 joint count (DAS28 score) at Week 24 and Week 52.

- The European League Against Rheumatism response at Week 24 and Week 52.
- AUC of the change in DAS28 from baseline up to Week 24.
- "Major clinical response" (ACR70 response for 6 consecutive months) at Week 52.
- Change from baseline in modified Total Sharp Score (mTSS) at Week 52.

The ACR20 response indicated:

• At least a 20% improvement from baseline in swollen joint count (66 joint count).

• At least a 20% improvement from baseline in tender joint count (68 joint count).

• At least a 20% improvement from baseline in at least three of the following five criteria:

- Subject pain assessment using a 100 mm visual analogue scale (VAS)
- Subject global assessment using a 100 mm VAS.
- Physician global assessment using a 100 mm VAS.
- Subjects assessment of disability using the Health Assessment Questionnaire - Disability Index (HAQ-DI).
- Acute phase reactant level (CRP).

The ACR50 and ACR70 indicated a 50% and 70% improvement, respectively, in the criteria. The DAS28 score was calculated using the following equation (four-variable equation):

DAS28 = 0.56 × √(tender 28 joint count) + 0.28 × √(swollen 28 joint count) + 0.70 × ln(ESR) +

0.014 × general health.

General health was subject global assessment using a 100 mm VAS. The EULAR response was based upon the DAS28 score. Subjects were classified as having either a good, moderate or no response

**Table 10. The EULAR Response Criteria Using DAS28**

| | Improvement in DAS28 from baseline | | |
|---|---|---|---|
| DAS28 at endpoint | > 1.2 | ≤ 1.2 and > 0.6 | ≤ 0.6 |
| ≤ 3.2 | Good response | Moderate response | No response |
| > 3.2 and ≤ 5.1 | Moderate response | Moderate response | No response |
| > 5.1 | Moderate response | No response | No response |

For the joint assessment for Calculation of American College of Rheumatology Response, independent joint assessors were assigned at each Investigator site. The 66/68 joint count included the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints of the hands, the metatarsal phalangeal and distal interphalangeal joints of the feet and the shoulder, elbow, wrist, hip, knee, ankle, tarsus and temporomandibular, sternoclavicular and acromio-clavicular joints [Sokka, 2005].

The 28 joint counts included the shoulders, elbows, wrists, knees and metacarpophalangeal and proximal interphalangeal joints of the hands.

Subjects were asked to assess their average pain during the past week on a VAS (0 to 100 mm). The scale ranged from 0 (no pain) to 100 (severe pain). Subjects were asked to complete an overall assessment of how their RA had affected them, rating how they were managing from 0 (very well) to 100 (very poorly).

The physician's assessment of the subject's current disease activity was documented on a VAS, ranging from 0 (no RA activity) to 100 (extremely active RA).

The physical function of the subject was assessed using the HAQ-DI questionnaire. It assessed the degree of difficulty a person has had in accomplishing tasks in eight functional areas over the previous 7 days, taking into account any aids or help required. The eight component sets were dressing and grooming, rising, eating, walking, hygiene, reach, grip and common daily activities. Responses in each functional area were scored from 0 (without any difficulty) to 3 (unable to do). The highest score recorded for any question in a category was the score for that category, unless aids, devices or help from another person was required. Dependence on aids or devices or help from others resulted in a minimum category score of 2. If a question was left blank, the category was scored based on the responses to the other question or questions. The HAQ-DI score was calculated as the sum of the category scores divided by the number of categories scored, giving a possible range of scores from 0 to 3.

At randomisation and end of treatment, subjects had a single posteroanterior radiographic assessment (X-ray) of the left and right hand/wrist and a single dorsoplantar radiographic image taken of the left and right foot. X-rays were reviewed centrally by two independent qualified readers under blinded conditions once images for all subjects had been obtained. The mean score from the two readers were used for all analyses. The joint erosion score, the joint space narrowing (JSN) score are given by the readers. The mTSS is the sum of the joint erosion score and JSN score [Van der Heijde, 1999]. The joint erosion score is a summary of erosion severity in 32 joints of the hands and 12 joints of the feet. Each joint is scored, according to the surface area involved, from 0 to 5, with 0 indicating no erosion, 1 indicating discrete erosions, 2 to 3 indicating larger erosions according to surface area involved, 4 indicating erosions extending over middle of the bone and 5 indicating extensive loss of bone from more than one half of the articulating bone. Because each side of a foot joint is graded on this scale, the maximum joint erosion score for a foot joint is 10. Thus, the maximal joint erosion score is 280. The JSN score summarises the severity of JSN in 30 joints of the hands and 12 joints of the feet. Assessment of JSN, including subluxation, is scored from 0 to 4, with 0 indicating normal, 1 indicating focal or doubtful, 2 indicating generalised, less than 50% of the original joint space, 3 indicating generalised, more than 50% of the original joint space or subluxation and 4 indicating bony ankylosis or complete luxation. The score for JSN ranges from 0 to 120 in the hands and from 0 to 48 in the feet. Thus, the maximal JSN score is 168 and the worst possible mTSS is 448.

***Sample size***

The ACR20 responses to patients treated with Enbrel from selected studies with regards to study population and treatment regimen were used for the equivalence margin and sample size calculation and are presented in **Table 11**.

**Table 11. ACR20 Responses in Pivotal Studies with Enbrel**

| | Enbrel® | Placebo | Absolute difference Enbrel® – placebo (%) | Time measurement | DMARD |
|---|---|---|---|---|---|
| | ACR20 response events/total (%) | ACR20 response events/total (%) | | | |
| Weinblatt (1999) | 42/59 (71%) | 8/30 (27%) | 44% | 24 weeks | MTX |
| Combe (2006) | 74/100 (74%) | 14/50 (28%) | 46% | 24 weeks | Sulfasalazine |
| Keystone*(2004) | 95/192 (49%) | 5/29 (17%) | 32% | 8 weeks | MTX |
| Overall | 211/351 (60%) | 27/109 (25%) | 35% | | |

** Data only represent results from subjects continuing MTX treatment. For Enbrel the subjects groups receiving 25 mg twice weekly and 50 mg once per week have been combined.*

A random-effects meta-analysis in the above studies estimated a risk difference of 0.4049 with a 95% CI (0.3103, 0.4996). To preserve at least 50% of the effect of Enbrel over and above placebo, an equivalence limit of 15% was used for the primary analysis.

The sample size of 249 per arm (overall sample size of 498) was to give 80% power accounting for the 12% drop rate when the expected ACR20 response rate was assumed as 60% at Week 24. Overall 596 subjects were randomised into the study due to the high number of subjects recruited during the last phase of the enrolment, which resulted in providing 87% power to the study.

The primary endpoint was assessed after the last subject completed 24 weeks of treatment or after the corresponding visit and statistical analyses were performed once all subjects have attended this visit. Available efficacy and safety data were also analysed and reported.

***Randomisation***

Subjects were assigned a unique subject number at Screening. The subject number was used to register the subject using the interactive web response system (IWRS) or the interactive voice response system (IVRS) and the subject was then randomised to either SB4 or Enbrel in a 1:1 ratio at a centre-level.

***Blinding (masking)***

This was a double-blind trial and subjects, investigators, joint assessors and other study personnel were to remain blinded throughout the entire treatment period. After the last subject completed the Week 24 visit, the study was unblinded for reporting purposes and efficacy, PK, safety and immunogenicity endpoints were evaluated.

***Statistical methods***

The following analysis data sets were defined:

Enrolled Set (ENR): ENR consisted of all subjects who provided informed consent for this study.

Randomised Set (RAN): RAN consisted of all subjects in the ENR who received a randomisation number at the Randomisation Visit. For analyses and displays based on RAN, subjects were classified according to the treatment they were assigned at randomisation.

Full Analysis Set (FAS): FAS consisted of all subjects who were randomised at the Randomisation Visit. Following the intent-to-treat principle, subjects were analysed according to the treatment they were assigned at randomisation. However, subjects who did not qualify for randomisation and were inadvertently randomised into the study were excluded from the FAS, provided these subjects did not receive any IP during that study phase.

Per-protocol Set 1 (PPS1): PPS1 consisted of all FAS subjects who completed the Week 24 visit and had an adherence (from baseline to Week 24) within the range 80-120% of both the expected number of IP injections and the expected sum of MTX doses without any major protocol deviations (PDs) that affected the efficacy assessment. Major PDs that led to exclusion from this set were pre-specified prior to unblinding the treatment codes for analyses.

Safety Set (SAF): The SAF consisted of all subjects who received at least one dose of double blind IP during the study phase. Subjects were analysed according to the treatment received. If there was any doubt whether a subject was treated or not, they were assumed treated for the purposes of analysis.

In addition to the above, Per-protocol Set 2 (PPS2) was defined, consisting of all FAS subjects who completed the Week 52 visit and had an adherence (from baseline to Week 52) within the range 80-120%

of both the expected number of IP injections and the expected sum of MTX doses without any major PDs that affected the efficacy assessment.

Primary Variable Analysis

The primary efficacy endpoint was the proportion of subjects meeting the ACR20 response criteria for RA at Week 24. The primary efficacy analysis for ACR20 response was performed for the Per Protocol Set 1 (PPS1, See "Numbers analysed Section of this report). No missing data was imputed into PPS1. The null hypothesis tested for the primary efficacy analysis was that either (1) SB4 is inferior to Enbrel or (2) SB4 was superior to Enbrel based on a pre-specified equivalence margin. Equivalence between the two treatment groups was declared if the two-sided 95% confidence interval (CI) of the difference in ACR20 response rate between SB4 and Enbrel was entirely contained within the equivalence margin of [–15%, 15%].

To estimate the 95% CIs of the treatment difference in terms of ACR20 response rate, a randomisation-based non parametric ANCOVA method (Koch et al., 1998 and Tangen et al., 1999)was used, controlling for region (pooled study centres) as a factor and baseline CRP value as a covariate, using Mantel-Haenszel weights for the strata. As the ACR20 response rate was expected to be around 50% at Week 24, the proportion of patients achieving ACR20 response approximately followed a normal distribution and therefore the proportion of ACR 20 responders was treated as a continuous variable. For subjects that dropped out before the expected end of treatment a "missing-at-random" approach was used, together with a number of sensitivity analyses

***Results***

**Participant flow**

Of the 596 subjects randomised to treatment, prior to Week 24, 45 (7.6%) subjects withdrew from the study of which, 16 subjects (5.4%) were from the SB4 treatment group and 29 (9.8%) were the Enbrel treatment group. In both treatment groups, the most common reasons for withdrawal were AEs (3.7%) and withdrawal of consent (2.7%). Patient disposition is shown in **Table 12**.

**Table 12. Disposition of subjects in Study SB4-G31-RA**

| | SB4 50 mg | Enbrel® 50 mg | Total |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Screened | | | 777 |
| Screening failures | | | 181 |
| Reasons for screening failures | | | |
| Does not meet inclusion criteria | | | 40 (22.1) |
| Does meet exclusion criteria | | | 113 (62.4) |
| Subject lost to follow up | | | 3 (1.7) |
| Withdrew consent | | | 18 (9.9) |
| Other | | | 16 (8.8) |
| Randomised | 299 | 297 | 596 |
| Completed Week 24 of treatment | 283 (94.6) | 268 (90.2) | 551 (92.4) |
| Withdrew before Week 24 | 16 (5.4) | 29 (9.8) | 45 (7.6) |
| Reason for withdrawal | | | |
| Adverse event | 8 (2.7) | 14 (4.7) | 22 (3.7) |
| Protocol deviation | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Lack of efficacy | 0 (0.0) | 3 (1.0) | 3 (0.5) |
| Investigator discretion | 2 (0.7) | 1 (0.3) | 3 (0.5) |
| Withdrew consent | 5 (1.7) | 11 (3.7) | 16 (2.7) |
| Completed Week 52 of treatment | 18 (6.0) | 12 (4.0) | 30 (5.0) |
| Withdrew before Week 52 | 25 (8.4) | 38 (12.8) | 63 (10.6) |
| Reason for withdrawal | | | |
| Adverse event | 11 (3.7) | 17 (5.7) | 28 (4.7) |
| Protocol deviation | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Lack of efficacy | 1 (0.3) | 3 (1.0) | 4 (0.7) |
| Subject lost to follow-up | 1 (0.3) | 1 (0.3) | 2 (0.3) |
| Investigator discretion | 2 (0.7) | 2 (0.7) | 4 (0.7) |
| Withdrew consent | 9 (3.0) | 15 (5.1) | 24 (4.0) |

**Recruitment**

The study was initiated on 11 June 2013 and the week 24 cut-off date was on 21 July 2014. Study completion date was on 28 November 2014. A total of 73 study centres across 10 countries worldwide enrolled patients.

