22 June 2017
EMA/CHMP/559383/2017
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Imraldi

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/004279/0000

## Note

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

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# List of abbreviations

| | |
|---|---|
| A280 | Absorbance at 280 nm |
| ACA | Anti-Clumping Reagent |
| ACR20/50/70 | American College of Rheumatology 20%/50%/70% improvement criteria |
| ACR-N | The numeric index of the ACR response |
| ADA | Anti-drug antibody |
| ADCC | Antibody dependent cell-mediated cytotoxicity |
| AE | Adverse effect |
| AlphaScreen | Amplified Luminescent Proximity Homogeneous Assay Screen |
| ALT | Alanine transaminase |
| ANCOVA | Analysis of covariance |
| API | Active Pharmaceutical Ingredient |
| Apoptosis | Programmed Cell Death |
| Asn | Asparagine |
| AST | Aspartate transaminase |
| ANOVA | Analysis of variance |
| AS | Ankylosing spondylitis |
| AU | Absorbance Unit |
| AUC | Area under the concentration-time curve |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero to infinity |
| $AUC_{last}$ | Area under the concentration-time curve from time 0 to the last quantifiable concentration |
| AZA | Azathioprine |
| BLQ | Below limit of quantification |
| BMI | Body mass index |
| BMWP | The Biosimilar Medicinal Products Working Party |
| CAPA | Corrective Action and Preventive Action |
| C1q | First subcomponent of the C1 complex |
| CD | Crohn's disease |
| CDC | Complement dependent cytotoxicity |
| CE-SDS | Capillary Electrophoresis-Sodium Dodecyl Sulfate |
| CE-SDS (NR) | Capillary Electrophoresis-Sodium Dodecyl Sulfate (Non-Reducing Condition) |
| CE-SDS (R) | Capillary Electrophoresis-Sodium Dodecyl Sulfate (Reducing Condition) |
| CEX-HPLC (CEX) | Cation Exchange-High Performance Liquid Chromatography |
| CFU | Colony Forming Unit |
| CHMP | The Committee for Medicinal Products for Human Use |
| CHO | Chinese hamster ovary |
| CI | Confidence interval |
| CIPC | Critical In-Process Control |
| CIPT | Critical In-Process Test |
| CL | Clearance |
| CL/F | Apparent total body clearance |
| $C_{max}$ | Maximum serum concentration |
| CMH | Cochran–Mantel–Haenszel |
| CRP | C-reactive protein |
| $C_t$ | Last observed concentration |
| $C_{trough}$ | pre-dose concentration |
| CV% | Coefficient of variation percentage |
| DAS28 | Disease activity score 28 |
| DLS | Dynamic Light Scattering |
| DMARD | Disease-modifying anti-rheumatic drugs |
| DP | Drug Product |
| DS | Drug Substance |
| EC | European community |
| ECD | Extracellular Domain |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| EMA/EMEA | European Medicines Agency |

| | |
|---|---|
| ESR | Erythrocyte sedimentation rate |
| ET | Early termination |
| EU | European Union |
| EULAR | European league against rheumatism |
| Fab | Fragment Antigen Binding Region |
| FAS | Full analysis set |
| FACS | Fluorescence-Activated Cell Sorting |
| FBDS | Formulated Bulk Drug Substance |
| FBS | Foetal Bovine Serum |
| Fc | Fragment, crystallizable region of antibody |
| FcγR | Fc Gamma Receptor |
| FcRn | Neonatal Fc Receptor |
| FcγRIa | Fc gamma Receptor Ia |
| FcγRIIa | Fc gamma Receptor IIa |
| FcγRIIb | Fc gamma Receptor IIb |
| FcγRIIIa | Fc gamma Receptor IIIa |
| FcγRIIIb | Fc gamma Receptor IIIb |
| FDA | Food and Drug Administration |
| FRET | Fluorescence Resonance Energy Transfer |
| GCP | Good clinical practice |
| GMP | Good Manufacturing Practice |
| HC | Heavy Chains |
| HCD | Host Cell DNA |
| HCP | Host Cell Protein |
| HM | High Mannose |
| HMW | High Molecular Weight Protein |
| HPLC | High Performance Liquid Chromatography |
| HS | Hidradenitis suppurativa |
| HT | Hypoxanthine and Thymidine |
| IBD | Inflammatory Bowel Disease |
| IC | Ion Chromatography |
| ICH | International council on harmonization |
| icIEF | Imaged Capillary Isoelectric Focusing |
| IgG | Immunoglobulin Gamma |
| IL | Interleukin |
| IMP | Investigational medicinal product |
| INN | International Non-proprietary Name |
| IP | Investigational product |
| IPA | Isopropyl Alcohol |
| IPS | In-Process Specification |
| IPT | In-Process Test |
| JSN | Joint space narrowing |
| $\lambda_z$ | Terminal rate constant |
| L | Litre |
| ln | Natural logarithm |
| KCP | Key Controlled Parameter |
| kg | Kilogram |
| LC | Light Chain |
| LC | Liquid Chromatography |
| LC-MS | Liquid Chromatography-Mass Spectrometry |
| LD | Lactate Dehydrogenase |
| LDAO | Lauryldimethylamine Oxide |
| LLOQ | lower limit of quantitation |
| LMW | Low Molecular Weight Protein |
| LoQ | List of questions |
| LTα3 | Lymphotoxin Alpha 3 |
| Lys | Lysine |
| MAA | Marketing authorisation application |
| mAb | Monoclonal antibody |
| MCB | Master Cell Bank |
| mg | Milligram |

| | |
|---|---|
| mL | Millilitre |
| MNAR | Missing not at random |
| 6-MP | 6-mercaptopurine |
| MPA | Mycophenolic Acid |
| MoA | Mechanism of Action |
| MRI | Magnetic resonance imaging |
| MS | Mass Spectrometry |
| MS/MS | Tandem Mass Spectrometry |
| mTSS | Modified total Sharp score |
| MTX | Methotrexate |
| MuLV | Murine Leukemia Viruses |
| n | Number of subjects |
| NA | Not Applicable |
| Nab | Neutralising antibody |
| NF-κB | Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells |
| NGHC | Non-Glycosylated Heavy Chain |
| N-Glycan | N-linked Glycosylation |
| NHP | Non-Human Primate |
| NK | Natural Killer |
| NOAEC | No Observed Adverse Effect Concentration |
| NOAEL | No Observed Adverse Effect Level |
| OOS | Out-Of-Specification |
| OQ | Operational Qualification |
| PCR | Polymerase Chain Reaction |
| PD | Pharmacodynamics |
| PFP | Pre-filled pen |
| PFS | Pre-filled syringe |
| PGA | Physician global assessment |
| PIP | Paediatric investigation plan |
| PK | Pharmacokinetic(s) |
| $\%AUC_{extrap}$ | The effect of extrapolated area |
| PPS1 | Per-protocol set 1 (Week 0 – Week 24) |
| PPS2 | Per-protocol set 1 (Week 24 – Week 52) |
| PsA | Psoriatic arthritis |
| PsO | Psoriasis |
| PVR | Process Validation Run |
| QC | Quality Control |
| QL | Quantitation Limit |
| R | Accumulation ratio |
| RA | Rheumatoid arthritis |
| RAN | Randomized set |
| RS | Reference standard |
| RSD | Relative Standard Deviation |
| RT | Reverse Transcription |
| RT | Room Temperature |
| SAF | Safety set |
| SAP | Statistical analysis plan |
| SAR | Structure Activity Relationship |
| SAWP | Scientific Advice Working Party |
| s.c. | subcutaneous |
| SB | Samsung Bioepis |
| SD | Standard Deviation |
| SE-HPLC | Size Exclusion-High Performance Liquid Chromatography |
| SEM | Standard error of the mean |
| SGA | Subject global assessment |
| SJC | Swollen joint count |
| SOC | Standard of care |
| SPA | Subject pain assessment |
| sTNF-α | Soluble tumor necrosis factor alpha |
| TB | Tuberculosis |
| TDI | Tolerable Daily Intake |
| Tg | Transgenic |

| | |
|---|---|
| TJC | Tender joint count |
| TK | Toxicokinetics |
| $T_{max}$ | Time to reach $C_{max}$ |
| tmTNF-α | transmembrane tumor necrosis factor alpha |
| TNF-α | Tumour necrosis factor alpha |
| TNFR | Tumor necrosis factor receptor |
| t½ | Elimination half-life |
| UC | Ulcerative colitis |
| ULN | Upper limit of normal |
| ULOQ | Upper limit of quantitation |
| VAS | Visual analogue scale |
| VCAM | Vascular Cell Adhesion Molecule |
| Vz/F | Apparent volume of distribution |
| WCB | Working Cell Bank |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Samsung Bioepis UK Limited (SBUK) submitted on 21 June 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Imraldi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Rheumatoid arthritis

Imraldi in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

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

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

Juvenile idiopathic arthritis

*Polyarticular juvenile idiopathic arthritis*

Imraldi in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Imraldi can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in patients aged less than 2 years.

*Enthesitis-related arthritis*

Imraldi is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

Axial spondyloarthritis

*Ankylosing spondylitis (AS)*

Imraldi is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

*Axial spondyloarthritis without radiographic evidence of AS*

Imraldi is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Imraldi is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

Psoriasis

Imraldi is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Imraldi is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Imraldi is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy.

Crohn's disease

Imraldi is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Imraldi is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

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

Uveitis

Imraldi is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

**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.

### *Scientific Advice*

The applicant received Scientific Advice from the CHMP on 25/07/2013, 11/09/2013 and 21/05/2015. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

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

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Milena Stain

- The application was received by the EMA on 21 June 2016.
- The procedure started on 14 July 2016.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 30 September 2016. The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 3 October 2016. The PRAC Rapporteur's Assessment Report was circulated to all PRAC members on 14 October 2016.
- During the meeting on 10 November 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 27 March 2017.
- During the PRAC meeting on 6 April 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 21 April 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 07 June 2017.
- During the meeting on 22 June 2017, 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 Imraldi on 22 June 2017.

# 2. Scientific discussion

## *2.1. Problem statement*

This centralized marketing authorization application concerns genetically engineered recombinant human monoclonal antibody product Imraldi 40 mg, solution for injection in pre-filled syringe, Article 3 (1) of Regulation EC No 726/2004, annex (1). The Sponsor has introduced the name Imraldi for the biosimilar in their D121 responses, but in the current assessment report the name Imraldi is mostly used for the biosimilar.

Imraldi is a biosimilar adalimumab with the EU Humira as the reference medicinal product. Imraldi is a genetically engineered recombinant human immunoglobulin IgG1 monoclonal antibody. Imraldi is currently available as a 40 mg prefilled syringe (PFS) presentation.

Adalimumab (Humira) was first approved in 2002 by the FDA and in 2003 by the European Commission (EC). Adalimumab is a well characterized drug substance by its pharmacological, efficacy and safety profile qualities.

Imraldi has been developed as a similar medicinal product according to Article 10(4) of Directive 2001/83/EC. The reference medicinal product used throughout the development program is Humira, sourced from the European Union.

### 2.1.1. Disease or condition

The marketing authorisation is applied in the following adult indications approved for EU Humira:

- **Rheumatoid arthritis (RA)**

  Imraldi in combination with methotrexate (MTX) is indicated for:

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

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

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

- **Axial spondyloarthritis, Ankylosing spondylitis (AS), Axial Spondyloarthritis without Radiographic Evidence of AS**

  Imraldi is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

  Imraldi is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

- **Psoriatic arthritis (PsA)**

  Imraldi is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

  Imraldi has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

- **Psoriasis (PsO)**

  Imraldi is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

- **Hidradenitis suppurativa (HS)**

  Imraldi is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy.

- **Uveitis**

  Imraldi is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid- sparing, or in whom corticosteroid treatment is inappropriate.

- **Crohn's disease (CD)**

  Imraldi is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

- **Ulcerative colitis (UC)**

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

As Imraldi is currently only available as a single dose 40 mg prefilled syringe (PFS) presentation, the Applicant intended initially to claim the paediatric indications only for those patients who are according to the body weight eligible to be administered the full 40 mg dose. However, similarly to other recent adalimumab biosimilar applications, the CHMP has recommended that these paediatric indications should be aligned with those of the EU Humira. Therefore the Applicant is now applying for all the same paediatric indications as approved for Humira:

- **Juvenile idiopathic arthritis polyarticular (JIA):**

  Imraldi in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Imraldi can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Imraldi has not been studied in patients aged less than 2 years."

- **Enthesitis-related arthritis (ERA):**

Imraldi is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

- **Paediatric plaque psoriasis**

  Imraldi is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

- **Paediatric Crohn's disease**

  Imraldi is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

- **Paediatric hidradenitis suppurativa (HS)**

  Imraldi is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy.

## 2.1.2. Biologic features

### *About the product*

Imraldi is a genetically engineered recombinant human immunoglobulin IgG1 monoclonal antibody produced in CHO cell lines. Its active substance is adalimumab, which neutralises the biological function of both soluble and transmembrane forms of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF receptors and modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.

TNF-α has been shown to be elevated in several disease states, including rheumatoid arthritis (RA), psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), axial spondyloarthritis without radiographic evidence of AS, Crohn's disease (CD), ulcerative colitis (UC), and hidradenitis suppurativa (HS).

Imraldi belongs to the pharmacotherapeutic group "Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors" (ATC code: L04AB04 ). Imraldi is presented in single dose pre-filled syringe containing 40 mg of adalimumab.

### *Type of Application and aspects on development*

This marketing authorization application is an abridged application for a similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC as amended by Directive 2004/27/EC and Article 3(3) of Regulation 726/2004/EC.

Imraldi by Samsung Bioepis UK Limited is a proposed similar biological medicinal product to Humira (adalimumab), authorized in the European Union (EU) via the Centralised Procedure in 2003. The Humira reference product used in the clinical program was provided by AbbVie Ltd and was sourced from within the European Union.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The active substance of Imraldi (referred to as active substance (DS) in the text) is adalimumab, a chimeric human immunoglobulin G1 (IgG1) monoclonal antibody produced in a Chinese Hamster Ovary (CHO) cell line. Imraldi has been developed by Samsung Bioepis as a similar biological medicinal product to the reference medicinal product, Humira (EMEA/H/C/481), which received a marketing authorisation in the EU via the centralised procedure on 08 Sep 2003. Adalimumab binds specifically to TNF-α and neutralises the biological function of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF-α receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF-α, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1 and ICAM-1).

Imraldi active substance is formulated with sodium citrate, citric acid monohydrate, histidine buffer, sorbitol, polysorbate 20 and water for injections. Imraldi is presented in a single-use pre-filled syringe (PFS) containing 40 mg adalimumab to be administered via subcutaneous (s.c.) injection. The proposed adult dosing and the recommended posology of Imraldi correspond with Humira containing 40 mg adalimumab; also the pediatric dosing follows that of EU-Humira, although it is not possible to administer Imraldi to paediatric patients that require less than a full 40 mg dose due to the absence of a vial presentation.

### 2.2.2. Active Substance

#### Structure

Imraldi (adalimumab) is a recombinant human monoclonal antibody, which is typically a "Y"- shaped large glycoprotein consisting of two kappa light chains each with a molecular weight of approximately 24 kDa and two IgG1 heavy chains each with a molecular weight of approximately 49 kDa. The total molecular weight of adalimumab is approximately 148 kDa. Each light chain consists of 214 amino acid residues and each heavy chain consists of 451 amino acid residues. Its molecular formula without the N-glycan moiety is $C_{6448}H_{9996}N_{1732}O_{2020}S_{42}$. One N-linked glycosylation site is located at Asn301 on each heavy chain and there are no O-linked glycosylation sites.

#### Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The manufacturing facility at Biogen Inc. (North Carolina, USA) is the intended site for commercial production.

Imraldi active substance is manufactured, packaged, stability tested, and quality-control tested in accordance with EU good manufacturing practices.

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 Imraldi 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 with a series of steps including chromatography, viral inactivation and viral filtration.

Control of materials

Materials used in the manufacture of the active substance have been listed together with information on the quality and control of these materials.

Cell banking system

The applicant is using a two-tiered cell bank system in overall accordance with ICH Q5A, Q5B, and Q5D guidelines. The host cell line is a Chinese Hamster Ovary cell line. Its safety is well established and it has been used as the host cell line in the production of numerous commercialised recombinant therapeutic antibodies. The generation of the expression is sufficiently detailed.

The genetic stability of the Imraldi cell substrate was confirmed by genetic and phenotypic analysis methods, as required by ICH Q5B and Q5D guidelines.

Control of critical steps and intermediates

For the control of the Imraldi active substance manufacturing process, the process controls are divided into controlled parameters (process inputs) and performance parameters (process outputs). For the input parameters, critical-, key- and non-key control parameters have been defined for each step in the process as well as the outputs, critical and process consistency in-process controls and in-process tests. The criticality is associated with impact on the defined critical quality attribute of the SB5 active substance.

Controlled parameters are input variables or conditions of the manufacturing process used to control the manufacturing process.

**Table 3.2.2.1 Descriptions of the critical-, key- and non-key control parameters**

| Controlled Parameter | Description |
|---|---|
| Non-key controlled parameter (N-KCP) | An input process parameter that is unlikely to impact either the process performance or product quality. |
| Key controlled parameter (KCP) | An input process parameter that may affect process performance, but is unlikely to affect product quality. |
| Critical controlled parameter (CCP) | An input process parameter that impacts product quality within a unit operation and may also affect process performance. |

Performance parameters are measured outputs from the process. Performance parameters indicate whether the process performs as expected. Outputs from one process step can be inputs to the next step. For the output parameters, most of the in-process controls / tests have action limits applied and a few have established in-process specifications. The definitions for the limits have been described. For some critical in-process tests and controls, specifications have not yet been established, but action limits are applied.

**Table 3.2.2.2 Descriptions of the performance parameters**

| Performance Parameter | Description |
|---|---|
| In-process control (IPC) | An output parameter used to assess process consistency and performance in real time. IPCs are tests or on-line measurements that are performed during processing that allow decisions to be made regarding the operation of the process or the progression to the next processing step. |
| Critical in-process control (CIPC) | A subset of IPCs used to assess product quality attributes. |
| In-process test (IPT) | An output parameter used to assess process consistency and process performance in which results are evaluated after batch or processing step completion. |
| Critical in-process test (CIPT) | A subset of IPTs used to directly assess product quality attributes or assess a process output, known to impact product quality. |

Full details of the process controls have been provided in the dossier.

Process validation

The commercial manufacturing process for Imraldi DS has been validated at Biogen large-scale manufacturing facility in USA. The validation of the cell culture process covered all steps from WCB thaw and cell expansion. With respect to the purification process, studies were conducted to confirm that each unit operation is able to show consistency of achieving product yield and reducing impurity content to an acceptable level. Overall, all controlled parameters were within the action limits and validation acceptance criteria were met.

A product risk assessment has been performed to determine the criticality of individual product attribute impacts on the overall quality of SB5 DS and to support the overall testing strategy. Justification for classification of the evaluated product attributes was appropriately provided. The rationale and methodology for the process risk assessments have been clearly presented and are considered acceptable.

Scale-down systems were used to model the full-scale Imraldi manufacturing cell culture and purification processes. The descriptions of the scale-down models have been provided in sufficient detail. The scale-down models have been qualified, based on comparisons with manufacturing scale data.

Clearance of process-related impurities was validated by using direct measurements as well as by using scale-down models The presented data demonstrate that the Imraldi active substance process for commercial production clears process-related impurities to acceptable levels considered safe for biopharmaceutical products.

A summary of test results for the process intermediate stability hold time studies were provided. The results of the hold time studies support the claimed maximum hold times.

Manufacturing process development

The modifications introduced to the manufacturing processes during the development have been adequately described and sufficient details and rationale for each step has been provided. The manufacturing process and control strategy were established during development. The risk assessment results were used to classify the process parameters and define the process control strategy.

Comparability assessments were performed to ensure that the batches used at each stage of Imraldi development are representative of subsequent development stages, and that changes in the manufacturing process at each stage of development do not affect product quality.

Characterisation

The characterisation of Imraldi involved determination of the structures (primary, secondary, and higher-order), glycosylation, charge variants, purity/impurities, cellular potency and binding activity. The results and conclusions of these studies are discussed in CTD section 3.2.R, Biosimilarity, as the characterisation studies are also part of the biosimilarity assessment.

## Specification

Specifications were set for quantity, identity, biological activity, purity and impurities, and safety taking the principles of the ICH Q6B guideline into account. Other general tests (appearance, pH, osmolality) are also included in the specification.

Overall, the test parameters proposed to be included in the Imraldi DS specification are considered appropriate and in line with relevant guidance.

Analytical methods

The analytical methods used for DS and DP release testing have been described in detail and validated according to ICH Q2. Validation summaries as well as detailed validation reports have been in submitted for those methods which are not conducted according to the Ph. Eur. In addition, the suitability of the compendial method addressing safety aspects (endotoxin and microbial enumeration) has been verified. The provided validation results indicate that the analytical methods for active substance release control are suitable for their intended use.

Batch analysis

The Applicant has provided batch analyses data. Almost all batches complied with the specifications set at the time of testing and thus support the conclusion of the Applicant that the active substance manufacturing process can perform effectively and reproducibly to produce active substance material meeting its predetermined specifications and quality attributes.

Reference materials

Reference standards are established to demonstrate consistency in the manufacturing process of each development stage through extensive set of analytical tests including biological and physicochemical assays. Also, reference standards are used for method development and validation, as well as assessment of continuity of reference standards themselves. In particular, reference standards are used to evaluate the system suitability of analytical methods.

## Stability

The Applicant has provided currently available real-time stability data at long-term, at intermediate, and at accelerated conditions. Supportive stability data was also provided. No critical changes or significant trends were observed in the tested parameters.

A shelf life of Imraldi DS is based on the long-term stability data. No clear trends can be observed in the provided data and all shelf-life acceptance criteria were met. Considering that the long-term storage condition can be agreed.

## 2.2.3. Finished Medicinal Product

## Description of the product and Pharmaceutical Development

The manufacture of SB5 bulk pre-filled syringes takes place at the finished product manufacturing facility. The manufacturing process of Imraldi finished product (referred to as finished product (DP) in the text) involves aseptic filling of pre-filled syringes, and no additional dilution steps are applied, thus the Imraldi finished product has the same composition as the Imraldi active substance.

Description and composition of the finished product

Imraldi finished product is a clear to opalescent, colourless to pale brown, sterile and preservative-free solution for injection. Imraldi finished product is presented as a single-use pre-filled syringe (PFS) which nominally contains 0.8 mL of solution and 40 mg of adalimumab.

The SB5 finished product has the same composition as the active substance (adalimumab, sodium citrate dihydrate, citric acid monohydrate, L-histidine, L-histidine hydrochloride monohydrate, sorbitol, and polysorbate 20) There are no novel excipients and no preservatives in the formulation.

Formulation development

In the developmental stage, formulation development studies were performed to confirm the effects of pH, buffer, excipient, and protein concentration on the stability of Imraldi finished product. The formulation development studies and the results were presented. From the results of the developmental studies above, the following conclusions were drawn for optimised Imraldi formulation. Finished product formulation robustness study was done to assess the formulation robustness of Imraldi finished product with variation of protein concentration, pH, L-histidine concentration and sorbitol concentration. Additionally, optimal formulation composition range was identified through this study. Results of the developmental robustness study showed that the Imraldi finished product formulation is robust within range of protein concentration, pH, and L-histidine concentration. The overall results of the formulation robustness study indicate that the formulation may be 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.

The Imraldi DP manufacturing process consists of DS thaw, pooling and mixing of the DS, sterile filtration, and aseptic syringe filling/stoppering. The manufacturing process of Imraldi finished product has been developed through process characterisation and an engineering run before process validation. The final process was verified by process validation.

For Imraldi finished product process characterisation, a risk assessment was conducted to select parameters that affect product quality and process consistency based on the development data and clinical GMP batch experience. As a result of the risk assessment, performed with Imraldi finished product, different manufacturing parameters were selected for further study during process characterisation.

Container closure integrity has been studied during development of Imraldi finished product and this test is included in the on-going stability studies.

Development studies on the finished product package for usability have been performed. A simulated-use human factors study was performed to confirm that the hazards associated with use of the product have been controlled.

## Manufacture of the product and process controls

The straightforward DP manufacturing process starts with active substance receipt and storage, involves thawing, pooling, and mixing of the active substance, followed by sterile filtration, aseptic syringe filling, and plunger placement. The DS has the same formulation as the DP, thus no dilution/formulation steps are applied. The controlled parameters and in-process tests and controls have been provided for all relevant manufacturing steps with associated In-process specifications and/or action limits, where applicable. The description of the Imraldi DP manufacturing process and the proposed control strategy for the manufacturing process are considered appropriate.

*Process validation*

The Imraldi DP manufacturing process was validated at the proposed commercial manufacturing site through input parameters (controlled process parameters) and output parameters (performance parameters) with predetermined acceptance criteria. Overall, all PVR batches met satisfactorily the

pre-determined acceptance criteria for all controlled process parameters, in-process tests and release tests.

## Product specification

Specifications were set for quantity, identity, biological activity, purity and impurities, and safety taking the principles of the ICH Q6B guideline into account. Other general tests (appearance, pH, osmolality) are also included in the specification.

The tests for quantity, identity, general tests, and the safety tests are considered appropriate and their acceptance limits are acceptable.

Container closure system

The syringe is a 1 mL syringe with needle and needle shield. This packaging is standard for pre-filled syringe presentations. The glass complies with Ph. Eur. 3.2.1, the silicone oil lubricant with Ph. Eur. 3.1.8 and the rubber part of the needle shield with Ph. Eur. 3.2.9. Appropriate drawings were provided.

## Stability of the product

The Applicant has provided data on stability studies performed at the long-term storage condition (5 ± 3°C), at the accelerated storage condition, and at the stress storage condition. All evaluated long-term stability parameters met the acceptance criteria supporting the Applicant's shelf-life claim. At accelerated condition, although slight changes in the purity of Imraldi DP were observed, all the results met the acceptance criteria. At stress condition, significant changes in the purity of Imraldi DP were observed for all studied batches. Based on the provided stability data the proposed shelf-life of 36 months when stored at 5 ± 3°C can be agreed. Temperature cycling studies have been performed where the finished product was exposed to several cycles of low and elevated temperatures. The results show that Imraldi finished product tolerates the applied excursions in temperature without significant degradation or other negative impact on quality attributes. The finished product sensitivity to light has been studied with the naked pre-filled syringes and with the commercial pack in ICH Q1B Option 2 conditions. The results show that Imraldi finished product solution is light sensitive and degradation is significant in the naked syringe.

In addition, the Applicant has performed a Patient convenience stability study to monitor the stability profile during exposure at ambient temperature (room temperature) conditions in use using Imraldi DP aged to 36 months. The Imraldi DP batches were subjected to accelerated condition up to 4 weeks. The observed changes were within the expected ranges based on the results from stability studies performed at accelerated condition, and met the acceptance criteria. The currently provided long-term stability data support the shelf-life of 36 months at the long-term storage condition (5 ± 3°C). Thus, the additional stability claim in SPC section 6.4 of "may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days" is considered to be supported by the provided data.

## Adventitious agents

The manufacturing process of the DS or the DP does not contain any material of human or animal origin and therefore the risk of adventitious agents entering the DP is considered low. The risk of microbial and mycoplasma contamination is adequately addressed, cell banks are demonstrated to be sterile, and sufficiently low bioburden is established for DS bulk.

The virus validation studies have been performed in accordance with the Note for guidance on virus validation studies (CPMP/BWP/268/95) and the choice of model viruses is considered appropriate. The manufacturing purification process includes virus inactivation steps as well as removal steps.

Overall the inactivation/removal of different types of viruses is considered to be sufficient.

## Biosimilarity

### Introduction

The biosimilarity between Imraldi and Humira, authorised in the European Union (EU), has been assessed through a comprehensive physicochemical and biological comparability exercise. The study follows the general principles as outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012).

### Physicochemical and biological characterisation studies to support biosimilarity

Similarity range

Similarity ranges for the side-by-side analyses have been established based on characterisation results. The available data is sufficient for evaluating the batch-to-batch variability present in EU Humira. It is noted that not all the quality attributes that are measured on a metric scale were assessed. For the side-by-side comparison of the additional biological properties of EU Humira included in the side-by-side comparison has been calculated, whereas the attributes characterizing the higher-order structure are required to be “similar to that of reference product within instrumental variability”. For certain quality attributes the statistical approach has resulted in wide similarity ranges, however, as characterisation results for the EU Humira batches are provided, an assessment independent of the chosen statistical approach is possible.

Similarity exercise summary

Comprehensive characterisation studies were performed using state-of-the-art analytical procedures to demonstrate similarity between Imraldi and Humira. As discussed below, the results of Imraldi were mostly within the similarity ranges defined based on characterisation results from EU Humira batches.

Primary structure

The primary structure of Imraldi and EU Humira was compared with regard to the molecular weight, amino acid sequence, N- and C-terminal sequence, peptide map, disulphide bridges, free sulphydryl groups, methionine oxidation and asparagine deamidation. The differences observed in molecular weight analyses due to slight differences in the glycosylation profile, as well as the differences in C-terminal lysine content, and the amount of free thiol group have been properly discussed and justified. In addition, for methionine oxidation a small difference is observed between Imraldi and Humira. This difference is considered to be of no clinical relevance.

Glycan profile

The glycosylation profiles of Imraldi and Humira were compared with regard to N-glycosylation site, glycan structures, as well as for relative quantities of %Afucose, %HM (high mannose), %G0F, %G1F, and %G2F. N-glycosylation site of Imraldi is identifided as identical to that of Humira. %G0F, %Afucose, %sialylation were found to be slightly different in Imraldi compared to Humira. The differences had been appropriately discussed and the differences can be considered clinically insignificant..

Purity and impurity profiles

In the comparisons of the purity and impurity profiles, similar low levels of HMW aggregates were measured both for Imraldi and for Humira. These results were confirmed by orthogonal analyses. Also another method shows similarity, although the %IgG is marginally lower for Imraldi compared to Humira.

A difference in non-glycosylated heavy chain (NGHC) levels was detected. The Applicant has provided experimental data demonstrating that the NGHC levels detected in Imraldi will not impact on biological activity.

Charge variants

The charged variant profiles of Imraldi and Humira differ to some degree. The percentage of acidic variants in Imraldi DP batches used in the side-by-side analysis is different fromHumira, although all batches are within the similarity ranges. The increase in acidic variants is accompanied by significantly lower levels of basic variants in Imraldi. These results have been confirmed by another analytical method.

In order to assess the impact of the differences, the Applicant has identified the variants present in the fractions, determined the glycan profiles, and studied biological activity. Based on the results from identity and biological activity studies conducted, it can be concluded that the remaining minor difference in acidic variants is of no clinical concern.

Higher order structures

The secondary structure was elucidated; the tertiary structure; the size distribution; the subvisible particles. The three-dimensional conformation was further analysed by antibody conformational array. No significant differences could be seen between Imraldi and Humira, therefore similarity with regard to higher order structures can be concluded.

Protein content

The protein contents were determined in terms of concentration by using an ultraviolet/visible spectroscopy (UV-Vis) spectrophotometer. The results showed that the protein concentration of Imraldi and EU Humira were similar.

Fab-related biological properties

As Fab-related properties, TNF-α binding, TNF-α neutralisation, and apoptosis activity were evaluated in the assessment. The results of all Imraldi batches included in the three assays are within both the historical min-max range of Humira, as well as within the established similarity ranges. Comparison of the relative binding of Imraldi and Humira to TNF-α has been measured, and the values derived thereof are given in % of relative binding activity. Additional studies confirmed similar TNF-α binding affinity between Imraldi and EU Humira.

Fc-related biological properties

As Fc-related functions, the Applicant has studied FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcRn, C1q binding, as well as ADCC and CDC activities. The binding activities of the Imraldi batches towards the Fc-receptors are all within the similarity ranges. For FcγRIIa binding, similarity was confirmed using a second orthogonal analytical method.

In the ADCC assay using the high affinity CD16 receptor, the activity of Imraldi DP batches relative to the reference standard, all tested batches being within the established similarity range. The ADCC activity of Humira ranged from. In the CDC assay, the relative activities of the Imraldi and Humira batches used in the side-by-side analysis do not overlap. However, based on the reported results, as well as the established similarity range, the claim for similarity with regard to CDC activity is supported.

Additional biological properties

As additional biological testing, the following properties have been compared; inhibition of cytokine release assay (in vitro IBD model), inhibition of apoptosis assay (in vitro IBD model), regulatory macrophage function assay, inhibition of adhesion molecule expression, transmembrane TNF-α binding assay, FcγRIIIa (158F/F) binding, FcγRIIIb binding, LTα3 binding assay, and conformational antibody array.

The additional biological testing, together with the Fab-related and Fc-related assays, address relevant mode of actions for adalimumab. The results support the similarity claim.

Comparative stability studies

To compare degradation profiles of Imraldi and Humira, the Applicant has conducted comparative stability studies under heat stressed and accelerated conditions, as well as oxidation and photostability studies. Overall, the changes that occurred under stress conditions and the degree at which they occurred were similar between Imraldi and EU Humira, showing that the degradation pattern was similar.

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

As detailed in the Quality overview, the quality part of the submission (module 3) is overall of good quality covering all main areas satisfactorily.