**Conduct of the study**

A total of 145 (24.3%) subjects had at least one major PD (**Table 13**); 73 (24.4%) subjects from the SB4 treatment group and 72 (24.2%) subjects from the Enbrel treatment group.

A total of 75 (12.6%) subjects were excluded from PPS1 due to a major protocol deviation . The most common major Protocol Deviations that led to exclusion from PPS1 were study procedures criteria (16 subjects in SB4 vs. 16 subjects in Enbrel) and concomitant medication criteria (9 subjects vs. 14 subjects).

**Table 13. Summary of major protocol deviations in Study SB4-G31-RA by treatment group (randomised set)**

| Protocol deviation | SB4 50 mg N=299 n (%) | Enbrel® 50 mg N=297 n (%) | Total N=596 n (%) |
|---|---|---|---|
| With at least one major protocol deviation | 73 (24.4) | 72 (24.2) | 145 (24.3) |
| Excluded from Per-protocol set 1 | 40 (13.4) | 35 (11.8) | 75 (12.6) |
| Concomitant medication criteria | 9 (3.0) | 14 (4.7) | 23 (3.9) |
| Eligibility and entry criteria | 7 (2.3) | 5 (1.7) | 12 (2.0) |
| Investigational product compliance | 9 (3.0) | 2 (0.7) | 11 (1.8) |
| Study procedures criteria | 16 (5.4) | 16 (5.4) | 32 (5.4) |
| Others | 45 (15.1) | 44 (14.8) | 89 (14.9) |
| Concomitant medication criteria | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Eligibility and entry criteria | 1 (0.3) | 4 (1.3) | 5 (0.8) |
| Investigational product compliance | 12 (4.0) | 13 (4.4) | 25 (4.2) |
| Study procedures criteria | 35 (11.7) | 31 (10.4) | 66 (11.1) |

**Baseline data**

Baseline demographic characteristics and disease characteristics are summarised in **Tables 14** and **15** respectively.

**Table 14. Demographic Characteristics in Study SB4-G31-RA (Randomised Set)**

| | SB4 50 mg N=299 | Enbrel® 50 mg N=297 | Total N=596 |
|---|---|---|---|
| **Age (years)** | | | |
| n | 299 | 297 | 596 |
| Mean (SD) | 52.1 (11.72) | 51.6 (11.63) | 51.8 (11.67) |
| **Age group n (%)** | | | |
| < 65 years | 253 (84.6) | 262 (88.2) | 515 (86.4) |
| ≥ 65 years | 46 (15.4) | 35 (11.8) | 81 (13.6) |
| **Gender n (%)** | | | |
| Male | 50 (16.7) | 44 (14.8) | 94 (15.8) |
| Female | 249 (83.3) | 253 (85.2) | 502 (84.2) |
| **Race, n (%)** | | | |
| White | 279 (93.3) | 273 (91.9) | 552 (92.6) |
| American Indian or Alaskan Native | 5 (1.7) | 7 (2.4) | 12 (2.0) |
| Asian | 11 (3.7) | 13 (4.4) | 24 (4.0) |
| Other | 4 (1.3) | 4 (1.3) | 8 (1.3) |
| **Ethnicity n (%)** | | | |
| Hispanic or Latino | 18 (6.0) | 19 (6.4) | 37 (6.2) |
| Other | 281 (94.0) | 278 (93.6) | 559 (93.8) |
| **Weight (kg)** | | | |
| n | 299 | 297 | 596 |
| Mean (SD) | 72.51 (15.926) | 70.98 (14.631) | 71.75 (15.300) |
| **Height (cm)** | | | |
| n | 299 | 297 | 596 |
| Mean (SD) | 164.39 (8.781) | 164.37 (8.551) | 164.38 (8.660) |
| **BMI (kg/m$^2$)** | | | |
| n | 299 | 297 | 596 |
| Mean (SD) | 26.81 (5.511) | 26.32 (5.296) | 26.57 (5.406) |

*BMI = Body Mass Index; SD = standard deviation*

**Table 15. Baseline Disease Characteristics in Study SB4-G31-RA**

| | SB4 50 mg | Enbrel® 50 mg | Total |
|---|---|---|---|
| | N=299 | N=297 | N=596 |
| **Swollen joint count (0-66)** | | | |
| n | 299 | 297 | 596 |
| Mean (SD) | 15.4 (7.48) | 15.0 (7.30) | 15.2 (7.39) |
| Min, Max | 6, 43 | 6, 48 | 6, 48 |
| **Tender joint count (0-68)** | | | |
| n | 299 | 297 | 596 |
| Mean (SD) | 23.5 (11.90) | 23.6 (12.64) | 23.5 (12.26) |
| Min, Max | 6, 66 | 6, 68 | 6, 68 |
| **Physician global assessment VAS (0-100)** | | | |
| n | 296 | 291 | 587 |
| Mean (SD) | 62.2 (15.09) | 63.2 (14.76) | 62.7 (14.92) |
| Min, Max | 2, 94 | 11, 95 | 2, 95 |
| **Subject global assessment VAS (0-100)** | | | |
| n | 298 | 297 | 595 |
| Mean (SD) | 61.7 (18.97) | 63.0 (17.70) | 62.4 (18.35) |
| Min, Max | 1, 97 | 12, 100 | 1, 100 |
| **Subject pain assessment VAS (0-100)** | | | |
| n | 298 | 297 | 595 |
| Mean (SD) | 61.8 (20.22) | 62.3 (19.22) | 62.1 (19.71) |
| Min, Max | 0, 100 | 7, 100 | 0, 100 |
| **HAQ-DI (0-3)** | | | |
| n | 298 | 297 | 595 |
| Mean (SD) | 1.4904 (0.55292) | 1.5097 (0.55983) | 1.5000 (0.55600) |
| Min, Max | 0.000, 3.000 | 0.000, 2.875 | 0.000, 3.000 |
| **C-reactive protein (mg/L)** | | | |
| n | 299 | 297 | 596 |
| Mean (SD) | 14.6 (20.01) | 12.7 (15.97) | 13.7 (18.12) |
| Min, Max | 1, 140 | 1, 76 | 1, 140 |
| **C-reactive protein n (%)**[a] | | | |
| ≥ 10 mg/L | 121 (40.5) | 114 (38.4) | 235 (39.4) |
| < 10 mg/L | 178 (59.5) | 183 (61.6) | 361 (60.6) |
| **Erythrocyte sedimentation rate (mm/h)** | | | |
| n | 299 | 297 | 596 |
| Mean (SD) | 46.5 (22.10) | 46.4 (22.62) | 46.5 (22.34) |
| Min, Max | 6, 140 | 2, 137 | 2, 140 |
| **Rheumatoid factor n (%)**[a] | | | |
| Positive | 237 (79.3) | 231 (77.8) | 468 (78.5) |
| Negative | 62 (20.7) | 66 (22.2) | 128 (21.5) |

**Prior and Concomitant Medications**

A similar proportion of subjects in the SB4 and Enbrel groups (46.2% vs. 47.1% respectively) had taken medication which started and stopped prior to the study (i.e., prior medication), and the majority of subjects received concomitant medication during the study (95.0% vs. 96.6%).

Reflective of the study population, the most commonly used prior medications were glucocorticoids (23.1% vs. 22.9% of subjects for the SB4 and Enbrel treated subjects respectively), also used by more than half of study subjects during the study (56.2% vs. 56.9% of subjects in the two treatment arms).

The use of prohibited prior or concomitant medications was reported in 4.9% of subjects; 4.3% of subjects in the SB4 treatment group used 18 prohibited medications and 5.4% subjects in the Enbrel group used 32 prohibited medications. The most commonly used prohibited medications were glucocorticoids (7 events in 4 subjects in both SB4 and Enbrel treatment groups), acetic acid derivatives and related substances (2 events in 2 subjects vs. 11 events in 6 subjects) and other opioids (4 events in 4 subjects vs. 8 events in 4 subjects). Protocol deviations related to concomitant medication criteria led to the exclusion of 3.9% of subjects from the PPS1 (3.0% vs. 4.7% of subjects in the SB4 and Enbrel treatment groups, respectively).

**Numbers analysed**

**Table 16. Data sets analysed**

| | SB4 50 mg | Enbrel® 50 mg | Total |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Randomised | 299 (100.0) | 297 (100.0) | 596 (100.0) |
| Full analysis set | 299 (100.0) | 297 (100.0) | 596 (100.0) |
| Safety set | 299 (100.0) | 297 (100.0) | 596 (100.0) |
| Per-protocol set 1 | 247 (82.6) | 234 (78.8) | 481 (80.7) |

**Outcomes and estimation**

Primary endpoint

The primary analysis of ACR20 response with the number of subjects who achieved ACR20 response at Week 24 for the PPS1 is presented in **Table 17**.

**Table 17. Primary Analysis of ACR20 Response Rate at Week 24 in Study SB4-G31-RA, PPS1**

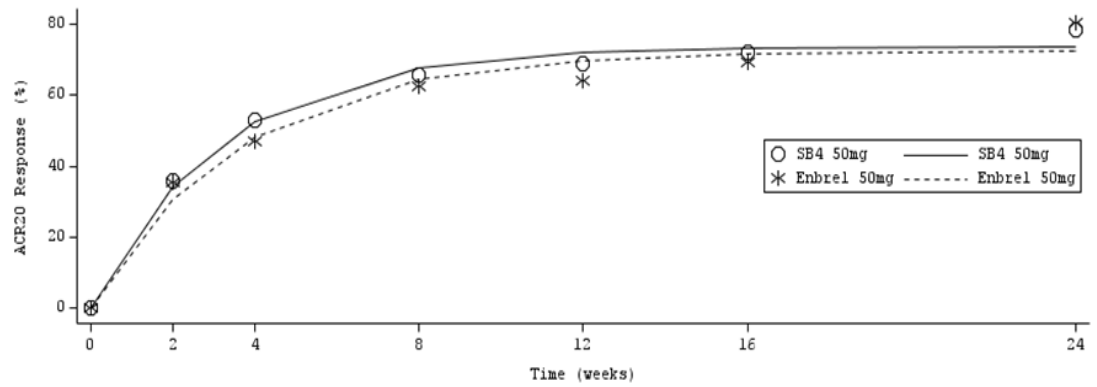
| Treatment | n/n' | (%) | Adjusted Difference Rate | 95% CI |
|---|---|---|---|---|
| SB4 50 mg (N=247) | 193/247 | (78.1) | –2.22% | (–9.41%, 4.98%) |
| Enbrel® 50 mg (N=234) | 188/234 | (80.3) | | |

CI = confidence interval. N = number of subjects in the per-protocol set 1; n' = number of subjects with an assessment; n = number of responders.