The manufacturing process has been described in sufficient detail; all raw and starting materials including the cell banks used in the manufacture of Imraldi material are listed identifying where each material is used in the process. Information on the quality and control of these materials has been provided. Also all excipients used for finished product formulation comply with the Ph. Eur. An adequate process control system, consisting of process input and process output parameters, is in place which ensures a consistent routine manufacture of Imraldi. Process validation supports the conclusion that the manufacturing process for active substance as well as for finished product can perform effectively and reproducibly to produce active substance respective finished product meeting its predetermined specifications and quality attributes. The provided active substance and finished product batch analyses data support this conclusion. Comparability of the clinical Imraldi batches used in the clinical studies and the process validation batches has been demonstrated.

The analytical similarity between Imraldi and Humira has been extensively addressed in accordance with relevant guidelines. The comparability studies address the primary, secondary, and tertiary structures, post-translational modifications, purity/impurity profile, biological activity, as well as the degradation profile. As expected, some differences in quality attributes were observed, these differences have, however, been satisfactorily discussed and justified not to be of clinical relevance.

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

Overall, the quality of Imraldi is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

Biosimilarity with the reference medicinal product Humira has been sufficiently demonstrated. From a quality point of view, the observed differences and levels of these differences have been well documented and are acceptable.

The overall Quality of Imraldi is considered acceptable.

### 2.2.6. Recommendation(s) for future quality development

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

## *2.3. Non-clinical aspects*

### 2.3.1. Pharmacology

A comprehensive panel of in vitro ligand binding studies and bioassays were conducted for demonstrating the similarity of Imraldi (also referred to as SB5 thoroughout this Report), and reference product EU Humira. The side-by-side characterisation studies are considered suitable for the demonstration of biosimilarity of monoclonal antibodies (Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues - EMA/CHMP/BMWP/403543/2010) and were categorized in Fab-related biological activities, Fc-related biological activities and additional supportive bioassays. In addition, the in vivo efficacy of SB5 and US Humira was compared in the Tg197 transgenic mouse model of arthritis.

Based on the *in vitro* data provided, SB5 appears to be similar to EU Humira in binding and functional characteristics (expressed as % of relative activities) regarding the primary mode of action for adalimumab *i.e.* TNF-α (soluble and transmembrane) binding and neutralisation activity. These also included the assessment of Tm-TNF-α related mechanism (apoptosis) and LTα3 binding. The data support the similar binding and functional characteristics in terms of Fc-related functions *i.e*. FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa (158V/V, 158F/F), FcγRIIIb, FcRn and C1Q binding, and complement dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC) activity. Additional studies were performed to support the similar functionality of SB5 and EU Humira on inflammatory bowel diseases. According to these studies and under the study conditions, effects on regulatory macrophages, inhibition of cytokine release (IL-8) and apoptotic activity in TNF-treated human colon carcinoma cells can be considered similar between the SB5 and EU Humira. In addition, there were no differences between SB5 and EU Humira on the inhibitory effects on TNF-α-induced endothelial VCAM expression.

The functional similarity was supported by the *in vivo* efficacy study in the Tg197 transgenic mouse model of arthritis, closely resembling human RA pathology as a consequence of overexpression of human TNF-α. Intraperitoneal administration of 0.5 mg/kg, 3 mg/kg and 10 mg/kg SB5 and US Humira (twice weekly) started before the onset of arthritic symptoms to evaluate the protective effect. The treatment was continued for 7 weeks. The treatment responses were evaluated weekly (from 3 to 10 weeks of age) macroscopically (macroscopic arthritis scores) and at the end of the treatment from histopathological samples (histopathological scores) in a blinded fashion from hind limb ankle joints. The *in vivo* efficacy of SB5 was similar to US Humira in inhibition of the arthritic pathology compared to the vehicle–treated mice. The studies on secondary PD, safety pharmacology and pharmacodynamic drug interactions were not conducted and are not deemed necessary.

## 2.3.2. Pharmacokinetics

The pharmacokinetics program consisted of a toxicokinetic profile comparison of SB5 and US Humira in cynomolgus monkeys included as part of the GLP-compliant 4-week repeat dose toxicity study, please see toxicology section below. Although pharmacokinetic studies are not formally requested for biosimilars in the EU, the toxicokinetic analysis was included for development of SB5 for the purposes of global markets.

The absence of studies evaluating the distribution, metabolism, excretion and pharmacokinetic drug interactions is consistent with CHMP guidance (Guideline on similar biological med icinal products containing monoclonal antibodies, EMA/CHMP/BMWP/403543/2010).

## 2.3.3. Toxicology

A 4-week comparative GLP-compliant repeat-dose toxicity study in cynomolgus monkeys was conducted to support the similarity of SB5 and originator Humira (US-sourced) in a reduced toxicology study package for a biosimilar application. The comparison of toxicokinetics, local tolerance and potential immunotoxic profiles were included to the study.

SB5 and US Humira were well tolerated at a dose level of 32 mg/kg (s.c., once weekly for 4 weeks), consistent with the results of originator adalimumab studies in cynomolgus monkeys and without unexpected findings. There were no significant or biologically meaningful treatment -related effects or differences between the SB5 and US Humira in clinical observations, body weights, food consumption, ophthalmoscopy examinations, electrocardiographs, haematology, coagulation, clinical chemistry or urinalysis endpoints, or peripheral blood leukocyte analysis, or macro/microscopic evaluations. The minor sporadic changes observed in this small scale monkey study were considered not to relate to the treatment, but be of biological inter-individual variation, within the range of historical control data, or incidental in nature or procedurally related.

Histopathology findings at injection site were similar (in type and incidence) across the SB5 and Humira-treated animals.

No significant differences were seen in the immunogenicity profile (in the ADA-formation) between the SB5 and US Humira in cynomolgus monkeys. None of SB5 or Humira-treated animals showed a confirmed positive anti-drug antibody response. 1/6 US Humira-treated animals were positive according to initial screening on Day 22 and Day 29, but was negative in the confirmatory analysis. However, this may present a potentially false negative finding. The ECL analysis method may not have been sufficient for detecting ADA due to the drug interference.

According to the immunophenotyping data, the SB5 is comparable to US Humira.

Full toxicity studies were not considered necessary as SB5 is a proposed biosimilar to Humira in agreement with the CHMP guidelines on similar biological medicinal products, and studies on single-dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity were not conducted.

In conclusion, SB5 can be considered similar to the originator US Humira in terms of toxicological, toxicokinetic and immunogenicity profiles.

## 2.3.4. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, a protein and therefore unlikely to pose a significant risk to the environment. This 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).

### 2.3.5. Discussion on non-clinical aspects

The comparability analyses were focused on array of *in vitro* ligand binding studies and bioassays assessing the primary pharmacology characteristics. Based on the data provided, SB5 appears to be similar to EU Humira in the *in vitro* characteristics. SB5 was developed for global markets and the non-clinical program included the *in vivo* efficacy study in the transgenic mouse model of arthritis and toxicological/toxicokinetics study in cynomolgus monkeys using an US sourced reference product as a comparator. These studies overall supported the *in vivo* functional similarity of SB5 and US Humira in inhibiting the arthritic symptoms and similarity in toxicological, toxicokinetic and immunogenicity profiles.

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

SB5 can be considered similar to originator Humira in terms of *in vitro* and *in vivo* functionality and of toxicological, toxicokinetic and immunogenicity profiles.

## *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.

### *Tabular overview of clinical studies*

| Study (Country) | Study Objectives | Design | Study Population | Primary Endpoint(s) |
|---|---|---|---|---|
| SB5-G11-NHV<br><br>Phase I<br><br>(Germany) | Comparative PK, safety, tolerability, and immunogenicity<br><br><u>For EMA:</u><br>To investigate and compare the PK profiles of SB5 and EU Humira® in healthy subjects.<br><br><u>For FDA:</u><br>To investigate and compare the PK profiles of SB5 to US Humira®, EU Humira® to US Humira® and SB5 to EU Humira® in healthy subjects | Randomised, single-blind, three-arm, parallel group, single-dose study;<br><br>Total duration: 10 weeks<br><br>Single dose *s.c.* injection of 40 mg of either SB5, EU Humira® or US Humira® | 189 healthy subjects (63/arm) | <u>For EMA:</u><br>$AUC_{inf}$, $C_{max}$<br><br><u>For FDA:</u><br>$AUC_{inf}$, $AUC_{last}$, $C_{max}$ |
| SB5-G31-RA<br><br>Phase III<br><br>(Bosnia, Bulgaria, Czech Republic, Korea, Lithuania, Poland, Ukraine) | Comparative efficacy, safety, tolerability, immunogenicity, and PK<br><br>To demonstrate the equivalence of SB5 to EU Humira® at Week 24, in terms of the ACR20 response rate in subjects with moderate to severe RA despite MTX therapy | Randomised, double-blind, parallel group, multicentre clinical study;<br><br>At Week 24, subjects receiving Humira® were randomised to either continue on Humira® or be transitioned to SB5 up to Week 50. Subjects receiving SB5 continued to receive SB5 40 mg up to Week 50, but they also followed the randomisation procedure to maintain blinding.<br><br>Total duration: 60 weeks (52 weeks of active treatment and 8 weeks of safety follow-up)<br>40 mg, *s.c.* injections of SB5 or EU Humira® every other week | 544 RA subjects (271 for SB5, 273 for EU Humira®) | ACR20 at Week 24 |

## 2.4.2. Pharmacokinetics

Two clinical studies were performed in which the PK of adalimumab from SB5 was compared to that of EU-sourced Humira.

- Pivotal PK study (SB5-G11-NHV) was a single-dose, phase 1, 3-way PK similarity study in healthy males and females comparing SB5 with EU-sourced Humira and US-sourced Humira.
- Randomized, double-blind, phase 3 study (SB5-G31-RA) in RA patients (having MTX medication), in which trough concentrations of adalimumab were compared between SB5 and EU-sourced Humira.

**Pivotal PK study in healthy subjects (SB5-G11-NHV)**

The study was conducted in Germany between May 02 (first subject signed informed consent) – Sept 02, 2014 (last subject last visit).

One amendment was made to the study protocol (dated Dec 09, 2013). In the amendment geometric means were updated to refer geometric LS Means to clarify the statistical analyses described in the statistical methods. This was the only change related to the PK.

This study was a randomised, single-blind, 3-arm, parallel group, single-dose phase 1 study. A total of 189 healthy subjects (aged 18-55 years) were enrolled to the study; 63 subjects in each of the 3 treatment groups (i.e. in SB5 group, in EU-sourced Humira group and in US-sourced Humira group). All subjects completed the study. In each group, all subjects received a single dose (40 mg) of SB5, EU-sourced Humira, or US-sourced Humira by deep s.c. injection via PFS in the periumbilical area while subjects were supine.

Blood samples for PK analysis were collected at 0 (pre-dose) and at 6, 12, 24, 48, 72, 96, 108, 120, 132, 144, 168, 336 (2 weeks), 504, 672, 1008 (6 weeks), 1344, and 1680 h (= 10 weeks) post-dose. Blood samples were collected for determination of ADA and Nabs to adalimumab at day 1 (pre-dose), day 15 (360 h) and day 71 (1704 h).

- Primary pharmacokinetic endpoints: $AUC_{inf}$, $C_{max}$
- Secondary pharmacokinetic endpoints: $AUC_{last}$, $AUC_{0-336}$, $T_{max}$, apparent volume of distribution based on the terminal phase (Vz/F), terminal rate constant ($\lambda_z$), $t_{½}$, CL/F and $\%AUC_{extrap}$.

For the EMA review, equivalence of the primary endpoints ($AUC_{inf}$, $C_{max}$) was determined if the 90% CI for the ratio of geometric LS Means of SB5 to EU-sourced Humira was within the acceptance interval of 0.8 to 1.25. Equivalence testing using the same margin and confidence interval was also provided for the secondary endpoint $AUC_{0-t}$ (co-primary EP for FDA application).

Point estimates of the mean and median values as well as SD, minimum and maximum values were presented for all secondary endpoints.

Summary statistics for calculated PK parameters included: n, mean, SD, CV%, SEM, geometric mean, geometric SD, geometric CV%, 90% CI of geometric mean, median, minimum, and maximum values. PK parameters were summarised by treatment group and listed by subject.

For exploratory purpose, the ANOVA for the PK parameters by ADA/NAb result were performed.

The demographic baseline characteristics were generally comparable across the three treatment groups.

The primary objective for the EMA review was to investigate and compare the PK profiles of SB5 and EU-sourced Humira in healthy subjects. The mean serum concentration-time profiles were similar following a single s.c. injection of the studied treatments (see Figures 3.4.1.1 and 3.4.1.2).

**Figure 3.4.1.1 Mean serum concentration (µg/ml) versus nominal times (h) on linear scale of SB5 and EU-sourced Humira.**

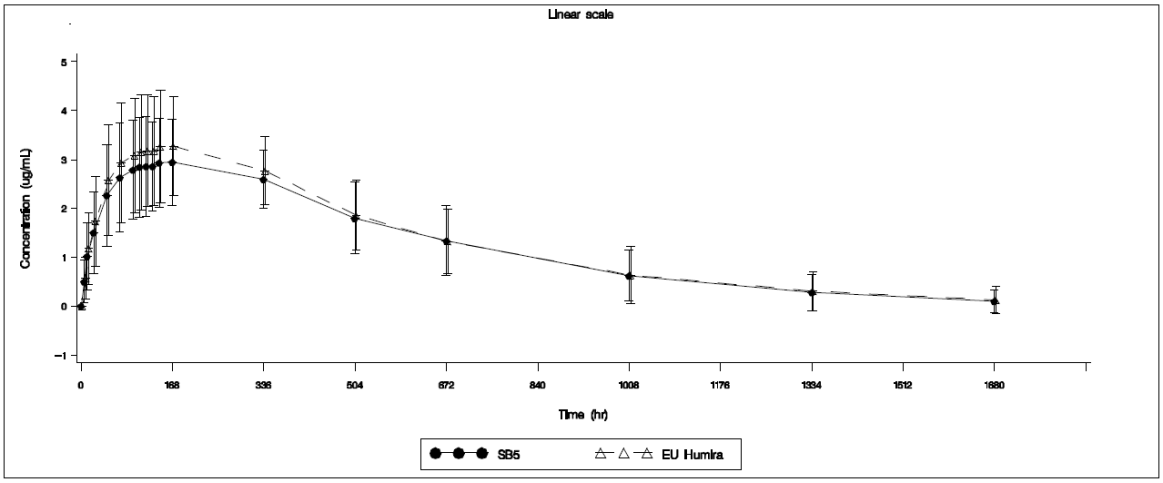
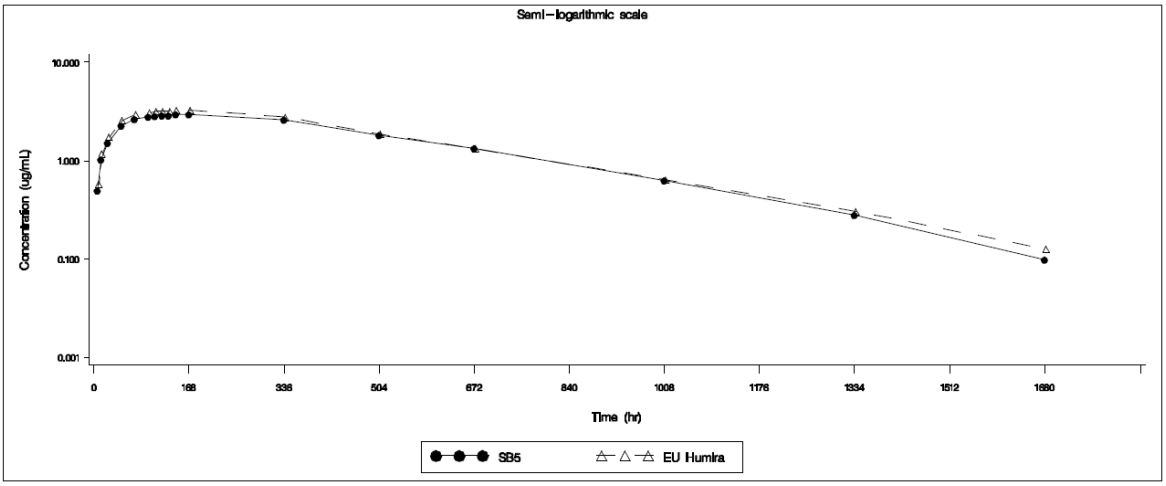



**Figure 3.4.1.2 Mean serum concentration (µg/ml) versus nominal times (h) on semi-logarithmic scale of SB5 and EU-sourced Humira.**




The secondary PK endpoints were also at the same level between SB5 group and EU-sourced Humira group (see Table 3.4.1.1).

No pre-dose concentrations were detected and no subjects reached the $T_{max}$ at the first sampling time-point.

The extrapolated AUC was less than 20% in most subjects (extrapolated AUC was > 20% in 3 subjects who received SB5, in 11 subjects who received EU-sourced Humira and in 9 subjects who received US-sourced Humira). Only 4 extrapolated AUCs were above 30% and the reason for the great difference between $AUC_{inf}$ vs $AUC_{last}$ was a short sampling period (in 3 cases up to 336 h and in one case up to 672 h). The sampling period has been long enough in most cases (no concern).

**Table 3.4.1.1 Summary of PK parameters for SB5 and EU-sourced Humira (PK analysis set)**

| PK Parameter (unit) | Statistics | SB5 N=62 | EU sourced Humira® N=63 |
|---|---|---|---|
| $AUC_{inf}$ | n | 53 | 61 |
| (µg·h/mL) | Mean | 2405.6 | 2435.5 |
| | SD | 825.93 | 915.66 |
| | Median | 2377 | 2264 |
| | Min | 852 | 1126 |
| | Max | 5049 | 5377 |
| $AUC_{last}$ | n | 53 | 61 |
| (µg·h/mL) | Mean | 2125.7 | 2096.0 |
| | SD | 689.92 | 791.28 |
| | Median | 2145 | 2012 |
| | Min | 796 | 657 |
| | Max | 4013 | 4151 |
| $C_{max}$ | n | 53 | 61 |
| (µg/mL) | Mean | 3.365 | 3.548 |
| | SD | 0.9796 | 1.1811 |
| | Median | 3.24 | 3.32 |
| | Min | 1.47 | 1.50 |
| | Max | 6.37 | 7.47 |
| $AUC_{0\text{-}336}$ | n | 53 | 61 |
| (µg·h/mL) | Mean | 914.0 | 956.6 |
| | SD | 234.81 | 293.36 |
| | Median | 906 | 920 |
| | Min | 382 | 394 |
| | Max | 1524 | 1861 |
| $T_{max}$ | n | 53 | 61 |
| (h) | Mean | 165.962 | 149.715 |
| | SD | 89.2503 | 76.6421 |
| | Median | 143.95 | 143.93 |
| | Min | 23.90 | 23.92 |
| | Max | 504.57 | 338.07 |
| $t_{½}$ | n | 53 | 61 |
| (h) | Mean | 342.46 | 357.58 |
| | SD | 153.499 | 181.168 |
| | Median | 319.4 | 341.7 |
| | Min | 120.7 | 101.3 |
| | Max | 740.7 | 830.8 |
| Vz/F | n | 53 | 61 |
| (mL) | Mean | 8279.2 | 8557.6 |
| | SD | 2563.93 | 3310.51 |
| | Median | 8180 | 7830 |
| | Min | 5096 | 2439 |
| | Max | 15986 | 20801 |
| CL/F | n | 53 | 61 |

The equivalence of the primary endpoints ($AUC_{inf}$, $C_{max}$) and also in $AUC_{last}$ was demonstrated; the 90% CI for the ratio of geometric LS Means of SB5 to EU-sourced Humira was within the acceptance interval of 0.8 to 1.25 and including the value 1.00 in the ratios (see Table 3.4.1.2).

**Table 3.4.1.2 ANOVA for PK parameters $AUC_{inf}$, $AUC_{last}$ and $C_{max}$ comparing SB5 to EU-sourced Humira (PK analysis set)**

| PK Parameter (unit) | Treatment | N | n | Geo-LS Means | Ratio A/B | 90% CI of Ratio |
|---|---|---|---|---|---|---|
| $AUC_{inf}$ (µg·h/mL) | SB5 | 62 | 53 | 2262.1 | 0.990 | 0.885; 1.108 |
| | EU sourced Humira® | 63 | 61 | 2284.3 | | |
| $AUC_{last}$ (µg·h/mL) | SB5 | 62 | 53 | 2007.0 | 1.027 | 0.915; 1.153 |
| | EU sourced Humira® | 63 | 61 | 1954.0 | | |
| $C_{max}$ (µg/mL) | SB5 | 62 | 53 | 3.229 | 0.957 | 0.870; 1.054 |
| | EU sourced Humira® | 63 | 61 | 3.373 | | |

A = SB5; B = EU sourced Humira®.
ANOVA = Analysis of variance; LS Means = least squares means; CI = confidence interval; N = number of subjects in PK population; n = number of subjects who contributed to analysis.
Subjects whose $T_{max}$ being 1 of the last 3 points in the respective profiles, were excluded from the ANOVA.

The post-dose ADA and NAb incidence was comparable between SB5 and EU-sourced Humira. (See for details under Clinical safety/ Immunological events).

However, the PK data of 16 subjects (n = 9 in the SB5 group, n = 2 in the EU-sourced Humira group and n = 5 in the US-sourced Humira group) were excluded from the initial PK analysis (the summary statistics and ANOVA for PK parameters) as the regression slope could not be estimated according to protocol ($T_{max}$ being 1 of the last 3 points in the respective profiles).

As there was no clear rationale to exclude $C_{max}$, $AUC_{last}$ and $AUC_{0-336}$ values from analysis, the Applicant has been asked to present a sensitivity analysis comparing $AUC_{0-t}$, $AUC_{0-336}$, and $C_{max}$ between treatment arms including these patients.

**Table 3.4.1.3 Analysis of Variance (ANOVA) for PK parameters including 16 subjects (PK population) (Study SB5-G11-NHV)**

| PK Parameter | Treatment | N | n | Mean | SD | Geo-LSMean | Ratio of SB5 to Reference Humira | | Ratio of EU Humira to US Humira | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Estimate | 90% CI | Estimate | 90% CI |
| $AUC_{inf}$ (h* µg/mL) | SB5 | 62 | 53 | 2405.6 | 825.93 | 2262.1 | | | | |
| | EU Humira | 63 | 61 | 2435.5 | 915.66 | 2284.3 | 0.990 | 0.885;1.108 | | |
| | US Humira | 62 | 57 | 2422.6 | 957.00 | 2259.4 | 1.001 | 0.890;1.126 | 1.011 | 0.904;1.131 |
| $C_{max}$ (µg/mL) | SB5 | 62 | 62 | 3.188 | 1.0226 | 3.027 | | | | |
| | EU Humira | 63 | 63 | 3.519 | 1.1729 | 3.347 | 0.905 | 0.822;0.996 | | |
| | US Humira | 62 | 62 | 3.451 | 1.0700 | 3.285 | 0.922 | 0.836;1.016 | 1.019 | 0.926;1.121 |
| $AUC_{last}$ (h*µg/mL) | SB5 | 62 | 62 | 1934.5 | 795.12 | 1748.6 | | | | |
| | EU Humira | 63 | 63 | 2062.8 | 800.38 | 1915.4 | 0.913 | 0.801;1.040 | | |
| | US Humira | 62 | 62 | 2015.9 | 822.42 | 1851.1 | 0.945 | 0.824;1.082 | 1.035 | 0.916;1.169 |
| $AUC_{0-336}$ (h*µg/mL) | SB5 | 62 | 61 | 865.6 | 259.80 | 820.8 | | | | |
| | EU Humira | 63 | 63 | 949.7 | 291.14 | 907.5 | 0.904 | 0.820;0.997 | | |
| | US Humira | 62 | 62 | 928.3 | 274.65 | 884.4 | 0.928 | 0.839;1.027 | 1.026 | 0.934;1.127 |

In addition, ANOVA was performed between the treatment groups for the $AUC_{inf}$, $C_{max}$, $AUC_{last}$ and $AUC_{0-336}$. The results presented in Table 3.4.1.3 show that the 90% confidence intervals of all the three

PK parameters are entirely contained in the [0.8; 1.25] interval. It was noted that the estimates in the SB5 group changed considerably.

Therefore, the Applicant was asked to investigate whether the differential exclusion may actually be related to differences in PK between SB5 and the reference medicinal product. A thorough investigation of the characteristics of excluded subjects (9 from the SB5 vs 2 from EU Humira group) showed that they tended to have higher BMIs and ADA titres compared with non-excluded subjects, which might result in lower absorption and faster clearance. While the development of ADAs is a post-randomisation event (and thus attributable to treatment), the distribution of height, weight and body mass index is very similar between groups (due to randomisation). Concerning ADA status, overall analyses [including the (PK) excluded subjects] do not reveal a meaningful difference in overall incidence and titres of ADAs between treatment.

Potential quality differences between SB5 and the reference product, which could also influence the absorption rate after extravascular administration, e.g. molecular weight or charge profiles, were also considered. However, data from extensive quality studies supports molecular similarity of SB5 and reference product, and the minor difference in acidic variants is not considered to translate into differences in biological activity. In summary, a difference in PK between SB5 and EU Humira cannot be concluded from this data.

**Clinical study in patients with moderate to severe RA despite MTX therapy (SB5-G31-RA)**

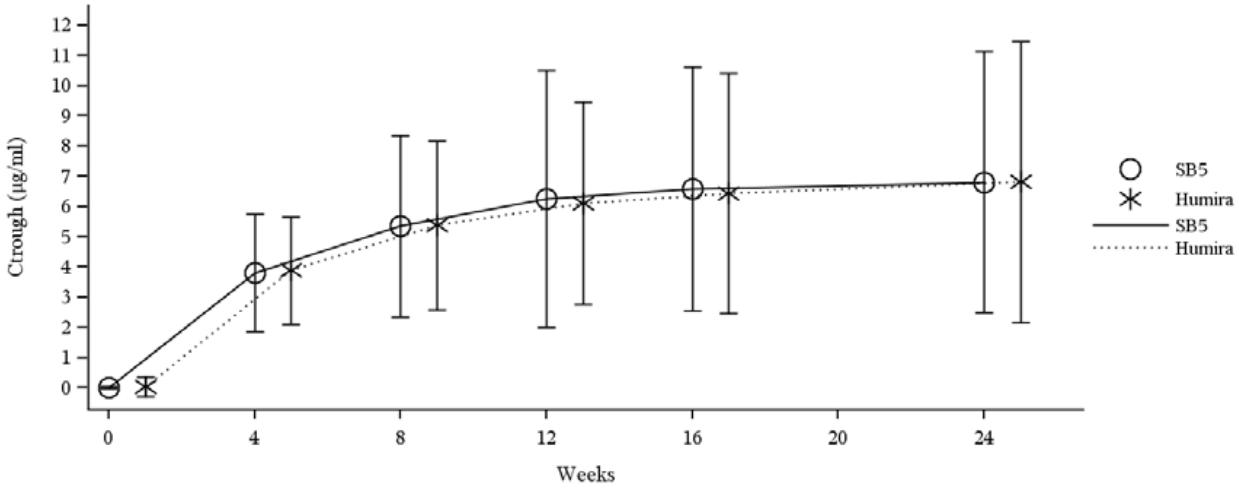
The study is described in Section 2.5.2. The PK results are summarized in this Section.

The first 65% of the enrolled subjects (356 subjects) had blood samples collected for PK analysis. The PK analysis set included 178 patients in the SB5 group and 178 patients in the Humira (EU-sourced) group. Subjects self-administered 40 mg of either SB5 or EU-sourced Humira every other week s.c., up to Week 50 (a total of 26 administrations of IP).

The serum concentrations of adalimumab ($C_{trough}$) were obtained prior to dosing at weeks 0, 4, 8, 12, 16 and 24. Blood samples for immunogenicity tests were collected at the same timepoints as the PK blood samples and additionally at weeks 32, 40 and 52.

Overall mean trough concentrations were similar at each time-point between the SB5 group and the Humira group (see Figure 3.4.1.3 and Table 3.4.1.3). The range of individual trough concentrations was also similar between the 2 treatment groups.

**Figure 3.4.1.3 Mean (SD) serum trough (pre-dose) concentration (µg/ml)-time profiles from week 0 to week 24.**




The serum trough concentrations up to week 24 were comparable between SB5 and Humira groups among those patients with an overall negative ADA result and among those patients with an overall positive ADA result.

Within each treatment group, overall mean trough concentrations in subjects with overall positive ADA results up to week 24 were remarkably lower than in subjects with overall negative ADA results up to Week 24. This was expected, as ADA formation against adalimumab is known to be accompanied by increased clearance and reduced exposure, as well as a possible loss of efficacy. Immunogenicity impact on pharmacokinetics is presented more detailed in the Safety part of this report.

**Table 3.4.1.4 Summary of serum trough (pre-dose) concentration (µg/ml) (PK analysis set)**

| Timepoint | Statistics | SB5 40 mg N=178 | Humira 40 mg N=178 |
|---|---|---|---|
| Week 0 | n | 164 | 166 |
| | *Mean (SD) | 0.004 (0.0404) | 0.035 (0.3399) |
| | CV% | 906.948 | 983.077 |
| | Min, Max | 0.00, 0.40 | 0.00, 4.33 |
| Week 4 | n | 165 | 170 |
| | *Mean (SD) | 3.850 (1.9687) | 3.892 (1.7833) |
| | CV% | 51.140 | 45.823 |
| | Min, Max | 0.00, 14.59 | 0.00, 8.66 |
| Week 8 | n | 167 | 169 |
| | *Mean (SD) | 5.224 (2.8888) | 5.378 (2.8075) |
| | CV% | 55.303 | 52.199 |
| | Min, Max | 0.00, 16.83 | 0.00, 13.43 |
| Week 12 | n | 167 | 162 |
| | *Mean (SD) | 6.244 (4.2736) | 6.034 (3.3600) |
| | CV% | 68.443 | 55.689 |
| | Min, Max | 0.00, 31.69 | 0.00, 17.44 |
| Week 16 | n | 164 | 157 |
| | *Mean (SD) | 6.526 (4.1034) | 6.409 (3.9340) |
| | CV% | 62.873 | 61.379 |
| | Min, Max | 0.00, 17.63 | 0.00, 16.98 |
| Week 24 | n | 159 | 162 |
| | *Mean (SD) | 6.761 (4.3869) | 6.773 (4.6675) |
| | CV% | 64.888 | 68.914 |
| | Min, Max | 0.00, 23.19 | 0.00, 18.22 |

N = number of subjects in the PK population; n = number of subjects
CV% = coefficient of variation; PK = pharmacokinetics; SD = standard deviation
*Means are arithmetic means

## 2.4.3. Pharmacodynamics

No pharmacodynamic data were evaluated in the bioequivalence studies in healthy volunteers since the validated PD markers do not exist for the efficacy of TNF-α inhibitors. Regarding the primary PD a set of non-clinical in vitro and in vivo studies has been performed. Studies on secondary PD have not been provided and are not required according to the EMA guideline (EMA/CHMP/BMWP/403543/2010).

Adalimumab is a human recombinant IgG monoclonal antibody (mAb) that exerts its effect by inhibiting TNF-α functional activity. TNF-α may exist as a soluble (sTNF-α) or a transmembrane (tmTNF-α) form.

Elevated levels of TNF-α have been detected in the serum and in the affected joints and tissues of patients with the various conditions for which Humira is approved. Therefore, the mechanism of action of adalimumab appears to be complex formation with TNF-α, which results in decrease of its availability to induce inflammatory effects and to facilitate its elimination. Complexes of adalimumab and TNF-α, particularly tmTNF-α, may also reduce the presence of disease-promoting inflammatory cells by

mediating processes such as reverse signalling (which initiates anti-inflammatory processes), apoptosis, antibody dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC).

In RA, PsA, and PsO, neutralisation of soluble and transmembrane TNF-α may play an important role. On the other hand, in CD and UC, inhibition of tmTNF-α signalling and Fcγ receptor-mediated functions may play an important role as well.

Extrapolation to originator indications is discussed in detail elsewhere in this AR.

**Table 3.4.2.1: Known and potential Mechanism of Actions of Humira in the licensed conditions of use**

| MOA of Humira | RA | AS | PsA | PsO | CD | UC | HS |
|---|---|---|---|---|---|---|---|
| *Mechanisms involving the Fab (antigen binding) region:* | | | | | | | |
| Blocking TNFR1 and TNFR2 activity via binding and neutralisation of s/tmTNF | Known | Known | Known | Known | Likely | Likely | Likely |
| Reverse (outside-to-inside) signalling via binding to tmTNF: | - | - | - | - | Likely | Likely | Possible |
| Apoptosis of lamina propria activated T cells | - | - | - | - | Likely | Likely | Possible |
| Suppression of cytokine secretion | - | - | - | - | Likely | Likely | Possible |
| *Mechanisms involving the Fc (constant) region* | | | | | | | |
| Induction of CDC on tmTNF-expressing target cells (via C1q binding) | - | - | - | - | Plausible | Plausible | Possible |
| Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells) | - | - | - | - | Plausible | Plausible | Possible |
| Induction of regulatory macrophages in mucosal healing | - | - | - | - | Plausible | Plausible | Possible |

ADCC=antibody-dependent cellular cytotoxicity; AS=ankylosing spondylitis; CD=Crohn's Disease; CDC=complement-dependent cytotoxicity; HS=Hidradenitis Suppurativa; MOA=mechanism of action; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; UC=ulcerative colitis; sTNF=soluble TNF; tmTNF=transmembrane TNF.
Source: adapted from: FDA Briefing Document, Arthritis Advisory Committee Meeting, 2016

## 2.4.4. Discussion on clinical pharmacology

### Analytical methods

The Applicant has used several bioanalytical methods for determination of circulating adalimumab, anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) from the serum samples of healthy volunteers (study SB5-G11-NHV) and patients with rheumatoid arthritis (RA, study SB5-G31-RA). For the ADA/Nab assays a single SB5 format is used for SB5 and Humira (EU, US) measurements both in validation and sample analysis. As part of the validation limited data demonstrating equal antigenicity of SB5 and Humira were provided, and thus further data from validation of both SB5 and Humira assays were requested together with information concerning the performance of both analytes in the two assay settings. The applicant has provided further data as requested and all of the issues are solved. For all assays validation reports have been provided, yet the data across assays was not fully clear and robust.

Concerning the drug measurements, validation of the phase 1 assay (pivotal PK study) was otherwise adequately performed, but the statistical analysis and the method used to define calibration curves raised questions. These have been adequately addressed by the applicant. Furthermore, possible ADA interference had not been evaluated at all, which raised concerns, as many of the study individuals have ADAs and NAbs (almost 100% of the healthy volunteers). The applicant has provided further data to demonstrate that the ADAs have not had impact on biosimilarity assessment. However, from the results it is clear that ADAs have a significant impact on PK measurements. Thus, it is recommended that for future regulatory submissions that involve PK and immunogenicity assessment, the ADA interference is clearly taken into account and described. For the phase 3 study ELISA assay validation data in RA matrix was missing, but has now been provided and the issue is solved.

Concerning the ADA and Nab assays, the screening and confirmatory methods for samples from healthy volunteers originally appeared more reliable and robust than those used for the Phase 3 RA samples. The applicant has provided further data and clarifications to address the identified problems in validation of the methods for RA samples. The issues concerning ADA drug tolerance testing and the impact of the difference in sensitivity to SB5 and Humira on the actual ADA results have been clarified and additional concordance data from earlier time points have been provided.

**PK data analysis and statistical analyses**

The PK parameters were adequately calculated. The handling of the BLQ concentrations was appropriate. The sample size calculations, randomisations and used analysis methods were appropriate. The original Statistical analysis plan (SAP) for the pivotal PK study (i.e. SB5-G11-NHV) was not included in the initially submitted dossier and the SAP and amendment were asked to be provided by the Applicant. The Applicant provided the above mentioned documents and the data related to the statistical analyses presented only summarised in the clinical study report.

**The PK studies**

Two clinical studies were performed in which the PK of adalimumab from SB5 was compared to that of Humira (EU-sourced). The doses of adalimumab administered s.c. were in the pivotal PK study 40 mg as a single-dose and 40 mg every other week up to week 50 in the clinical study in RA patients. The administration device was the PFS in both studies.

In the pivotal PK study (SB5-G11-NHV) the primary objective was to investigate and compare the PK profiles of SB5 and EU-sourced Humira in healthy subjects. The healthy subjects are an adequate population to show the PK similarity. The choice of parallel study design was adequately justified. Adalimumab has approximately a two week half-life and there may have been safety concerns on repeated dosing due to potential immunogenicity. There were originally no exact data of the protein content of the test and reference product batches used in the clinical study. Consequently, the protein content data for the test and the reference products was asked to be provided by the Applicant. The Protein contents of the test product batch and the reference product batch are almost similar.

For the primary PK parameters (i.e. $AUC_{inf}$ and $C_{max}$) the 90%CI for the ratio of the test and reference products was within the pre-specified bioequivalence acceptance range of 80.0%-125.00% (including the 100.00% in the ratios). The $AUC_{last}$ and partial $AUC_{0-336}$ were also at the similar level between studied treatments.

The Applicant presented a sensitivity analysis comparing $AUC_{0-t}$, $AUC_{0-336}$, and $C_{max}$ between treatment arms including 16 patients who had been formally excluded from the primary statistical analysis per protocol, as $t_{max}$ was one of the 3 last measurable time points, which was an exclusion criterion for the regression slope estimation. This was requested since there is no compelling rationale for excluding the $C_{max}$, $AUC_{last}$ and $AUC_{0-336}$ values of 9 subjects with SB5 and 2 subjects from the EU Humira treatment

arm from statistical analysis, as the measurements of almost all time points necessary to evaluate these parameters are available. While the 90% CIs of these three PK parameters are still entirely contained in the [0.8; 1.25]acceptance range, the estimates in the SB5 group changed considerably.Therefore, the Applicant was asked to investigate whether the differential exclusion may actually be related to differences in PK between SB5 and the reference medicinal product. A thorough investigation of the characteristics of excluded subjects showed that they tended to have higher BMIs and ADA titres compared with non-excluded subjects, which might result in lower absorption and faster clearance. While the development of ADAs is a post-randomisation event (and thus attributable to treatment), the distribution of height, weight and body mass index is very similar between groups (due to randomisation). Overall analyses [including the (PK) excluded subjects] do not reveal a meaningful difference in overall incidence and titres of ADAs between treatment.

Potential quality differences between SB5 and the reference product, which could also influence the absorption rate after extravascular administration, e.g. molecular weight or charge profiles, were also considered. However, data from extensive quality studies supports molecular similarity of SB5 and reference product, and the minor difference in acidic variants is not considered to translate into differences in biological activity. In summary, a difference in PK between SB5 and EU Humira cannot be concluded from this data.

The PK data were obtained also from phase 3 study in RA patients, which is in line with guideline recommendations.

Overall mean trough concentrations were similar between the SB5 group and the Humira group. The range of individual trough concentrations was also similar between the two treatment groups. The inter-patient variabilities in the trough concentrations were high (at steady-state the CV%s were 56-69%), however, at the same level in both studied treatments. The Applicant was requested to perform direct comparison of the trough concentrations between SB5 and EU-sourced Humira, presenting point estimates and 90%CIs. This comparative analysis was to be provided for all visits where the PK measurements were done. The Applicant performed the comparative analysis in the trough concentrations between SB5 and EU-sourced Humira at all visits as requested. The trough concentrations have been within the bioequivalence criteria (i.e. within 0.8-1.25 including 1.0) at each week except at baseline. Consequently, the trough concentrations have been similar in RA patients.

There were several patients both in SB5 and Humira group having no trough concentrations in one time-point or even in all time-points. Consequently, the reason for trough concentrations of below limit of quantification (BLQ) and some discussion of these low concentrations and their impact on the efficacy was asked to be provided. The Applicant provided very comprehensive discussion of the trough concentration below the BLQ. It was thought that immunogenicity had also an impact to the low concentrations, because most of the patients with at least one post-dose BLQ had overall ADA-positive results up to week 24 (i.e. the clearance of adalimumab was higher in these patients).

The Applicant thought that the existence of at least one BLQ might have an influence in efficacy; however, the efficacy profiles were comparable. The Applicant presented the ACR20/50/70 response rates for RA patients, who had at least one post-dose BLQ up to week 24 and it can be seen that the efficacy profiles were quite comparable. The impact of the low concentrations to the efficacy can be considered to have been similar in both treatment groups (the number of patients with at least one post-dose BLQ was quite comparable between studied treatments, The distribution of ADA and Nab status in patients having at least one post-dose BLQ between the two treatment groups was comparable and the efficacy was comparable between the treatment groups).

There were also some excluded trough concentrations on the data at different time-points, which needed explanation (the number of patients in the PK population was 178 in both groups; however, the number

of patients having pre-dose concentrations in different weeks varied from 157 to 169 in both groups. The reasons of exclusions were as follows: patients were discontinued from the study, due to a protocol deviation of PK blood sampling (i.e. within 60 minutes prior to the investigational product administration; drug concentration was analysed, but not included for the summary statistics for trough concentration analysis) and due to the PK sampling not being performed. The exclusion of the data from summary statistics for trough concentration analysis was in accordance with the study protocol.

The Applicant was requested to clarify open questions regarding the patients not allocated to the PK population, in which PK samples were taken by mistake. The Applicant clarified adequately that none of the non-PK patients have undergone the complete sampling period of 24 weeks and the PK analysis has not been performed on these samples.

The serum trough concentrations up to week 24 were comparable between SB5 and Humira groups among those patients with an overall negative ADA result and among those patients with an overall positive ADA result. Within each treatment group, overall mean trough concentrations in subjects with overall positive ADA results up to week 24 were markedly lower than in subjects with overall negative ADA results up to Week 24, which is consistent with the Humira SmPC.

No clinical studies in special populations and no *in vitro* or *in vivo* drug-drug interaction studies were conducted with the SB5 and this is acceptable.

In the proposed SB5 SmPC the PK text in the Section 5.2 “Pharmacokinetic properties” is from the Humira SmPC. As the SB5 and Humira are considered to be biosimilar it is acceptable to use Humira SmPC text.

**The PD studies and extrapolation**

No specific PD biomarkers are available for TNFα functional studies and the data provided has been based on non-clinical primary pharmacodynamics studies. This is approvable since the question here is about biosimilar development and not of a novel treatment entity. Regarding extrapolation, the Applicant has provided data on the cytokine profiles in the various indications and explained TNF-α overexpression as being the common denominator in the Humira approved medical conditions.

Regarding the recently approved new indications of EU-Humira, the Applicant has justified in their responses the extrapolation to hidradenitis suppurativa (HS) indication and in both RA and HS similar cytokine targets are proposed. It has been reported that cytokines IL-17 and IL-22 releasing T helper cells (Th17), after induction by IL-23 and IL-1β, infiltrate the dermal HS lesions. RA is considered to be one of the Th17-mediated diseases and the effector cytokines of Th17 cells are known to induce characteristic findings of RA. Thus the extrapolation between RA and HS can be considered acceptable. Also, in uveitis Th17 function is believed to be central in pathogenesis, which is also implied by the cytokine profile with elevated IL-17 and IL-22 levels in Uveitis, although their direct correlation to the Th17 pathogenesis has been disputed. Nevertheless, it has been shown that he numbers of TH17 cells increased during active uveitis/scleritis and decreased following treatment in animal experiments and IL-17 blockade reduced severity of inflammation in uveitis rodent models.

## 2.4.5. Conclusions on clinical pharmacology

In the pivotal PK study the 90%CIs for the GM ratios of the primary PK parameters (i.e. $AUC_{inf}$ and $C_{max}$) of the test and reference products was within the pre-specified bioequivalence acceptance range of 80.0%-125.00% (including the 100.00% in the ratios).

Initial concerns based on the differential exclusion of subjects between the SB5 and EU Humira arm and the results of a PK sensitivity analysis including all subjects, have been resolved.

Further information on the assessment of drug concentration and ADA/NAb results and validation of the analytical methods has been provided and all bioanalytical questions are resolved.

## *2.5. Clinical efficacy*

### 2.5.1. Dose response study(ies)

### 2.5.2. Main study

### SB5-G31-RA: A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity of SB5 Compared to Humira in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy *Methods*

#### *Study Participants*

The Applicant has recruited patients with active, moderate to severe RA despite MTX therapy for at least 6 months from a total of 51 centres, 48 in Europe (both inside and outside the EU) and in Korea. To reduce efficacy and safety outcome variability, subjects had to be on both a stable route of MTX administration (oral or parenteral) and a stable dose of MTX and continue to take MTX throughout the study.

**Inclusion Criteria**

Subjects had to meet all of the following criteria to be eligible for the study:

1. Were male or female aged 18-75 years at the time of signing the informed consent form.

2. Had been diagnosed as having RA according to the revised 1987 ACR criteria for at least 6 months but not exceeding 15 years prior to Screening.

3. Had moderate to severe active disease, despite MTX therapy, defined as:

    a. More than or equal to 6 swollen joints and more than or equal to 6 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) ≥ 10 mg/L at Screening.

4. Had been treated with MTX for a total of at least 6 months prior to Randomisation and must have been on both: a stable route of administration (oral or parenteral) and stable dose of MTX (10-25 mg/week) for at least 4 weeks prior to Screening.

5. If using non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics for RA, must have been on a stable dose for at least 4 weeks prior to Randomisation. If taking oral glucocorticoids, must have been on a stable dose (equivalent to ≤ 10 mg prednisolone daily) for at least 4 weeks prior to Randomisation. Low potency topical, otic and ophthalmic glucocorticoid preparations were permitted.

6. Female subjects who were not pregnant or nursing at Screening and Randomisation and who were not planning to become pregnant from Screening until 5 months after the last dose of IP.

7. Subjects and their partners of childbearing potential (female or male) must have agreed to use at least 2 forms of appropriate contraception (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, physical barrier, male sterilisation or true abstinence) from Screening until 5 months after the last dose of IP. True abstinence was to be considered sufficient for subjects who do not have a partner.

8. Were able to, in the opinion of the Investigator, understand the implications of taking part in the study and be willing to follow the study requirements.

9. Had provided informed consent, which had to be obtained prior to any study related procedures.

**Exclusion Criteria**

Subjects meeting any of the following criteria were not eligible for the study:

1. Had been treated previously with any biological agents including any TNF inhibitor.

2. Had a known hypersensitivity to human immunoglobulin proteins or other components of Humira or SB5.

3. Had been taking any of the following concomitant medications, within the timeframe specified:

    a. Corticosteroids for the treatment of RA above levels equivalent to 10 mg prednisolone daily within 4 weeks prior to Randomisation.

    b. Any DMARDs/systemic immunosuppressive agents (other than MTX) including, but not limited to, hydroxy-chloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus 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 3 times daily (alternatively with 50 g of activated powdered charcoal 4 times daily) for at least 11 days.

    d. Alkylating agents including, but not limited to, chlorambucil, cyclophosphamide, nitrogen mustard within 12 months prior to Randomisation.

    e. Injectable corticosteroids for the treatment of RA within 4 weeks prior to Randomisation.

    f. IP from another study within 5 half-lives of that product prior to Randomisation or use of an investigational device at Screening.

4. Had been taking or were expected to receive any live or live-attenuated vaccine within 8 weeks prior to Randomisation or during the study.

5. Had abnormal renal or hepatic function at Screening defined as the following:

    a. Serum creatinine $\geq$ 2 $\times$ the upper limit of normal (ULN).

    b. Serum alanine transaminase or aspartate transaminase $\geq$ 2 x ULN.

6. Had abnormal haematological parameters at Screening defined as the following:

    a. Haemoglobin < 8.0 g/dL.

    b. White blood cell count < 3.5 × 103 cells/µL (< 3.5 × 109 cells/L).

    c. Neutrophil count < 1.5 × 103 cells/µL.

    d. Platelet count < 100 × 103 cells/µL.

7. Had a positive serological test for hepatitis B or hepatitis C or had a known history of infection with human immunodeficiency virus.

8. Had a current diagnosis of active TB, had been recently exposed to a person with active TB, or were considered to have latent TB as indicated by a positive QuantiFERON® Gold test result.

9. Had had a serious infection (such as sepsis, abscess, opportunistic infections, or invasive fungal infections such as histoplasmosis) or had been treated with intravenous antibiotics for an infection within 8 weeks or oral antibiotics within 2 weeks prior to Randomisation. Nonsignificant infections did not need to be considered exclusionary at the discretion of the Investigator.

10. Had a history of chronic or recurrent infection (such as chronic renal infection, chronic chest infection, or recurrent urinary infection).

11. Had a history of an infected joint prosthesis which had not been removed or replaced.

12. Had any of the following conditions:

    a. History of congestive heart failure (New York Heart Association Class III/IV).

    b. History of acute myocardial infarction or unstable angina within the previous 12 months prior to Screening.

    c. Uncontrolled diabetes mellitus or uncontrolled hypertension which, in the opinion of the Investigator, would have put the subject at risk if they were enrolled.

    d. History of demyelinating disorders (such as multiple sclerosis or Guillain-Barré syndrome).

    e. History of any malignancy within the previous 5 years prior to Screening except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.

    f. History of lymphoproliferative disease including lymphoma.

    g. History of organ transplantation.

    h. Significant systemic RA involvement (e.g., vasculitis, pulmonary fibrosis, etc.) which, in the opinion of the Investigator, would have put the subject at risk if they were enrolled.

    i. Other inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, AS, systemic lupus erythematosus, Lyme disease, or fibromyalgia, which may have confounded the evaluation of the efficacy or safety of IP.

    j. Any conditions significantly affecting the nervous system (e.g., neuropathic conditions or nervous system damage) which may have interfered with the Investigator's assessment on disease activity scores including joint counts.

    k. Any other disease or disorder which, in the opinion of the Investigator, would have put the subject at risk if they were enrolled.

13. Had physical incapacitation (ACR functional Class IV or wheelchair-/bed-bound).

14. Have had a substance abuse (alcohol or drug) problem within the previous 3 years prior to Screening.

## *Treatments*

**Test product**: SB5

Presentation: prefilled syringe

Dose: 40 mg every other week

Administration route: subcutaneous injection

**Reference product**: Humira provided by Abbvie Ltd (EU-sourced)

Presentation: prefilled syringe

Dose: 40 mg every other week

Administration route: subcutaneous injection

Subjects had to take MTX for at least 6 months prior to Randomisation. A stable dose of oral or parenteral MTX (10-25 mg/week) was to be taken by all subjects from 4 weeks before Screening until End-of-Treatment visit (Week 52). The route of administration was not to be changed in this period.

As MTX can cause folic acid deficiency, during this period subjects also had to take folic acid 5-15 mg/week.

## *Objectives*

The primary objective of this study was to demonstrate the equivalence of SB5 to Humira at Week 24, in terms of American College of Rheumatology 20% response criteria (ACR20) response rate in subjects with moderate to severe RA despite MTX therapy.

The secondary objectives were:

- To evaluate efficacy of SB5 compared to Humira 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 SB5 compared to Humira in subjects with moderate to severe RA despite MTX therapy.
- To evaluate PK of SB5 compared to Humira in subjects with moderate to severe RA despite MTX therapy.
- To evaluate immunogenicity of SB5 compared to Humira in subjects with moderate to severe RA despite MTX therapy.
- To evaluate safety and immunogenicity in subjects who transitioned to SB5 and who maintained Humira at Week 24 for transition sub-study.

## *Outcomes / endpoints*

The main efficacy variable for the study is the ACR20 response. Other efficacy endpoints include the American College of Rheumatology 50% response criteria (ACR50), the American College of Rheumatology 70% response criteria (ACR70), individual components of the ACR improvement criteria, DAS28, major clinical response, and the European League Against Rheumatism (EULAR) response (good response, moderate response or no response). The ACR20 response indicates:

- 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 3 of the following 5 criteria:
    - Subject pain assessment using a 100 mm VAS
    - Subject global assessment using a 100 mm VAS
    - Physician global assessment using a 100 mm VAS
    - Subject assessment of disability using the HAQ-DI
    - Acute phase reactant level (CRP)

The ACR50 and ACR70 indicate a 50% and 70% improvement, respectively, in the criteria.

Other secondary outcome measures were individual components of the ACR improvement criteria; decrease in Disease Activity Score 28 (DAS28); major clinical response; the European League Against Rheumatism (EULAR) response (good response, moderate response or no response); continuous ACR-N and the AUC of ACR-N; AUC of change from baseline in DAS28; numeric index of the ACR response (ACR-N); structural joint damage (single posteroanterior and dorsoplantar X-ray image of each wrist and foot respectively) and the joint erosion score, the joint space narrowing (JSN) score and the modified total Sharp score (mTSS).

### *Randomisation and Blinding (masking)*

A unique subject number was assigned to subjects at Screening. The subject number was used to register the subject using the Interactive Web Response System (IWRS) and the subject was then randomised (in a ratio of 1:1) to either SB5 or Humira. At Week 24, subjects receiving Humira were randomised again in a 1:1 ratio to either continue on Humira or be transitioned to SB5. Subjects receiving SB5 continued to receive SB5 but they also followed the randomisation procedure to maintain blinding. These randomisations occurred according to a computer-generated randomisation scheme which randomised subjects at a centre-level. If a subject was withdrawn the randomisation number(s) were not re-used. At each study visit the Investigator or designee contacted the IWRS and an appropriate number of codes was provided. These codes indicated which prefilled syringes should be dispensed to the subject.

### *Statistical methods*

Randomised set (RAN) consisted of all subjects who received a randomisation number at the Randomisation visit. Full analysis set (FAS) consisted of all subjects who were randomised at the Randomisation visit. Subjects who did not qualify for randomisation and were inadvertently randomised into the study were excluded from the FAS, provided these subjects do not receive IP during that study phase. Per-protocol set 1 (PPS1) consisted of all FAS subjects who completed the Week 24 visit and adhered to the IP regimen within the range of 80-120% of both the expected number of IP administrations and the expected sum of MTX doses without any major protocol deviations that have impact on the efficacy assessment. The PPS1 was considered the primary analysis set. Per-protocol set 2 (PPS2) consisted of all FAS subjects who completed the Week 52 visit and had an adherence (through Week 52) within the range of 80-120% of both the expected number of IP administrations and the expected sum of MTX doses without any major protocol deviations that have impact on the efficacy assessment. Safety set (SAF) comprised subjects who received at least one dose of IP during the study

phase. Pharmacokinetic population comprised all subjects in the SAF who had at least one pharmacokinetic sample collected.

The primary objective of this study was to demonstrate equivalence in the ACR20 response rate between SB5 and Humira at Week 24 for the PPS1 by employing a randomisation-based nonparametric analysis of covariance.

The corresponding 95% CIs of the treatment difference in terms of ACR20 response rate were estimated using non-parametric analysis that controlled for region as a factor and baseline CRP value as a covariate. Equivalence between the two treatment groups was declared if the 2-sided 95% CI of the difference in ACR20 response rate between SB5 and Humira was entirely contained within the equivalence margin of [-15%, 15%].

As the ACR20 response rate is expected to be around 50% at Week 24 based on the historic data, the proportion of patients achieving ACR20 response approximately follows a normal distribution. Hence the proportion was treated as a continuous variable. The difference in proportions was weighted by the number of observations pertaining to each region and the variance was estimated under the assumption of the different variation between two treatment groups within region.

A supportive analysis using a time-response model with the ACR20 response was used to further investigate the treatment difference during the time course of the study period up to Week 24 for the PPS1. A time-response model estimates the separate time-response curves for each treatment group over the time course of the study. The 2-norm measures squared differences across all time-points for the two treatment group. Using the time-response modelling on the historical data, the 95% CI for the 2-norm of the treatment difference was calculated as [128.61%, 201.53%]. The equivalence margin was defined as 64.31%, which is half of the lower bound of the 95% CI for the treatment effect. The equivalence was concluded if the upper limit of 95% CI for the 2-norm of the difference between SB5 and Humira was less than 64.31%.

The same analysis conducted for the PPS1 population was performed for the FAS to explore the robustness of the results, i.e. available data analysis (no imputation, i.e., subjects with missing data at Week 24 excluded from the analysis). The other scheduled sensitivity analyses were: non-responder analysis and multiple imputation method for missing data imputation and Cochran-Mantel-Haenszel (CMH) and ANCOVA methods to get 95% CI for the difference.

For the primary efficacy analysis and a supportive analysis using a time-response model, missing American College of Rheumatology 20% response criteria (ACR20) was not imputed. Non-responder imputation method was used for missing ACR20 responses for the FAS population.

When the same analysis as the primary efficacy analysis was repeated for the FAS, missing components in each American College of Rheumatology (ACR) response were imputed using multiple imputation method that assumes missing-at-random (MAR) and the missing data of subjects who withdrew from the study with the primary reasons of an adverse event (AE) or lack of efficacy were imputed with the assumption of missing-not-at-random (MNAR). If subjects were discontinued due to an AE or lack of efficacy, these subjects were assumed to have their change worsen by certain degree of score in the ACR20 components.

## *Results*

## Participant flow

**Table 2.5.2.1.** Participant Flow for study SB5-G31-RA

| | SB5 40 mg | Humira® 40 mg | | | Total |
|---|---|---|---|---|---|
| | | Overall | SB5 40 mg | Humira® 40 mg | |
| | n (%) | n (%) | n (%) | n (%) | n (%) |
| Screened | | | | | 747 |
| Randomised at Week 0[a] | 271 (100.0) | 273 (100.0) | | | 544 (100.0) |
| Completed Week 24[a] | 254 (93.7) | 254 (93.0) | | | 508 (93.4) |
| Discontinued prior to Week 24[a] | 17 (6.3) | 19 (7.0) | | | 36 (6.6) |
| Reason for discontinuation | | | | | |
| Withdrawal of consent | 11 (4.1) | 8 (2.9) | | | 19 (3.5) |
| Adverse event | 2 (0.7) | 9 (3.3) | | | 11 (2.0) |
| Lack of efficacy | 1 (0.4) | 2 (0.7) | | | 3 (0.6) |
| Other | 3 (1.1) | 0 (0.0) | | | 3 (0.6) |
| Randomised at Week 24[b] | 254 (100.0) | 254 (100.0) | 125 (100.0) | 129 (100.0) | 508 (100.0) |
| Completed Week 52[b] | 248 (97.6) | 241 (94.9) | 117 (93.6) | 124 (96.1) | 489 (96.3) |
| Discontinued from Week 24 to Week 52[b] | 6 (2.4) | 13 (5.1) | 8 (6.4) | 5 (3.9) | 19 (3.7) |
| Reason for discontinuation | | | | | |
| Adverse event | 2 (0.8) | 5 (2.0) | 2 (1.6) | 3 (2.3) | 7 (1.4) |
| Withdrawal of consent | 2 (0.8) | 5 (2.0) | 4 (3.2) | 1 (0.8) | 7 (1.4) |
| Lack of efficacy | 0 (0.0) | 2 (0.8) | 1 (0.8) | 1 (0.8) | 2 (0.4) |
| Other | 1 (0.4) | 1 (0.4) | 1 (0.8) | 0 (0.0) | 2 (0.4) |
| Subject lost to follow-up | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) |

n = number of subjects

[a] Percentages were based on the number of randomised subjects at Week 0.

[b] Percentages were based on the number of randomised subjects at Week 24.

Source: Table 14.1-1.1

## Baseline data

Baseline characteristics between groups regarding demographic characteristics as well as medical history were balanced between groups as shown below.

**Table 2.5.2.2**: Demographic Characteristics (Randomized Set).

| | SB5 40 mg | Humira® 40 mg | | | Total |
|---|---|---|---|---|---|
| | | Overall | SB5 40 mg | Humira® 40 mg | |
| | N=271 | N=273 | N=125[a] | N=129[a] | N=544 |
| **Age (years)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 49.8 (12.67) | 52.5 (11.91) | 51.7 (11.29) | 52.8 (12.34) | 51.2 (12.36) |
| **Age group, n (%)** | | | | | |
| < 65 years | 242 (89.3) | 233 (85.3) | 111 (88.8) | 107 (82.9) | 475 (87.3) |
| ≥ 65 years | 29 (10.7) | 40 (14.7) | 14 (11.2) | 22 (17.1) | 69 (12.7) |
| **Gender, n (%)** | | | | | |
| Male | 54 (19.9) | 49 (17.9) | 20 (16.0) | 26 (20.2) | 103 (18.9) |
| Female | 217 (80.1) | 224 (82.1) | 105 (84.0) | 103 (79.8) | 441 (81.1) |
| **Race, n (%)** | | | | | |
| White | 271 (100.0) | 269 (98.5) | 123 (98.4) | 127 (98.4) | 540 (99.3) |
| Asian | 0 (0.0) | 4 (1.5) | 2 (1.6) | 2 (1.6) | 4 (0.7) |
| **Ethnicity, n (%)** | | | | | |
| Hispanic or Latino | 2 (0.7) | 2 (0.7) | 1 (0.8) | 1 (0.8) | 4 (0.7) |
| Chinese | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Indian (Indian subcontinent) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Japanese | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Mixed ethnicity | 6 (2.2) | 5 (1.8) | 2 (1.6) | 3 (2.3) | 11 (2.0) |
| Other | 263 (97.0) | 266 (97.4) | 122 (97.6) | 125 (96.9) | 529 (97.2) |
| **Weight (kg)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 72.45 (14.779) | 73.95 (14.978) | 74.94 (15.523) | 73.46 (14.252) | 73.20 (14.884) |
| **Height (cm)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 166.22 (9.025) | 165.47 (8.189) | 165.84 (7.422) | 165.28 (8.814) | 165.84 (8.615) |
| **BMI (kg/m$^2$)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 26.18 (4.759) | 26.99 (5.101) | 27.23 (5.274) | 26.90 (4.962) | 26.59 (4.945) |

N = number of subjects in the Randomised Set; n = number of subjects
BMI = body mass index; SD = standard deviation
[a] Based on the subjects who had re-randomisation at Week 24; Humira®/SB5 and Humira®/Humira® may not add up to Humira® overall due to discontinuation prior to Week 24.

**Table 2.5.2.3: Baseline Disease Characteristics for Rheumatoid Arthritis Measures (Randomised Set)**

| | SB5 40 mg | Humira® 40 mg | | | Total |
|---|---|---|---|---|---|
| | | Overall | SB5 40 mg | Humira® 40 mg | |
| | N=271 | N=273 | N=125[a] | N=129[a] | N=544 |
| **Disease duration (years)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 5.44 (4.363) | 5.46 (4.336) | 5.32 (4.105) | 5.63 (4.526) | 5.45 (4.345) |
| Min, Max | 0.5, 21.0 | 0.5, 21.0 | 0.5, 19.0 | 0.5, 21.0 | 0.5, 21.0 |
| **Duration of MTX use (months)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 39.47 (38.377) | 37.81 (34.861) | 38.25 (33.768) | 39.51 (37.212) | 38.64 (36.631) |
| Min, Max | 6.0, 211.1 | 6.0, 179.7 | 6.1, 151.8 | 6.0, 179.7 | 6.0, 211.1 |
| **Weekly dose of MTX at baseline (mg)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 15.13 (4.623) | 15.35 (4.411) | 15.44 (4.457) | 15.21 (4.420) | 15.24 (4.515) |
| Min, Max | 10.0, 25.0 | 10.0, 25.0 | 10.0, 25.0 | 10.0, 25.0 | 10.0, 25.0 |
| **SJC (0-66)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 15.8 (8.03) | 15.5 (7.54) | 14.5 (6.37) | 16.3 (8.33) | 15.7 (7.78) |
| Min, Max | 6, 48 | 6, 46 | 6, 32 | 6, 46 | 6, 48 |
| **TJC (0-68)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 23.9 (11.69) | 24.1 (10.82) | 23.8 (10.46) | 24.3 (11.29) | 24.0 (11.25) |
| Min, Max | 6, 66 | 7, 58 | 7, 57 | 8, 58 | 6, 66 |
| **PGA VAS (0-100)** | | | | | |
| n | 269 | 272 | 125 | 129 | 541 |
| Mean (SD) | 59.8 (16.87) | 60.6 (15.38) | 60.6 (14.68) | 61.0 (16.13) | 60.2 (16.13) |
| Min, Max | 3, 100 | 18, 91 | 25, 89 | 18, 91 | 3, 100 |

| | | | | | |
|---|---|---|---|---|---|
| **SGA VAS (0-100)** | | | | | |
| n | 270 | 273 | 125 | 129 | 543 |
| Mean (SD) | 58.5 (20.29) | 59.4 (18.65) | 59.1 (18.02) | 59.9 (19.60) | 58.9 (19.47) |
| Min, Max | 5, 100 | 14, 100 | 18, 100 | 14, 100 | 5, 100 |
| **SPA VAS (0-100)** | | | | | |
| n | 270 | 273 | 125 | 129 | 543 |
| Mean (SD) | 59.2 (20.70) | 60.8 (19.71) | 61.0 (19.60) | 60.6 (19.96) | 60.0 (20.21) |
| Min, Max | 4, 100 | 10, 100 | 10, 96 | 10, 100 | 4, 100 |
| **HAQ-DI (0-3)** | | | | | |
| n | 270 | 273 | 125 | 129 | 543 |
| Mean (SD) | 1.3343 (0.60796) | 1.3585 (0.64175) | 1.3790 (0.63121) | 1.3556 (0.66593) | 1.3465 (0.62472) |
| Min, Max | 0.000, 2.875 | 0.000, 3.000 | 0.000, 3.000 | 0.000, 2.875 | 0.000, 3.000 |
| **CRP (mg/L)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 11.47 (19.043) | 12.64 (18.989) | 13.01 (20.819) | 11.90 (15.725) | 12.05 (19.007) |
| Min, Max | 0.5, 144.4 | 0.5, 128.8 | 0.5, 128.8 | 0.5, 91.5 | 0.5, 144.4 |
| **CRP, n (%)** | | | | | |
| ≥ 10 mg/L | 81 (29.9) | 93 (34.1) | 40 (32.0) | 48 (37.2) | 174 (32.0) |
| < 10 mg/L | 190 (70.1) | 180 (65.9) | 85 (68.0) | 81 (62.8) | 370 (68.0) |
| **ESR (mm/h)** | | | | | |
| n | 271 | 273 | 125 | 129 | 544 |
| Mean (SD) | 39.6 (13.27) | 39.6 (13.86) | 40.5 (14.27) | 39.3 (14.03) | 39.6 (13.55) |
| Min, Max | 8, 110 | 14, 108 | 16, 108 | 14, 108 | 8, 110 |
| **mTSS** | | | | | |
| n | 244 | 250 | 119 | 128 | 494 |
| Mean (SD) | 29.51 (46.518) | 31.39 (51.284) | 29.56 (50.719) | 33.65 (52.377) | 30.46 (48.947) |
| Min, Max | 0.0, 253.0 | 0.0, 321.3 | 0.0, 321.3 | 0.0, 273.0 | 0.0, 321.3 |

The proportions of subjects with medical/surgical history and continuing medical conditions were 78.2% vs. 88.3% in the SB5 and Humira treatment groups, respectively. The most commonly reported medical history and continuing medical conditions by SOC were surgical and medical procedures (48.0% of subjects in the SB5 treatment group vs. 55.7% of subjects in the Humira treatment group), musculoskeletal and connective tissue disorders (35.1% vs. 39.6% of subjects), and vascular disorders (33.6% vs. 45.1% of subjects).