**Supportive Analysis of Primary Efficacy Analysis**

The time-response curves of SB4 and Enbrel up to Week 24 showing the ACR20 response over time were estimated to be equivalent and supported the robustness of the primary efficacy analysis. The treatment difference of the 2-norm was 12.7 and the 95% CI of the treatment difference was (‑4.6, 30.0), where the upper limit 30.0 was less than the pre-specified equivalence margin of 83.28. The time-response graphs for the ACR20 response for the PPS1 are presented in **Figure 7.**

**Figure 7. Time-Response Model for ACR20 Response up to Week 24 (Per-protocol Set 1)**



**Sensitivity Analysis of Primary Efficacy Variable**

To explore the robustness of the ACR20 responses for the PPS1, the same analysis was performed for the FAS (**Table 18**).

**Table 18. Analysis of ACR20 Response Rate at Week 24 in Study SB4-G31-RA, Full Analysis Set (Non-responder analysis)**

| Treatment | n/n' | (%) | Adjusted Difference Rate | 95% CI |
|---|---|---|---|---|
| SB4 50 mg (N=299) | 220/298 | (73.8) | 1.92% | (–5.24%, 9.07%) |
| Enbrel® 50 mg (N=297) | 213/297 | (71.7) | | |

*CI = confidence interval. N = number of subjects in the full analysis set; n' = number of subjects with an assessment; n = number of responders Subjects with missing ACR20 response at Week 24 were considered as non-responders at Week 24.*

To further assess the sensitivity of the primary analysis method in detecting differences between the treatments, additional logistic and a log-binomial regression models using the factors and covariates as in the primary analysis (PP and FAS) was submitted. The results with logistic regression are presented in **Tables 19** (PPS1) and **20** (FAS).

**Table 19. Logistic regression analysis for ACR 20 response rates at week 24, in Study SB4-G31-RA (PPS1)**

| Treatment | Responder | | | Adjusted Rate (%) | | Adjusted Difference (SB4 – Enbrel®) (%) | | |
|---|---|---|---|---|---|---|---|---|
| | n' | n | Percent (%) | Mean | SE | Rate | SE | 95% CI |
| SB4 (N=247) | 247 | 193 | 78.1 | 82.4 | 3.219 | -2.06 | 4.378 | (-10.64, 6.52) |
| Enbrel® (N=236) | 236 | 190 | 80.5 | 84.4 | 2.968 | | | |

N = number of patients in per-protocol set 1
n' = number of patients with available results; n = number of responders; percentage was based on n'.

**Table 20. Logistic regression for ACR 20 response rates at week 24, in Study SB4-G31-RA (FAS)**

| Treatment | Responder | | | Adjusted Rate (%) | | Adjusted Difference (SB4 – Enbrel®) (%) | | |
|---|---|---|---|---|---|---|---|---|
| | n' | n | Percent (%) | Mean | SE | Rate | SE | 95% CI |
| **Available data analysis** | | | | | | | | |
| SB4 (N=299) | 287 | 220 | 76.7 | 79.9 | 2.845 | -1.40 | 3.950 | (-9.14, 6.35) |
| Enbrel® (N=297) | 272 | 213 | 78.3 | 81.3 | 2.739 | | | |
| **Non-responder imputation** | | | | | | | | |
| SB4 (N=299) | 299 | 220 | 73.6 | 76.3 | 2.862 | 1.54 | 4.100 | (-6.49, 9.58) |
| Enbrel® (N=297) | 297 | 213 | 71.7 | 74.8 | 2.935 | | | |

N = number of patients in per-protocol set 1
n' = number of patients with available results; n = number of responders; percentage was based on n'.

Secondary endpoints

*ACR20 Response at Week 52*

The analysis of ACR20 response rate at Week 52 for the FAS is presented in **Table 21.**

**Table 21. Analysis of ACR 20 Response rate at week 52 in in Study SB4-G31-RA Non-responder analysis (FAS)**

| Treatment | n/n' | (%) | Adjusted Difference Rate | 95% CI |
|---|---|---|---|---|
| SB4 50 mg (N=299) | 210/299 | (70.2) | 4.48% | (–2.90%, 11.87%) |
| Enbrel® 50 mg (N=297) | 195/297 | (65.7) | | |

CI = confidence interval; N = number of subjects in the per-protocol set 2; n' = number of subjects with an assessment; n = number of responders.

*ACR50 and ACR70 Response at Week 24 and Week 52*

**Table 22. Analysis of ACR50 and ACR70 Response Rates at Week 24 and Week 52; Non-responder Analysis (FAS)**

| Time-point | ACR response | Treatment | n/n' | (%) | Adjusted Difference Rate | 95% CI |
|---|---|---|---|---|---|---|
| Week 24 | ACR50 | SB4 50 mg (N=299) | 128/299 | (42.8) | 3.84% | (–3.91%, 11.60%) |
| | | Enbrel® 50 mg (N=297) | 116/297 | (39.1) | | |
| | ACR70 | SB4 50 mg (N=299) | 69/299 | (23.1) | 3.25% | (–3.20%, 9.70%) |
| | | Enbrel® 50 mg (N=297) | 59/297 | (19.9) | | |
| Week 52 | ACR50 | SB4 50 mg (N=299) | 143/299 | (47.8) | 5.48% | (–2.32%, 13.29%) |
| | | Enbrel® 50 mg (N=297) | 125/297 | (42.1) | | |
| | ACR70 | SB4 50 mg (N=299) | 91/299 | (30.4) | 5.90% | (–1.12%, 12.93%) |
| | | Enbrel® 50 mg (N=297) | 73/297 | (24.6) | | |

CI = confidence interval; N = number of subjects in the full analysis set; n' = number of subjects with an assessment; n = number of responders.
Subjects with missing ACR50 or ACR70 responses were considered as non-responders at Week 24 and/or Week 52.

The ACR 50 and 70 response rates at Week 52 for the per protocol analysis set 2 is presented in **Table 23**.

**Table 23. Analysis of ACR50 and ACR 70 response rates at week 52 in Study SB4-G31-RA, PPS2**

| ACR response | Treatment | n/n' | (%) | Adjusted Difference Rate | 95% CI |
|---|---|---|---|---|---|
| ACR50 | SB4 50 mg (N=224) | 131/224 | (58.5) | 4.50% | (–4.67%, 13.67%) |
| | Enbrel® 50 mg (N=216) | 115/216 | (53.2) | | |
| ACR70 | SB4 50 mg (N=224) | 84/224 | (37.5) | 7.02% | (–1.69%, 15.74%) |
| | Enbrel® 50 mg (N=216) | 67/216 | (31.0) | | |

CI = confidence interval; N = number of subjects in the per-protocol set 2; n' = number of subjects with an assessment; n = number of responders.
Percentages were based on the number of subjects in the per-protocol set 2.

*ACR-N at Week 24 and Week 52*

The mean ACR-N at Week 24 was 45.03% in the SB4 treatment group and 43.72% in the Enbrel treatment group. The mean ACR-N at Week 52 was 52.08% for the SB4 treatment group and 49.17% for the Enbrel treatment group.

*DAS28 Score at Week 24 and Week 52*

The mean change in DAS28 score from Baseline at Week 24 was 2.5697 in the SB4 treatment group and 2.5037 in the Enbrel treatment group. The mean change in DAS28 score from baseline at Week 52 was 2.9108 in the SB4 treatment group and 2.7990 in the Enbrel treatment Group.

**Ancillary analyses**

Subgroup analyses for the primary endpoint were performed by ADA status, baseline CRP (≥10 mg/L vs. < 10 mg/L) and patient demographics (i.e. EU vs. non-EU, < 65 years vs. ≥ 65 years and gender interactions, all in PPS1):

*ADAs*

Among subjects who had an overall post-dose negative ADA result at Week 24 (for detailed results on ADA, see Section Clinical Safety of this Report) 78.0% (191/245) subjects and 81.5% (167/205) subjects achieved an ACR20 response in the SB4 and Enbrel treatment groups, respectively. The adjusted treatment difference and its 95% CI in ACR20 response rate at Week 24 among subjects with an overall post-dose negative ADA result was -3.57% (-11.12%, 3.99%) which was also contained within the equivalence margin of [-15%, 15%].

At Week 24, the proportion of subjects who achieved ACR20 response among subjects with an overall post-dose positive ADA result was 100% (2/2) in the SB4 treatment group and 72.4% (21/29) in the Enbrel treatment group. The adjusted treatment difference and its 95% CI in ACR20 response rate at Week 24 among subjects with an overall post-dose positive ADA result was 22.14% (-54.79%, 99.07%).

*CRP levels*

Of the 107 subjects whose baseline CRP level was ≥ 10 mg/L in the SB4 treatment group, 87 subjects (81.3%) achieved an ACR20 response at Week 24. Of the 95 subjects whose baseline CRP level was ≥ 10 mg/L in the Enbrel treatment group, 82 subjects (86.3%) achieved an ACR20 response at Week 24. The adjusted treatment difference and its 95% CI in ACR20 response rate at Week 24 within subjects whose baseline CRP level was ≥ 10 mg/L was -3.11% (-13.32%, 7.10%).

Of the 140 subjects in the SB4 treatment group whose baseline CRP level was < 10 mg/L, 106 subjects (75.7%) achieved an ACR20 response at Week 24. Of the 139 subjects in the Enbrel treatment group whose baseline CRP level was < 10 mg/L, 106 subjects (76.3%) achieved an ACR20 response at Week 24. The adjusted treatment difference and its 95% CI in ACR20 response rate at Week 24 within subjects whose baseline CRP level was < 10 mg/L was 0.84% (-11.05%, 9.37%).

*Demographics*

There was no statistically significant interaction in ACR20 response rate at Week 24 between treatment and region, age group or gender.

**Summary of main study**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 24. Summary of Efficacy for trial SB4-G31-RA**

| Title: A Randomised, Double-blind, Parallel Group, Multicentre ClinicalStudy to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB4Compared to Enbrel in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy | |
|---|---|
| Study identifier | SB4-G31-RA |

| | | | |
|---|---|---|---|
| Design | This was a randomised, double-blind, parallel group, multicentre clinical study. A total of 498 subjects with moderate to severe RA despite MTX therapy were to be randomised in a 1:1 ratio to receive either<br>SB4 50 mg (n=249) or Enbrel 50 mg (n=249) once-weekly for 52 weeks via subcutaneous injection. Subjects were enrolled in the study for up to 56 weeks after Randomisation, consisting of 52 weeks of active treatment and 4 weeks of safety follow-up. The primary endpoint (ACR20 response at Week 24) was assessed in all subjects who completed 24 weeks of study treatment. Secondary endpoints included other relevant efficacy parameters, safety, PK and immunogenicity parameters. | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | 52 weeks<br>not applicable<br>4 weeks safety follow up | |
| Hypothesis | Equivalence in terms of ACR20 responder% | | |
| Treatments groups | SB4 | 50 mg s.c., once weekly, 52 weeks, 299 subjects randomised | |
| | Enbrel (EU sourced) | 50 mg s.c., once weekly, 52 weeks, 297 subjects randomised | |
| | | | |
| Endpoints and definitions | Primary endpoint | ACR 20 at 24 weeks | The primary objective of this study was to demonstrate the equivalence of SB4 to Enbrel at Week 24, in terms of American College of Rheumatology 20% response criteria (ACR20) response rate in subjects with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) therapy. |
| | Secondary efficacy endpoints | ACR 50, ACR 70 at 24 and 52 weeks, ACR20 at 52 weeks | ACR20, ACR 50% response criteria (ACR50) and ACR 70% response criteria (ACR70) response at Week 24 and Week 52, as well as ACR20 at 52 weeks |
| | | ACR-N | The numeric index of the ACR response (ACR-N) at Week 24 and Week 52. |
| | | AUC of ACR-N | The area under the curve (AUC) of ACR-N up to Week 24. |
| | | DAS28 score | The disease activity score based on a 28 joint count (DAS28 score) at Week 24 and Week 52. |
| | | EULAR Response | The European League Against Rheumatism response at Week 24 and Week 52. |
| | | AUC DAS28 | The AUC of the change in DAS28 from baseline up to Week 24. |
| | | Major clinical response | ACR70 response for 6 consecutive months at Week 52. |
| | | Change in Total Sharp Score | Change from baseline in modified Total Sharp Score at Week 52. |