### *Conduct of the Study*

There was 1 amendment made to the protocol. This amendment made only administrative changes to the protocol.

A total of 225 (41.4%) subjects had at least 1 major PD; 107 subjects in the SB5 treatment group and 118 subjects in the Humira treatment group. A total of 39 (7.2%) subjects were excluded from PPS1 due to major PDs. The most common major PDs that led to exclusion from PPS1 were eligibility and entry criteria (14 [5.2%] subjects in the SB5 vs. 7 [2.6%] subjects in the Humira treatment groups) and visit schedule criteria (3 [1.1%] subjects in the SB5 vs. 5 [1.8%] subjects in the Humira treatment groups). A total of 67 (12.3%) subjects were excluded from PPS2 due to major PDs. The most common major PDs that led to exclusion from PPS2 were visit schedule criteria (25 [9.2%] subjects in the SB5 vs. 15 [5.5%] subjects in the Humira overall treatment groups; among subjects in Humira overall, 7 [5.6%] subjects in the Humira/SB5 vs. 8 [6.2%] subjects in the Humira/Humira treatment groups) and eligibility and entry criteria (14 [5.2%] subjects in the SB5 vs. 7 [2.6%] subjects in the Humira overall treatment groups; among subjects in Humira overall, 4 [3.2%] subjects in the Humira/SB5 vs. 3 [2.3%] subjects in the Humira/Humira treatment groups).

### *Numbers analysed*

Below (Table 2.5.2.4) are shown the subjects analyzed in each analysis set (as defined above).

**Table 2.5.2.4: Data Sets Analysed (Randomized Set)**

| | SB5 40 mg | Humira® 40 mg | | | Total |
|---|---|---|---|---|---|
| | | Overall | SB5 40 mg | Humira® 40 mg | |
| | N=271 | N=273 | N=125[a] | N=129[a] | N=544 |
| | n (%) | n (%) | n (%) | n (%) | n (%) |
| Full analysis set | 269 (99.3) | 273 (100.0) | 125 (100.0) | 129 (100.0) | 542 (99.6) |
| Per-protocol set 1 | 239 (88.2) | 237 (86.8) | 118 (94.4) | 119 (92.2) | 476 (87.5) |
| Per-protocol set 2 | 212 (78.2) | 217 (79.5) | 106 (84.8) | 111 (86.0) | 429 (78.9) |
| Safety set 1 | 268 (98.9) | 273 (100.0) | 125 (100.0)[b] | 127 (98.4)[b] | 541 (99.4) |
| Safety set 2 | 254 (93.7) | 252 (92.3) | 125 (100.0) | 127 (98.4) | 506 (93.0) |
| PK population | 178 (65.7) | 178 (65.2) | | | 356 (65.4) |

N = number of subjects in the Randomised Set; n = number of subjects
PK = pharmacokinetics
[a] Based on the subjects who had re-randomisation at Week 24; Humira®/SB5 and Humira®/Humira® may not add up to Humira® overall due to discontinuation prior to Week 24.
[b] Based on the subjects in the Safety Set 2 who administered at least 1 IP after re-randomisation at Week 24.
Percentages were based on the number of randomised subjects.
Source: Table 14.1-2.1

## Outcomes and estimation

Primary efficacy endpoint:

The groups were equivalent in efficacy in the primary analysis (PPS1 population) for the adjusted difference in the ACR20 response rate at Week 24, the 95% CI for difference being well within ±15% acceptance range (Table 3.4.5.7). The sensitivity of the analysis was shown in the FAS population, the

outcome meeting the pre-defined equivalence criteria as well (Table 3.4.5.8). Thus, the primary objective for the study was met. The responder rates were 72.4% (173/239) for SB5 and 72.2% (171/237) for Humira. The adjusted treatment difference in ACR20 response rate at Week 24 was 0.1% and the 95% CI of the adjusted treatment difference was [−7.83%, 8.13%]. This data supports the equivalence in efficacy between the treatments.

**Table 2.5.2.5**: Primary Analysis of ACR20 Response Rate at Week 24 (Per-protocol Set 1)

| Treatment | n/n' | (%) | Estimated Difference in Proportions | 95% CI |
|---|---|---|---|---|
| SB5 40 mg (N=239) | 173/239 | (72.4) | 0.1% | [−7.83%, 8.13%] |
| Humira® 40 mg (N=237) | 171/237 | (72.2) | | |

N = number of subjects in the Per-protocol Set 1; n = number of responders; n' = number of subjects with an assessment
ACR20 = American College of Rheumatology 20% response criteria; CI = confidence interval
Nonparametric randomisation-based analysis of covariance was used with region as a stratification factor and baseline C-reactive protein (CRP) value as a covariate.

In the FAS population the proportion of subjects achieving ACR20 response at Week 24 was 68.0% (183/269) for SB5 and 67.4% (184/273) for Humira with the estimated difference in proportions of 0.8% when the non-responder analysis was applied and the 95% CI of the adjusted treatment difference of [−7.03%, 8.56%] (Table 2.5.2.6).

**Table 2.5.2.6: Analysis of ACR20 Response Rate at Week 24; Non-responder Analysis (Full Analysis Set)**

| Treatment | n/n' | (%) | Estimated Difference in Proportions | 95% CI |
|---|---|---|---|---|
| SB5 40 mg (N=269) | 183/269 | (68.0) | 0.8% | [−7.03%, 8.56%] |
| Humira® 40 mg (N=273) | 184/273 | (67.4) | | |

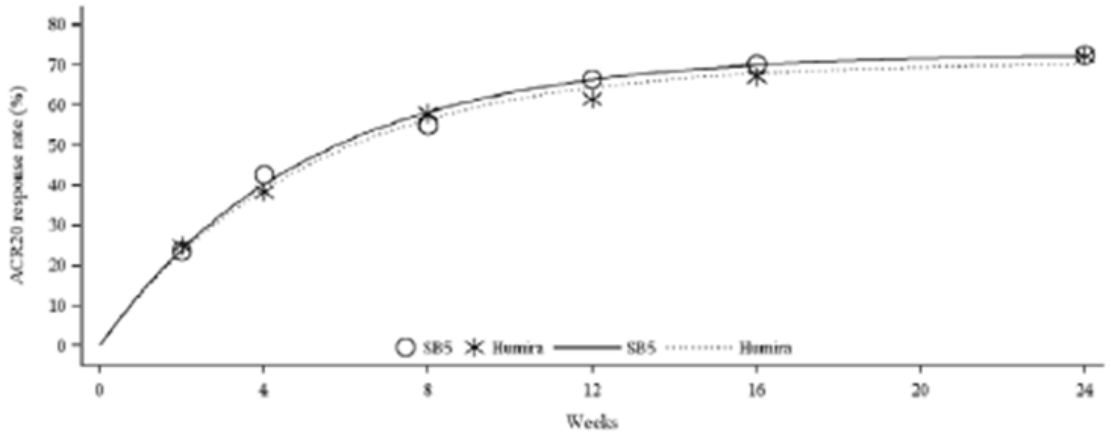
N = number of subjects in the Full Analysis Set; n = number of responders; n' = number of subjects with an assessment
ACR20 = American College of Rheumatology 20% response criteria; CI = confidence interval
Nonparametric randomisation-based analysis of covariance was used with region as a stratification factor and baseline CRP value as a covariate.
Subjects with missing ACR20 response at Week 24 were considered as non-responders at Week 24.

The data was equivalent also in the FAS population when no imputation of the missing data of the patients withdrawn was performed, the responder rate being 71.5% (183/256) for SB5 and 71.3% (184/258) for Humira, resulting in the 95% CI of -7.733- 7.789 for the difference between the groups when a missing-at-random was assumed and to the 95% CI of -8.03 - 7.59 with the pattern mixture model.

The time-response curves of SB5 and Humira 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 8.07 and the 95% CI of the treatment difference was −11.884 - 28.022, where the upper limit 28.022 was less than the pre-specified equivalence margin of 64.31. Thus, the robustness of the primary analysis was also corroborated by this analysis.

Since at week 24 a plateau in treatment effect seems to be evident, it is also of interest to evaluate the earlier time course of this measure, which appears fairly similar also in the sensitive, steep part of the response curve (see below).

**Figure 3.4.5.2 Time-Response Model for ACR20 Response up to Week 24 (PPS1)**




Secondary efficacy endpoints

The secondary efficacy variables at Week 24 (ACR50 and ACR70 response, ACR-N, AUC of ACR-N up to Week 24, DAS28 score, AUC of the Change in DAS28 from Baseline up to Week 24, EULAR response) were comparable between the SB5 and Imralditreatment groups.

The secondary efficacy variables at Week 52 comparing SB5 group and the subjects continuing with Humira after Week 24 showed results slightly exceeding upper boundary in 95% CI for the difference in the ACR20 response. The other secondary outcomes at Week 52 (ACR50 and ACR70, ACR-N, DAS28, EULAR) between the groups were comparable.

ACR50 and ACR70 Response Rates at Week 24 were comparable in both PPS1 (Table 2.5.2.7) and FAS population (Table 2.5.2.8).

**Table 2.5.2.7: Analysis of ACR50 and ACR70 Response Rates at Week 24 (PPS1)**

| ACR response | Treatment | n/n' | (%) | Estimated Difference in Proportions | 95% CI |
|---|---|---|---|---|---|
| ACR50 | SB5 40 mg (N=239) | 91/239 | (38.1) | –2.0% | [–10.69%, 6.75%] |
| | Humira® 40 mg (N=237) | 94/237 | (39.7) | | |
| ACR70 | SB5 40 mg (N=239) | 46/239 | (19.2) | –1.3% | [ –8.41%, 5.80%] |
| | Humira® 40 mg (N=237) | 48/237 | (20.3) | | |

N = number of subjects in the Per-protocol Set 1; n = number of responders; n' = number of subjects with an assessment

ACR50 = American College of Rheumatology 50% response criteria; ACR70 = American College of Rheumatology 70% response criteria; CI = confidence interval

Nonparametric randomisation-based analysis of covariance was used with region as a stratification factor and baseline CRP value as a covariate.

**Table 2.5.2.8: Analysis of ACR50 and ACR70 Response Rates at Week 24; Non-responder Analysis (Full Analysis Set)**

| ACR response | Treatment | n/n' | (%) | Estimated Difference in Proportions | 95% CI |
|---|---|---|---|---|---|
| ACR50 | SB5 40 mg (N=269) | 98/269 | (36.4) | –0.3% | [–8.34%, 7.80%] |
| | Humira® 40 mg (N=273) | 100/273 | (36.6) | | |
| ACR70 | SB5 40 mg (N=269) | 47/269 | (17.5) | –1.0% | [–7.37%, 5.45%] |
| | Humira® 40 mg (N=273) | 50/273 | (18.3) | | |

N = number of subjects in the Full Analysis Set; n = number of responders; n' = number of subjects with an assessment
ACR50 = American College of Rheumatology 50% response criteria; ACR70 = American College of Rheumatology 70% response criteria; CI = confidence interval
Nonparametric randomisation-based analysis of covariance was used with region as a stratification factor and baseline CRP value as a covariate.
Subjects with missing ACR50 or ACR70 responses were considered as non-responders at Week 24.

The proportion of subjects achieving ACR20 response rate at Week 52 for the PPS2 was 76.9% (163/212) in the SB5 and 71.2% (79/111) in the Humira/Humira treatment groups. The adjusted treatment difference in ACR20 response rate at Week 52 was 5.6% [95% CI: −4.63%, 15.90%] between the SB5 and Humira/Humira treatment groups. In the FAS population the proportion of subjects achieving ACR20 response at Week 52 was 71.7% (193/269) in the SB5 and 70.5% (91/129) in the Humira/Humira treatment groups. The adjusted treatment difference in ACR20 response rate at Week 52 with the non-responder analysis was 1.2% [95% CI: −8.34%, 10.75%] between the SB5 and Humira/Humira treatment groups.

The proportion of subjects achieving ACR50 response rate at Week 52 for the PPS2 was 49.1% (104/212) in the SB5 and 51.4% (57/111) in the Humira/Humira treatment groups. The adjusted treatment difference in ACR50 response rate at Week 52 was −2.9% [95% CI: −14.46%, 8.69%] between the SB5 and Humira/Humira treatment groups. The respective adjusted treatment difference in ACR70 response rate at Week 52 was 0.3% [95% CI: −10.25%, 10.86%]. Both ACR 50 and ACR 70 were preserved within the exploratory equivalence margins (defined for ACR20, week 24: -15%,15%) This was observed in the PPS2 as well as in the FAS and underlines similarity of long term efficacy of SB5 and Humira. Of note, patients who switched from Humira to SB5 at week 24 were not considered for this assessment. The mean ACR-N at Week 24 was 40.17 in the SB5 treatment group and 39.58 in the Humira treatment group. The mean ACR-N at Week 52 was 48.42 in the SB5 and 46.14 in the Humira/Humira treatment groups. The treatment difference in the LSMeans and its 95% CI for ACR-N at Week 24 was 0.4 [−4.61, 5.34]. The treatment difference in the LSMeans and its 95% CI for ACR-N at Week 52 was 2.2 [−4.33, 8.82] between the SB5 and Humira/Humira.

The mean AUC of ACR-N up to Week 24 was 4834.85 in the SB5 treatment group and 4688.04 in the Humira treatment group. The treatment difference in the LSMeans and its 95% CI for AUC of ACR-N up to Week 24 was 127.7 [−461.07, 716.37].

The mean AUC of the change in DAS28 from Baseline up to Week 24 was −333.74 in the SB5 treatment group and −324.86 in the EU Humira treatment group. The treatment difference in LSMeans and its 95% CI for AUC of change in DAS28 from Baseline up to Week 24 was −7.7 [−36.02, 20.66]. The mean change in the DAS28 score from Baseline at Week 24 was −2.74 in the SB5 treatment group and −2.68 in the Humira treatment group. The mean change in DAS28 from Baseline at Week 52 was −3.05 in the SB5 and −2.92 in the Humira/Humira treatment groups. The treatment difference in the LSMeans and its 95% CI

for DAS28 at Week 24 was −0.04 [−0.26, 0.17], which was contained within the pre-defined equivalence margins of [−0.6, 0.6]. The treatment difference in the LSMeans and its 95% CI for DAS28 at Week 52 was −0.10 [−0.38, 0.18] between the SB5 and Humira/Humira, which was contained within the pre-defined equivalence margins of [−0.6, 0.6]. Similarity in both secondary DAS28 measures could hence been shown. Data was only provided for FAS. Furthermore no relevant changes between Humira and SB5 can be derived from an analysis of the AUC of the change in DAS28 from baseline to week 24.

At Week 24, the proportion of subjects who had a good EULAR response was 34.1% in the SB5 and 34.6% in the Humira treatment groups, and a moderate EULAR response was 59.2% and 58.8%, respectively. The proportion of subjects who had no EULAR response was 6.7% and 6.6% in the SB5 and Humira treatment groups, respectively. At Week 52, the proportion of subjects who had a good EULAR response was 47.8% in the SB5, 46.3% in the Humira overall, 46.6% in the Humira/SB5, and 46.0% in the Humira/Humira treatment groups, and a moderate EULAR response was 45.7%, 46.3%, 47.5%, and 45.2%, respectively. The proportion of subjects who had no EULAR response was 6.5%, 7.4%, 5.9%, and 8.9%, respectively.

The mean change in mTSS from Baseline at Week 52 was 0.17 in the SB5 and 0.50 in the Humira/Humira treatment groups. The adjusted treatment difference in LSMeans and the 95% CI in mTSS at Week 52 was −0.31 [95% CI: −0.843, 0.224] between the SB5 and Humira/Humira treatment groups.

**Table 2.5.2.9: Summary statistics of Structural Joint Damage Assessment (FAS)**

| | | SB5 40 mg | Humira® 40 mg | | | Total |
|---|---|---|---|---|---|---|
| | | | Overall | SB5 40 mg | Humira® 40 mg | |
| | | N=269 | N=273 | N=125[a] | N=129[a] | N=542 |
| **Modified total Sharp score** | | | | | | |
| Week 0 | n | 244 | 250 | 119 | 128 | 494 |
| | Mean (SD) | 29.51 (46.518) | 31.39 (51.284) | 29.56 (50.719) | 33.65 (52.377) | 30.46 (48.947) |
| Week 52[b] | n | 241 | 238 | 114 | 124 | 479 |
| | Mean (SD) | 29.93 (47.186) | 31.38 (51.986) | 29.21 (51.144) | 33.38 (52.877) | 30.65 (49.583) |
| Change from Baseline[b] mean (SD) | | 0.17 (2.489) | 0.38 (2.562) | 0.25 (2.732) | 0.50 (2.401) | 0.27 (2.525) |
| **Joint erosion score** | | | | | | |
| Week 0 | n | 244 | 250 | 119 | 128 | 494 |
| | Mean (SD) | 15.56 (24.380) | 16.45 (27.789) | 14.93 (26.577) | 18.14 (29.137) | 16.01 (26.138) |
| Week 52[b] | n | 241 | 238 | 114 | 124 | 479 |
| | Mean (SD) | 15.77 (24.709) | 16.48 (28.104) | 14.95 (27.033) | 17.88 (29.093) | 16.12 (26.425) |
| Change from Baseline[b] mean (SD) | | 0.11 (1.563) | 0.17 (1.268) | 0.18 (1.388) | 0.16 (1.152) | 0.14 (1.423) |
| **Joint space narrowing score** | | | | | | |
| Week 0 | n | 244 | 250 | 119 | 128 | 494 |
| | Mean (SD) | 13.95 (23.401) | 14.93 (24.591) | 14.63 (25.249) | 15.52 (24.271) | 14.45 (23.991) |
| Week 52[b] | n | 241 | 238 | 114 | 124 | 479 |
| | Mean (SD) | 14.17 (23.787) | 14.90 (24.743) | 14.26 (24.984) | 15.49 (24.606) | 14.53 (24.244) |
| Change from Baseline[b] mean (SD) | | 0.06 (1.321) | 0.21 (1.760) | 0.07 (1.539) | 0.34 (1.938) | 0.14 (1.555) |

N = number of subjects in the Full Analysis Set; n = number of subjects with an assessment
SD = standard deviation
[a] Based on the subjects who had re-randomisation at Week 24; Humira®/SB5 and Humira®/Humira® may not add up to Humira® overall due to discontinuation prior to Week 24.
[b] For subjects who completed Week 52 visit.

## Ancillary analyses

### *Subgroup analysis by anti-drug antibody status*

The ACR20 response rate at Week 24 was similar between the SB5 and EU Humira treatment groups among subjects who had an overall negative ADA result up to Week 24, with 78.7% (118/150) subjects and 74.1% (117/158) subjects achieving an ACR20 response in the SB5 and EU Humira treatment groups, respectively. The adjusted treatment difference and its 95% CI in ACR20 response rate at Week 24 among subjects with an overall negative ADA result was 5.7% [−3.8%, 15.2%]. The ACR20 response rate at Week 24 was lower in the SB5 treatment group than in the EU Humira treatment group among subjects who had an overall positive ADA result up to Week 24, with an overall positive ACR20 result in 57.5% of patients (42/73) in the SB5 treatment group and in 71.2% of patients (52/73) in the EU Humira

treatment group. The adjusted treatment difference and its 95% CI in ACR20 response rate at Week 24 among subjects with an overall positive ADA result was −17.5% [−33.3%, −1.8%]. There was a significant interaction in ACR20 response rate at Week 24 between treatment and ADA status (p-value = 0.015).

Within the SB5 treatment group, the ACR20 response rate at Week 24 in subjects with an overall positive ADA result up to Week 24 (57.5%) was lower than in subjects with an overall negative ADA result up to Week 24 (78.7%). However, the ACR20 response rate at Week 24 was comparable within the EU Humira treatment group between subjects with an overall positive ADA result up to Week 24 (71.2%) and subjects with an overall negative ADA result up to Week 24 (74.1%).

The ACR50 and ACR70 response rates at Week 24 were similar between the SB5 and Humira treatment groups in both overall positive and negative ADA subjects.

**Table 2.5.2.10: ANCOVA for ACR20 Response at Week 24 by 24-week ADA Results and Treatment (Per-Protocol Set 1)**

| 24-week ADA Result | Treatment | n/n' | (%) | LS Mean | 95% CI of LsMean | Estimated Difference in Proportions | 95% CI of Adjusted Treatment Difference | *p*-value |
|---|---|---|---|---|---|---|---|---|
| Positive | SB5 (N=73) | 42/73 | (57.5) | 49.1 | [36.9, 61.4] | −17.5% | [−33.3%,−1.8%] | 0.015 |
| | EU Humira® (N=73) | 52/73 | (71.2) | 66.6 | [54.5, 78.8] | | | |
| Negative | SB5 (N=150) | 118/150 | (78.7) | 81.2 | [73.9, 88.5] | 5.7% | [−3.8%, 15.2%] | |
| | EU Humira® (N=158) | 117/158 | (74.1) | 75.5 | [68.2, 82.9] | | | |

N = number of subjects in the per-protocol set 1; n' = number of subjects with available assessment results; n = number of responders. The *p*-value is for the interaction term.

(For further details, see under Clinical safety/ immunogenicity events)

The subgroup analysis by baseline CRP level, age, and demographic characteristics (region and gender) did not show significant interaction with the treatment.

The Applicant has presented comparative data whether the difference between groups in ADA positive patients in favour of Humira will remain in longer term after Week 24. Since the quality data robustly demonstrates the similarity between the products, and since the incidence of neutralizing antibody formation as well as titers and neutralizing capacity are similar between the products, the chance finding could be assumed. Furthermore, even though the ACR response (categorical variable) in ADA positive treatment groups was consistently lower in the SB5 treated patients, the difference was very small when DAS28 (continuous variable) analysis was used. Thus, the higher ACR responses in ADA positive Humira group could be considered an isolated finding that is not compatible with ADA results, pharmacokinetics or the DAS28 results. Based on the ACR20 score in each visit up to Week 52 the ACR score improved even though the increased number of NAb positive patients was diagnosed. Thus, any clear withering effect in NAb-positive patients was not seen. Furthermore, in DAS28 score no NAb associated difference was seen between SB5 and Humira groups up to Week 52. In addition, fluctuation in ACR scores was seen excluding systematic impact of NAb positivity on outcome between treatments. Thus, these findings do not exclude the biosimilarity claim.

## Summary of main study(ies)

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 2.5.2.11: Summary of Efficacy for trial SB5-G31-RA**

| | | | |
|---|---|---|---|
| **Title:** A Randomized, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity of SB5 Compared to Humira in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy | | | |
| Study identifier | SB5-G31-RA (protocol number), 2013-005013-13 (EudraCT number) | | |
| Design | Randomized, double-blind, parallel group, multicentre clinical study<br><br>The study was composed of two distinct periods. A total of 544 subjects with moderate to severe RA despite MTX therapy were first randomized in a 1:1 ratio to receive either SB5 40 mg (n=271) or EU Humira 40 mg (n=273) every other week via subcutaneous injection. At Week 24, subjects receiving EU Humira were randomized again in a 1:1 ratio to either continue on Humira 40 mg (Humira/Humira) (n=129) or transitioned to SB5 40 mg (Humira/SB5) (n=125) every other week up to Week 50. Subjects receiving SB5 continued to receive SB5 40 mg up to Week 50 but they also followed the randomization procedure to maintain blinding. The expected study duration per individual subject was 60 weeks after randomization (52 weeks of active treatment and 8 weeks of safety follow-up). | | |
| | Duration of main phase:<br><br>Duration of Run-in phase: | | 24 weeks (primary endpoint),<br>52 weeks (end of active treatment)<br>6 weeks (screening) |
| Hypothesis | Equivalence; equivalence margin for the difference in ARC20 response rate at week 24: [-15%, 15%] | | |
| Treatments groups | SB5 | | SB5 40 mg, SC, every other week, up to week 50, randomized: n=271 |
| | Humira | | Humira 40 mg, SC, every other week, up to week 22, randomized: n=273 |
| | Humira/Humira | | Humira 40 mg, SC, every other week, from week 24 to week 50, randomized: n=129 |
| | Humira/SB5 | | SB5 40 mg, SC, every other week, from week 24 to week 50, randomized: n=125 |
| | All subjects received 10-25 mg/week of oral or parenteral MTX | | |
| Endpoints and definitions | Primary efficacy endpoint | ACR20 | American College of Rheumatology 20% response criteria (ACR20) response rate at Week 24 |
| | Supportive analysis of primary efficacy analysis | Time Response Model for ARC20 | ACR20 response over time up to Week 24 |
| | Secondary efficacy endpoint | ACR20 | ACR20 response rate at Week 52 |
| | Secondary efficacy endpoint | ACR50 | ACR 50% response criteria (ACR50) response rate at Week 24 and Week 52 |
| | Secondary efficacy endpoint | ARC70 | ACR 70% response criteria (ACR70) response rate at Week 24 and Week 52 |

| | | | |
|---|---|---|---|
| | Secondary efficacy endpoint | ACR-N | The numeric index of the ACR response (ACR-N) at Week 24 and Week 52 |
| | Secondary efficacy endpoint | AUC of ACR-N | The area under the curve (AUC) of ACR-N up to Week 24 |
| | Secondary efficacy endpoint | DAS28 | Change in the disease activity score based on a 28 joint count (DAS28 score) from baseline at Week 24 and Week 52 |
| | Secondary efficacy endpoint | AUC of the change in DAS28 from Baseline | AUC of the change in DAS28 from baseline up to Week 24 |
| | Secondary efficacy endpoint | EULAR Response | The European League Against Rheumatism (EULAR) response at Week 24 and Week 52 |
| | Secondary efficacy endpoint | Major Clinical Response | ACR70 response for 6 consecutive months at Week 52 |
| | Secondary efficacy endpoint | mTSS | Change in modified Total Sharp Score (mTSS) from baseline to Week 52 |
| Database lock | Interim DB lock: Jul 01, 2015; Final DB lock: Dec 01, 2015<br><br>The interim DB lock was for the 24-week interim clinical study report mainly for assessing and reporting the primary endpoint. Full clinical outcomes were analysed after the final DB lock. | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Per protocol Set 1 (primary analysis set)<br><br>**Week 24** | | |
| Descriptive statistics and estimate variability | Treatment group | SB5 | Humira |
| | Number of subjects | 239 | 237 |
| | ACR20 response rate at Week 24 | 72.4% (173/239) | 72.2% (171/237) |
| | Time Response Model for ARC20 | 72.9 | 70.8 |
| | ACR50 response rate at Week 24 | 38.1% (91/239) | 39.7% (94/237) |
| | ARC70 response rate at Week 24 | 19.2% (46/239) | 20.3% (48/237) |
| Effect estimate per comparison | ACR20 response rate at Week 24 | Comparison groups | SB5 - Humira |
| | | Adjusted treatment difference | 0.1% |
| | | 95% CI | [-7.83%, 8.13%] |
| | | P-value | 0.97 |
| | Time Response Model for ARC20 | Comparison groups | SB5 - Humira |
| | | Treatment difference of the 2-norm | 8.07 |
| | | 95% CI | [-11.884, 28.022] |
| | | Pre-specified equivalence margin | 64.31 |
| | | P-value | 0.40 |
| | ACR50 response | Comparison groups | SB5 - Humira |

| | | | |
|---|---|---|---|
| | rate at Week 24 | Adjusted treatment difference | -2.0% |
| | | 95% CI | [-10.69%, 6.75%] |
| | | P-value | 0.66 |
| | ARC70 response rate at Week 24 | Comparison groups | SB5 - Humira |
| | | Adjusted treatment difference | -1.3% |
| | | 95% CI | [-8.41%, 5.80%] |
| | | P-value | 0.72 |
| **Analysis description** | **Sensitivity analysis** | | |
| Analysis population and time point description | Full Analysis Set (FAS) (non-responder analysis)<br>**Week 24** | | |
| Descriptive statistics and estimate variability | Treatment group | SB5 | Humira |
| | Number of subjects | 269 | 273 |
| | ACR20 response rate at Week 24 | 68.0%<br>(183/269) | 67.4%<br>(184/273) |
| | ACR50 response rate at Week 24 | 36.4%<br>(98/269) | 36.6%<br>(100/273) |
| | ARC70 response rate at Week 24 | 17.5%<br>(47/269) | 18.3%<br>(50/273) |
| | ACR-N<br>mean<br>SD<br>median | <br>40.17<br>28.731<br>38.15 | <br>39.58<br>29.180<br>37.45 |
| | AUC of ACR-N<br>mean<br>SD<br>median | <br>4834.85<br>3547.975<br>4270.20 | <br>4688.04<br>3567.037<br>4176.70 |
| | DAS28<br>mean<br>SD<br>median | <br>-2.74<br>1.297<br>-2.70 | <br>-2.68<br>1.277<br>-2.50 |
| | AUC of the change in DAS28 from Baseline<br>mean<br>SD<br>median | <br><br>-333.74<br>172.552<br>-330.65 | <br><br>-324.86<br>171.783<br>-315.10 |
| | EULAR Response<br>Good<br>Moderate<br>No response | <br>34.1% (87/255)<br>59.2% (151/255)<br>6.7% (17/255) | <br>34.6% (89/257)<br>58.8% (151/257)<br>6.6% (17/257) |
| Effect estimate per comparison | ACR20 response rate at Week 24 | Comparison groups | SB5 - Humira |
| | | Adjusted treatment difference | 0.8% |
| | | 95% CI | [-7.03%, 8.56%] |
| | | P-value | 0.85 |
| | ACR50 response rate at Week 24 | Comparison groups | SB5 - Humira |
| | | Adjusted treatment difference | -0.3% |
| | | 95% CI | [-8.34%, 7.80%] |
| | | P-value | 0.95 |
| | ARC70 response | Comparison groups | SB5 - Humira |

| | | | | | |
|---|---|---|---|---|---|
| | rate at Week 24 | Adjusted treatment difference | -1.0% | | |
| | | 95% CI | [-7.37%, 5.45%] | | |
| | | P-value | 0.77 | | |
| | ACR-N | Comparison groups | SB5 - Humira | | |
| | | Treatment difference in the LSMeans | 0.4 | | |
| | | 95% CI | [-4.61, 5.34] | | |
| | | P-value | 0.88 | | |
| | AUC of ACR-N | Comparison groups | SB5 - Humira | | |
| | | Treatment difference in the LSMeans | 127.7 | | |
| | | 95% CI | [-461.07, 716.37] | | |
| | | P-value | 0.67 | | |
| | DAS28 | Comparison groups | SB5 - Humira | | |
| | | Treatment difference in the LSMeans | -0.04 | | |
| | | 95% CI | [-0.26, 0.17] | | |
| | | P-value | 0.69 | | |
| | AUC of the change in DAS28 from Baseline | Comparison groups | SB5 - Humira | | |
| | | Treatment difference in LSMeans | -7.7 | | |
| | | 95% CI | [-36.02, 20.66] | | |
| | | P-value | 0.59 | | |
| | EULAR Response | Statistical analysis has not been conducted. | | | |
| **Analysis description** | **Secondary Analysis** | | | | |
| Analysis population and time point description | Per-protocol set 2<br>**Week 52** | | | | |
| Descriptive statistics and estimate variability | Treatment group | SB5 | Humira/ Humira | Humira/SB5 | Humira Overall |
| | Number of subjects | 212 | 111 | 106 | 217 |
| | ACR20 response rate at Week 52 | 76.9% (163/212) | 71.2% (79/111) | 81.1% (86/106) | 76.0% (165/217) |
| | ACR50 response rate at Week 52 | 49.1% (104/212) | 51.4% (57/111) | 53.8% (57/106) | 52.5% (114/217) |
| | ARC70 response rate at Week 52 | 31.1% (66/212) | 30.6% (34/111) | 26.4% (28/106) | 28.6% (62/217) |
| Effect estimate per comparison | ACR20 response rate at Week 52 | Comparison groups | SB5 – Humira/ Humira | Humira/SB5 -Humira/ Humira | SB5 - Humira Overall |
| | | Adjusted treatment difference | 5.6% | 10.1% | 0.8% |
| | | 95% CI | [-4.63%, 15.90%] | [-1.24%, 21.45%] | [-7.27%, 8.91%] |
| | | P-value | 0.28 | 0.08 | 0.84 |
| | ACR50 response rate at Week 52 | Comparison groups | SB5 - Humira/ Humira | Humira/SB5 -Humira/ Humira | SB5 - Humira Overall |