| | | | |
|---|---|---|---|
| | Secondary<br>Safety endpoints | SAEs | Incidence of serious adverse events (SAEs). |
| | | AEs | Incidence of adverse events (AEs, graded as mild, moderate and severe). |
| | | Clinical abnormality | Incidence of clinical laboratory abnormalities.<br>Vital signs abnormalities. |
| | | Immunogenicity | Incidence of anti-drug antibodies (ADA).<br>Incidence of neutralising antibodies. |
| | PK Endpoints | | Serum concentration at baseline (prior to dosing) at Weeks 2, 4, 8, 12, 16 and 24 (trough concentration [Ctrough]).<br><br>The following PK parameters were calculated at Week 8:<br>• Area under the concentration-time curve during the dosing interval ($AUC_T$).<br>• Maximum concentration ($C_{max}$).<br>• Minimum concentration ($C_{min}$).<br>• Peak-trough concentration ratio.<br>• Average serum concentration ($C_{av}$) during the dosing interval.<br>• Degree of fluctuation during the dosing interval.<br>• Swing during the dosing interval.<br>• Time to reach Cmax ($T_{max}$).<br>• Apparent total body clearance (CL/F).<br>Terminal half-life ($t_{½}$). |
| Database lock | Cut-off date Jul 21, 2014 | | |

Main Results and Analyses

| | | | |
|---|---|---|---|
| Analyses description | Primary/Secondary Analyses | | |
| Analysis population and time point description | Full Analysis Set (pattern mixture analysis using multiple imputation) and Per Protocol Set 1<br>at week 12 & 24 | | |
| Descriptive statistics and estimate variability | Treatment group | SB4 | Enbrel |
| | Number of subjects | FAS: 299<br>PPS1: 247 | FAS: 297<br>PPS1: 234 |
| | ACR20 at w24 (%)<br>PPS1 | 193/247 (78.1) | 188/234 (80.3) |
| | ACR20 at w24 (%)<br>FAS | 227/299 (75.9) | 225/297 (75.8) |
| | ACR20 at w12 (%)<br>PPS1 | 170/247 (68.8) | 150/234 (64.1) |
| | ACR50 at w24 (%)<br>PPS1 | 115/247 (46.6) | 99/234 (42.3) |

| | | | |
|---|---|---|---|
| | ACR50 at w12 (%)<br>PPS1 | 99/247 (40.1) | 80/234 (34.2) |
| | ACR70 at w24 (%)<br>PPS1 | 63/247 (25.5) | 53/234 (22.6) |
| | ACR70 at w12 (%)<br>PPS1 | 46/247 (18.6) | 34/234 (14.5) |
| | DAS28 at w24<br>Mean change (SD)<br>FAS | -2.5696<br>(1.3720) | -2.5037<br>(1.3175) |
| | DAS28 at w12<br>Mean change (SD)<br>FAS | -2.4270<br>(1.3536) | -2.2415<br>(1.2941) |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint<br>ACR20 at w24<br>PPS1 | Comparison groups | SB4 vs. Enbrel |
| | | Treatment difference | -0.0222 |
| | | 95% CI | -0.0941; 0.0498 |
| | | Test | -0.15 < CI < 0.15 |
| | Primary endpoint<br>ACR20 at w24<br>FAS | Comparison groups | SB4 vs. Enbrel |
| | | Treatment difference | 0.0016 |
| | | 95% CI | -0.0689; 0.0721 |
| | | Test | -0.15 < CI < 0.15 |
| | Secondary endpoint<br>ACR50 at w24<br>PPS1 | Comparison groups | SB4 vs. Enbrel |
| | | Treatment difference | 0.0479 |
| | | 95% CI | –0.0392; 0.1349 |
| | | Test | N/A* |
| | Secondary endpoint<br>DAS28 at w24<br>FAS | Comparison groups | SB4 vs. Enbrel |
| | | Treatment difference | 0.072 |
| | | 95% CI | -0.135 to 0.279 |
| | | Test | -0.555 < CI < 0.555** |
| Notes | *No equivalence margin has been determined for ACR50 at week 24.<br>** The margin assumed here has not been formally defined for confirmatory purposes but was discussed during Scientific Advice.<br><br>No statistical comparison of primary/secondary endpoints at time points prior to week 24 has been provided. | | |

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

Not applicable.

**Supportive studies**

No supportive efficacy trials were performed.

## 2.5.3. Discussion on clinical efficacy

**Design and conduct of clinical studies**

The pivotal efficacy and safety clinical trial, SB4-G31-RA was a randomised double-blind multicentre, parallel group study to demonstrate equivalence in efficacy and safety of Benepali (SB4) and Enbrel when co-administrated with methotrexate in patients with active RA. The choice of the clinical setting for the single pivotal equivalence trial, i.e. rheumatoid arthritis patients not adequately controlled with methotrexate was in line with CHMP guidance. This clinical model was considered sufficiently sensitive to enable the detection of differences between biosimilar candidate and originator, as among the approved therapeutic indications of Enbrel RA has been the most thoroughly studied. In addition, there are validated and reasonably sensitive methods to study the disease activity of RA which would therefore allow for the detection of any possible differences between the compared products. ACR20 response rate at week 24 as primary efficacy endpoint were considered acceptable and representative of the clinical status in RA and an equivalence margin in the range of 10-15% had also been agreed upon in Scientific Advice.

To derive an equivalence margin of +/-15%, the applicant conducted a meta-analysis of three RA trials. A risk difference of 0.4049 with a 95% CI (0.3103, 0.4996) between Enbrel and placebo (both given in addition to MTX or sulfasalazin) was estimated across the trials. An equivalence limit of 0.155 would thus allow retaining 50% of the lower boundary of the risk difference CI. Even though such an approach to margin determination is not formally foreseen in applicable guidance documents, it was considered acceptable by the CHMP.

The ACR20 response rate was expected to be around 60% at Week 24. It was nevertheless noted that a higher than expected response rate for ACR 20 at week 24 was observed in the pivotal efficacy trial compared to the cited references (i.e. between 70 and 80% depending on the analysis set). The applicant stated that some differences in baseline characteristics (e.g. tender/swollen joint counts, CRP), i.e. less severe disease in their pivotal RA sample compared to historic data might have contributed to the higher absolute ACR response rate in both treatment arms.

There was therefore some uncertainty as to whether the observed differences between absolute responses or the potentially underlying differences with regards to disease characteristics in the investigated population compared to the reference studies might have implications on the applicability of the used equivalence margin. This however was sufficiently mitigated by the fact, that for the primary outcome as well as for most secondary analyses, the point estimates and corresponding 95% CIs were well contained within the equivalence margin boundaries and not borderline results.

Additional analyses showed very similar results to the primary analysis.

Main inclusion and exclusion criteria were comparable with the referenced trials. Relevant demographic and disease- or treatment-related baseline characteristics were well balanced between study arms.

There were no important concerns raised regarding the conduct of the trial.

**Efficacy data and additional analyses**

The pivotal trial has demonstrated comparable efficacy of Benepali (SB4) and the originator product

Enbrel in terms of proportion of ACR20 responders at week 24. The fact that upper and lower 95% CI bounds of difference in fact do not exceed 10% provided further assurance for Benepali (SB4) being similar to Enbrel, and would even accommodate a more stringent equivalence margin which had been proposed in the Scientific Advice procedure EMA/CHMP/SAWP/9771/2012.

Main secondary outcomes, i.e. higher responder thresholds ACR50 and ACR70, as well as DAS28 at week 24 and the response profile over the initial 24 weeks for primary and secondary endpoints have been reported. Based on these data Benepali (SB4) consistently exerts slightly higher efficacy at time points prior to week 24. It appears that week 24 might not be the most sensitive time point to show differences between Benepali (SB4) and Enbrel in terms of ACR20 responder rate.
Overall, the reported discrepancies are of small magnitude and can ultimately be deemed negligible in the context of a comprehensive biosimilarity comparison.

Analyses on the secondary efficacy endpoints supported the primary efficacy analysis further supporting biosimilarity, with the result being similar between the treatment groups. Subgroup analyses overall supported claims on the primary and secondary analyses. The results from the non-parametric analysis were also confirmed with a logistic regression model and a log-binomial model however providing further evidence of strength of biosimilarity.

The 52-week results showed that after week 24, ACR20 had effectively reached a plateau whereas there was further improvement for the higher response thresholds (ACR50 and ACR70) as well as the DAS28 in both treatment arms.

For ACR20/50/70, the adjusted treatment differences in response rates and 95% confidence intervals were, with the exception of ACR70 (only for the PPS2 set but not for the FAS), contained within the pre-specified margins of +/- 15% for both analysis sets after 52 weeks.

However, the CHMP stated that applying uniform equivalence margins across multiple time points, responder thresholds and corresponding point estimates presents challenges, and therefore careful interpretation of findings is required.

A high adjusted difference between point estimates for the highest response threshold ACR70 (i.e. 7.02%, 95% CI: –1.69%, 15.74% in the PPS) at week 52 was noted. Within the context of the ACR response pattern over time and further week 52 outcomes (including DAS-28) the CHMP considered that this isolated result was not sufficient to challenge the notion of biosimilarity between Benepali and Enbrel over a prolonged course of treatment, as established by the totality of the evidence which had been submitted by the Applicant.

## 2.5.4. Conclusions on the clinical efficacy

The pivotal efficacy study SB4-G31-RA conducted in RA patients provided robust evidence of equivalence between Benepali and Enbrel based on ACR20 response at Week 24, the primary endpoint, and this was supported by most secondary efficacy parameters and sensitivity analyses.

In addition, PK was similar in the most sensitive model (PK study in healthy volunteers).

Therefore these results are sufficient to demonstrate equivalence in efficacy between the proposed biosimilar Benepali and the reference product Enbrel.

## *2.6. Clinical safety*

Safety information was derived from the clinical study SB4-G31-RA in RA patients as an appropriate study population for showing biosimilarity, and further supported by the clinical study SB4-G11-NHV in healthy subjects. A pooled safety analysis was not applicable due to the heterogeneity of study populations (RA patients vs. healthy subjects) and duration of treatment / exposure (long-term vs. single-dose).

**Patient exposure**

**SB4-G31-RA**

A total of 596 patients were randomised in a 1:1 ratio to receive either SB4 50 mg (n=299) or EU Enbrel 50 mg (n=297) once weekly for up to 52 weeks via self-administered SC injection. All 596 patients received at least 1 injection of Benepali (SB4) or EU Enbrel; the mean duration of exposure was 338.9 days in the Benepali (SB4) and 323.5 days in the EU Enbrel treatment groups (**Table 25**).

**Table 25. Duration of exposure to study drug (Safety Set), in Study SB4-G31-RA**

| | SB4 50 mg | | EU Enbrel 50 mg | | Total | |
|---|---|---|---|---|---|---|
| **Duration of exposure (days)** | **N=299** | | **N=297** | | **N=596** | |
| **Statistics** | | | | | | |
| n | 299 | | 297 | | 596 | |
| Mean (SD) | 338.9 (58.00) | | 323.5 (87.53) | | 331.2 (74.54) | |
| Min, Max | 34, 371 | | 14, 371 | | 14, 371 | |
| **Exposure, n (%)** | | | | | | |
| ≥ 1 day | 299 | (100.0) | 297 | (100.0) | 596 | (100.0) |
| ≥ 8 days | 299 | (100.0) | 297 | (100.0) | 596 | (100.0) |
| ≥ 15 days | 299 | (100.0) | 296 | (99.7) | 595 | (99.8) |
| ≥ 29 days | 299 | (100.0) | 291 | (98.0) | 590 | (99.0) |
| ≥ 57 days | 297 | (99.3) | 286 | (96.3) | 583 | (97.8) |
| ≥ 85 days | 295 | (98.7) | 281 | (94.6) | 576 | (96.6) |
| ≥ 113 days | 291 | (97.3) | 276 | (92.9) | 567 | (95.1) |
| ≥ 169 days | 289 | (96.7) | 271 | (91.2) | 560 | (94.0) |
| ≥ 225 days | 283 | (94.6) | 263 | (88.6) | 546 | (91.6) |
| ≥ 281 days | 270 | (90.3) | 253 | (85.2) | 523 | (87.8) |
| ≥ 358 days | 212 | (70.9) | 222 | (74.7) | 434 | (72.8) |

*SD = standard deviation. Max = maximum; Min = minimum;.*
*Duration of exposure (days) was calculated as follows:*
*If the last investigational product administration date was known: (last IP administration date – first IP administration date) + 1*
*If the last investigational product administration date was unknown: (last visit date – first IP administration date) + 1*

**SB4-G11-NHV**

In the clinical study SB4-G11-NHV, a total of 138 healthy subjects were randomised to receive single etanercept doses (50 mg via SC injection), with 46 and 45 subjects exposed to Benepali (SB4) in Part A and Part B, respectively. The safety set comprised all subjects who received at least one dose of the study drug.

In Part A, one subject discontinued the study after Benepali (SB4) administration in the first period. In Part B, one subject discontinued the study after US Enbrel administration in the first period. In Part C, 3 subjects and 1 subject discontinued the study after EU Enbrel and US Enbrel administration, respectively,

in the first period. The characteristics of the study population were comparable between the sequences in each part.

### Adverse events

### SB4-G31-RA

A total of 354 (59.4%) patients reported 1179 treatment emergent adverse events (TEAEs) at any time after the first dose of the study drugs: 533 TEAEs in 175 (58.5%) patients in the Benepali (SB4) treatment group vs. 646 TEAEs in 179 (60.3%) patients in the EU Enbrel treatment group (**Table 26**).

**Table 26. Number (%) of Patients with TEAEs and Number of Events by Preferred Term That Occurred in ≥ 2% of Patients in any Treatment Group (Safety Set) (Study SB4-G31-RA)**

| Treatment | SB4 50 mg N=299 | | | EU Enbrel 50 mg N=297 | | | Total N=596 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Preferred term** | **n** | **(%)** | **E** | **n** | **(%)** | **E** | **n** | **(%)** | **E** |
| Any TEAEs | 175 | (58.5) | 533 | 179 | (60.3) | 646 | 354 | (59.4) | 1179 |
| Upper respiratory tract infection | 24 | (8.0) | 28 | 16 | (5.4) | 18 | 40 | (6.7) | 46 |
| Alanine aminotransferase increased | 18 | (6.0) | 25 | 17 | (5.7) | 26 | 35 | (5.9) | 51 |
| Nasopharyngitis | 15 | (5.0) | 17 | 16 | (5.4) | 17 | 31 | (5.2) | 34 |
| Headache | 13 | (4.3) | 15 | 8 | (2.7) | 16 | 21 | (3.5) | 31 |
| Hypertension | 11 | (3.7) | 16 | 11 | (3.7) | 12 | 22 | (3.7) | 28 |
| Rheumatoid arthritis | 9 | (3.0) | 10 | 10 | (3.4) | 11 | 19 | (3.2) | 21 |
| Aspartate aminotransferase increased | 8 | (2.7) | 13 | 9 | (3.0) | 10 | 17 | (2.9) | 23 |
| Viral infection | 7 | (2.3) | 7 | 5 | (1.7) | 5 | 12 | (2.0) | 12 |
| Injection site erythema | 6 | (2.0) | 16 | 33 | (11.1) | 85 | 39 | (6.5) | 101 |
| Bronchitis | 6 | (2.0) | 6 | 6 | (2.0) | 6 | 12 | (2.0) | 12 |
| Rash | 6 | (2.0) | 6 | 4 | (1.3) | 4 | 10 | (1.7) | 10 |
| Rhinitis | 6 | (2.0) | 6 | 4 | (1.3) | 5 | 10 | (1.7) | 11 |
| Leukopenia | 6 | (2.0) | 7 | 3 | (1.0) | 4 | 9 | (1.5) | 11 |
| Pharyngitis | 5 | (1.7) | 5 | 8 | (2.7) | 9 | 13 | (2.2) | 14 |
| Diarrhoea | 5 | (1.7) | 5 | 7 | (2.4) | 8 | 12 | (2.0) | 13 |
| Urinary tract infection | 5 | (1.7) | 5 | 7 | (2.4) | 9 | 12 | (2.0) | 14 |
| Cough | 4 | (1.3) | 4 | 10 | (3.4) | 11 | 14 | (2.3) | 15 |
| Lymphocyte count decreased | 4 | (1.3) | 4 | 6 | (2.0) | 8 | 10 | (1.7) | 12 |
| Erythema | 2 | (0.7) | 4 | 10 | (3.4) | 10 | 12 | (2.0) | 14 |
| Dizziness | 2 | (0.7) | 3 | 7 | (2.4) | 7 | 9 | (1.5) | 10 |
| Injection site rash | 2 | (0.7) | 2 | 6 | (2.0) | 11 | 8 | (1.3) | 13 |
| Injection site reaction | 1 | (0.3) | 1 | 8 | (2.7) | 13 | 9 | (1.5) | 14 |

The majority of AEs were mild to moderate in severity. Of those, 29.4% of the ones reported in the SB4 treated patients and 36.7% in the Enbrel treated patients and are summarised in **Table 27.**

**Table 27. Summary of Treatment-Emergent Adverse Events by Severity and causality (Safety Set) (Study SB4-G31-RA)**

| | SB4 (N=299) | | | EU Enbrel (N=297) | | |
|---|---|---|---|---|---|---|
| | n | (%) | E | n | (%) | E |
| Any TEAEs | 175 | (58.5) | 533 | 179 | (60.3) | 646 |
| TEAE Severity | | | | | | |
| Mild | 78 | (26.1) | 307 | 91 | (30.6) | 445 |
| Moderate | 83 | (27.8) | 199 | 77 | (25.9) | 189 |
| Severe | 14 | (4.7) | 27 | 11 | (3.7) | 12 |
| TEAE Causality | | | | | | |
| Related | 88 | (29.4) | 180 | 109 | (36.7) | 314 |
| Not related | 87 | (29.1) | 353 | 70 | (23.6) | 332 |

The TEAEs considered causally related to the study drug occurring in ≥ 2% of patients in any treatment group are presented in **Table 28.**

**Table 28. Number (%) of Patients with TEAEs Considered Causally Related and Number of Events by Preferred Term in ≥ 2% of Patients in Any Treatment Group (Safety Set) (Study SB4-G31-RA)**

| | SB4 (N=299) | | | EU Enbrel (N=297) | | |
|---|---|---|---|---|---|---|
| **Preferred term** | **n** | **(%)** | **E** | **n** | **(%)** | **E** |
| Any TEAE | 175 | (58.5) | 533 | 179 | (60.3) | 646 |
| ALT increased | 12 | (4.0) | 14 | 11 | (3.7) | 15 |
| Injection site erythema | 6 | (2.0) | 16 | 33 | (11.1) | 84 |
| Upper respiratory tract infection | 6 | (2.0) | 6 | 4 | (1.3) | 4 |
| Rheumatoid arthritis | 6 | (2.0) | 7 | 1 | (0.3) | 1 |
| AST increased | 4 | (1.3) | 5 | 6 | (2.0) | 6 |
| Erythema | 2 | (0.7) | 4 | 6 | (2.0) | 6 |
| Injection site rash | 2 | (0.7) | 2 | 6 | (2.0) | 11 |
| Injection site reaction | 1 | (0.3) | 1 | 8 | (2.7) | 13 |

*ALT: alanine aminotransferase; AST: aspartate aminotransferase; E: frequency of adverse events; TEAE: treatment-emergent adverse event. Percentages were based on the number of patients in the safety set.*

Adverse Events Leading to Discontinuation

The TEAEs leading to discontinuation reported in more than 2 patients overall at the PT level were RA (2 events in 2 [0.7%] patients in the SB4 treatment group and 5 events in 5 [1.7%] patients in the EU Enbrel treatment group, 2 [1 in each treatment group] of which were considered to be related to IP) and injection site erythema (1 event in 1 [0.3%] patient in the SB4 treatment group and 4 events in 4 [1.3%] patients in the EU Enbrel treatment group, all of which were considered to be related to IP)

**Serious adverse event / deaths / other significant events**

Deaths

Two deaths were reported during the study from the SB4 treatment group, one case each of gastric adenocarcinoma and cardiorespiratory failure. In both cases, the events were not considered related to the treatment.

Serious adverse events

The proportion of patients who experienced any SAEs was comparable between the Benepali (SB4) and EU Enbrel treatment groups. A total of 38 SAEs were reported in 33 (5.5%) of the patients, with 18

(6.0%) patients reporting 23 SAEs in the Benepali (SB4) treatment group vs. 15 (5.1%) patients reporting 15 SAEs in the EU Enbrel treatment group however only 3 SAE were considered treatment related in the Benepali (SB4) group :

- A case of breast cancer on Day 189, which led to discontinuation of the study drug and required hospitalisation.
- Two cases of Still's disease adult onset in one patient both reported on Day 305, both of which required hospitalisation and one of which was severe and led to discontinuation of IP.

while 7 treatment related SAEs occurred in the Enbrel group:

- One case of pneumonia on Day 63, which led to discontinuation of the study drug and required hospitalisation;
- One case of neutropenia on Day 15, which led to discontinuation of the study drug and required hospitalisation;
- Two cases of cellulitis on Day 228, one on day 280, which required hospitalisation;
- One case of chorioretinopathy on Day 64, which led to discontinuation of the study drug and was considered to be an important medical event;
- One case of invasive ductal breast carcinoma on Day 147, which led to discontinuation of the study drug and was considered to be an important medical event;
- One case of erysipelas on Day 135, which required hospitalisation.

Malignancies were reported in 4 (1.3%) patients in the Benepali (SB4) vs. 1 (0.3%) patient in the EU Enbrel treatment group. In the Benepali (SB4) treatment group, gastric adenocarcinoma, basal cell carcinoma, breast cancer and lung cancer metastatic were each reported by one patient, while in the EU Enbrel treatment group, invasive ductal breast carcinoma was reported by one patient.

**Adverse events of special interest (AESI)**

There were 8 AESIs (i.e., serious infection, TB) reported in 6 patients overall. All were serious infections whereas no cases of active TB were reported. The incidence of AESIs was comparable between the Benepali (SB4) and EU Enbrel group.