| | | | | | |
|---|---|---|---|---|---|
| | | Adjusted treatment difference | -2.9% | 2.0% | -3.8% |
| | | 95% CI | [−14.46%, 8.69%] | [−11.34%, 15.29%] | [−13.09%, 5.56%] |
| | | P-value | 0.63 | 0.77 | 0.43 |
| | ACR70 response rate at Week 52 | Comparison groups | SB5 - Humira/ Humira | Humira/SB5 -Humira/ Humira | SB5 - Humira Overall |
| | | Adjusted treatment difference | 0.3% | -4.4% | 2.5% |
| | | 95% CI | [-10.25%, 10.86%] | [-16.42%, 7.66%] | [-6.08%, 11.12%] |
| | | P-value | 0.95 | 0.46 | 0.57 |
| **Analysis description** | **Sensitivity Analysis** | | | | |
| Analysis population and time point description | Full analysis set (FAS) (non-responder analysis)<br>**Week 52** | | | | |
| Descriptive statistics and estimate variability | Treatment group | SB5 | Humira/ Humira | Humira/SB5 | Humira Overall |
| | Number of subjects | 269 | 129 | 125 | 273 |
| | ACR20 response rate at Week 52 | 71.7% (193/269) | 70.5% (91/129) | 74.4% (93/125) | 67.4% (184/273) |
| | ACR50 response rate at Week 52 | 46.1% (124/269) | 48.8% (63/129) | 51.2% (64/125) | 46.5% (127/273) |
| | ARC70 response rate at Week 52 | 29.4% (79/269) | 27.1% (35/129) | 24.8% (31/125) | 24.2% (66/273) |
| | ACR-N<br>mean<br>SD<br>median | <br>48.42<br>30.882<br>49.45 | <br>46.14<br>30.718<br>50.00 | <br>49.58<br>29.506<br>52.65 | <br>47.82<br>30.120<br>50.45 |
| | DAS28<br>mean<br>SD<br>median | <br>-3.05<br>1.387<br>-3.10 | <br>-2.92<br>1.434<br>-3.00 | <br>-3.02<br>1.161<br>-3.05 | <br>-2.97<br>1.306<br>-3.00 |
| | EULAR response<br>Good<br><br>Moderate<br><br>No response | <br>47.8% (118/247)<br>45.7% (113/247)<br>6.5% (16/247) | <br>46.0% (57/124)<br>45.2% (56/124)<br>8.9% (11/124) | <br>46.6% (55/118)<br>47.5% (56/118)<br>5.9% (7/118) | <br>46.3% (112/242)<br>46.3% (112/242)<br>7.4% (18/242) |
| | Major Clinical Response at Week 52 | 15.7% (39/248) | 9.7% (12/124) | 15.3% (18/118) | 12.4% (30/242) |
| | mTSS<br>mean change from Baseline<br>SD | <br><br>0.17<br>2.489 | <br><br>0.50<br>2.401 | <br><br>0.25<br>2.732 | <br><br>0.38<br>2.562 |
| Effect estimate per comparison | ACR20 response rate at Week 52 | Comparison groups | SB5 – Humira/ Humira | Humira/SB5 - Humira/ Humira | SB5 - Humira Overall |
| | | Adjusted treatment difference | 1.2% | 3.9% | 4.4% |
| | | 95% CI | [-8.34%, 10.75%] | [-7.13%, 14.86%] | [-3.37%, 12.18%] |

| | | | | | |
|---|---|---|---|---|---|
| | | P-value | 0.80 | 0.49 | 0.27 |
| | ACR50 response rate at Week 52 | Comparison groups | SB5 - Humira/ Humira | Humira/SB5 – Humira/ Humira | SB5 - Humira Overall |
| | | Adjusted treatment difference | -3.2% | 2.3% | -0.6% |
| | | 95% CI | [-13.70%, 7.33%] | [-9.85%, 14.53%] | [-8.86%, 7.67%] |
| | | P-value | 0.55 | 0.70 | 0.89 |
| | ACR70 response rate at Week 52 | Comparison groups | SB5 - Humira/ Humira | Humira/SB5 – Humira/ Humira | SB5 - Humira Overall |
| | | Adjusted treatment difference | 1.7% | -2.5% | 5.0% |
| | | 95% CI | [-7.71%, 11.05%] | [-13.38%, 8.35%] | [-2.42%, 12.39%] |
| | | P-value | 0.73 | 0.65 | 0.19 |
| | ACR-N at Week 52 | Comparison groups | SB5 - Humira/ Humira | Humira/SB5 – Humira/ Humira | SB5 - Humira Overall |
| | | Treatment difference in the LSMeans | 2.2 | 3.4 | 0.6 |
| | | 95% CI | [-4.33, 8.82] | [-4.34, 11.06] | [-4.75, 6.01] |
| | | P-value | 0.50 | 0.39 | 0.82 |
| | DAS28 | Comparison groups | SB5 - Humira/ Humira | Humira/SB5 – Humira/ Humira | SB5 - Humira Overall |
| | | Treatment difference in the LSMeans | -0.10 | -0.08 | -0.06 |
| | | 95% CI | [-0.38, 0.18] | [-0.40, 0.24] | [-0.29, 0.16] |
| | | P-value | 0.48 | 0.61 | 0.59 |
| | EULAR Response | Data was summarized only descriptively. | | | |
| | Major Clinical Response | Data was summarized only descriptively. | | | |
| | mTSS | Comparison groups | SB5 - Humira/ Humira | Humira/ SB5 – Humira/ Humira | SB5 - Humira Overall |
| | | Adjusted treatment difference in LSMeans | -0.31 | -0.22 | -0.20 |
| | | 95% CI | [-0.843, 0.224] | [-0.883, 0.435] | [-0.655, 0.247] |
| | | P-value | 0.25 | 0.50 | 0.38 |

## Clinical studies in special populations

The primary concern in designing biosimilarity study is to select a target population that is the most sensitive and homogeneous in detecting differences between the test and reference products. Separate

study in paediatric patients is not usually required in the biosimilarity setting. The applicant has selected the population to cover the age group from 18 to 75 years, which is acceptable.

## *Supportive study(ies)*

### Extrapolation of indications

The Applicant intends to claim the same therapeutic indications for the proposed biosimilar SB5 as granted for Humira in the EU. The SB5 development program included direct physicochemical and biological comparisons of SB5, EU and US sourced Humira, a three-way comparison of the three products in a Phase I PK study as well as a confirmatory clinical Phase III study to evaluate the efficacy, safety/tolerability, and immunogenicity of SB5 compared to EU Humira in subjects with moderate to severe RA despite Methotrexate therapy. In the dossier, a reference is made to the "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), which outlines the possibility for extrapolation for clinical data to other indications of the reference product, when biosimilar comparability has been demonstrated by thorough physicochemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication.

To support this strategy the Applicant has provided a separate document which includes the result of a thorough literature review of the mechanism of action of adalimumab to justify extrapolation of the efficacy and safety data across all its approved therapeutic indications.

Firstly the role of TNF-α and its receptors in the pathogenesis of the different authorised indications is discussed, followed by a discussion on the current knowledge of the relationship between adalimumab structure and target/receptor interactions, and its relevance for the extrapolation of indications, including a discussion on the similarity exercise focusing on these attributes. Finally, the known efficacy and safety profiles of the reference product in the extrapolated indications will be discussed. The Applicant considers that the data provided in this MAA provides adequate justification to extrapolate the date obtained in RA patients to all other claimed indications.

**Table 2.5.2.11: Evidence supporting extrapolation of indications of SB5**

| Factors Considered to Justify Extrapolation of Indications | Data Provided |
|---|---|
| The MoA in each condition of use for which licensure is sought | • Discussion on the MoA of TNF-α in approved Humira® indications<br>• Comparative physicochemical analyses and biological assays demonstrating analytical and functional similarity between SB5 and Humira®. The various assays covered different domains of the molecule considered to be particularly important in CD/UC and possibly HS. |

| | |
|---|---|
| The PK, PD, and bio-distribution of the product in different patient populations | • Similarity in structure and function, similarity in binding to TNF-α and FcRn<br>• PK similarity demonstrated in healthy subject studies, supported by data in a subset of RA-patients<br>• Efficacy similarity in RA patients<br>• Analysis of PK and PD characteristics of Humira® across the different approved indications |
| Differences in expected safety concerns in each condition of use and patient population (including whether expected safety concerns are related to the pharmacological activity of the product or to off-target activities)<br>Any other factor that may affect the safety or effectiveness of the product in each condition of use and patient population for which licensure is sought | • Analysis of known safety profiles of adalimumab across indications.<br>• An analysis of immunogenicity and safety profile across indications<br>• Supportive evidence of comparative immunogenicity of SB5 and Humira® |

CD=Crohn's disease; FcRn=Neonatal Fc-receptor; HS=hidradenitis suppurativa; IV=Intravenous; MoA=mechanism of action; PD=pharmacodynamic; PK=pharmacokinetic; TNF-α=Tumour necrosis factor-α; UC=ulcerative colitis.

From the quality perspective (including the *in-vitro* assays) the Company has performed a sound and comprehensive biosimilarity exercise. Up to 47 batches of EU Humira have been extensively characterised and the data were used for a statistical evaluation of the similarity ranges. The side-by side comparison of SB5 clinical and process validation batches with EU -(as well as with US- and Korean sourced) Humira batches included a quite exhaustive panel of standard and state-of-the art techniques which has been used for characterisation and comparison of relevant quality attributes of the adalimumab molecule. This panel includes analytical tests for physicochemical features whereas the biological profile of adalimumab was covered by tests for Fab activities (TNF-α binding and neutralisation assays, apoptosis assay) and Fc activities (binding to the FcγRs and FcRn, binding to C1q, ADCC and CDC assays).

It is believed that neutralisation of sTNF and tmTNF is of key relevance for the efficacy of adalimumab in RA by preventing TNF from inducing TNFR-mediated cellular functions. Regarding IBD it is currently considered that more mechanisms are likely involved. Therefore, a panel of additional biological assays was submitted for justifying extrapolation of indications (inhibition of IL-8 cytokine release, induction of regulatory macrophages, T-cell anti-proliferation, inhibition of adhesion molecule expression, binding to transmembrane TNF-α, FcγRIIIa 158 F/F type binding, FcγRIIIb binding, and LTα3 (TNF-β) binding). The necessity of studying these mechanisms comparatively is primarily deducted from observations that other TNF alpha antagonists display differing levels (or even lack) of efficacy in IBD indications, suggesting that a wider range of mechanisms could be involved. However, it needs to be emphasized that the relative contribution of these various effects is currently unknown.

From a non-clinical perspective the extrapolation of indications seems appropriate for this type of monoclonal antibody based targeted therapy. It also needs to be recognised that available non-clinical pharmacological models for the proposed indications are developed for proof of concept purposes and usually lack discriminatory power for purposes of testing biosimilarity. Consequently, physicochemical comparability together with comparative *in vitro* studies are considered sensitive and appropriate comparative testing parameters for extrapolation purposes.

There are no significant differences in the pharmacokinetic characteristics of Humira between healthy subjects and patients across the various approved Humira indications, hence comparatively evaluating PK in a single dose healthy volunteer study and in a subset of RA patients supports. Comparable PK of SB5 and Humira has been demonstrated in both models (a pivotal comparative PK study in healthy volunteers, supported by similar results of mean $C_{trough}$ levels in a representative subset of RA patients). A drug level

of 5 µg/mL has been reported to have a predictive value of good clinical response in both RA and PsA patients (Pouw et al., 2015; Vogelzang et al., 2014). Also in CD and UC patients, adalimumab serum levels were related to clinical response (Karimiris et al., 2009; Roblin et al., 2014).

For the choice of its efficacy and safety models the company refers to EU guidance recommending comparative parallel design in treatment-naïve patients as the most sensitive design for a premarketing study to assess potential differences in the risk of immunogenicity (EMA "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues") and reiterates that the choice of patient population for the comparative clinical efficacy/safety study has been endorsed during scientific advice (EMA/CHMP/SAWP/430098/2013).

Indeed RA is the indication for which Humira obtained initial marketing authorization and it is the indication for which most clinical trial experience has been accumulated, hence the external validity of results, can be considered high. The disease pathology of RA and the role of TNF-α inhibition are known. Furthermore adalimumab exhibits a reasonable effect size in moderate to severe RA, which among the indications for which Humira is indicated for is only topped by PASI 75 response rates in Psoriasis studies. The company argues that, in terms of representativeness, by far most patients treated with Humira suffer from RA. This argument can only be partly followed, since the model most sensitive to allow for extrapolation to other indications should be chosen, not the model representative of what most adalimumab treated patients suffer from. However, the chosen model together with the convincing clinical similarity data is considered sensitive enough to allow for extrapolation to all other indications of Humira.

Safety related outcomes mediated by TNFα suppression are considered comparable across indications. Comparative immunogenicity has clinically been evaluated in two populations (healthy volunteers and RA patients) in addition to structural and functional analyses in earlier drug development stages.

In summary, provided outstanding issues can be clarified, the totality of data suggests that SB5 is biosimilar to Humira. Complemented by the results obtained by functional assays to comparatively study the mechanism of action proposed for IBD indications (inhibition of IL-8 cytokine release, induction of regulatory macrophages, T-cell anti-proliferation, inhibition of adhesion molecule expression, binding to transmembrane TNF-α, FcγRIIIa 158 F/F type binding, FcγRIIIb binding, and LTα3 (TNF-β) binding) and clinical models chosen to investigate biosimilarity are considered sufficiently sensitive to support extrapolation.

Regarding the extrapolation to Hidradenitis Suppurativa (HS) the Applicant has addressed that the elevated skin tissue TNF-α level has been observed in this condition. The pathogenesis in this condition is proposed to be different, but it has similar elements with the rheumatoid conditions regarding the tmTNF signaling, apoptosis characteristics and in suppression of cytokine secretion. The cytokine expression profile between HS and rheumatoid conditions is though somewhat different, TNF-α overexpression, however, being the common denominator between these diseases. It has been reported that T helper cells (Th17) releasing cytokines IL-17 and IL-22 infiltrate the dermal HS lesions. RA is considered to be Th17-mediated disease as well. The target for adalimumab, TNF-α induces CD4+ T cell IL-17 production indirectly in response to increased IL-1β and IL-6 levels by monocytes in a TNFRI and TNFRII dependent manner. Thus, the described pathogenesis supports the similar primary mechanism of action for adalimumab in both conditions. The non-clinical results in tmTNF-α related binding activity did not show significant differences between SB5 and US Humira. The extrapolation to HS is sufficiently justified by the same target molecules and similar pathomechanisms. The Applicant has extended the claim for indication to uveitis, in which Th17 function is also believed to be central in its pathogenesis.

**Usability of the device**

The Applicant has performed three formative studies in users in parallel with the device development. The purpose of these studies was to get response from the users in the understanding of the instructions of use, on their practical ability to use the device by injection on a practice pad and to design outer and inner carton by user preferences. The Applicant had made corrective actions after each study and these improvements were implemented prior to human factors validation study.

Altogether 83 subjects were enrolled and they represented patients, healthcare professionals and caregivers. The group of patients included those with and without previous experience of PFS use and those who did not have any experience on injections. The patients were selected appropriately to cover the most of the indications applied for the current product, the largest group being RA patients (25) and the majority of the patients (31 of 40) had disease-related impairment reflecting adequately the target population for the SB5 single-dose Safety PFS device.

According to the Applicant no device failures or use-related risks (adverse events or needle sticks) to necessitate further changes to the PFS device were observed during the human factors validation study. The Applicant has provided full Formative and Human Factor Validation study reports and the data on the improvements performed to the device based on the risks observed during the Formative studies. The HFS was considered adequate to mitigate the possible risks in the use of the device and the corrections performed are appropriate for the improved usability of the device.

## 2.5.3. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

The pivotal phase 3 clinical efficacy and safety study (SB5-G31-RA) was a randomised, double-blind, parallel group, multicentre study to demonstrate biosimilarity between the SB5 adalimumab and EU Humira in moderate to severe rheumatoid arthritis patients receiving concomitant methotrexate therapy and folic acid supplement. The primary objective of this study was to demonstrate the equivalence of SB5 to Humira at Week 24, in terms of American College of Rheumatology 20% response criteria (ACR20) response rate in subjects with moderate to severe RA despite MTX therapy. The secondary objectives included the evaluation of efficacy, safety, tolerability, immunogenicity and PK of SB5 compared to Humira using several other endpoints (e.g. ACR20 at 52 weeks, ACR50, ACR70, and DAS28) at Weeks 24 and 52. At week 24, patients in the Humira treatment group were re-randomised either to continue with Humira or to switch to SB5, to evaluate the efficacy, safety and immunogenicity in subjects after switching the treatment. The presented primary and secondary objectives were typical of this type of study and are considered acceptable. The switch of the treatments to clarify the interchangeability between the biosimilar and originator is not a requirement within EU, but supports the Applicants global program, and is as such acceptable. The main long term data for the EU marketing authorization consists of the comparison between SB5 and Humira/Humira treatment groups at Week 52.

The selection of the study target population of moderate to severe rheumatoid arthritis patients having incomplete response from the methotrexate treatment was approved in the CHMP scientific advice and was also according to the EMA guidance on the selection of sensitive clinical models in biosimilar mAb development, and as such is acceptable. By the CHMP scientific advice the study population was considered to be sensitive enough model to allow observation of clinically relevant differences between the biosimilar candidate and the reference medicinal product. Overall the study design (target population and primary outcome time point) can be considered sensitive to detect differences between treatments.

The equivalence margin of ±15% for the difference in the ACR20 response rate between groups was approved by the CHMP scientific advice and was statistically justified by the Applicant in the dossier. The

Applicant conducted a meta-analysis of two studies by Keystone (2004) and Weinblatt (2003) and derived an equivalence margin of ±15% based on fixed-effects model estimate of 0.3832 for the difference between adalimumab and placebo with a 95% CI [0.3060, 0.4605] using the Mantel-Haenszel weight. By the rule to preserve 50% of the clinical effect the lower boundary of the 95% CI was selected resulting in 0.15 (= 0.5 × 0.3060) and ±15% margin for the equivalence and is considered justified by the statistical rational. However, the justification of the clinical non-relevance of the equivalence margin is not explained by the Applicant as required by the EMA guideline on biosimilars (EMEA/CHMP/BMWP/42832/2005 Rev1). The 95% CI ACR20 proportion rate being well within the predefined equivalence margin no concerns pertaining to biosimilarity are present, and therefore further justification from the applicant is not required. Furthermore, the clinical justification of non-relevance might be difficult to prove for the endpoint, which is a proportional unit and does not directly measure the improvement in the effect size for the continuous variable. The ACR20 response rate in the current Phase 3 study was slightly (~5%) higher, but of the same magnitude, compared to the respective values in the two studies referred to in the equivalence margin estimation, supporting the selected criteria for the biosimilarity. From the statistical standpoint in the primary endpoint analysis the adjusted estimates of the treatment effect should be compared to unadjusted estimates as addressed by the EMA guidance on adjustment for baseline covariates (EMA/CHMP/295050/2013). The Applicant has provided the requested data, which shows comparable results between the adjusted and unadjusted estimates. The selection of baseline CRP as a covariate for the pivotal study ANCOVA analysis is supported, since it correlates with the RA disease activity.

The sensitivity analyses applied by the Applicant are acceptable, and the approach to first study the primary outcome in the PPS population with the sensitivity analysis evaluating the robustness of results in FAS population, is acceptable. The handling of the missing data is according to the EMA Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1.).

The study was un-blinded for a limited number of prospectively selected sponsor representatives to conduct the Week 24 pivotal efficacy analysis. The personnel were prospectively assigned to the blinded and unblinded staff members by their functions to carry out interim pivotal analysis. Some of the duties of the unblinded members were transferred to the blinded staff members not participating in the Week 24 analysis. The Applicant confirms that the trial was kept blinded up to 52 weeks. Treatment codes and results were protected for blinding up to Week 52. The computer-generated randomization at centre level was conducted by using Interactive Web Response system (IWRS). The Applicant has provided biostatistical addendum undersigned at the 11th of February, 2014, and full randomization protocol, which describes the use of blocked randomization schedule with stratifying factors and on demand allocation of blocks in both initial and re-randomization randomization scheme. In general, the statistical protocol was according to the guidelines and the CHMP scientific advice received.

The study population for the primary analysis (PPS1) contained 239 and 237 study subjects in the SB5 and Humira groups, respectively. For the FAS population 269 and 273 patients were randomised to the SB5 and Humira groups, respectively. The discontinuation rate was low in both groups being under 10% and no significant imbalance between the groups was observed regarding the discontinuations although the withdrawal rate due to adverse events was somewhat higher in the Humira group. Demographic and disease- or treatment-related baseline characteristics were well balanced between the study arms. However, it seems that surgical treatments and other continuing medical conditions were slightly more frequently reported in the Humira group, but the difference in numbers is not expected to have impact on the study outcome. However, a significant difference in mean age (49.8 (SB5) vs. 52.5 years (Humira), p-value = 0.010) was present. There was also a numerical, but not statistically significant trend for a higher number of patients aged ≥ 65 in the Humira treatment arm 10.7% (SB5) vs. 14.7% (Humira). Subgroup analyses performed by the applicant revealed that among the subjects aged ≥ 65 years, 68.0% (17/25) and 71.4% (25/35) of the subjects achieved an ACR20 response at Week 24 in the SB5 and

Humira treatment groups, respectively and thus there was no significant interaction in ACR20 response rate at Week 24 between treatment and age group (p-value = 0.865).

The Applicant addresses that no rescue medicines were provided to the patients during the study and the criteria for the prohibited and permitted concomitant treatment were pre-determined. The mean weekly dose level of MTX was similar at the initiation between the groups. However, several major protocol deviations in the MTX treatment were seen. The protocol deviation in the MTX treatment criteria was observed in 24 events in the Imraldi group and 26 events in the Humira group. The Applicant has clarified the criteria to exclude subjects from the study based on the IP and MTX compliance criteria, which have been followed consistently in the respective study populations (PPS, FAS, PK, and SAS). In addition, since the study outcome is comparable in FAS and PPS populations the patients excluded by these criteria do not have any impact on the results. The reported use of concomitant medication did not differ significantly between the groups during the study. According to the Applicant glucocorticoids were used by approximately half of the study subjects (49.6% vs. 45.1% of subjects in SB5 and Humira groups respectively) and acetic acid derivatives and related substances by 23.9% and 20.5% of subjects in SB5 and Humira groups, respectively.

Based on the Applicants notification the clinical studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and they were consistent with the International Conference on Harmonisation (ICH) “Guideline for Good Clinical Practice (GCP)” (ICH E6(R1)) and applicable local regulatory requirements and laws. A high number of protocol deviations was reported with a possibility to variable practices in the clinical trial conduct in the countries outside EU (Bosnia and Herzegovina, Ukraine, South Korea), the overall major protocol deviation frequency being 39.5% and 43.2% in SB5 and Humira groups, respectively, in the pivotal efficacy trial (SB5-G31-RA). Regarding the center or region effect on the results the Applicant had performed an Analysis of Covariance for ACR20 response at Week 24 with treatment by Region (EU vs. non-EU) in PP population, which gave non-significant statistical significance. In addition, the same most highly recruiting site of the current pivotal study was included in the pivotal study of the same Company for an earlier biosimilar application for the same indication, without critical issues to be found in the recent GCP-inspection. Therefore, the GCP-inspection of the current pivotal study was not pursued further. The Applicant has appropriately explained the discrepancy in the number of centres reported to be included in the study by the slow CTA approval and late start of the trial in some planned trial sites.

The study data was collected for 52 weeks which is considered adequate for comparing the long term efficacy and safety between the biosimilar and reference medicinal product.

### *Efficacy data and additional analyses*

A single pivotal clinical study (SB5-G31-RA) conducted showed equivalence in the primary outcome, ACR20 response rate at Week 24, in both PPS1 and FAS populations attesting the robustness of the outcome. The proportion of subjects in PPS1 population reaching the ACR20 response rate at week 24 were 72.4% (173/239) and 72.2% (171/237) in the SB5 and EU Humira groups, respectively. The estimated difference in proportions was 0.1% and its 95% CI -7.83% - 8.13%, and was well contained within the pre-specified equivalence margin of ±15%. In FAS population the corresponding response rates were 68.0% (183/269) and 67.4% (184/273) leading to the adjusted difference in proportions of 0.8% and 95% CI of -7.03 – 8.56%. Thus, regarding the primary outcome the study fulfilled the biosimilarity criteria. In addition, although the plateau in ACR20 response rate was reached at Week 24 the earlier time course of ACR20 response did not reveal relevant differences either, thus confirming similarity also in the sensitive, steep part of the time/response curve. Also the secondary endpoints ACR50 and ACR70 were confined within the equivalence margin at week 24.

Longer-term secondary outcomes ACR20 and ACR50 at Week 52 showed a trend of a modestly better response in the SB5 group compared to the EU Humira and also in the switched SB5/Humira group compared to the group of patients continuing with Humira. Thus, when evaluating ACR20 response at week 52, in the PPS1, the lower limits of the 95% CI of the adjusted treatment differences in ACR20 response rate at Week 52 (-4.63%) between the SB5 and Humira /Humira treatment group was preserved within the exploratory equivalence margin of [-15%, 15%] pre-defined for Week 24, however not the upper limits (15.90%). This finding is not confirmed, when looking at the FAS [-8.34%,10.75%]. Since the study was not planned to show similarity at week 52 these measures are considered not indicative of a higher response rate of SB5, at week 52, especially, since ACR50 (−2.9% [95% CI: −14.46%, 8.69%]), ACR70 (0.3% [95% CI: −10.25%, 10.86%]), and DAS28 score (−0.10 [−0.38, 0.18], margin: -0.6/0.6), once more show strong support of similarity in long term efficacy.

The percentage of subjects who achieved a major clinical response, which is defined as ACR70 response for 6 consecutive months at Week 52 was 15.7% (39/248) in the SB5 and 9.7% (12/124) in the Humira/Humira treatment groups. This might indicate that major clinical response is more likely to occur under SB5 compared to Humira. In addition the difference vanishes in patients switched from Humira to SB5, where 15.3% (18/118) show major clinical response.

To claim similar long-term efficacy between the products, the Applicant has looked at the components of ACR in different time points up to Week 52. In each ACR criteria the products had similar scores and at Week 52 no clear difference in any criteria was seen, supporting the biosimilarity regarding the primary outcome. The trend of seemingly better ACR20 response and major clinical response at Week 52 in SB5 treatment compared to the reference product treatment group was temporal, which fell into normal variability of the ACR response. Moreover, efficacy parameters other than ACR20 response rate and major clinical response were comparable across the treatment groups at Week 52.

Altogether, the secondary outcomes encompassing also structural endpoint were in line with the primary efficacy analysis supporting the biosimilarity claim. Some modest differences between groups were observed in the secondary outcome analyses, but these being descriptive analyses not adequately powered they do not change the overall impression on biosimilarity. The Applicant has submitted the comparative statistical analysis of the individual ACR components, which indicates biosimilarity in each ACR component analysed.

The difference in ACR20 response between the SB5 and EU Humira groups was seen in ADA-positive subgroup comparison. Instead, treatment responses were highly comparable between the SB5 and EU Humira treatment groups for the ADA-negative subgroup. If ADA positive groups are compared the ACR20 level was reached only by 57.5% (42/73) of the subjects in the SB5 group and 71.2% (52/73) of the subjects in the Humira group, which brings estimated difference in proportions of -17.5% (95% CI -33.3%, -1.8%) between the groups, while in ADA negative subjects the difference in proportions between the groups was 5.7% (95% CI -3.8%, 15.2%). However, in long-term efficacy no clear withering effect in ADA positive patients was seen, which would have been expected when more patients will turn out to be ADA positive with longer exposure time. Furthermore, clear fluctuation in ACR scores was seen and no correlation between worsening of the response and increasing number of NAb-positivity was seen. Moreover, the results between treatment groups in both ADA positive and negative subgroups were similar in DAS28 score. Thus, the observed difference does not exclude the biosimilarity claim between the products. Other subgroup analyses of baseline CRP, age, and demographic characteristics showed no interaction with treatment.

Overall ANCOVA for ACR20 response at Week 24 by the ADA results (PPS1) resulted in statistically significant difference (p-value 0.015) between the groups. The efficacy difference in ADA positive groups was less in ACR50 (SB5 28.8%, Humira 35.6%); and pointing in the opposite direction for ACR 70 (SB5 19.2%, Humira 16.4%). Based on the ACR response rate curve for the group continuing with Humira after

week 24 and SB5 group, the ACR responses seem to be consistently lower in the SB5 ADA positive subgroup in each time-point evaluated. This observation, however, cannot be considered clinically important since the difference in the ACR20 responses was highest at week 24, but narrowed towards week 52, which is contradictory if the difference would be due to increased immunogenicity.

In the ADA-positive subgroups, the Humira group had better efficacy as determined by AUC of ACR responses (categorical variables), whereas no difference was seen when DAS28 AUC (continuous variable) was used. Furthermore, the incidence of ADAs, titers and neutralizing capacity were comparable between the groups. Regarding the kinetics the exposure to adalimumab was similarly decreased in both ADA-positive groups. Thus, based on these data the increased ACR responses in ADA positive Humira group could be considered an isolated finding that is not compatible with ADA results, pharmacokinetics or the DAS28 results. In addition, any long-term withering of the efficacy outcome was not seen in overall population and even improved efficacy in a group who switched from Humira to SB5 was seen.

The Applicant is claiming the same indications as granted for the originator Humira. Since the primary adalimumab mechanism of action is similar between rheumatoid, psoriasis and HS indications and the quality and pre-clinical data have shown comparable physicochemical and functional characteristics between the SB5 and Humira, extrapolation can be agreed in these indications granted for the originator. The comparative functional analyses performed included also the binding and effector functions of membrane bound TNF-α, demonstrating comparable bioanalytical behaviour between the SB5 and Humira, further on supporting the similar mechanistic functions of the products also in IBD indications. Regarding the uveitis indication recently granted for the Humira originator and applied by the Applicant the provided justification for extrapolation is sufficient for the claim of this indication.

Since only the 40 mg/0.8 ml strength has been studied and the MA is only sought for that PFS presentation and the product is intended to be marketed as a fixed dose product without the graduation in the syringe the product is suitable only to those children for whom this dose level is applicable. The Applicant has amended the posology Section 4.2 of the SmPC to conform with the limitations in the paediatric use and included the advice to use other formulations and presentations of adalimumab products in the paediatric patients not suited for the current dose. According to the recent principle recommendation by the CHMP related to paediatric indications of biosimilar products, the Section 4.1 of the SmPC should include paediatric indications in full, as with the originator, and Section 4.2 should include explanatory details on which patients can be dosed with the existing presentation. The Applicant has updated the SmPC accordingly.

The Applicant had performed improvement to the SB5 single-dose Safety PFS device based on the data obtained from three formative studies prior to human factors validation study. No device failures or use-related risks were observed in human factor study. The Applicant had provided the full study reports from the formative studies and the human factors validation study. Based on the documentation provided, the study and the performed improvements based on the formative study results seem adequate to support the safe use and usability of the device.

## 2.5.4. Conclusions on the clinical efficacy

The results presented on efficacy support the biosimilarity claim between the test product SB5 and the reference product EU Humira.

## 2.6. Clinical safety

### Patient exposure

The applicant has submitted safety data on 189 healthy volunteers exposed to a single 40 mg s.c. dose of adalimumab and on 544 RA patients exposed to at least one dose of 40 mg every other week [EOW] via s.c. injection for up to 52 weeks:

In the clinical Phase I study SB5-11-NHV, a total of 189 healthy subjects were randomised to receive a single dose of adalimumab (40 mg via s.c. injection), with 63 subjects in each of the three treatment groups (SB5, EU Humira and US Humira). The SAF comprised all subjects who received at least one dose of investigational product (IP).

In the clinical Phase III study SB5-G31-RA, 544 patients were randomised to receive adalimumab (40 mg every other week [EOW] via s.c. injection) for up to 52 weeks. Safety Set 1 (**SAF1**) consisted of all subjects who received at least 1 dose of IP during the study. Safety Set 2 (**SAF2**) consisted of all SAF1 subjects who received at least 1 dose of IP after re-randomisation at Week 24. 271 subjects were randomised to the SB5 treatment group and 273 subjects were randomised to the EU Humira treatment group. 254 (93.7%) subjects in the SB5 and 254 (93.0%) subjects in the EU Humira treatment groups completed 24 weeks of the study. Prior to Week 24, 36 (6.6%) subjects withdrew from the study, including 17 subjects (6.3%) from the SB5 treatment group and 19 (7.0%) subjects from the EU Humira treatment group.