**Table 29. Adverse events of special interest in in Any Treatment Group (Safety Set) (Study SB4-G31-RA)**

| System organ class | SB4 (N=299) | | | EU Enbrel (N=297) | | |
|---|---|---|---|---|---|---|
| Preferred term | n | (%) | E | n | (%) | E |
| Any AESI | 1 | (0.3) | 3 | 5 | (1.7) | 5 |
| HEPATOBILIARY DISORDERS | 1 | (0.3) | 1 | 0 | (0.0) | 0 |
| Cholecystitis | 1 | (0.3) | 1 | 0 | (0.0) | 0 |
| INFECTIONS AND INFESTATIONS | 1 | (0.3) | 2 | 5 | (1.7) | 5 |
| Liver abscess | 1 | (0.3) | 1 | 0 | (0.0) | 0 |
| Peritonitis | 1 | (0.3) | 1 | 0 | (0.0) | 0 |
| Appendicitis | 0 | (0.0) | 0 | 1 | (0.3) | 1 |
| Cellulitis | 0 | (0.0) | 0 | 2 | (0.7) | 2 |
| Erysipelas | 0 | (0.0) | 0 | 1 | (0.3) | 1 |
| Pneumonia | 0 | (0.0) | 0 | 1 | (0.3) | 1 |

**Immunological events**

Anti-drug antibodies (ADAs) were assayed by two electrochemiluminescence assays, using SB4 as both capturing and detection antigen. In the single-dose PK study, none of the 45 individuals in the SB4 arm had ADAs whereas 7 out of 45 in the Enbrel arm had antibodies, one with neutralising capacity.

In Study SB4-G31-RA, blood samples for the analysis of immunogenicity were collected at baseline and Weeks 2, 4, 8, 12, 16, 24, and 52 and tested for anti-drug antibodies (ADA). Serum samples in which ADA were detected would be reflexed to a neutralising antibody (Nab) assay to evaluate the effects of ADAs on the ability of etanercept to provide competitive inhibition of TNF-α.

The overall ADA result was defined as positive if the subject had at least 1 positive ADA result up to that time point regardless of the ADA test result at baseline (Week 0). These results, between weeks 8-52 are summarised in **Table 30.**

**Table 30. Incidence of anti-drug antibodies and neutralising antibodies to etanercept, safety set in Study SB4-G31-RA**

| | | SB4 50 mg | | | Enbrel® 50mg | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N=299 | | | N=297 | | | N=596 | | |
| Timepoint | Parameter | n' | n | (%) | n' | n | (%) | n' | n | (%) |
| Week 0 | ADA | 299 | 0 | (0.0) | 297 | 0 | (0.0) | 596 | 0 | (0.0) |
| | NAb | | 0 | | | 0 | | | 0 | |
| Week 8 overall | ADA | 299 | 2 | (0.7) | 296 | 38 | (12.8) | 595 | 40 | (6.7) |
| | NAb | | 0 | | | 1 | | | 1 | |
| Week 24 overall | ADA | 299 | 2 | (0.7) | 296 | 39 | (13.2) | 595 | 41 | (6.9) |
| | NAb | | 0 | | | 1 | | | 1 | |
| Week 52 overall | ADA | 299 | 3 | (1.0) | 296 | 39 | (13.2) | 595 | 42 | (7.1) |
| | NAb | | 0 | | | 1 | | | 1 | |

ADA=anti-drug antibody, NAb=neutralising antibody.
ADA was determined as positive if at least one ADA positive result was obtained up to the timepoint regardless of the ADA result at Week 0.
n': number of subjects with available ADA results against SB4 at each timepoint.
Percentages were based on n'.

There was a significant (p-value < 0.001) difference in overall ADA formation at week 24.

The drug tolerance level of ADA assay was close to the mean trough concentrations. There was a difference in the mean trough concentrations at weeks 4 and 8. This difference may have caused a bias in the ADA results. As most of the positive samples were obtained at week 4 and 8, the Applicant submitted a re-analysis of the ADA prevalence by treatment arm by ignoring samples taken at weeks 4 and 8. Results from this analysis, are presented in **Table 31.**

**Table 31. Incidence of Overall ADA by Treatment Group by Ignoring Samples Taken at Weeks 4 and 8 (Safety Set, Study SB4-G31-RA)**

| Overall ADA Status | SB4 n/n' (%) | EU Enbrel n/n' (%) | *p*-value |
|---|---|---|---|
| 24-week Overall ADA Incidence | 0/299 (0.0) | 2/296 (0.7) | 0.2471 |
| 52-week Overall ADA Incidence | 1/299 (0.3) | 2/296 (0.7) | 0.6225 |

The results of the ADA assays demonstrate that SB4 is not more immunogenic than Enbrel. However, based on the current knowledge of the low drug tolerance of the ADA assay and the possibility of more

false negative results in the SB4 arm, it is premature to conclude that SB4 is less immunogenic than Enbrel.

### Injection Site Reactions

There was 1 (0.3%) patient in the Benepali (SB4) group vs. 17 (5.7%) patients in the EU Enbrel group who reported at least 1 injection site reaction up to Week 24. In addition, there were 2 (0.7%) patients in the Benepali (SB4) group vs. 17 (5.7%) patients in the EU Enbrel group reporting at least 1 injection site reaction up to Week 52 (**Table 32).** Most of the injection site reactions were mild and patients recovered.

**Table 32. Incidence of Injection Site Reaction by Visit and Treatment Group (Safety Set) in Study SB4-G31-RA)**

| Time point | SB4 (N=299) n/n' (%) | EU Enbrel (N=297) n/n' (%) | Total (N=596) n/n' (%) |
|---|---|---|---|
| Week 0 | 0/299 (0.0) | 0/297 (0.0) | 0/596 (0.0) |
| Week 1 | 0/294 (0.0) | 0/296 (0.0) | 0/590 (0.0) |
| Week 2 | 0/294 (0.0) | 2/291 (0.7) | 2/585 (0.3) |
| Week 4 | 0/294 (0.0) | 8/279 (2.9) | 8/573 (1.4) |
| Week 8 | 1/280 (0.4) | 10/275 (3.6) | 11/555 (2.0) |
| Week 12 | 1/272 (0.4) | 6/260 (2.3) | 7/532 (1.3) |
| Week 16 | 0/273 (0.0) | 2/257 (0.8) | 2/530 (0.4) |
| Week 24 | 0/260 (0.0) | 0/250 (0.0) | 0/510 (0.0) |
| Week 24 overall | 1/299 (0.3) | 17/297 (5.7) | 18/596 (3.0) |
| Week 32 | 1/257 (0.4) | 0/241 (0.0) | 1/498 (0.2) |
| Week 40 | 0/253 (0.0) | 0/238 (0.0) | 0/491 (0.0) |
| Week 52 | 0/199 (0.0) | 0/193 (0.0) | 0/392 (0.0) |
| Week 52 overall | 2/299 (0.7) | 17/297 (5.7) | 19/596 (3.2) |

*n': number of patients who have available assessment results. Percentages were based on n'.*
*n: number of patients who have an injection site reaction defined as "Reaction" if reported as clinically significant abnormal, adverse events due to abnormality worsening or both.*
*Week 24/52 overall assessment results were determined as "Reaction" for patients with at least one "Reaction" up to Week 24/52 respectively*

The incidence of injection site reaction did not appear to be correlated with ADA development with a similar percentage of patients reported with an injection site reaction between patients with an overall positive ADA result and patients with an overall negative ADA result (for SB4 treated patients: 0.0% in overall ADA-positive vs. 0.3% in overall ADA-negative; for EU Enbrel treated patients: 5.1% in overall ADA-positive vs. 5.8% in overall ADA-negative).

### Laboratory findings

Overall, there were no notable differences in mean and median values of clinical chemistry, haematology and urinalysis assessments observed between the Benepali (SB4) and Enbrel treatment groups.

The most commonly reported significant biochemical abnormality was high ALT, reported in 16 (5.4%) patients in the SB4 treatment group vs. 10 (3.4%) patients in the EU Enbrel treatment group. High AST was reported in 8 (2.7%) vs. 4 (1.4%) patients, respectively, and high GGT was reported in 7 (2.3%) vs. 2 (0.7%) patients, respectively.

The most commonly reported significant abnormality in haematology was high neutrophil (reported in 5 [1.7%] patients in the SB4 treatment group vs. 2 [0.7%] patients in the EU Enbrel treatment group)

and low neutrophil and lymphocyte (each reported in 3 [1.0%] patients in the SB4 treatment group vs. 4 [1.4%] patients in the EU Enbrel treatment group).

**Safety in special populations**

No studies in special populations were submitted.

**Safety related to drug-drug interactions and other interactions**

In accordance with the EMA biosimilar guideline (EMEA/CHMP/BMWP/42832/2005), no further specific studies on the potential impact of drug interactions were submitted with Benepali (SB4).

**Post marketing experience**

No post-marketing data were submitted.

## 2.6.1. Discussion on clinical safety

Most available comparative safety data of Benepali (SB4) are derived from the pivotal trial in RA (SB4-G31-RA) involving 299 patients exposed to Benepali, out of whom 283 (94.6%) completed 24 weeks (time of primary endpoint), and 212 patients (70.9%) completed 52 weeks. A comparable number of patients was exposed to EU Enbrel.

Additionally 91 subjects received one dose of Benepali (SB4) in a PK trial in healthy volunteers (SB4-G11-NHV) which however can only contribute to evaluate short term safety, due to the short study duration and its inherent cross over design.

Overall, the type and incidence of ADRs to the test and reference products appeared similar and in line with those expected on the basis of the Enbrel SmPC.

In study SB4-G31-RA, serious adverse events were slightly less frequent under Enbrel (15 SAEs in 5.1% of patients) than under SB04 (23 SAEs in 6.0% of the patients), however only one SAE was considered treatment related in the Benepali (SB4) group versus six treatment-related SAEs in the Enbrel group.

There were 2 deaths reported during the study, both were assessed as not related to the IP. AESIs and malignancies were equally distributed and no cases of active tuberculosis were reported across the clinical program.

The most frequent ADRs were injection site erythema (6 [2.0%] patients in the Benepali (SB4) vs. 33 [11.1%] patients in the EU Enbrel group), upper respiratory tract infection (24 [8.0%] vs. 16 [5.4%] patients), alanine aminotransferase (ALT) increased (18 [6.0%] vs. 17 [5.7%] patients) and nasopharyngitis (15 [5.0%] vs. 16 [5.4%] patients).

Injection site reactions in general and upper respiratory tract infections have also been described as the most common AEs in the SmPC of Enbrel.

In the pivotal efficacy and safety trial, the patient incidence of injection-site reactions (5.7%) at week 24 appeared lower than expected (36% in Enbrel SmPC). This difference could have been at least partly due to an extensive split of the way that such reactions were reported (e.g. injection site erythema, injection site rash, injection site reactions etc.) Grouping of such terms would have resulted in an overall incidence of injection site reactions of 17.2%. Further parameters which could have contributed to the observed variation of risk were the lack of L-Arginine and the lack of latex in the needle shield in Benepali.

A subgroup analysis revealed that their incidence was, not influenced by positive or negative ADA status. All injection site associated AEs were generally mild and resolved within a few days. Therefore even if the exact cause of the observed imbalance could not be established, the CHMP considered that it was not of

clinical significance. The incidence of injection site reactions was similar (2 vs 3 events) between Benepali (SB4) and EU Enbrel in the PK study in healthy volunteers.

Three (1.0%) of Benepali (SB4) treated patients tested positive for ADAs at least once in Study SB4-G31-RA, compared to 39 (13.1%) patients in the EU Enbrel group, one of which also tested positive for neutralizing antibodies. There was a significant (p-value < 0.001) difference in overall ADA formation at week 24. The potential impact of ADA status on administration site reactions was also investigated but did not demonstrate any correlation between the two.

Based on information from the ADA assays that were conducted, Benepali (SB4) showed a favourable immunogenicity profile compared to Enbrel. However, this finding is uncertain because of the low drug tolerance of the ADA assay that led to a low sensitivity and a potential bias. The ADA formation did not seem to cause a different efficacy profile, neither in ADA positive nor negative patients and therefore does not have a bearing in establishing biosimilarity between Benepali and Enbrel. This is also supported by published literature in which it has been suggested, that etanercept antibodies do not impact on the safety and efficacy profile of the drug (Genovese et al., 2002). Possible explanations for the differences in ADA incidence between Benepali and Enbrel could be the slightly different drug concentrations in samples or differences in the sensitivities of the corresponding analytical methods.

Subgroup analysis did not show differences in the incidence of TEAEs in ADA negative patients (any TEAEs incidence: 58.1% in the Benepali (SB4) vs. 57.6% in the EU Enbrel group). In ADA positive patients, more patients suffered from any TEAE compared to ADA negative patients (3/3, 100% in the Benepali (SB4) and 31/39, 79.5% in the EU Enbrel group). However, these differences were considered to be of limited significance due to the small number of ADA positive patients, especially in the Benepali (SB4) group.

The CHMP considered that from the safety (and efficacy) point of view, it is more important to consider sustained immune responses. Therefore as the observed differences with respect to ADA formation between Benepali and Enbrel appeared to be transient, with almost no differences after 8 weeks of treatment, their clinical significance was considered minimal. The applicant however, is encouraged to further investigate the potential reasons for the observed differences especially with regards to the sensitivity and robustness of the ADA assays.

There was a difference between the treatment groups in the ‘hepatobiliary disorders’ SOC AEs: 17 TEAEs in 11 patients were reported in the Benepali (SB4) group, compared with no AEs in the EU Enbrel group (4 events of cholelithiasis in 4 subjects, 3 events of liver disorder in 3 subjects, 3 events of cholecystitis chronic in 2 subjects, 2 events of bile duct stone in 1 subject and 1 event of biliary colic, cholangitis, cholecystitis, gall bladder perforation and hypertransaminasaemia each reported in 1 subject).

Most of the AEs were mild or moderate in severity; only 1 event was severe and 2 events in 2 subjects were considered related to the investigational product. Six events from 4 subjects were reported as SAE.

The observed imbalance in the SOC hepatobiliary events in the Benepali (SB4) treatment arm was caused by a higher incidence of biliary disorders. Further investigations revealed that biliary risk factors were more common in the Benepali (SB4) compared to the Enbrel treatment arm. It was therefore concluded, that the observed difference in the incidence of AEs in the SOC “hepatobiliary events” was not treatment related.

Malignancies were reported in five subjects in the pivotal study: four subjects in the Benepali (SB4) treatment group (basal cell carcinoma, breast cancer, gastric cancer and lung cancer metastatic) and 1 subject in the Enbrel treatment group (invasive ductal breast carcinoma). While the mode of action of TNF alpha inhibitors could influence the incidence of malignancy, the difference between the two treatment arms is perceived as too low to conclude on a significant difference.

### 2.6.2. Conclusions on the clinical safety

The size of the safety database and duration of exposure is considered appropriate for the evaluation of the general safety profile of Benepali. The safety profile observed for etanercept was consistent with previous studies in these study populations of RA patients and healthy volunteers and this class of drugs.

A numerical imbalance in injection site reactions, malignancies and hepatobiliary events was observed in the RA pivotal trial SB4-G31-RA. However, the numbers involved were small and a thorough review of all available data suggested that the observed difference were most likely chance findings. Rare adverse reactions known for Enbrel, such as malignancies, will also be closely monitored as part of the registries which are described in the RMP.

Finally, an extensive analysis of the immunogenicity profile of Benepali has been conducted in the clinical trials, which demonstrated that the immune response to etanercept and its impact on safety and efficacy is comparable between Benepali and Enbrel.

## *2.7. Risk Management Plan*

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.1 with the following content:

***Safety concerns***

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Malignancy (including lymphoma and leukaemia)<br>Serious and opportunistic infections (including TB, Legionella, Listeria, parasitic infection)<br>Lupus-like reactions<br>Sarcoidosis and/or granulomas Injection site reactions<br>Allergic reactions<br>Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome)<br>Systemic vasculitis (including ANCA positive vasculitis) Macrophage activation syndrome<br>Central demyelinating disorders<br>Peripheral demyelinating events (CIDP and GBS) Aplastic anaemia and pancytopenia<br>Interstitial lung disease (including pulmonary fibrosis and pneumonitis) Autoimmune hepatitis<br>Liver events in patients with history of viral hepatitis (including hepatitis B virus reactivation) |
| Important identified risks – specific indications | Change in morphology and/or severity of psoriasis<br>Worsening of CHF in adult subjects |
| Important potential risks – all indications | Autoimmune renal disease<br>Pemphigus/pemphigoid<br>Amyotrophic lateral sclerosis<br>Myasthenia gravis<br>Encephalitis/leukoencephalomyeli tis<br>Progressive multifocal leukoencephalopathy Liver failure<br>Hepatic cirrhosis and fibrosis Severe hypertensive reactions<br>Adverse pregnancy outcomes<br>Potential for medication errors (pre-filled pen) Potential for male infertility<br>Weight gain |
| Important potential risks – specific indications | Acute ischemic CV events in adult subjects Potential for paediatric off-label use |
| Missing information | Use in hepatic and renal impaired subjects Use in different ethnic origins<br>Use in pregnant women |

Abbreviations: ANCA= anti-neutrophil cytoplasmic antibodies; CHF=congestive heart failure; CIDP=chronic inflammatory demyelinating polyneuropathy; CV=cardiovascular; GBS=Guillain-Barré Syndrome; TB=tuberculosis.

***Pharmacovigilance plan***

| Study / activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| 1 SB4-G31- RA | A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB4 (Benepali) Compared to Enbrel in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy<br>The first 52 weeks is a double blind, randomised equivalence study comparing SB4 (Benepali) and Enbrel in MTX-resistant RA patients, and the next 48 weeks is an open label study switching the Enbrel arm to SB4 (Benepali) | Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous adverse reactions, systemic vasculitis, macrophage activation syndrome, central demyelinating disorders, peripheral demyelinating events, aplastic anaemia and pancytopenia, interstitial lung disease, autoimmune hepatitis, liver events in patients with history of viral hepatitis, autoimmune renal disease, pemphigus/pemphigoid, amyotrophic lateral sclerosis, myasthenia gravis, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, liver failure, hepatic cirrhosis and fibrosis, severe hypertensive reactions, weight gain, and acute ischemic cardiovascular (CV) events. | Started | Week 24 CSR: October 2014 (submitted with MAA)<br><br>Week 52 CSR: March 2015 (completed)<br><br>Week 100 CSR: March 2016 (planned) |

| Study / activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| 2 BSRBR-RA Category 3 | An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice. | Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous adverse reactions, systemic vasculitis, macrophage activation syndrome, central demyelinating disorders, peripheral demyelinating events, aplastic anaemia and pancytopenia, interstitial lung disease, autoimmune hepatitis, liver events in patients with history of viral hepatitis, change in morphology and/or severity of psoriasis, worsening of congestive heart failure (CHF), autoimmune renal disease, pemphigus/pemphigoid, amyotrophic lateral sclerosis, myasthenia gravis, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, liver failure, hepatic cirrhosis and fibrosis, severe hypertensive reactions, adverse pregnancy outcomes, potential for male infertility, weight gain, acute ischemic CV events, and use in pregnant women. | Planned for 2016 4Q | Final report planned for 2027<br><br>Annual interim reports with PSUR/RMP updates where applicable |

| | | | | |
|---|---|---|---|---|
| 3 RABBIT<br>Category 3 | A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with | Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous adverse reactions, systemic vasculitis, macrophage activation syndrome, central demyelinating disorders, peripheral demyelinating | Planned for 2016 4Q | Final report planned for 2027<br><br>Annual interim reports with PSUR/RMP updates where applicable |
| Study/activity Type, title<br>and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |

| | | | | |
|---|---|---|---|---|
| | tumour necrosis factor-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs. | events, aplastic anaemia and pancytopenia, interstitial lung disease, autoimmune hepatitis, liver events in patients with history of viral hepatitis, change in morphology and/or severity of psoriasis, worsening of CHF, autoimmune renal disease, pemphigus/pemphigoid, amyotrophic lateral sclerosis, myasthenia gravis, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, liver failure, hepatic cirrhosis and fibrosis, severe hypertensive reactions, adverse pregnancy outcomes, potential for male infertility, weight gain, acute ischemic CV events, and use in pregnant women. | | |

| | | | | |
|---|---|---|---|---|
| 4. ARTIS Category 3 | A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, juvenile idiopathic arthritis, and other rheumatic disease patients treated with etanercept. | Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous adverse reactions, systemic vasculitis, macrophage activation syndrome, central demyelinating disorders, peripheral demyelinating events, aplastic anaemia and pancytopenia, interstitial lung disease, autoimmune hepatitis, liver events in patients with history of viral hepatitis, change in morphology and/or severity of psoriasis, worsening of CHF, autoimmune renal disease, pemphigus/pemphigoid, amyotrophic lateral sclerosis, myasthenia gravis, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, liver failure, hepatic cirrhosis and fibrosis, severe hypertensive reactions, adverse pregnancy outcomes, potential for male infertility, weight gain, acute ischemic CV events, and use in pregnant women. | Planned for 2016 4Q | Final report planned for 2027<br><br>Annual interim reports with PSUR/RMP updates where applicable |

| | | | | |
|---|---|---|---|---|
| 5. BADBIR Category 3 | A nationwide registry which seeks to assess the long-term safety of biologic treatments for psoriasis. Recommended by NICE that all patients in the UK receiving new therapies for psoriasis be registered in BADBIR. | Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous adverse reactions, systemic vasculitis, macrophage activation syndrome, central demyelinating disorders, peripheral demyelinating events, aplastic anaemia and pancytopenia, interstitial lung disease, autoimmune hepatitis, liver events in patients with history of viral hepatitis, change in morphology and/or severity of psoriasis, worsening of CHF, autoimmune renal disease, pemphigus/pemphigoid, amyotrophic lateral sclerosis, myasthenia gravis, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, liver failure, hepatic cirrhosis and fibrosis, severe hypertensive reactions, adverse pregnancy outcomes, potential for male infertility, weight gain, acute ischemic CV events, and use in pregnant women. | Planned for 2016 4Q | Final report planned for 2027<br><br>Annual interim reports with PSUR/RMP updates where applicable |