At Week 24, of the 254 subjects receiving EU Humira, 125 (49.2%) were randomised to transition to SB5 40 mg (Humira/SB5) and 129 (50.8%) were randomised to continue on EU Humira In total, 248 (97.6%) subjects in the SB5, 117 (93.6%) subjects in the Humira/SB5, and 124 (96.1%) subjects in the Humira/Humira treatment group completed 52 weeks of the study. Between Week 24 and Week 52, 19 (3.7%) subjects withdrew from the study; 6 (2.4%) subjects from the SB5 treatment group, 8 (6.4%) subjects from the Humira/SB5, and 5 (3.9%) subjects from the Humira/Humira treatment group. 40 mg (hereinafter Humira/Humira)

Duration of exposure

541 subjects included in the SAF1 received at least 1 injection of SB5 or EU Humira. Up to Week 24, the mean duration of exposure was 150.7 days in the SB5 treatment group and 148.7 days in the EU Humira treatment group. Up to Week 52, the duration of exposure to the IP was comparable between the SB5 and Humira overall treatment groups and between the SB5 and Humira/Humira treatment groups. The mean duration of exposure was 333.6 days in the SB5, 324.6 days in the Humira overall, 343.3 days in the Humira/SB5, and 348.3 days in the Humira/Humira treatment groups.

**Table 2.6.1 Treatment exposure**

| | N (receiving at least 1 dose) | | |
|---|---|---|---|
| | **SB5** | **Adalimumab** (of which switched to SB5) | Total |
| PK Healthy Subjects | | | |
| SB5-G11-NHV | 63 | 126* | 189 |
| Patients (RA) | | | |
| SB5-G31-RA | 271 | 273 (125) | 544 |
| Total | 334 | 399 | 733 |

* 63 subjects were exposed to adalimumab (US) and a further 63 subjects were exposed to adalimumab (EU).

## *Adverse events*

### Study SB5-11-NHV

The safety end-points of this healthy volunteer-study included:

- Vital signs abnormalities (semi-supine position)
- Abnormalities in physical examination
- Incidence of abnormalities in clinical laboratory values
- including haematology, chemistry and urinalysis
- Abnormalities in 12-lead electrocardiogram (ECG)
- Incidence of adverse events (AEs) and serious AEs (SAEs)
- Injection site assessment

There were no deaths or discontinuation due to TEAEs (treatment emergent adverse events) during the study. Among healthy volunteers, TEAEs were observed in 57.1%, 46.0% and 61.9% of subjects in the SB5 group, EU Humira and US Humira groups, respectively, most commonly nasopharyngitis (19.0% and 12.7% in SB5 and Humira-groups, respectively) and headache (17.5% and 6.3%).

Most AEs were mild or moderate, with only one severe event observed in the US Humira group.

**Table 2.6.2. Treatment-emergent adverse events which occurred in at least 5% of subjects**

| Treatment | SB5 N=63 | | | EU Humira® N=63 | | | US Humira® N=63 | | | Total N=189 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%) | E | n | (%) | E | n | (%) | E | n | (%) | E |
| Any TEAEs | 36 | (57.1) | 66 | 29 | (46.0) | 55 | 39 | (61.9) | 58 | 104 | (55.0) | 179 |
| Preferred term | | | | | | | | | | | | |
| Nasopharyngitis | 12 | (19.0) | 12 | 8 | (12.7) | 8 | 11 | (17.5) | 11 | 31 | (16.4) | 31 |
| Headache | 11 | (17.5) | 15 | 4 | (6.3) | 4 | 7 | (11.1) | 7 | 22 | (11.6) | 26 |
| Oral herpes | 4 | (6.3) | 4 | 1 | (1.6) | 1 | 4 | (6.3) | 4 | 9 | (4.8) | 9 |
| Rhinitis | 2 | (3.2) | 2 | 4 | (6.3) | 4 | 3 | (4.8) | 3 | 9 | (4.8) | 9 |

N = number of subjects in the safety set; Subjects n = number of subjects who experienced each event; E = number of events experienced.
Percentages were subjects n divided by N.
Source: Section 5.3.3.1 CSR SB5-G11-NHV, Table 12-1

**Study SB5-G31-RA**

The safety endpoints of this study in RA-patients included:

- Incidence of SAEs
- Incidence of AEs (graded as mild, moderate and severe)
- Incidence of clinical laboratory abnormalities
- Vital signs abnormalities
- AEs of special interest **(AESI):** Serious infections, Active tuberculosis

AEs were assessed with regards to severity, causality, and expectedness. Protocol section 8.1.5. defines causality assessment as follows: "The causal relationship between the IP and the AE should be defined as not related (no) or related (yes). Events should be classified as "related" if there is a reasonable possibility that the IP caused the AE. This means that there are facts (evidence) or arguments to suggest a causal relationship. Events should be classified as "not related" if there is not a reasonable possibility that the IP caused the AE."

A total of 207 (38.3%) subjects reported 457 TEAEs at any time after the first dose of IP until Week 24; 96 (35.8%) subjects in the SB5 and 111 (40.7%) subjects in the Humira treatment groups reported TEAEs. The most common TEAE was nasopharyngitis (4.9% and 9.2% in the SB5 and Humira groups).

**Table 2.6.3. Number (%) of Subjects with TEAEs and Number of Events by PT That Occurred in ≥ 2% of Subjects up to Week 24 in Any Treatment Group**
**(SAF1)**

| Treatment | SB5 N=268 | | EU Humira® N=273 | | Total N=541 | |
|---|---|---|---|---|---|---|
| Preferred Term | n (%) | E | n (%) | E | n (%) | E |
| Any TEAEs | 96 (35.8) | 193 | 111 (40.7) | 264 | 207 (38.3) | 457 |
| Nasopharyngitis | 13 (4.9) | 15 | 25 (9.2) | 27 | 38 (7.0) | 42 |
| Headache | 9 (3.4) | 10 | 7 (2.6) | 7 | 16 (3.0) | 17 |
| Bronchitis | 7 (2.6) | 7 | 7 (2.6) | 7 | 14 (2.6) | 14 |
| Alanine aminotransferase increased | 6 (2.2) | 6 | 8 (2.9) | 8 | 14 (2.6) | 14 |
| Spinal pain | 6 (2.2) | 7 | 7 (2.6) | 8 | 13 (2.4) | 15 |
| Nausea | 5 (1.9) | 8 | 6 (2.2) | 14 | 11 (2.0) | 22 |

N = number of subjects in the Safety Set 1; n = number of subjects with TEAEs; E = frequency of the adverse events started before Week 24; TEAE = treatment-emergent adverse event
Percentages were based on the number of subjects in the Safety Set 1.
Source: Section 5.3.5.1 CSR SB5-G31-RA, Table 12-2, Table 14.3.1-3.2

A total of 294 (54.3%) subjects reported 727 TEAEs at any time until week 52 after the first dose of IP; 140 (52.2%) subjects in the SB5, 154 (56.4%) subjects in the Humira overall, and 69 (54.3%) subjects in the Humira/Humira treatment groups. A total of 17.2% of subjects experienced a TEAE judged as related to the IP, and 37.2% of subjects experienced a TEAE judged as not related to the IP by the investigator; there was no obvious difference between the SB5 and Humira groups. The most common TEAE was nasopharyngitis (9%, 12.6%). Upper respiratory tract infection was seen in 3.7% and 0.8% of patients in the SB5 and Humira/Humira groups.

**Table 2.6.4. TEAEs (Occurring in ≥ 2% of subjects in any Treatment Group) at the PT Level up to Week 52 (SAF1)**

| Treatment | SB5 N=268 | | EU Humira® | | | | Total N=541 | |
|---|---|---|---|---|---|---|---|---|
| | | | Overall N=273 | | EU Humira® N=127[a] | | | |
| Preferred term | n (%) | E | n (%) | E | n (%) | E | n (%) | E |
| Any TEAEs | 140 (52.2) | 325 | 154 (56.4) | 402 | 69 (54.3) | 193 | 294 (54.3) | 727 |
| Nasopharyngitis | 24 (9.0) | 27 | 30 (11.0) | 34 | 16 (12.6) | 19 | 54 (10.0) | 61 |
| Headache | 11 (4.1) | 13 | 14 (5.1) | 15 | 6 (4.7) | 6 | 25 (4.6) | 28 |
| Bronchitis | 11 (4.1) | 12 | 11 (4.0) | 11 | 5 (3.9) | 5 | 22 (4.1) | 23 |
| Latent tuberculosis | 11 (4.1) | 11 | 8 (2.9) | 8 | 7 (5.5) | 7 | 19 (3.5) | 19 |
| Upper respiratory tract infection | 10 (3.7) | 10 | 8 (2.9) | 11 | 1 (0.8) | 1 | 18 (3.3) | 21 |
| Alanine aminotransferase increased | 9 (3.4) | 9 | 12 (4.4) | 12 | 7 (5.5) | 7 | 21 (3.9) | 21 |
| Spinal pain | 8 (3.0) | 14 | 9 (3.3) | 13 | 6 (4.7) | 7 | 17 (3.1) | 27 |
| Urinary tract infection | 8 (3.0) | 10 | 7 (2.6) | 7 | 2 (1.6) | 2 | 15 (2.8) | 17 |
| Nausea | 8 (3.0) | 11 | 6 (2.2) | 14 | 4 (3.1) | 12 | 14 (2.6) | 25 |
| Back pain | 7 (2.6) | 7 | 4 (1.5) | 4 | 3 (2.4) | 3 | 11 (2.0) | 11 |
| Arthralgia | 7 (2.6) | 9 | 2 (0.7) | 2 | 0 (0.0) | 0 | 9 (1.7) | 11 |
| Rheumatoid arthritis | 4 (1.5) | 4 | 7 (2.6) | 7 | 4 (3.1) | 4 | 11 (2.0) | 11 |
| Aspartate aminotransferase increased | 3 (1.1) | 3 | 6 (2.2) | 6 | 3 (2.4) | 3 | 9 (1.7) | 9 |

N = number of subjects in the Safety Set 1; n = number of subjects with TEAEs; E = frequency of the adverse events;
TEAE = treatment-emergent adverse event
[a] Based on the subjects in the Safety Set 2.
Percentages were based on N.
Source: Section 5.3.5.1 CSR SB5-G31-RA, Table 14.3.1-1.2

**Other Significant Adverse Events up to Week 24 for the Safety Set 1**

There were 3 AESIs up to Week 24 in 3 subjects (0.6%) overall. In the SB5 treatment group, 1 (0.4%) subject was reported with 1 AESI:

• A 51-year-old female white subject was reported with Escherichia urinary tract infection on Day 128, which was noted as resolved on Day 143. The event was moderate in severity, required hospitalisation and led to temporary discontinuation of IP. The event was considered to be related to the IP.

In the Humira treatment group, 2 (0.7%) subjects were each reported with 1 AESI up to Week 24:

• A 58-year-old female white subject was reported with bronchopneumonia on Day 24, which was noted as resolved on Day 52. The event was severe in severity, required hospitalisation and led to temporary discontinuation of IP. The event was considered to be related to the IP.

• A 63-year-old male white subject was reported with staphylococcal sepsis on Day 109, which was resolving. The event was severe in severity, and required hospitalisation. The event led to discontinuation of IP and was considered not to be related to the IP.

Malignancies

3 events in 2 subjects in the Humira treatment group were malignancies: 1 subject was reported with lymphoma and metastases to spine and 1 subject was reported with papillary thyroid cancer. There were no malignancies reported in the SB5 treatment group up to Week 24.

**Other Significant Adverse Events up to Week 52 for the Safety Set 1**

There were 5 AESIs up to Week 52 in 5 subjects (0.9%) overall. In the SB5 treatment group, 1 (0.4%) subject was reported with 1 AESI:

• 1 subject was reported with Escherichia urinary tract infection.

In the Humira overall treatment group, 4 (1.5%) subjects each reported 1 AESI:

• 1 subject was reported with bronchopneumonia.

• 1 subject was reported with staphylococcal sepsis.

• A 58-year-old female white subject was reported with a urinary tract infection on Day 386, which was noted as resolved on Day 403. The last dose of IP had been given on Day 358. The event was severe in severity, and required hospitalisation. The event was considered not to be related to the IP.

• A 21-year-old female white subject was reported with pneumonia on Day 245, which was noted as resolved on Day 256. The event was severe in severity, and required hospitalisation. The event led to temporary discontinuation of IP and was considered to be related to the IP.

Malignancies

Malignancies were reported in a total of 5 (0.9%) subjects up to Week 52; 1 malignancy was reported in 1 (0.4%) subject in the SB5 treatment group, 5 malignancies in 4 (1.5%) subjects in the Humira overall treatment group, and 1 malignancy in 1 (0.8%) subject in the Humira/Humira treatment group.

In the SB5 treatment group, 1 (0.4%) subject was reported with a malignancy:

• A 52-year-old male white subject was reported with small cell lung cancer on Day 329, which was noted as resolving. The event was severe in severity, medically important, and required hospitalisation. The event was not considered to be related to the IP.

In the Humira overall treatment group, 5 malignancies were reported in 4 (1.5%) subjects:

• A 48-year-old female white subject was reported with papillary thyroid cancer on Day 62, which was noted as recovered with sequelae on Day 181. The event was mild in severity, medically important, and required hospitalisation. The event was not considered to be related to the IP. IP was permanently discontinued.

• 1 subject was reported with lymphoma and metastases to spine.

• 1 subject was reported with glioblastoma multiforme.

• A 45-year-old male white subject was reported with seminoma on Day 313, which was noted as resolved with sequelae on Day 314. The event was mild in severity and required hospitalisation. The event was not considered to be related to the IP.

**Newly occurred AEs after week 24 (SAF2)**

A total of 265 AEs were reported in 171 (33.8%) subjects; 82 (32.3%) subjects in the SB5/SB5 treatment group, 47 (37.6%) subjects in the Humira/SB5 treatment group and 42 (33.1%) subjects in the Humira /Humira treatment group reported any kind of AEs. For Humira /SB5 treatment group, if a lag time window overlapped with pre-transition IP (Humira) exposure time period (28 days), the AE was considered to be undetermined. Otherwise, the AE was considered to be attributed to post-transition IP (SB5).

**Table 2.6.5. Number (%) of Subjects with TEAEs and Number of Events by PT Newly Occurred after Week 24 in ⩾ 2% of Subjects in Any Treatment Group (SAF 2)**

| Treatment | SB5/SB5 N=254 | | EU Humira®/SB5 N=125 | | | | | | EU Humira®/ EU Humira® N=127 | | Total N=506 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Overall | | SB5[a] | | Undetermined[a] | | | | | |
| Preferred term | n (%) | E | n (%) | E | n (%) | E | n (%) | E | n (%) | E | n (%) | E |
| Any TEAEs | 82 (32.3) | 128 | 47 (37.6) | 70 | 15 (12.0) | 20 | 38 (30.4) | 50 | 42 (33.1) | 67 | 171 (33.8) | 265 |
| Nasopharyngitis | 11 (4.3) | 12 | 4 (3.2) | 4 | 0 (0.0) | 0 | 4 (3.2) | 4 | 3 (2.4) | 3 | 18 (3.6) | 19 |
| Latent tuberculosis | 8 (3.1) | 8 | 1 (0.8) | 1 | 0 (0.0) | 0 | 1 (0.8) | 1 | 7 (5.5) | 7 | 16 (3.2) | 16 |
| Spinal pain | 5 (2.0) | 7 | 3 (2.4) | 3 | 0 (0.0) | 0 | 3 (2.4) | 3 | 2 (1.6) | 2 | 10 (2.0) | 12 |
| Bronchitis | 5 (2.0) | 5 | 2 (1.6) | 2 | 0 (0.0) | 0 | 2 (1.6) | 2 | 2 (1.6) | 2 | 9 (1.8) | 9 |
| Urinary tract infection | 5 (2.0) | 6 | 3 (2.4) | 3 | 1 (0.8) | 1 | 2 (1.6) | 2 | 0 (0.0) | 0 | 8 (1.6) | 9 |
| Rheumatoid arthritis | 4 (1.6) | 4 | 3 (2.4) | 3 | 1 (0.8) | 1 | 2 (1.6) | 2 | 4 (3.1) | 4 | 11 (2.2) | 11 |
| Upper respiratory tract infection | 4 (1.6) | 4 | 5 (4.0) | 6 | 1 (0.8) | 1 | 5 (4.0) | 5 | 0 (0.0) | 0 | 9 (1.8) | 10 |
| Alanine aminotransferase increased | 3 (1.2) | 3 | 1 (0.8) | 1 | 1 (0.8) | 1 | 0 (0.0) | 0 | 3 (2.4) | 3 | 7 (1.4) | 7 |
| Headache | 2 (0.8) | 3 | 3 (2.4) | 4 | 0 (0.0) | 0 | 3 (2.4) | 4 | 4 (3.1) | 4 | 9 (1.8) | 11 |
| Mycobacterium tuberculosis complex test positive | 2 (0.8) | 2 | 4 (3.2) | 4 | 1 (0.8) | 1 | 3 (2.4) | 3 | 1 (0.8) | 1 | 7 (1.4) | 7 |

N = number of subjects in the Safety Set 2; n = number of subjects with TEAEs; E = frequency of the adverse events; TEAE = treatment-emergent adverse event
[a] For Humira®/SB5 treatment group, if a lag time window overlapped with pre-transition IP (Humira®) exposure time period (28 days), then the AE was considered to be undetermined. Otherwise, the AE was considered to be attributed to post-transition IP (SB5).
Percentages were based on the number of subjects in the Safety Set 2.
Source: Section 5.3.5.1 CSR SB5-G31-RA, Table 12-4, Table 14.3.1-2.2

The most common new AE after week 24 was nasopharyngitis (4.3 and 2.4% in SB5 and Humira/Humira-groups). The AEs seen in the undetermined group, i.e. immediately after the switch from EU-Humira to SB5 (*if a lag time window overlapped with pre-transition IP/ Humira exposure time period (28 days), then the AE was considered to be undetermined*), included e.g. upper respiratory tract infections, headache, spinal pain, and importantly 3 patients (2.4%) had Mycobacterium tuberculosis complex test positive and 1 had latent tuberculosis. The Applicant had provided detailed information on these patients and concluded that it is not related to switching from EU Humira to SB5

## Serious adverse events and deaths

Study SB5-11-NHV

There were no deaths during the study. Two SAEs occurred in 2 subjects; 1 subject from the SB5 treatment group suffered from a psychotic disorder on day 21 day after administration of the IP and was hospitalized, and 1 subject from the US sourced Humira treatment group who developed appendicitis on 15 day after administration of the IP and underwent laparoscopic appendicectomy; both events were assessed by the Investigator not to be related to the IP.

Study SB5-G31-RA

Deaths

There were 2 deaths reported during the study from the Humira treatment group:

- 60-year-old female white subject in the Humira treatment group was reported with cardiac arrest on Day 137 (or Week 20). The last IP administration prior to death was on Day 128. On study Day 125, the subject had been hospitalised with paraplegia. After the diagnostic procedures (tumour assessment results were unavailable), the subject was diagnosed with serious adverse events (SAEs) of lymphoma and metastases to spine. On study Day 137, the subject experienced a fatal adverse event of cardiac arrest. Autopsy was not performed. The Investigator considered the event of lymphoma and metastases to spine to be related to IP and the event of cardiac arrest to be unrelated to IP.

-63-year-old male white subject in the Humira treatment group was reported with pulmonary embolism on Day 126 (or Week 18). The last IP administration prior to death was on Day 111. On study day 108, the subject had experienced an SAE of vascular pseudoaneurysm, and undergone surgery (distal prosthetic anastomosis of right limb), and was diagnosed with Staphylococcal sepsis and treatetd with antibiotics and lower leg incisions on both sides. Due to long immobilization and infection, on study day 126, the subject experienced pulmonary embolism with fatal outcome. Autopsy was not performed. The Investigator considered the events of vascular pseudoaneurysm, Staphylococcal sepsis and pulmonary embolism to be unrelated to IP.

A total of 15 SAEs were reported in 11 (2.0%) of the subjects; 3 (1.1%) subjects reported 3 SAEs in the SB5 treatment group, and 8 (2.9%) subjects reported 12 SAEs in the EU Humira treatment group.

Of the 15 SAEs reported, 2 from the Humira treatment group were fatal and 2 in the neoplasm benign, malignant and unspecified (including cysts and polyps) SOC from the Humira treatment group only were not resolved (mediastinal lymph nodes tumor and metastatic spinal tumor).

**Table 2.6.6. Serious Adverse Event by Preferred Term up to Week 24 (SAF1)**

| Treatment | SB5 40 mg N=268 | | Humira® 40 mg N=273 | | Total N=541 | |
|---|---|---|---|---|---|---|
| Preferred term | n (%) | E | n (%) | E | n (%) | E |
| Any SAEs | 3 (1.1) | 3 | 8 (2.9) | 12 | 11 (2.0) | 15 |
| Acute myocardial infarction | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Escherichia urinary tract infection | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Viral infection | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Bronchopneumonia | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Cardiac arrest | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Eosinophilia | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Lymphoma | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Metastases to spine | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Nasal inflammation | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Papillary thyroid cancer | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Pneumonia | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Pulmonary embolism | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Staphylococcal sepsis | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Ulna fracture | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |
| Vascular pseudoaneurysm | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.2) | 1 |

N = number of subjects in the Safety Set 1; n = number of subjects with SAEs
E = frequency of the AEs started before Week 24; SAE = serious adverse event
Adverse events were coded by system organ class and preferred term using the MedDRA Version 17.0 coding dictionary.
Percentages were based on the number of subjects in the Safety Set 1.

Up to week 52, total of 29 SAEs were reported in 25 (4.6%) subjects; 9 (3.4%) subjects reported 9 SAEs in the SB5, 16 (5.9%) subjects reported 20 SAEs in the Humira overall, and 6 (4.7%) subjects reported 6 SAEs in the Humira/Humira treatment groups. Of the 29 SAEs reported, 2 were fatal (see above). Of the 9 SAEs reported in the SB5 treatment group up to Week 52, 2 SAEs were considered to be related to the IP. Of the 20 SAEs reported in the Humira overall treatment group up to Week 52, 5 SAEs were considered to be related to the IP.

**Table 2.6.7. Serious Adverse Event by Preferred Term up to Week 52 (SAF1)**

| Treatment | SB5 N=268 | | EU Humira® Overall N=273 | | EU Humira® N=127[a] | | Total N=541 | |
|---|---|---|---|---|---|---|---|---|
| Preferred term | n (%) | E | n (%) | E | n (%) | E | n (%) | E |
| Any SAEs | 9 (3.4) | 9 | 16 (5.9) | 20 | 6 (4.7) | 6 | 25 (4.6) | 29 |
| Acute myocardial infarction | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Chronic obstructive pulmonary disease | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Escherichia urinary tract infection | 1 (0.4) | 1 | ρ (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |

| Treatment | SB5 N=268 | | EU Humira® | | | | Total N=541 | |
|---|---|---|---|---|---|---|---|---|
| | | | Overall N=273 | | EU Humira® N=127[a] | | | |
| Preferred term | n (%) | E | n (%) | E | n (%) | E | n (%) | E |
| Femoral hernia, obstructive | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Lumbar radiculopathy | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Retinal oedema | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Rheumatoid arthritis | 1 (0.4) | 1 | 1 (0.4) | 1 | 1 (0.8) | 1 | 2 (0.4) | 2 |
| Small cell lung cancer | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Viral infection | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Pneumonia | 0 (0.0) | 0 | 2 (0.7) | 2 | 0 (0.0) | 0 | 2 (0.4) | 2 |
| Bronchitis | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Bronchopneumonia | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Cardiac arrest | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Craniocerebral injury | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Eosinophilia | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Glioblastoma multiforme | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Lymphoma | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Metastases to spine | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Multiple sclerosis | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Nasal inflammation | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Papillary thyroid cancer | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Pulmonary embolism | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Seminoma | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Staphylococcal sepsis | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Ulna fracture | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Urinary tract infection | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Vascular pseudoaneurysm | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |

N = number of subjects in the Safety Set 1; n = number of subjects with SAEs; E = frequency of the SAEs; SAE = serious adverse event
[a]Based on the subjects in the Safety Set 2.
Percentages were based on N.
Source: Section 5.3.5.1 CSR SB5-G31-RA, Table 12-6, Table 14.3.1-1.5.

**SAEs after week 24**

The proportion of subjects who experienced SAEs after Week 24 for the SAF2 was 2.4% (6 events in 6 subjects) in the SB5/SB5 treatment group, 3.2% (4 events in 4 subjects) in the Humira/SB5 treatment group, and 3.1% (4 events in 4 subjects) in the Humira /Humira treatment group.

| Treatment | SB5 N=268 | | EU Humira® | | | | Total N=541 | |
|---|---|---|---|---|---|---|---|---|
| | | | Overall N=273 | | EU Humira® N=127[a] | | | |
| Preferred term | n (%) | E | n (%) | E | n (%) | E | n (%) | E |
| Femoral hernia, obstructive | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Lumbar radiculopathy | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Retinal oedema | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Rheumatoid arthritis | 1 (0.4) | 1 | 1 (0.4) | 1 | 1 (0.8) | 1 | 2 (0.4) | 2 |
| Small cell lung cancer | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Viral infection | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Pneumonia | 0 (0.0) | 0 | 2 (0.7) | 2 | 0 (0.0) | 0 | 2 (0.4) | 2 |
| Bronchitis | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Bronchopneumonia | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Cardiac arrest | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Craniocerebral injury | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Eosinophilia | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Glioblastoma multiforme | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Lymphoma | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Metastases to spine | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Multiple sclerosis | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Nasal inflammation | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Papillary thyroid cancer | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Pulmonary embolism | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Seminoma | 0 (0.0) | 0 | 1 (0.4) | 1 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Staphylococcal sepsis | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Ulna fracture | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Urinary tract infection | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Vascular pseudoaneurysm | 0 (0.0) | 0 | 1 (0.4) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |

N = number of subjects in the Safety Set 1; n = number of subjects with SAEs; E = frequency of the SAEs; SAE = serious adverse event

[a]Based on the subjects in the Safety Set 2.

Percentages were based on N.

Source: Section 5.3.5.1 CSR SB5-G31-RA, Table 12-6, Table 14.3.1-1.5.

**Table 2.6.8. Newly Occurred Serious Adverse Events after Week 24 by Preferred Term (SAF2)**

| Treatment | SB5/SB5 N=254 | | EU Humira®/SB5 N=125 | | | | | | EU Humira®/EU Humira® N=127 | | Total N=506 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Overall | | SB5[a] | | Undetermined[a] | | | | | |
| Preferred term | n (%) | E | n (%) | E | n (%) | E | n (%) | E | n (%) | E | n (%) | E |
| Any SAEs | 6 (2.4) | 6 | 4 (3.2) | 4 | 1 (0.8) | 1 | 3 (2.4) | 3 | 4 (3.1) | 4 | 14 (2.8) | 14 |
| Rheumatoid arthritis | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.8) | 1 | 2 (0.4) | 2 |
| Chronic obstructive pulmonary disease | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Femoral hernia, obstructive | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Lumbar radiculopathy | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Retinal oedema | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Small cell lung cancer | 1 (0.4) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Bronchitis | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Craniocerebral injury | 0 (0.0) | 0 | 1 (0.8) | 1 | 0 (0.0) | 0 | 1 (0.8) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Glioblastoma multiforme | 0 (0.0) | 0 | 1 (0.8) | 1 | 0 (0.0) | 0 | 1 (0.8) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Multiple sclerosis | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Pneumonia | 0 (0.0) | 0 | 1 (0.8) | 1 | 0 (0.0) | 0 | 1 (0.8) | 1 | 0 (0.0) | 0 | 1 (0.2) | 1 |
| Seminoma | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.8) | 1 | 1 (0.2) | 1 |
| Urinary tract infection | 0 (0.0) | 0 | 1 (0.8) | 1 | 1 (0.8) | 1 | 0 (0.0) | 0 | 0 (0.0) | 0 | 1 (0.2) | 1 |

N = number of subjects in the Safety Set 2; n = number of subjects with SAEs, E = frequency of the SAEs; SAE = serious adverse event
[a] For Humira®/SB5 treatment group, if a lag time window overlapped with pre-transition IP (Humira®) exposure time period (28 days), then the AE was considered to be undetermined. Otherwise, the AE was considered to be attributed to post-transition IP (SB5).
Percentages were based on the number of subjects in the Safety Set 2.
Source: Section 5.3.5.1 CSR SB5-G31-RA, Table 12-7, Table 14.3.1-2.5

## Laboratory findings

Study SB5-G11-NHV

Among healthy volunteers, the mean and median values of all parameters of haematology, biochemistry and urinalysis did not show any changes over time. Minor alterations were comparable to those usually seen in a healthy population. There were no clinically meaningful post-dose changes in these parameters from baseline after SB5, EU Humira or US Humira administrations.

Study SB5-G31-RA

The values and changes from baseline for each laboratory parameter for haematology, biochemistry (including rheumatoid factor and CRP), and urinalysis were comparable between the SB5 and Humira overall treatment groups and between the SB5 and Humira /Humira treatment groups (SAF1).

Up to Week 24, the most commonly reported significant abnormal haematology parameter was low neutrophils, reported in 4 (1.5%) subjects in the SB5 and 4 (1.5%) subjects in the EU Humira treatment groups. Low lymphocytes were reported in 3 (1.1%) vs. 1 (0.4%) subject, and high neutrophils was reported in 3 (1.1%) vs. 0 subjects, respectively.

The number of subjects with at least 1 post-dose significant abnormality in any of the haematology parameters up to Week 52 for the SAF1 are summarised in table below.

The only difference between the groups was in the number of patients with high neutrophil accounts, i.e. 4 patients in SB5 and none in Humira-group.

**Table 2.6.9. Number (%) of Subjects with at Least 1 Post-dose Significant Abnormality in Haematology Parameters up to Week 52 (SAF1)**

| Parameters | Criteria | SB5 N=268 | EU Humira® | | | Total N=541 |
|---|---|---|---|---|---|---|
| | | | Overall N=273 | SB5 N=125[a] | EU Humira® N=127[a] | |
| | | n (%) | n (%) | n (%) | n (%) | n (%) |
| Haemoglobin (g/L) | L2 | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| | H2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Haematocrit (L/L) | L2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | H2 | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| Leukocytes ($\times 10^9$/L) | L2 | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| | H2 | 2 (0.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.4) |
| Neutrophils ($\times 10^9$/L) | L2 | 5 (1.9) | 4 (1.5) | 3 (2.4) | 1 (0.8) | 9 (1.7) |
| | H2 | 4 (1.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (0.7) |
| Lymphocytes ($\times 10^9$/L) | L2 | 3 (1.1) | 2 (0.7) | 0 (0.0) | 2 (1.6) | 5 (0.9) |
| | H2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Platelets ($\times 10^9$/L) | L2 | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| | H2 | 1 (0.4) | 1 (0.4) | 0 (0.0) | 1 (0.8) | 2 (0.4) |

N = number of subjects in the Safety Set 1; n = number of subjects with available assessment results
L2 = below the significant abnormal range; H2 = above the significant abnormal range
[a] Based on the subjects in the Safety Set 2; Humira®/SB5 and Humira®/Humira® may not add up to Humira® overall.
Percentages were based on N.
Overall results at Week 52 were determined if at least 1 abnormality from Week 0 to Week 52.
Significant abnormalities were defined with L2/H2. For haemoglobin, L2 was < 90 g/L for males and < 80 g/L for females and H2 was > 200 g/L; for haematocrit, L2 was < 0.3 L/L for males and < 0.2 L/L for females and H2 was > 0.6 L/L; for leukocytes, L2 was < $2.0 \times 10^9$/L and H2 was > $20 \times 10^9$/L; for neutrophils, L2 was < $1.2 \times 10^9$/L and H2 was > $15 \times 10^9$/L; for lymphocytes, L2 was < $0.5 \times 10^9$/L; and for platelets, L2 was < $50 \times 10^9$/L and H2 was > $600 \times 10^9$/L.
Source: Section 5.3.5.1 CSR SB5-G31-RA, Table 12-8, Table 14.3-2.7

Up to Week 24, the most commonly reported significant abnormal biochemistry parameter was high ALT, reported in the 8 (3.0%) subjects in the SB5 treatment group and 13 (4.8%) subjects in the EU Humira treatment group. High AST was reported in 4 (1.5%) vs. 5 (1.8%) subjects, and high γGT was reported in 2 (0.7%) vs. 3 (1.1%) subjects, respectively.

The number of subjects with at least 1 post-dose significant abnormality in any of the biochemistry parameters for the SAF1 up to Week 52 are summarised in the table below.