***Risk minimisation measures***

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| **Important Identified risks: All Indications** | | |
| Malignancy (including lymphoma and leukaemia) | **SmPC**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects | None proposed |
| Serious and opportunistic infections (including TB, Legionella, Listeria, parasitic infection) | **SmPC**<br>Section 4.3 Contraindications<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects | Patient Alert Card |
| Lupus-like reactions | **SmPC**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects | None proposed |
| Sarcoidosis and/or granulomas | **SmPC**<br>Section 4.8 Undesirable effects | None proposed |
| Injection site reactions | **SmPC**<br>Section 4.8 Undesirable effects | None proposed |
| Allergic reactions | **SmPC**<br>Section 4.3 Contraindications<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects | None proposed |
| Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson | **SmPC**<br>Section 4.8 Undesirable effects | None proposed |
| Systemic vasculitis (including ANCA positive vasculitis) | **SmPC**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects | None proposed |
| Macrophage activation syndrome | **SmPC**<br>Section 4.8 Undesirable effects | None proposed |
| Central demyelinating disorders | **SmPC**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects | None proposed |
| Peripheral demyelinating events (CIDP and GBS) | **SmPC**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects | None proposed |

| | | |
|---|---|---|
| Aplastic anaemia and pancytopenia | **SmPC**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects | None proposed |
| Interstitial lung disease (including pulmonary fibrosis and | **SmPC**<br>Section 4.8 Undesirable effects | None proposed |
| Autoimmune hepatitis | **SmPC**<br>Section 4.8 Undesirable effects | None proposed |
| Liver events in patients with history of viral hepatitis (including HBV reactivation) | **SmPC**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects | None proposed |
| **Important Identified Risks: Specific Indications** | | |
| Change in morphology and/or severity of psoriasis | **SmPC**<br>Section 4.8 Undesirable effects | None proposed |

| | | |
|---|---|---|
| Worsening of CHF in adult subjects | **SmPC**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects | Patient Alert Card |
| **Important Potential Risks: All Indications** | | |
| Autoimmune renal disease | None proposed | None proposed |
| Pemphigus/pemphigoid | None proposed | None proposed |
| Amyotrophic lateral sclerosis | None proposed | None proposed |
| Myasthenia gravis | None proposed | None proposed |
| Encephalitis/leukoencephalomyel | None proposed | None proposed |
| Progressive multifocal leukoencephalopathy | None proposed | None proposed |
| Liver failure | None proposed | None proposed |
| Hepatic cirrhosis and fibrosis | None proposed | None proposed |
| Severe hypertensive reactions | None proposed | None proposed |
| Adverse pregnancy outcomes | **SmPC**<br>Section 4.6 Fertility, Pregnancy and Lactation | None proposed |
| Potential for medication errors (PFP) | Clear Package Leaflet<br>Instructions for use of the PFP | Educational programme for healthcare professionals and patients. |
| Potential for male infertility | None proposed | None proposed |
| Weight gain | None proposed | None proposed |
| **Important Potential Risks: Specific Indications** | | |
| Acute ischemic cardiovascular events in adult subjects | None proposed | None proposed |

| | | |
|---|---|---|
| Potential for paediatric off-label use | **SmPC**<br>Section 4.2 Posology and method of administration<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>**Package leaflet**<br>Children and adolescents Side effects in children and | Patient Alert Card<br>Educational programme for healthcare professionals and patients. |
| **Missing Information: All Indications** | | |
| Use in hepatic and renal impaired subjects | **SmPC**<br>Section 4.2 Posology and method of administration<br>Section 4.4 Special warnings and precautions for use | None proposed |
| Use in different ethnic origins | None proposed | None proposed |

| | | |
|---|---|---|
| Use in pregnant women | **SmPC**<br>Section 4.6 Fertility, Pregnancy and Lactation | None proposed |

## *2.8. Pharmacovigilance*

**Pharmacovigilance system**

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

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

### 2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Benepali (etanercept) is included in the additional monitoring list as a new biological product.

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

# 3. Benefit-Risk Balance

In the development of a biosimilar product, there is no requirement to demonstrate benefit to the patient per se as this has been shown for the reference product. The benefits and risks are inferred from the similarity of the test product to the reference product in terms of quality, efficacy and safety.

The purpose of a biosimilar application is to demonstrate similarity to the reference product.

***Benefits***

**Beneficial effects**

From the quality perspective, the applicant has demonstrated that the overall manufacturing process for Benepali, operated within established parameters, can perform effectively and reproducibly to produce material meeting its predetermined specifications and quality attributes. Implemented process controls will ensure that the process operates consistently and will also ensure the consistency and quality of the Benepali DS. In addition the applicant could sufficiently demonstrate comparability of Benepali material derived from different manufacturing scales during process development.

Finally, a comprehensive similarity exercise including clinical and PVR Benepali batches was also submitted. Based on these results it can be concluded that Benepali is at the quality level similar to EU Enbrel. Observed differences were sufficiently justified to have no impact on efficacy and safety when comparing Benepali with Enbrel.

From the pre-clinical perspective, it was considered that available data support biosimilarity between Benepali and EU-Enbrel based on:

- *in vitro* ligand binding studies and bioassays on primary pharmacology;
- mechanism of action (MOA)-related assays TNF-α, LT-α3 Binding Assays and TNF-α Neutralisation Cell Based Assay;
- selected Fc-related non-MOA-related binding assays including: FcγRIa-, FcγRIIa-, FcγRIIb-, FcγRIIIa(V-type)-, and FcRn binding assays.

From a clinical perspective, available data support biosimilarity between Benepali and Enbrel based on:

- The primary pharmacokinetic endpoints, $AUC_{inf}$ and $C_{max}$ with their 90% confidence intervals are well within the predefined acceptance range of 80-125%, therefore Benepali was shown to be bioequivalent to EU-Enbrel;
- The pivotal efficacy trial in patients with rheumatoid arthritis achieved its primary endpoint since the 95% confidence interval for the difference in ACR20 was contained within the predefined equivalence margin (± 15%) in both the FAS and the PPS1 population; secondary outcomes at week 24, and virtually all outcomes at week 52 were in support of primary findings.

**Uncertainty in the knowledge about the beneficial effects**

- None

***Risks***

**Unfavourable effects**

No major concerns regarding specific unfavourable effects became apparent in the development of Benepali (SB4). The type and incidence of ADRs observed with Benepali in the clinical studies were generally similar and in line with those expected on the basis of the Enbrel SmPC.

**Uncertainty in the knowledge about the unfavourable effects**

In contrast to full length anti TNF-α mAbs etanercept shows absent or strongly reduced ADCC activity, which is speculated of being responsible for differences in their clinical safety and efficacy profiles. A slightly increased content of afuscosylated structures may be responsible for slightly higher affinities of Benepali batches to FcγRIIIa and FcγRIIIb (although still meeting the comparability ranges). A slightly increased ADCC activity for Benepali in comparison to EU Enbrel was detectable, but not considered of clinical relevance, as in comparison to full length anti TNF-α Infliximab the difference appears negligible.

A numerical imbalance in malignancies (4 vs. 1), was observed with Benepali compared to Enbrel. Based on a detailed analysis of these cases this difference is considered to be likely a chance finding. Malignancies will be closely monitored on a longer term and in larger set of population as part of registries as described in the RMP.

In addition there was a significant (p-value < 0.001) difference in overall ADA formation at week 24. While only 3 of Benepali treated patients tested positive for ADAs at some point of the study, 39 patients tested positive in the EU Enbrel group, one of which also tested positive for neutralizing antibodies. The clinical impact of the difference in ADAs seems however negligible, especially as this difference is almost extinct after 8 weeks of treatment. In addition, the applied electrochemiluminescence assay suffers from a low drug tolerance that renders the ADA results of the Study SB4-G31-RA somewhat uncertain.

***Benefit-risk balance***

**Importance of favourable and unfavourable effects**

A comprehensive biosimilarity exercise, which covered almost all relevant structural and functional characteristics of the etanercept molecule, was submitted. The presented results support the biosimilarity claim for most of the quality attributes. Detected differences were sufficiently discussed and justified to have no impact on the efficacy/safety profile of Benepali.

Both the PK trial in healthy volunteers ($AUC_{inf}$ and $C_{max}$) and the pivotal efficacy trial in patients with rheumatoid arthritis (ACR20 at week 24) achieved their respective primary and important secondary endpoints (e.g. DAS28 and ACR 20 across whole study period) which is considered crucial for the biosimilar exercise. Additionally, the safety profile of Benepali (SB4) seems similar compared to Enbrel with any observed differences in antibody formation not having any clinical meaningful impact on the efficacy.

**Benefit-risk balance**

For a biosimilar, the benefit-risk conclusion is based on the totality of evidence collected from the quality, non-clinical, and clinical comparability exercise. For Benepali the benefit-risk is considered positive based on the submitted data.

***Discussion on the benefit-risk balance***

The acceptance of a biosimilar product is based on the overall similarity of quality, pharmaco-toxicological, pharmacokinetic and pharmacodynamic aspects and clinical efficacy and safety. This includes comprehensive physicochemical, biological characterisation and comparison and requires knowledge on how to interpret any differences between a biosimilar and its reference medicinal product. Any observed differences have to be justified also with regard to their potential effect on efficacy and safety of the biosimilar medicinal product.

Biosimilarity at the quality level was demonstrated on the basis of a very comprehensive comparability exercise; detected differences in the charged variants and glycan structure have been appropriately

justified to have no impact on biological activity by in-depth characterisation. Considering the mode of action for etanercept and the justifications provided by the applicant, the CHMP considered that these differences do not have any impact on the efficacy/safety profile of Benepali.

From a preclinical perspective comparative PD, PK and toxicology data between Benepali and the reference product Enbrel demonstrated biosimilarity. The evaluation of primary pharmacology by *in vitro* ligand binding studies and bioassays was regarded as appropriate. In addition, PK was similar in the most sensitive model (PK study in healthy volunteers).

The efficacy of Benepali was shown to be similar to that of Enbrel in the primary endpoint (ACR20, week 24) and the other secondary endpoints in a model of acceptable sensitivity (moderate to severe RA in combination with MTX in Study SB4-G31-RA). Therefore these results are sufficient to demonstrate equivalence in efficacy between the proposed biosimilar Benepali and the reference product Enbrel.

Extrapolation of the pharmacokinetic, efficacy and safety data generated in the two clinical trials in healthy volunteers and RA to the other authorised indications of Enbrel is sufficiently justified.

As the PK of etanercept is comparable in patients with RA, ankylosing spondylitis (AS), psoriasis, and healthy subjects (McCormack and Wellington, 2004; Nestorov et al., 2006; Zhou, 2005; Zhou et al., 2011), the PK results obtained with Benepali, demonstrating its biosimilarity with the reference product Enbrel in healthy subjects can be reasonably extrapolated to the approved therapeutic indications of Enbrel.

With regards to the efficacy, it is well established that an uncontrolled inflammatory process is common to all therapeutic indications of Enbrel. These indications share a common mechanism of action, i.e. the competitive inhibition of TNF-α binding and blockade of the ensuing inflammatory processes. Therefore, and in line with the EMA guidelines on the similar biological medicinal products, the efficacy results obtained with Benepali, demonstrating equivalence of Benepali and Enbrel in RA patients can be reasonably extrapolated to the other approved therapeutic indications of Enbrel.

Finally, with regards to safety, the adverse event profiles, clinical laboratory data, and other safety parameters did not show any significant safety issues which are not expected with etanercept treatment. There were no obvious relevant differences in the safety profile of Benepali as compared to Enbrel with no obvious no indication of any safety imbalance in disadvantage of Benepali. The safety outcomes obtained with Benepali in RA patients can be reasonably extrapolated to the other approved therapeutic indications of EU Enbrel. There appears to be no relevant differences in the safety profile of etanercept throughout the approved therapeutic indications. As a biosimilar, the safety-related product information for Enbrel also applies to SB4.

The applicant intends to claim the same therapeutic indications for adult patients for the biosimilar Benepali as granted for Enbrel in the EU. However, due to the sole proposed pharmaceutical strength which contains 50 mg etanercept per dose, the applicant does not intend to claim the approved paediatric indications for Enbrel (paediatric PsO, JIA). Adequate risk minimisation measures to avoid the potential pediatric off-label use have been included in the RMP. Although only the adult indication is applicable to SB4, the product has been considered as being biosimilar.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Benepali in the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing

spondylitis, non-radiographic axial spondyloarthritis and plaque psoriasis in adult patients is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

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

***Conditions and requirements of the Marketing Authorisation***

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Prior to launch in each Member State, the MAH shall agree the final educational material with the competent authority in that Member State, consisting of information provided to all healthcare professionals expected to prescribe the product on the correct and safe use of the pre-filled pen and to inform them that the product is not for paediatric use, and a Patient Alert Card which is to be given to patients using Benepali.

The healthcare professional's educational material should contain the following key elements:

- Teaching guide to facilitate training of the patients in the safe use of the pre-filled pen/prefilled syringes
- A needle-free demonstration device
- Material to remind healthcare professionals that Benepali is not for paediatric use
- Instructional materials to share with patients

The Patient Alert Card should contain the following key elements for patients treated with Benepali:

- The risk of opportunistic infections and tuberculosis (TB)

- The risk of Congestive Heart Failure (CHF).
- SB4 is not for use in children

- **Obligation to complete post-authorisation measures**

None.