**Table 2.6.10. Number (%) of Subjects with at Least 1 Post-dose Significant Abnormality in Biochemistry Parameters up to Week 52 (SAF1).**

| Parameters | Criteria | SB5 N=268 | EU Humira® | | | Total N=541 |
|---|---|---|---|---|---|---|
| | | | Overall N=273 | SB5 N=125[a] | EU Humira® N=127[a] | |
| | | n (%) | n (%) | n (%) | n (%) | n (%) |
| Bilirubin (µmol/L) | L2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | H2 | 2 (0.7) | 2 (0.7) | 1 (0.8) | 1 (0.8) | 4 (0.7) |
| AST (U/L) | L2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | H2 | 4 (1.5) | 5 (1.8) | 4 (3.2) | 1 (0.8) | 9 (1.7) |
| ALT (U/L) | L2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | H2 | 10 (3.7) | 15 (5.5) | 8 (6.4) | 7 (5.5) | 25 (4.6) |
| γGT (U/L) | L2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | H2 | 4 (1.5) | 4 (1.5) | 2 (1.6) | 2 (1.6) | 8 (1.5) |
| ALP (U/L) | L2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | H2 | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| LDH (U/L) | L2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | H2 | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| Glucose (mmol/L) | L2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | H2 | 2 (0.7) | 2 (0.7) | 2 (1.6) | 0 (0.0) | 4 (0.7) |
| Phosphorus (mmol/L) | L2 | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| | H2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

N = number of subjects in the Safety Set 1; n = number of subjects with available assessment results
AST = aspartate aminotransferase; ALT = alanine aminotransferase; γGT = gamma-glutamyl transferase; ALP = Alkaline phosphatase; LDH = lactate dehydrogenase; L2 = below the significant abnormal range; H2 = above the significant abnormal range
[a] Based on the subjects in the Safety Set 2; Humira®/SB5 and Humira®/Humira® may not add up to Humira® overall.
Percentages were based on N.
Overall results at Week 52 were determined if at least 1 abnormality from Week 0 to Week 52.
Significant abnormalities were defined with L2/H2. For bilirubin, H2 was > 34.2 µmol/L; for AST, H2 was > 123 U/L for males and > 99 U/L for females; for ALT, H2 was > 123 U/L for males and > 99 U/L for females; for γGT, H2 was > 305 U/L for males and > 180 U/L for females; for ALP, H2 was > 300 U/L; for LDH, H2 was > 750 U/L; for glucose, H2 was > 13.9 mmol/L; and for phosphorus, L2 was < 0.29 mmol/L.
Source: Section 5.3.5.1 CSR SB5-G31-RA, Table 12-9, Table 14.3-2.8

**Auto-antibodies**

Anti-nuclear Antibodies

At Baseline, the majority of subjects in the SB5 and EU Humira treatment groups had negative anti-nuclear antibody (ANA): 254 (95.1%) and 258 (94.9%), respectively.

At Week 24, 5 (1.9%) subjects in the SB5 and 3 (1.2%) subjects in the EU Humira treatment groups had a shift from positive ANA at baseline to negative. Shifts from negative ANA at baseline to positive at Week 24 were reported in 12 (4.6%) subjects and 13 (5.0%) subjects, respectively. At Week 52, shifts from positive ANA at baseline to negative were reported in 2 (0.8%) subjects in the SB5, 3 (1.2%) subjects in the Humira overall, 1 (0.8%) subjects in the Humira/SB5, and 2 (1.6%) subjects in the Humira/Humira treatment groups. Shifts from negative ANA at baseline to positive at Week 52 were reported in 21 (8.4%) vs. 25 (10.0%) vs. 14 (11.4%) vs. 11 (8.8%), respectively.

Anti-double Stranded DNA Antibodies

At Week 24, a total of 3 and 5 subjects in the SB5 and EU Humira treatment groups, respectively, tested positive for anti-dsDNA antibodies. At Week 52, 6 subjects in the SB5, 2 in the Humira overall, 1 in the Humira/SB5, and 1 in the Humira/Humira treatment groups tested positive. None of the subjects who were positive for anti-dsDNA antibodies developed a lupus-like syndrome.

Urinalysis

There were no notable differences in the proportion of subjects with abnormal (not clinically significant or clinically significant) urinalysis parameters (erythrocytes, glucose, haemoglobin, ketones, leukocytes, nitrite, protein, and urobilinogen) up to Week 52 observed between the SB5 and Humira overall treatment groups, and between the SB5 and the Humira/Humira treatment groups.

No meaningful differences were observed for laboratory evaluations in the different treatment groups.

## Safety in special populations

The Applicant has not conducted specific studies on assessing the potential impact of intrinsic factors on safety of SB5, and relies on the documentation of the reference product Humira.

## Immunological events

### Anti-adalimumab antibody assay methodology

Anti-Drug-Antibodies (ADAs) were measured by a bridging ligand-binding electro-chemiluminescent (ECL) assayin both Humira- and SB5-treated patients. (For validation of these methods, see Analytical methods in the Discussion on Clinical pharmacology section of this AR and Clinical AR.)

#### Neutralising antibodies

Neutralising antibodies (Nabs) were measured. The neutralising activity was assessed by inhibition of TNF-$\alpha$ binding to immobilised SB5 by circulating ADAs.

#### Antigenicity of SB5 and Humira

The Applicant claims that adalimumab of EU-Humira and SB5 are antigenically equivalent by showing a similar inhibition of the signal by a monoclonal human anti-adalimumab antibody. In addition, the Applicant has used dilution curves of polyclonal rabbit anti-SB5 and rabbit anti-adalimumab (from EU Humira) to demonstrate similar reactivity in the ECL assay.

### ADAs in clinical samples from healthy individuals and patients with rheumatoid arthritis

Immunogenicity was studied in both clinical studies. The single dose study in healthy volunteers (Study SB5-G11-NHV) is part of a global development program and compared the PK profiles of SB5 with Humira sourced either from the EU or the USA. The confirmatory efficacy, safety and immunogenicity study SB5-G31-RA included also a pharmacokinetic sub-study.

Study SB5-G11-NHV

Study "A Randomised, Single-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Three Formulations of adalimumab (SB5, EU Humira and US Humira ) in Healthy Subjects" involved 189 subjects (63 per arm) who were randomized into the three study arms, all of whom were included in the safety analysis. After administration of a single subcutaneous 40mg adalimumab dose, the pharmacokinetic profile was similar between SB5, EU-Humira and US-Humira. The PK results do not suggest any significant bias in the analysis of immunogenicity in terms of drug tolerance.

ADA- and Nab-positivity was defined as at least one post-dose positive sample. The post-dose incidence of ADAs was 62/63 (98.4%), 60/63 (95.2%), and 63/63 (100%) in subjects administered with SB5, EU Humira, and US Humira, respectively. The frequency of positive samples was comparable in the groups at all sampling points (Table below).

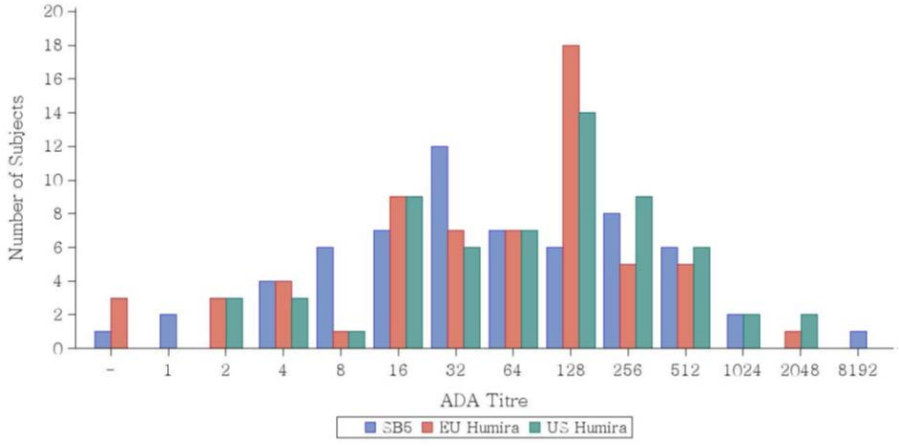
**Table 2.6.11. Summary of study SB5-G11-NHV Immunogenicity Results**

| Study ID (design) | Title | Duration | Treatment | Overall ADAs[a] n/n' (%) | Overall NAbs n/n' (%) | eCTD Location |
|---|---|---|---|---|---|---|
| SB5-G11-NHV (Phase I) | A Randomised, Single-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Three Formulations of adalimumab (SB5, EU Humira® and US Humira®) in Healthy Subjects | 10 weeks (post dose 71 days) | Single dose *s.c.* injection of 40 mg SB5 | 62/63 (98.4%) | 49/62 (79.0%) | 5.3.3.1 |
| | | | Single dose *s.c.* injection of 40 mg EU Humira® | 60/63 (95.2%) | 48/60 (80.0%) | |
| | | | Single dose *s.c.* injection of 40 mg US Humira® | 63/63 (100%) | 52/63 (82.5%) | |

n'= number of subjects with available immunogenicity assessment results;
[a] Overall ADA results were determined as 'Positive' if subject had at least 1 ADA-positive result until the relevant timepoint

The titers were comparable in the groups (see figure below).

**Figure 2.6.2. Subject Distribution by ADA Titer Including ADA-negative (PK population) (Study SB5-G11-NHV)**



Nabs were detected in 49/62 (79.0%), 48/60 (80.0%), and 52/63 (82.5%) of subjects in the SB5, EU-Humira, and US-Humira groups, respectively. The incidence was comparable in all groups at all sampling points.

Study SB5-G31-RA

The confirmatory Study SB5-G31-RA, "A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB5 Compared to Humira in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy" involved a total of 544 RA patients, 271 subjects to the SB5 treatment group and 273 to the EU-Humira treatment group. Blood samples for the determination of ADAs and NAbs were collected at baseline and Weeks 4, 8, 16, 24, 32, 40 and 52.

ADAs were found in 32% and 31% of patients treated with SB5 and EU-Humira, respectively, by week 24. At week 52, the numbers among SB5-treated and Humira-treated patients were 36% and 37%, respectively (see table below).

**Table 2.6.12 Summary of Study SB5-G31-RA Immunogenicity Results**

| Study ID (design) | Title | Duration | Treatment | ADAs[a] n/n' (%) | eCTD Location |
|---|---|---|---|---|---|
| SB5-G31-RA (Phase III) | A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity of SB5 Compared to Humira® in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy | 24 weeks overall (Safety set 1) | *s.c.* injections of SB5 40 mg EOW | 79/246 (32.1) | 5.3.5.1 |
| | | | *s.c.* injections of Humira® 40 mg EOW continuously | 81/260 (31.2) | |
| | | 52 weeks overall (Safety set 2) | *s.c.* injections of SB5 40 mg EOW continuously | 85/236 (36.0) | |
| | | | *s.c.* injections of SB5 40 mg EOW in patients previously receiving Humira and transitioned to SB5 at Week 24 | 47/122 (38.5) | |
| | | | *s.c.* injection of Humira® 40 mg EOW continuously | 46/123 (37.4) | |
| | | After Week 24 overall[a,b] | *s.c.* injection of SB5 40 mg EOW continuously | 9/160 (5.6) | |
| | | | *s.c.* injections of SB5 40 mg EOW in patients previously receiving Humira® and transitioned to SB5 at Week 24 | 5/80 (6.3) | |
| | | | *s.c.* injection of Humira® 40 mg EOW continuously | 11/87 (12.6) | |

n'= number of subjects with available immunogenicity assessment results; EOW= every other week
Source: Section 5.3.5.1 SB5-G31-RA CSR Table 12-10, Table 14.3-3.1 (SAF1) and Table 14.3-3.2 (SAF2).
[a] Values were from the Safety Set 2.
[b] After transition overall were determined as 'Positive' if subject had at least one ADA-positive result from Week 32 to Week 52 among subjects with the overall ADA-negative at Week 24 among subjects with an overall ADA-negative status at Week 24. Percentages were based on n'.

Immunogenicity after the switch in study SB5-G31-RA

At Week 24, 254 subjects receiving Humira were re-randomised in a 1:1 ratio to either continuing on Humira 40 mg (Humira/Humira , n=129) or to switching to SB5 (Humira/SB5, n=125) up to Week 50. The 254 subjects initially randomized to SB5 continued to receiving SB5 40 mg up to Week 50.

Five (6.3%) subjects in the Humira/SB5 and 11 (12.6%) subjects in the Humira/Humira treatment groups converted to ADA-positive after Week 24.

Among the 45 subjects in the Humira/SB5 treatment group with an overall ADA positive result at Week 24, 16 subjects (35.6%) had transitioned-treatment-boosted ADA (ADA titer was increased at any time after Week 24 compared with the highest ADA titer up to Week 24), 22 subjects (48.9%) had positive ADAs after Week 24 where the titer was the same or decreased from the highest titer from Week 0 to Week 24, and 7 subjects (15.6%) had ADA negative results at all visits after Week 24.

Among 39 subjects in the Humira/Humira treatment group with an overall ADA positive result at Week 24 or an ADA positive or missing result at Week 0 (there was 1 subject with a missing result in this treatment group), 12 subjects (30.8%) had transitioned-treatment-boosted ADA, 23 subjects (59.0%) had positive ADAs after Week 24 where the titer was the same or decreased from the highest titer between Week 0 and Week 24, and 4 subjects (10.3%) had ADA negative results at all visits after Week 24.

**Pre-existing antibodies (study SB5-G31-RA)**

Among the 20 subjects in the SB5 treatment group with an ADA positive or missing result at Week 0, 9 subjects (45.0%) had treatment-boosted ADA (ADA titer was increased at any time post-baseline compared with the baseline titer), 9 subjects (45.0%) had positive ADAs where the titer was the same or decreased compared with the baseline titer at any time after onset of SB5 administration, and 2 subjects (10.0%) had ADA negative results at all visits after IP administration.

Among 9 subjects in the Humira treatment group with an ADA positive or missing result at Week 0, 5 subjects (55.6%) had treatment-boosted ADA (including a subject who had a missing value at baseline and positive results post-baseline), 1 subject (11.1%) had positive ADAs where the titer was the same or decreased compared with the baseline titer at any time after IP administration, and 3 subjects (33.3%) had ADA negative results at all visits after IP administration.

**Impact of ADAs on the pharmacokinetics of adalimumab**

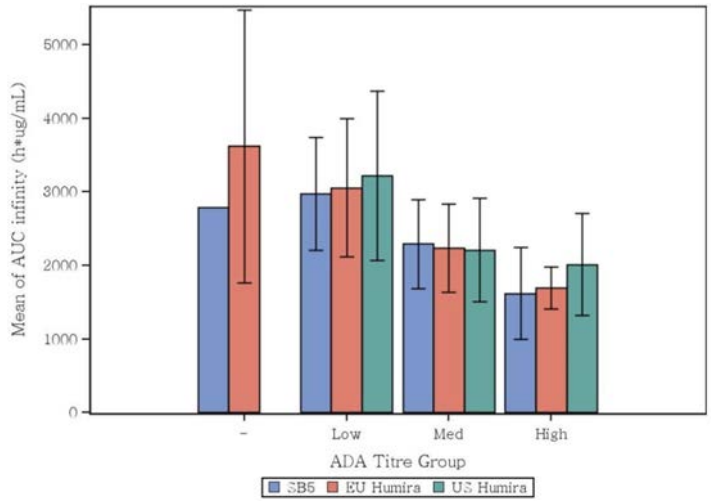
In the single-dose pharmacokinetic study in healthy individuals (SB5-G11-NHV), the number of ADA-negative individuals was too low for comparisons. Therefore, the Applicant divided the subjects to low, medium, and high titer groups. The $AUC_{inf}$ and $AUC_{last}$ had an inverse correlation to the titers of ADAs. High titer ADA-positive patients had higher adalimumab clearance rates. The impact of high titer ADAs was also seen on Cmax. The effect appeared similar in SB5-, EU-Humira, and US-Humira subgroups (see Table and Figure below for example).

**Table 2.6.13 AUC inf in low, medium, and high ADA titer groups of individuals**

| ADA titer | SB5 (N=52/62) | | EU-Humira (N=58/63) | | US-Humira (N=57/62) | |
|---|---|---|---|---|---|---|
| Sub group | n | Mean | n | Mean | n | Mean |
| Low | 19 | 2973 | 17 | 3057 | 15 | 3218 |
| Medium | 22 | 2291 | 30 | 2236 | 27 | 2209 |
| High | 11 | 1621 | 11 | 1697 | 15 | 2013 |

PK parameters did not differ between SB5-, EU-Humira-, and US-Humira-treated patients when ADA-positive and –negative patients were analysed separately (see Figure below).

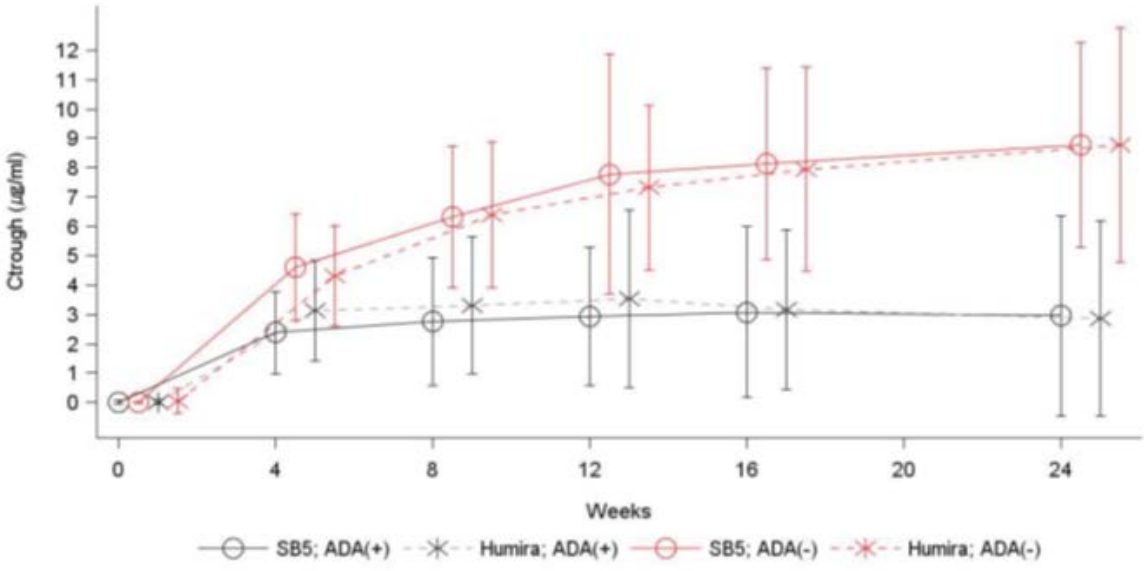
**Figure 2.6.3 Comparison of AUCinf Mean (SD) across ADA Titer Subgroups (Study SB5-G11-NHV)**




The confirmatory Study SB5-G31-RA, there were a total of 544 RA patients, 271 subjects to the SB5 treatment group and 273 to the EU-Humira treatment group. Pre-dose trough concentrations were measured in 178 patients both in the SB5- and EU-Humira groups, respectively. Fifty-five patients were ADA-positive in the PK-groups of both treatment arms. At week 52, the numbers among SB5-treated and Humira-treated patients were 36% and 39%, respectively.

The trough (pre-dose) levels were comparable in the SB5- and EU-Humira treated patients in both ADA- and ADA+ patient populations. In general, trough concentrations were lower in ADA+ population (see Figure below).

**Figure 2.6.4. Arithmetic Mean Predose (Trough) Concentration-time Profiles by Week 24 Anti-drug Antibody Result and Treatment Group Linear Scale (PK Population) (Study SB5-G31-RA)**



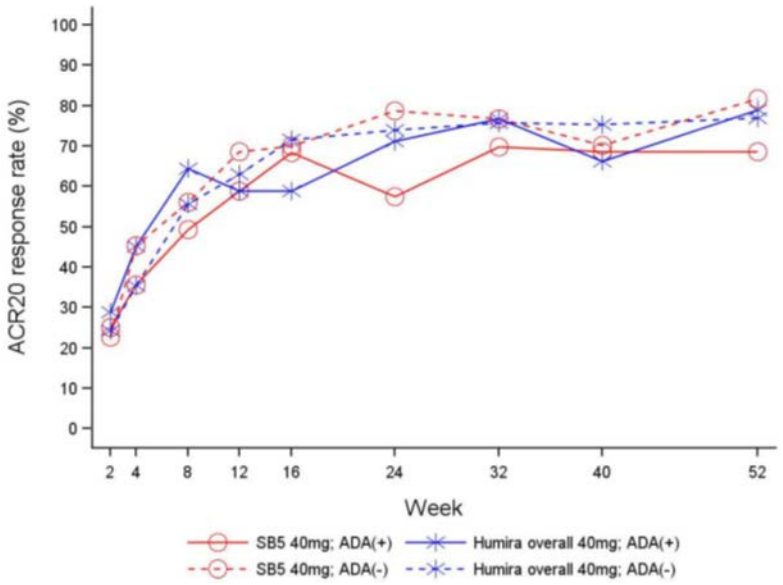
The ACR20 response at week 24 in ADA positive patients showed a slight drop in subjects treated with SB5 compared to Humira. When comparing mean $C_{trough}$ levels at week 24 in the ADA positive subgroup (51/178 subjects treated with SB5 as well as with Humira), however, mean $C_{trough}$ levels were slightly higher with SB5 compared to Humira (2.95 µg/ml vs. 2.86 µg/ml). Thus, no correlation between the observed temporary decline in ACR20 at week 24 and PK (mean $C_{trough}$ level) is seen, although it is noticed that $C_{trough}$ levels were only taken in a subset of patients. The mean through concentrations did not change significantly in the steady state until week 24.

**Impact of ADAs on efficacy**

At week 24, the percentages of ACR20-responses were comparable in ADA-negative SB5- and EU-Humira-treated patients. However, there was a statistically significant difference in the ADA-positive population; 57.5% in the SB5 treated patients and 71.2% in EU-Humira-treated patients. A similar trend was also found in ACR50 and ACR70 responses but the differences were not statistically significant. (See Table 3.4.5.12)

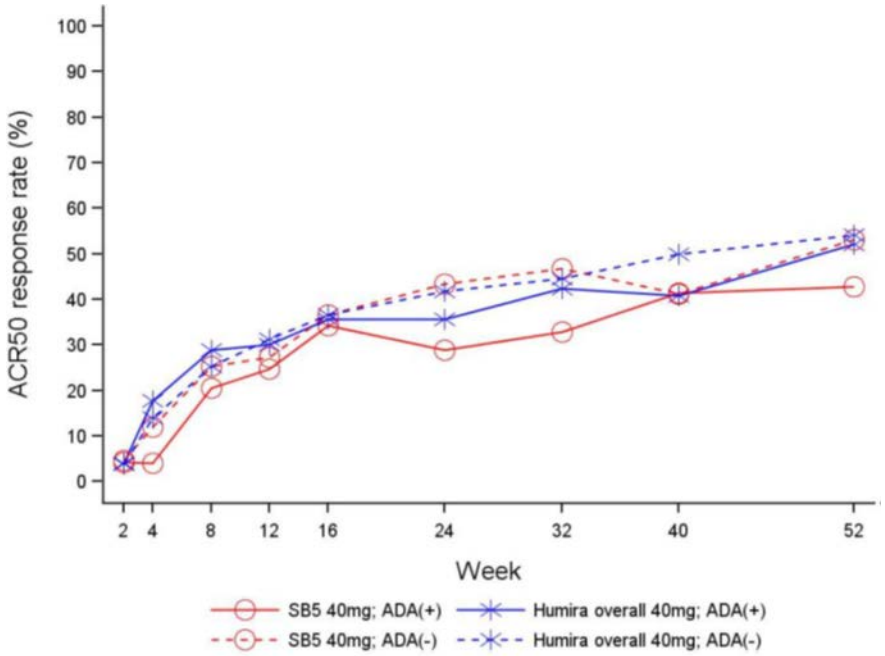
The ACR20 response rate in ADA-positive patients was 68.5% at Week 16, 57.5% at Week 24, 69.9% at Week 32, 68.6% at Week 40, and 68.6% at Week 52, for the SB5 treatment group, compared to 58.9% at Week 16, 71.2% at Week 24, 76.7% at Week, 66.2% at Week 40 and 78.9% at Week 52 for the Humira overall treatment group (Figure below).

**Figure 2.6.5. ACR20 Response up to Week 52 by Overall ADA Status up to Week 24 and Treatment Group (Per-Protocol Set 1) (Study SB5-G31-RA)**




The ACR50 response rate in ADA-positive patients was 34.2% at Week 16, 28.8% at Week 24, 32.9% at Week 32, 41.4% at Week 40 and 42.9% at Week 52 for the SB5 treatment group, compared to 35.6% at Week 16, 35.6% at Week 24, 42.5% at Week 32, 40.8% at Week 40 and 52.1% at Week 52 for the Humira overall treatment group (Figure below).

**Figure 3.4.8.6 ACR50 Response up to Week 52 by Overall ADA Status up to Week 24 and Treatment Group (Per-Protocol Set 1) (Study SB5-G31-RA)**




At week 52, the difference between ADA-positive SB5-treated patients was not seen in ACR70 responses.

The finding that ACR responses were lower in ADA-positive patients at week 24 in SB5 compared to Humira group is unexpected. In Weeks 1-24, the AUC of ACR20 was 10% higher in the Humira group whereas the AUC DAS28 was similar. ACR responses of SB5-treated patients in the whole (per protocol) population were within the pre-specified equivalence range. The difference between the ADA-positive groups is not widening towards week 52. The ADA-positive subgroups are small and vulnerable for fluctuation. It seems obvious that the ACR20-difference between the ADA-positive groups is a chance finding since a difference is not seen in the ADA-prevalence, exposure or DAS28 results. In fact, the behavior of both ADA-positive groups is unexpected with regard to ARC20 responses. The ADA-positive SB5 group had an unexpected drop in the ACR responses at week 24 whereas the ADA-positive Humira group had almost the same ACR responses as the ADA-negative group. This contradicts previous data on adalimumab.

The incidence, titers and neutralizing capacity of ADAs seem comparable between the groups. Interestingly, there was no significant difference in ACR20 responses in patients with neutralizing antibodies. Thus, there is no evidence of an increased immunogenicity of SB5.

ADAs are known to reduce the exposure and efficacy of adalimumab. ADA-positive patients in both SB5 and adalimumab treatment groups had lower trough concentrations than the ADA-negative patients but there were no difference between ADA-positive groups. The Applicant divided the patients into two groups on the basis of the trough level (above and below1.274 µg/mL) that has been shown to distinguish patients with good and poor response to adalimumab. In both groups, a better response was seen in the high trough level group by all efficacy endpoints, except in the ACR20 response in the Humira group (where the response was similar in those with above and below 1.274 µg/mL threshold; this is unusual finding, as discussed above). Taken together, data on DAS28, exposure, and ADAs as well historical data on efficacy and exposure in ADA-positive patients suggest that the difference in the ACR responses between the ADA-positive groups is most likely a chance finding.

**Injection site reactions**:

Among healthy volunteers, only one injection site reaction occurred classified according to applicant´s scaling system (scale 0-15, score of ≥ 2 classified as an AE).

In study SB5-G31-RA, up to Week 24, injection site reactions (3.0% in the SB5 vs. 2.9% in the EU Humira treatment group) were comparable between the SB5 and EU Humira treatment groups. Up to Week 52, the proportions of subjects who experienced injection site reactions for the SAF1 were comparable between the SB5 and Humira overall treatment groups and between the SB5 and Humira/Humira treatment groups. The number of reactions was higher in the Humira overall and Humira/Humira treatment groups, due to high numbers of events of 'injection site reaction' and 'injection site erythema'. In the SB5 treatment group, 8 (3.0%) subjects reported 9 injection site reactions, in the Humira overall treatment group, 8 (2.9%) subjects reported 45 injection site reactions, and in the Humira/Humira treatment group, 4 (3.1%) subjects reported 32 injection site reactions when the high-level group term of administration site reaction was regarded as injection site reaction.

For the Safety Set 2 (after Week 24), Injection site reactions after Week 24 were reported in 2 (1.6%) subjects in the Humira/Humira treatment group only in the SAF2.

Two subjects discontinued the study due to hypersensitivity reactions (PT allergic dermatitis), both in Humira group.

**Incidence of Injection Site Reactions by ADA Status**

The overall incidence of injection site reactions (i.e., TEAEs with 'administration site reactions' as the high level group term) was 2.4% in the SB5 vs. 3.9% in the Humira treatment group in subjects with an overall negative ADA result up to Week 24 and 5.1% vs. 0.0%, in subjects with an overall positive ADA result up to Week 24.

The overall incidence of injection site reactions was 2.5% in the SB5 vs. 4.3% in the Humira overall vs. 3.9% in the Humira/Humira treatment groups among subjects with an overall negative ADA result up to Week 52 and 4.5% vs. 0.0% vs. 0.0%, respectively, among subjects with an overall positive ADA result up to Week 52.

For both the overall ADA results up to Week 24 and Week 52, within the SB5 treatment group, there was a higher incidence of injection site reactions in subjects with an overall positive ADA result. However, within the Humira overall and Humira/Humira treatment groups, there was a higher incidence of injection site reactions in subjects with an overall negative ADA result.

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

The Applicant has not conducted further specific studies on the potential impact of drug interactions with SB5. This is in line with EMA guideline for biosimilar products

## Discontinuation due to AES

Study SB5-G11-NHV

There were no discontinuations due to AEs in Study SB5-G11-NHV.

Study SB5-G31-RA

The overall discontinuation rate due to AEs was 2.0% during the first 24 weeks, and 1.4% during weeks 24-52 (see Table "Subject disposition). At week 24 0.7% and 3.3% of patients had discontinued due to

AEs in the SB5 and Humira groups. At week 52 there were 26 events that had led to discontinuation of IP; 8 events in 4 (1.5%) subjects in the SB5 treatment group, 18 events in 15 (5.5%) subjects in the Humira overall treatment group, and 3 events in 3 (2.4%) subjects in the Humira /Humira treatment group.

TEAEs leading to IP discontinuation at the SOC level most commonly reported were skin and subcutaneous tissue disorders (0 events in the SB5 vs. 4 events in 4 [1.5%] subjects in the Humira treatment groups), nervous system disorders (1 event in 1 [0.4%] subject vs. 2 events in 1 [0.4%] subject, respectively), and neoplasms benign, malignant and unspecified (including cysts and polyps) (0 events vs. 3 events in 2 [0.7%] subjects, respectively). At the PT level, the TEAEs leading to IP discontinuation reported in ≥ 2 subjects were headache (1 event in 1 [0.4%] subject each in the SB5 and Humira treatment groups) and dermatitis allergic (0 events in the SB5 vs. 2 events in 2 [0.7%] subjects in the Humira treatment groups).

In the SB5 treatment group, all 6 TEAEs reported which led to discontinuation of IP up to Week 24 were considered to be related to the IP:

• A 65-year-old female white subject was reported with abdominal pain, nausea, vomiting, musculoskeletal pain, and headache on Day 57, which all resolved on Day 63.

• A 53-year-old female white subject was reported with injection site urticaria on Day 16, which was not resolved.

In the Humira treatment group, 10 of the 13 TEAEs leading to discontinuation of IP before Week 24 were considered to be related to the IP:

• A 55-year-old male white subject was reported with rash on Day 142, which was not resolved.

• A 58-year-old female white subject was reported with dermatitis allergic on Day 8, which was resolving.

• A 50-year-old female white subject was reported with dermatitis allergic on Day 72, which was not resolved.

• A 48-year-old male white subject was reported with drug hypersensitivity on Day 12, which resolved on Day 17.

• A 60-year-old female white subject was reported with lymphoma and metastases to spine on Day 125, which were not resolved.

• A 32-year-old female white subject was reported with dizziness, headache, and hypertension on Day 32, which were resolved (headache and hypertension on Day 56 and dizziness on Day 58).

• A 51-year-old female white subject was reported with injection site reaction on Day 27, which resolved on Day 33.

3 events leading to discontinuation of IP in 3 subjects in the Humira treatment group were considered not related to the IP: staphylococcal sepsis, papillary thyroid cancer and dermatitis.

## 2.6.1. Discussion on clinical safety

The number of subjects (altogether 189 healthy volunteers out of which 63 were administered SB5; and 544 RA-patients out of which 271 were administered SB5) is sufficient for comparing the safety profile of the biosimilar candidate SB5 and reference medicinal product EU-Humira and studying the safety of a biosimilar product for up to one year, in line with the EMA guideline to establish immunogenicity of

biosimilar product and in line with the given scientific advice. No information is available on exposure >12 months.

A pooled safety analysis was not performed due to the heterogeneity of study populations (RA patients versus healthy subjects) and the difference in duration of treatment/exposure (multiple-dose versus single-dose), which is acceptable.

The most frequently reported TEAEs observed in SB5 group are in line with the known safety profile for Humira.

Among healthy volunteers, TEAEs were observed in 57.1%, 46.0% and 61.9% of subjects in the SB5 group, EU Humira and US Humira groups, respectively, most commonly nasopharyngitis (19% and 12.7% in SB5 and EU-Humira groups) and headache (17.5 and 6.3%). No obvious signal of safety differences between SB5 and Humira was observed in the healthy volunteers; the difference in headache is considered a chance finding, as the same is not seen in the RA-study.

In RA patients, a total of 207 (38.3%) subjects reported 457 TEAEs at any time after the first dose of IP until Week 24; 96 (35.8%) subjects in the SB5 and 111 (40.7%) subjects in the Humira treatment groups reported TEAEs. The most frequently reported TEAEs (e.g. nasopharyngitis 4.9% and 9.2%; headache 3.4% and 2.6% in SB5 and Humira-groups) are in line with the know safety profile for Humira, and no obvious signal for safety differences between SB5 and Humira was observed. There were 5 AESIs reported during the study (1 in SB5-group, 0 in Humira/Humira-group, 4 in the overall Humira group), all were infections. The results up to week 52 were broadly similar, although there were slightly more upper respiratory tract infections in the SB5 group (3.7%) compared to Humira/Humira-group (0.8%), but this is considered a chance finding (in some other respiratory tract infection AE-groups the figures were on the opposite direction).

The most common new AE after week 24 was nasopharyngitis (4.3 and 2.4% in SB5 and Humira/Humira-groups). The AEs seen in the undetermined group, i.e. immediately after the switch from EU-Humira to SB5 (if a lag time window overlapped with pre-transition IP/ Humira exposure time period (28 days), then the AE was considered to be undetermined), included e.g. upper respiratory tract infections, headache, spinal pain. In addition, importantly, 3 patients (2.4%) had Mycobacterium tuberculosis complex test positive and 1 had latent tuberculosis. However, it was clarified that tuberculosis test was actually performed prior to IP administration at Week 24 visit, and categorized as “undetermined” due to a time discrepancy between laboratory testing and reporting of AE.

The Applicant was asked to clarify the guidance given to investigators with regards to causality assessment as the majority of AEs were classified as “not related” to the IP. However, it is concluded that the way causality was determined was not likely to cause bias between the treatment groups and to affect reliability of the study results with regards to safety. Furthermore, while of importance, the causality assessment is still considered secondary to detection and accurate documentation of TEAEs as a whole regardless of causality.

A total of 11 TEAEs “rheumatoid arthritis” occurred in SAF1 and SAF2. It was confirmed that 11 cases represent worsening/exacerbation of pre-existing RA.

There were two SAEs among the healthy volunteers, 1 in the SB5 and 1 in the Humira-group, both judged as not related to the IP by the investigator.

In RA patients, the overall occurrence of SAEs was 2.0% during the first 24 weeks, and 2.4% during weeks 24-52. Two deaths occurred (both in Humira group, one case of cardiac arrest at week 20 and one case of pulmonary embolism at week 18) among RA patients, both events were judged as not related to the IP by the investigator (however, the case of cardiac arrest was preceded with the event of lymphoma and metastases to spine, judged as related to the IP). The overall occurrence of SAEs was low and the

SAEs reported are in line with the known safety profile of adalimumab, with no obvious differences between the SB5 and Humira-groups.

There were no discontinuations due to AEs in the healthy volunteer-Study SB5-G11-NHV. In RA-patients the rate of discontinuations due to AEs was low (0.7% SB5, 3.3% Humira at 24 weeks; 1.5% and 2.4% at 52 weeks). The AEs leading to discontinuation were in line with the known safety profile for adalimumab and thus with no major differences between the SB5 and Humira groups.

Among healthy volunteers, the mean and median values of all parameters of haematology, biochemistry and urinalysis did not show any changes over time. In RA patients, the changes in hematologic and biochemical parameters were comparable between treatment groups, and in line with the known safety profile for adalimumab. The only difference between the groups was in the number of patients with high neutrophil accounts, i.e. 4 patients in SB5 and none in Humira-group; however, the numbers are small and this is a known ADR of adalimumab –thus this is considered a chance finding.

The Applicant has not conducted specific studies on assessing the potential impact of intrinsic factors on safety of SB5, and relies on the documentation of the reference product Humira. This is considered acceptable as reference can be made to the innovator product regarding safety in special populations.

With regard to immunogenicity, discussed here with an integrated holistic approach (See also under Clinical efficacy and Clinical pharmacology), in the single dose study in healthy volunteers, almost all patients were ADA-positive. The distribution of low, medium and high ADA titers was similar in SB5- and EU-Humira-treated patients. Most ADA-positive patients had NAbs in both treatment arms suggesting that ADAs are mainly anti-idiotypic. In the confirmatory equivalence study SB5-G31-RA, the incidences of ADAs were 32% and 31% in the SB5- and EU-Humira arms, respectively. According to the Applicant, the lower ADA-incidence in RA patients as compared to healthy individuals may be explained by the lower sensitivity of the RA-adapted ADA assay. Approximately half of the ADA-positive sera were positive in the NAb-assay. The titers of the ADA at different time points appeared similar in the treatment arms and increased over time. There was no indication that the switch from Humira to SB5 induced excess immunogenicity. This is in line with previous switch studies of biosimilars and their reference products.

In healthy volunteers, exposure decreased by increasing ADA titers in both SB5- and EU-Humira groups. The exposure was similar between groups in ADA-positive and -negative groups. In RA patients who were ADA-positive, the trough levels were reduced, but in a comparable manner in both treatment groups. The ACR responses were comparable in the ADA-negative population. In ADA-positive population, there was a trend for a lower ACR20 and -50 response rates in ADA-positive population until week 52 as compared to the ADA-negative population (see under Clinical efficacy).

Overall, the safety profiles of ADA-positive SB5 and Humira-treated patients were comparable. In RA patients, approximately 3% of subjects in both treatment groups experienced injection site reactions during the first 24 weeks, and the occurrence decreased thereafter. However, the number of reactions was higher in the Humira treated patients, compared to SB5 treated patients (up to week 52, 9 reactions in 8 subjects (3.0%) in SB5 group vs 32 reactions in 4 subjects (3.1%) in Humira/Humira group). Thus, there was an imbalance between the treatment groups in the number of injection site reactions, although the proportion of patients with injection site reactions seemed comparable. The Applicant explained that the difference in number of ISRs was mainly derived from 4 patients reporting repeated ISRs –in particular 2 patients reporting 12 and 13 events, respectively- thereby contributing to the imbalance in terms of higher number of ISRs in the Humira arm.

Further, in ADA negative subjects, the incidence of injection site reactions was higher for the Humira treatment group while in ADA positive subjects a higher incidence for SB5 treatment was noticeable. The Applicant was asked to comment on the higher incidence of injection site reactions in the SB5 vs the Humira group for subjects with ADA. The response by the Applicant clarified that 2 of the 4 local AEs

observed in ADA positive SB5 subjects were injection site reactions that can be caused by any intravenous administration of a medicinal product (i.e. injection site haematoma and phlebitis), and that the incidence of 2 local AEs in the SB5 group vs. zero in the Humira group was most likely a chance finding.

The scaling system for injection site reactions used in Study SB5-11-NHV, was not employed in study SB5-G31-RA. The reason why the scoring system was not employed in study SB5-G31-RA was that a detailed scoring system would not have been feasible in a phase III setting with 51 centres where injections are self-administered at home. However, a simplified, yet more systematic approach to guide investigators in the evaluation of ISRs could have been used to capture ISRs in the phase III setting, to decrease potential variability of assessment of ISRs as AEs by individual investigators/centres.

In addition, the Applicant was asked to provide a table comparing the incidence of all TEAEs related to hypersensitivity reactions for the SAF1 and SAF2 overall and with regard to ADA status according to the MedDRA SMQ 'Anaphylactic reaction' Incidences were low both in ADA positive as well as ADA negative patients. No striking differences could be observed for SB5 and Humira treated patients. Similarly, after transition from SB5 to Humira no increased incidence of ADAs was seen.

Finally, the Applicant analysed the sera for antinuclear and double-stranded DNA-antibodies. There were a few positive samples in both treatment arms. The autoantibodies were not associated with signs or symptoms suggesting systemic lupus erythematosus.

### 2.6.2. Conclusions on the clinical safety

The number of subjects is sufficient for comparing the safety profile of the biosimilar candidate SB5 and reference medicinal product EU-Humira and studying the safety of a biosimilar product for up to one year. Broadly, the number, severity and type of TEAEs, SAEs, AEs of special interest, treatment discontinuations due to AEs, laboratory findings were comparable between SB5 and Humira and mirroring the safety profile as described in the SmPC of Humira. The frequency of related AEs, severity of AEs and AESIs remained similar for the group who transitioned from Humira to SB5 at week 24. More detailed data on injection site reactions, hypersensitivity and anaphylactic reactions were requested in order to allow a thorough assessment of this issue both in subjects with and without ADAs. The submitted additional analyses further support the comparability of the safety profile of SB5 and Humira.

With regard to immunogenicity, the incidence and titre distribution of ADAs were compared and seemed similar for SB5 and Humira, with about half of all subjects developing neutralising antibodies in each treatment group. No worsening of the immunogenicity profile was observed after transitioning from Humira to SB5.

## *2.7. Risk Management Plan*

### Safety Concerns

**Table 2.7.1: Summary of the Safety Concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB);<br><br>Reactivation of hepatitis B; |

| Summary of safety concerns | |
|---|---|
| | Pancreatitis;<br>Lymphoma;<br>Hepatosplenic T-cell lymphoma (HSTCL);<br>Leukaemia;<br>Non-melanoma skin cancer (NMSC);<br>Melanoma;<br>Merkel cell carcinoma (Neuroendocrine carcinoma of the skin);<br>Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS] and optic neuritis);<br>Immune reactions (including lupus-like reactions and allergic reactions);<br>Sarcoidosis;<br>Congestive heart failure (CHF);<br>Myocardial infarction (MI);<br>Cerebrovascular accident (CVA);<br>Interstitial lung disease (ILD);<br>Pulmonary embolism;<br>Cutaneous vasculitis;<br>Stevens-Johnson syndrome (SJS);<br>Erythema multiforme;<br>Worsening and new onset of psoriasis (PsO);<br>Haematologic disorders;<br>Intestinal perforation;<br>Intestinal stricture in Crohn's disease (CD);<br>Liver failure and other liver events;<br>Elevated alanine aminotransferase (ALT) levels;<br>Autoimmune hepatitis;<br>Medication errors and maladministration. |
| Important potential risks | Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma);<br>Vasculitis (non-cutaneous);<br>Progressive multifocal leukoencephalopathy (PML);<br>Reversible posterior leukoencephalopathy syndrome (RPLS);<br>Amyotrophic lateral sclerosis (ALS);<br>Adenocarcinoma of colon in ulcerative colitis (UC) patients;<br>Infections in infants exposed to adalimumab in utero;<br>Off-label use; |
| Missing information | Subjects with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications; |

| Summary of safety concerns | |
|---|---|
| | Pregnant and lactating women;<br>Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in PsO, CD, UC and juvenile idiopathic arthritis (JIA).<br>Long-term safety information in the treatment of adults with HS<br>Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD and pedERA<br>Long-term safety data in the treatment of adults with uveitis |

## Pharmacovigilance Plan

**Table 2.7.2: Table of ongoing / planned PV studies /activities in the 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) |
|---|---|---|---|---|
| ARTIS<br>Category 3 | A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, JIA, and other rheumatic disease patients treated with adalimumab. | Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB; Merkel cell carcinoma; elevated ALT levels; autoimmune hepatitis; pregnant and lactating women; remission-withdrawal-retreatment nr-axSpA data and episodic treatment in PsO and JIA | Planned for 2019 2Q | Final report planned for 2025<br><br>Annual interim reports will be submitted during the study period and until submission of the final report. |
| Spanish Registry of Adverse Events of Biological Therapies (BIOBADASER)<br>Category 3 | 1. To identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, and to estimate the frequency of their occurrence<br>2. To identify unexpected adverse events<br>3. To identify relevant adverse events that occur following the suspension of the treatment<br>4. To estimate | Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB; Merkel cell carcinoma; elevated ALT levels; autoimmune hepatitis; pregnant and lactating women; remission-withdrawal-retreatment nr-axSpA data and episodic treatment in PsO and JIA | Planned for 2019 2Q | Final report planned for 2025<br><br>Annual interim reports will be submitted during the study period and until submission of the final report. |

| 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) |
|---|---|---|---|---|
| | the relative risk of occurrence of adverse events with biological therapies in patients with RA compared to those not exposed to these treatments<br>5. To identify risk factors for suffering adverse reactions with these treatments<br>6. To evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment | | | |

## Risk Minimisation Measures

**Table 2.7.3: Summary of the Risk Minimisation Measures**

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| **Important Identified Risk** | | |
| Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB | Proposed text in SmPC:<br>**Section 4.3 Contraindications**<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | Patient Alert Card<br>HCP Educational Programme<br>Imraldi Safety Monograph and TB screening and checklist brochure |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Reactivation of hepatitis B | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Pancreatitis | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Lymphoma | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | Patient Alert Card<br>HCP Educational Programme |
| HSTCL | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | Patient Alert Card<br>HCP Educational Programme |
| Leukaemia | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>Proposed text is also present in the PL. | Patient Alert Card<br>HCP Educational Programme |
| NMSC | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | Patient Alert Card<br>HCP Educational Programme |
| Melanoma | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects** | Patient Alert Card<br>HCP Educational Programme |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Proposed text is also present in the PL. | |
| Merkel cell carcinoma (neuroendocrine carcinoma of the skin) | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | Patient Alert Card<br>HCP Educational Programme |
| Demyelinating disorders (including MS, GBS, and optic neuritis) | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | Patient Alert Card<br>HCP Educational Programme |
| Immune reactions (including lupus-like reactions and allergic reactions) | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Sarcoidosis | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| CHF | Proposed text in SmPC:<br>**Section 4.3 Contraindications**<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | Patient Alert Card<br>HCP Educational Programme |
| MI | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| CVA | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| ILD | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Pulmonary embolism | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Cutaneous vasculitis | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| SJS | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Erythema multiforme | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Worsening and new onset of PsO | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Haematologic disorders | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Intestinal perforation | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Intestinal stricture in CD | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>Proposed text is also present in the PL. | None proposed |
| Liver failure and other liver events | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Elevated ALT levels | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Autoimmune hepatitis | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | None proposed |
| Medication errors and maladministration | None proposed<br>Proposed text in SmPC:<br>**Section 4.2 Posology and method of administration**<br>Proposed text is also present in the PL. | None proposed |
| **Important Potential Risks** | | |
| Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma) | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in the PL. | Patient Alert Card<br>HCP Educational Programme |
| Vasculitis (non-cutaneous) | Proposed text in SmPC:<br>**Section 4.8 Undesirable effects**<br>Proposed text is also present in | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | the PL. | |
| PML | None proposed | None proposed |
| RPLS | None proposed | None proposed |
| ALS | None proposed | None proposed |
| Adenocarcinoma of colon in UC patients | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>Proposed text is also present in the PL. | None proposed |
| Infections in infants exposed to adalimumab in utero | Proposed text in SmPC:<br>**Section 4.6 Fertility, pregnancy and lactation**<br>Proposed text is also present in the PL. | None proposed |
| Off-label use | None proposed | None proposed |
| **Missing Information** | | |
| Subjects with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications | Proposed text in SmPC:<br>**Section 4.4 Special warnings and precautions for use**<br>Proposed text is also present in the PL. | None proposed |
| Pregnant and lactating women | Proposed text in SmPC:<br>**Section 4.6 Fertility, pregnancy and lactation**<br>Proposed text is also present in the PL. | None proposed |
| Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in PsO, CD, UC and juvenile idiopathic arthritis (JIA) | None proposed | None proposed |
| Long-term safety information in the treatment of adults with HS | None proposed | None proposed |
| Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD and pedERA | None proposed | None proposed |
| Long-term safety data in the treatment of adults with uveitis | None proposed | None proposed |

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

## *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, Imraldi (adalimumab) is included in the additional monitoring list as 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

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

SB5 has been developed by Samsung Bioepis as a similar biological medicinal product to Humira. This marketing authorisation application (MAA) is therefore an abridged application submitted under the legal basis of Article 10 (4) of the Directive 2001/83/EC as amended by Directive 2004/27/EC.

It is noteworthy that SB5 is currently only available as a single dose 40 mg prefilled syringe (PFS) presentation, as thus not all paediatric patients can be dosed with SB5 (this is reflected in the SmPC Section 4.2).

Clinical studies to demonstrate similarity of SB5 to EU sourced Humira were presented in healthy volunteers (PK, safety and tolerability), as well as in patients with Rheumatoid Arthritis (efficacy, safety, tolerability, PK). In addition the applicant presented a sophisticated discussion on the extrapolation of the different indications, justified by thorough physicochemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in RA patients and a thorough literature review of the mechanism of action (MoA) of adalimumab to justify extrapolation efficacy and safety data across all its approved therapeutic indications. This extrapolation is in agreement with the “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) as well as former CHMP Scientific Advice. The Applicant is also claiming the recently approved indications of Humira, namely hidradenitis suppurativa and uveitis to harmonize labelling with the originator EU Humira. Based on the product mode of action and target molecules the biosimilarity claim can be extrapolated to these conditions.

### 3.1.2. Available therapies and unmet medical need

This is a biosimilar application to Humira.

### 3.1.3. Main clinical studies

SB5-G11-NHV

Phase I study: A randomized, single-blind, three-arm, parallel group, single dose study in 189 healthy volunteers (63/arm) to demonstrate comparative PK, safety, tolerability, and immunogenicity

In each group, all subjects received a single dose (40 mg) of SB5, EU-sourced Humira, or US-sourced Humira by s.c. administration route. The primary PK endpoints were AUCinf and Cmax and the equivalence criteria were met if 90% CI for the ratio of geometric LS Means of SB5 to EU-sourced Humira was within the acceptance interval of 0.8 to 1.25.

SB5-G31-RA

Phase III trial: A randomized, double-blind, parallel group, multicentre clinical study in 544 adult adalimumab-naïve patients (271 for SB5 and 273 for EU Humira) with moderate to severe active RA and with inadequate response to methotrexate, a pivotal clinical trial to demonstrate similarity in efficacy, safety, PK, and immunogenicity.

The subjects received 40 mg of SB5 or EU Humira every other week by s.c. administration route. The subjects received concomitant MTX treatment, the dosing (10-25 mg/week) remaining stable and unchanged throughout the study. The primary efficacy endpoint was ACR20 response rate at week 24 in the PPS1 population and the biosimilarity was demonstrated if the 95% confidence interval (CI) of the difference of the two proportions was entirely contained within the pre-justified equivalence margin of [-15%, 15%].

The supportive analysis in the FAS population was conducted to explore the robustness of the ACR20 responses. The equivalence margin was based on two RA studies by Keystone (2004) and Weinblatt (2003). After 24 weeks the Humira group was re-randomized 1:1 to continue with Humira or to switch to SB5. The study was continued up to 52 Weeks to explore long-term safety, immunogenicity and efficacy. After 52 Weeks of active treatment the study continued with 8 weeks safety follow-up period. The primary PK endpoint was $C_{trough}$.

## *3.2. Favourable effects*

From Quality and non-clinical perspective,

Module 3 of the SB5 dossier is of good quality and adequately provides information on the manufacturing and control of SB5. The Applicant demonstrates that when operating within the established input ranges for process parameters, a high quality medicinal product fulfilling its specifications can be reproducibly manufactured. The minor changes introduced into the manufacturing process during product development have been adequately described and demonstrated to have no impact on product quality.

In order to demonstrate biosimilarity on the quality level between SB5 and the reference medicinal product Humira, comprehensive physicochemical and biological comparability studies using state-of-the art analytical methods have been carried out. The comparability studies address the primary, secondary, and tertiary structures, post-translational modifications, purity/impurity profile, biological activity, as well as the degradation profile. Based on the studies, it can be concluded that for most quality attributes, SB5 is similar to Humira. Where differences exist, these differences have been properly discussed and justified not to be of clinical relevance.

In addition, from the non-clinical perspective, it is considered that the similarity between SB5 and Humira is supported in terms of in vivo functionality (inhibition of the arthritic symptoms) and toxicological, toxicokinetic and immunogenicity profiles.

From the pharmacokinetic perspective, in the PK pivotal study the primary endpoints (i.e. $AUC_{inf}$ and $C_{max}$) with their 90% CIs are within the predefined acceptance range of 80-125%. This applies to the initial analysis as well as the analysis with previously excluded subjects. The estimates of the geometric LS means ratios for the comparison of SB5 and EU sourced Humira for $AUC_{inf}$, $AUC_{last}$ and $C_{max}$ of the sensitivity analysis are 0.990, 0.905 and 0.913 and the corresponding 90%CIs ([0.885-1.108], [0.822-0.996], [0.801-1.040], respectively).

The number of ADA-negative patients in study SB5-G12-NHV was very low and a meaningful assessment of the impact of ADA formation on PK parameters therefore was limited. The applicant analysed the influence of ADA formation on PK according to three different ADA titre subgroups. No meaningful difference was seen when comparing the means of AUCinf, Cmax, and AUClast across the three treatment groups (SB5, EU Humira, US Humira) in the ADA titre Low subgroup, ADA titre Med subgroup, and ADA titre High subgroup.

From the clinical perspective, the proportion of subjects in PPS1 population reaching the ACR20 response rate at week 24 were 72.4% (173/239) and 72.2% (171/237) in the SB5 and EU Humira groups, respectively. The estimated difference in proportions was 0.1% and its 95% CI -7.83% - 8.13%, it being well contained within the pre-specified equivalence margin of ±15%. In the FAS population the corresponding response rates were 68.0% (183/269) and 67.4% (184/273) leading to the adjusted difference in proportions of 0.8% and 95% CI of -7.03 – 8.56%. Thus, regarding the primary outcome the study fulfilled the biosimilarity criteria.

Also the secondary endpoints ACR50 and ACR70 were confined within the equivalence margin at week 24. At Week 52 the ACR20 for the PPS2 was 76.9% (163/212) in the SB5 and 71.2% (79/111) in the Humira/Humira treatment groups; the adjusted treatment difference was 5.6% [95% CI: −4.63%, 15.90%] between the SB5 and Humira/Humira treatment groups.

The similarity demonstrated in the primary endpoint is confirmed by secondary measures at week 24 such as DAS28 [treatment difference and its 95% CI for DAS28 at Week 24 was −0.04 [−0.26, 0.17], which was contained within the pre-defined equivalence margin of [−0.6, 0.6] as well as ACR50 and ACR70 (−2.0% [−10.69%, 6.75%] and −1.3% [−8.41%, 5.80%], respectively).

## *3.3. Uncertainties and limitations about favourable effects*

From Quality and Non-clinical perspective

From the Quality perspective all uncertainties have been adequately addressed by the Applicant, no concerns remain.

In addition in the non-clinical PK evaluation an up to 30 % higher $C_{max}$ was observed in Humira in comparison to SB5-treated animals. The difference in exposure was not statistically significant due to the small group size. There was also considerable higher variation in mean serum concentrations for the Humira-treated animals than SB5-treated animals on Day 22. However, these nonclinical PK data are superseded by clinical PK data.

From the pharmacokinetic perspective, several uncertainties related to bioanalytical methods were originally observed. The Applicant has provided further data and clarifications as requested and all remaining issues are solved.

A PK sensitivity analysis was requested including the 16 subjects (9/2/5 from the SB5/EU Humira/US Humira treatment arms, respectively), who were excluded from the PK analysis according to protocol defined criteria (not enough concentration data in the elimination phase), but could still contribute data for calculation of $C_{max}$. The analysis shows estimates of the GM ratio of the $C_{max}$ of SB5 vs EU Humira of 0.905, the 90% CI (0.822; 0.996) being entirely contained in the acceptance range. A thorough investigation of the characteristics of excluded subjects (9 from the SB5 vs 2 from EU Humira group) showed that they tended to have higher BMIs and ADA titres compared with non-excluded subjects, which might result in lower absorption and faster clearance. Potential quality differences between SB5 and the reference product, which could also influence the absorption rate after extravascular administration, e.g. molecular weight or charge profiles, were also considered. However, data from extensive quality studies supports molecular similarity of SB5 and reference product, and the minor difference in acidic variants is not considered to translate into differences in biological activity. In summary, a difference in PK between SB5 and EU Humira cannot be concluded from this data.

From the Clinical perspective the following uncertainties were observed:

- A 20% difference in the ACR20 response rate at Week 24 in the SB5 group with ADA positive patients in comparison to the ADA negative patients was observed while in the Humira group similar efficacy regardless of ADA status was seen; the frequency of ADA positivity was similar in Humira and SB5 groups. The estimated difference between the SB5 and Humira group in ACR20 responses in ADA positive patients at Week 24 was −17.5% (95% CI −33.3%, −1.8%; p= 0.015). In ADA negative group the result was approximately comparable by 4.7% difference in ACR20 response rate (CI −3.8% - 15.2%). However, after further analyses this could be considered to be a chance finding.

## *3.4. Unfavourable effects*

From a quality and non-clinical perspective no issues which contribute to unfavourable effects have been raised.

The overall rate of TEAEs, SAEs, treatment discontinuations due to AEs, laboratory findings was similar for SB5 and Humira. The adverse events captured mirrored those already described in the SmPC for Humira. Patients who switched from Humira to SB5 demonstrated a similar safety profile to those subjects who stayed on their treatment for the whole study duration.

Among healthy volunteers, TEAEs were observed in 57.1%, 46.0% and 61.9% of subjects in the SB5 group, EU Humira and US Humira groups, respectively, most commonly nasopharyngitis and headache. No obvious signal of safety differences between SB5 and Humira was observed in the healthy volunteers.

In RA patients, a total of 207 (38.3%) subjects reported 457 TEAEs at any time after the first dose of IP until Week 24; 96 (35.8%) subjects in the SB5 and 111 (40.7%) subjects in the Humira treatment groups, with no obvious differences between the SB5 and Humira-groups. The findings were similar up to

52 weeks (52.2% SB% and 54.3% Humira/Humira group reported TEAEs). The most frequently reported TEAEs during the 52 week period were nasopharyngitis (9%, 12.6% in the SB5 and Humira/Humira-groups), headache (4.1%, 4.7%), bronchitis (4.1%, 3.9%), alanine aminotransferase increased (3.4%, 5.5%), latent tuberculosis (4.1%, 5.5%), and upper respiratory tract infection (3.7%, 0.8%); the most frequently reported TEAEs are in line with the know safety profile for Humira. There were 5 AESIs reported during the study, all were infections. The overall rate of TEAEs was similar for SB5 and Humira.

Immunogenicity seemed markedly higher than observed in the initial licensing studies for Humira. In the single dose study in healthy volunteers almost all patients were ADA-positive; the distribution of low, medium and high ADA titers was similar in SB5- and EU-Humira-treated patients. In RA-patients the incidences of ADAs were 32% and 31% in the SB5- and EU-Humira groups, respectively. Approximately half of the ADA-positive sera were positive in the NAb-assay. The occurrence of hypersensitivity reactions and injection site reactions (proportion of patients) was low and overall comparable. However, the number of reactions in these patients was higher in the Humira treated patients, compared to SB5 treated patients (up to week 52, 9 reactions in 8 subjects (3.0%) vs 32 reactions in 4 subjects (3.1% in Humira/Humira group).

## *3.5. Uncertainties and limitations about unfavourable effects*

From a quality and preclinical perspective no issues which contribute to unfavourable effects have been raised.

Although the submitted data do not give a reason for suspicion of differences in safety profile, no long-term data beyond 12 months are available. Post-marketing data gathering is important to obtain further information regarding the relative safety of SB5. Two registries for the follow-up of safety of relevant selected AEs, ARTIS (Anti-Rheumatic Treatment in Sweden) and BIOBADASER (Spanish Registry of Adverse Events of Biological Therapies), are proposed post marketing.

The way causality was assessed in study SB5-G31-RA, could have led to variability of interpretation by investigators, and surprisingly high proportion of TEAEs were classified as “not related” to the IP, despite that these AEs represent typical adverse reactions associated with Humira. However, this is not considered to be of major importance to the assessment of safety, as safety is assessed mainly based on TEAEs (i.e. all AEs regardless of causality), the investigators were blinded to the IP during the study, and the main purpose in this study was to compare the safety of the biosimilar to that of the reference product, and thus most likely no bias has been introduced here between the groups.

With regard to immunogenicity, the applicant has provided further information and data concerning assessment of ADA/NAb results and the issues are resolved.

## *3.6. Benefit-risk assessment and discussion*

### 3.6.1. Importance of favourable and unfavourable effects

When evaluating a biosimilar application, it is of importance that all parts of the comparability exercise point in the same direction, which is the case here.

An overall robust and adequately controlled manufacturing process for drug substance as well as for drug product is in place which can perform effectively and reproducibly to produce drug substance respective drug product meeting its predetermined specifications and quality attributes. The provided drug

substance and drug product batch analyses data support this conclusion. An appropriate control strategy ensures that material of sufficient high quality will enter the market.

Concerning the biosimilarity exercise a comparable profile for the majority of the quality attributes could be shown. A potential impact of differences in certain physicochemical characteristics has been ruled out by demonstrated similarity for the biological activity investigated by a broad panel of binding and in-vitro assays. It is not expected that the differences reported would impact the clinical performance of SB5. Therefore, from an analytical and biological point of view, similarity has been demonstrated.

From a non-clinical perspective the similarity of SB5 and Humira has been shown with regard to in vivo PD, PK and toxicology. Statistically not significant differences in the PK of SB5 as compared to Humira are most probably attributable to the small group size of experimental animals and, thus, of no clinical relevance.

On the clinical level, the company followed a stepwise approach and was able to demonstrate similarity between SB5 and Humira across the whole clinical development. In the single dose PK trial in healthy volunteers, the primary analysis revealed biosimilarity between the products.

Evaluation of mean serum trough concentrations in a subgroup of patients in study SB5-G31-RA were comparable between treatment arms. Similarity was shown in most primary and secondary efficacy measures in study SB5-G31-RA, where the proportion of patients reaching ACR20 at week 24 was almost identical and the CI of the treatment difference well preserved within the predefined equivalence margins. Further, the ACR20 results were comparable between the groups across the whole study duration, also at the more sensitive earlier time points of the study.

These results are affirmed by similarity in key secondary measures such as DAS28 at week 24, ACR50 and ACR70, at week 24 as well as week 52. Those findings, among others, emphasize that SB5 and Humira exhibit comparable efficacy profiles.

A difference in ACR response between the subgroups of ADA positive patients was seen. In this subgroup a lower ACR response rate was observed in the SB5 treatment group compared to the EU Humira treatment group at Week 24. This finding was most pronounced for ACR20 (SB5 57.5%, Humira 71.2%). The company considers this to be a chance finding. The position of the Applicant is supported by the trend of decreased difference in ACR20 responses towards Week 52 and no difference observed between ADA positive treatment groups in DAS28 AUC (continuous variable), while in ACR AUC responses (categorical variables) the EU Humira group showed better response. Furthermore, the incidence, titres and neutralizing capacity of ADAs were comparable between the groups. Altogether, based on these data, and also taking into account the small number of patients in these different ADA-subgroups and somewhat fluctuating results in different endpoints at different time points, the difference between the groups in ACR20 responses could be assumed to be an isolated finding that is not compatible with ADA results, pharmacokinetics or the DAS28 results. Also the fact that efficacy was similar in ADA-negative and ADA-positive patients in the Humira group was an unusual finding contradicting previous data on adalimumab and thus pointing towards a chance finding.

Based on the data provided by the Applicant on ACR and DAS28 response in NAb-positive and –negative patients in different time points showed no clear correlation between increased number of NAb-positive patients and efficacy. These data did not show any indication on the withering effect with increasing ADA positivity in long-term.

In addition to clinical efficacy also safety looks comparable between SB5 and Humira. This is true for the incidence, kind and severity of AES, as well as the incidence and quality of ADA, across both trials.

Extrapolation to all indications approved for the EU Humira is suggested. Adequate justification of the similarity in mechanism of action and in relevant target molecules for the disease development also

between the newest indications of EU-Humira, namely HS and uveitis, and RA, has been provided to allow extrapolation. Complemented by the results obtained by functional assays to comparatively study the mechanism of action proposed for IBD indications (e.g., binding to tmTNF, apoptosis assay, inhibition of IL-8 cytokine release, regulatory macrophage function) and clinical models chosen to investigate biosimilarity are considered sufficiently sensitive to support extrapolation.

### 3.6.2. Balance of benefits and risks

Biosimilarity from the quality, non-clinical, clinical PK, safety, and efficacy point of view has been demonstrated.

The benefit-risk balance of SB5 is regarded as equal to the BR balance of Humira, which is positive.

### *3.7. Conclusions*

The overall B/R of Imraldi is positive.

## 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 Imraldi is favourable in the following indication:

Rheumatoid arthritis

Imraldi in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

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

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

Juvenile idiopathic arthritis

*Polyarticular juvenile idiopathic arthritis*

Imraldi in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Imraldi can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in patients aged less than 2 years.

*Enthesitis-related arthritis*

Imraldi is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy

Axial spondyloarthritis

*Ankylosing spondylitis (AS)*

Imraldi is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

*Axial spondyloarthritis without radiographic evidence of AS*

Imraldi is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Imraldi is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

Psoriasis

Imraldi is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Imraldi is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Imraldi is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy.

Crohn’s disease

Imraldi is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Imraldi is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

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

contraindications for such therapies.

Uveitis

Imraldi is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

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

## *Conditions or restrictions regarding supply and use*

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

## *Other conditions and requirements of the marketing authorisation*

### Periodic Safety Update Reports

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

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

### Risk Management Plan (RMP)

The 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 of Imraldi in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Imraldi is marketed, all healthcare professionals who are expected to prescribe Imraldi have are provided with the following educational package:

- Physician educational material

- Patient information

**The physician educational material** should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient alert card

**The Guide for healthcare professionals** shall contain the following key elements:

- Relevant information on the safety concerns of serious infections, sepsis, tuberculosis and opportunistic infections; congestive heart failure; demyelinating disorders; malignancies to be addressed by the additional risk minimisation measures (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable).

**The patient alert card** shall contain the following key messages:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Imraldi.
- That Imraldi treatment may increase the potential risks of serious infections, sepsis, tuberculosis and opportunistic infections; congestive heart failure; demyelinating disorders; malignancies.
- Signs or symptoms of the safety concern and when to seek attention from a HCP
- Contact details of the prescriber

**The patient information pack should contain:**

- Patient information leaflet

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

Not applicable.