1 April 2016
EMA/CHMP/272283/2016
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Flixabi

International non-proprietary name: INFLIXIMAB

Procedure No. EMEA/H/C/004020/0000

Note

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

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Administrative information

Name of the medicinal product:	Flixabi
Applicant:	Samsung Bioepis UK Limited (SBUK) Regus Building 3000 Hillswood Drive Surrey Chertsey KT16 0RS UNITED KINGDOM
Active substance:	INFLIXIMAB
International Non-proprietary Name:	INFLIXIMAB
Pharmaco-therapeutic group (ATC Code):	immunosuppressants, tumor necrosis factor alpha (TNF-α) inhibitors (L04AB02)
Therapeutic indications:	<u>Rheumatoid arthritis</u> Flixabi, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in: • adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate. • adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs. In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see section 5.1). <u>Adult Crohn's disease</u> Flixabi 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. • treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy). <u>Paediatric Crohn's disease</u> Flixabi is indicated for treatment of severe, active Crohn's disease in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy. <u>Ulcerative colitis</u> Flixabi 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. <u>Paediatric ulcerative colitis</u> Flixabi is indicated for treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. <u>Ankylosing spondylitis</u> Flixabiis indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy. <u>Psoriatic arthritis</u> Flixabi is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Flixabi should be administered - in combination with methotrexate - or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated. Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint

	damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1). <u>Psoriasis</u> Flixabi is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen ultra-violet A (PUVA) (see section 5.1).
Pharmaceutical form:	Powder for concentrate for solution for infusion
Strength:	100 mg
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

ACR20	American College of Rheumatology 20% Response Criteria
ACR50	American College of Rheumatology 50% Response Criteria
ACR70	American College of Rheumatology 70% Response Criteria
ACR-N	Numeric Index of the ACR Response
ADA	Anti-drug Antibody
ADCC	Antibody-dependent Cell-mediated Cytotoxicity
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-time Curve
AUCinf	Area Under the Concentration-time Curve from Time Zero to Infinity
AUClast	Area Under the Concentration-time Curve from Time Zero to the Last Quantifiable Concentration
AZA	Azathioprine
BLQ	Below the Lower Limit of Quantitation
BMI	Body Mass Index
BPD	Biological Product Development
BSE	Bovine Spongiform Encephalopathy
C1q	Complement Component 1, q Subcomponent, A Chain
CCP	Critical Controlled Parameter
CD	Crohn's Disease
CDC	Complement-dependent Cytotoxicity
CI	Confidence Interval
CIPC	Critical In-process Controls
CIPT	Critical In-process Tests
CL	Clearance
CLB	Competitive Ligand Binding
Cmax	Maximum Observed Concentration at Tmax
CQA	Critical Quality Attribute
CRP	C-reactive Protein
CSR	Clinical Study Report
Ctrough	Serum Concentration Immediately prior to Next Infusion
CV	Coefficient of Variation
DAS28	Disease Activity Score Based On A 28 Joint Count
DHFR	Dihydrofolate Reductase
DMARD	Disease-modifying Antirheumatic Drug
DoE	Design of Experiments
ELISA	Enzyme-linked Immunosorbent Assay
ET	Early Termination
EULAR	European League Against Rheumatism
Fab	Fragment Antigen-Binding
FACS	Fluorescence-activated Cell Sorting
FAS	Full Analysis Set
FRET	Fluorescence Resonance Energy Transfer
HCP	Host Cell Protein
HM	High Mannose
IBD	Inflammatory Bowel Disease
IPC	In-process Control

IPS	In-process Specifications
IPT	In-process Test
ITT	Intention-to-Treat
KCP	Key Controlled Parameter
Kel	Terminal Rate Constant
LMW	Low Molecular Weight
mAb	Monoclonal Antibody
MoA	Mechanism of Action
MSD	Meso Scale Discovery
mTSS	Modified Total Sharp Score
Nab	Neutralising Antibody
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells
NK	Natural Killer
N-KCP	Non-key Controlled Parameter
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PK	Pharmacokinetic
PPD	Pharmaceutical Product Development
PPS	Per-Protocol Set
PsA	Psoriatic Arthritis
PVR	Process Validation Run
RA	Rheumatoid Arthritis
RSD	Relative Standard Deviation
SAE	Serious Adverse Event SOC
SD	Sprague Dawley
sTNF-α	Soluble Tumour Necrosis Factor Alpha
t½	Elimination Half Life
TB	Tuberculosis
Tg	Transgenic
Tmax	Time to Reach Maximum (Peak) Plasma Concentration (Cmax)
tmTNF-α	Transmembrane Tumour Necrosis Factor Alpha
TNFR	Tumour Necrosis Factor Receptor
TNF-α	Tumour Necrosis Factor Alpha
UC	Ulcerative Colitis

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Samsung Bioepis UK Limited (SBUK) submitted on 3 March 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Flixabi through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 May 2014.

The applicant applied for the following indications:

Rheumatoid arthritis
Flixabi in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see section 5.1).

Adult Crohn's disease
Flixabi 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.
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Paediatric Crohn's disease
Flixabi is indicated for treatment of severe, active Crohn's disease in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Ulcerative colitis
Flixabi 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.

Paediatric ulcerative colitis
Flixabi is indicated for treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

Ankylosing spondylitis
Flixabi is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis
Flixabi is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.
Flixabi should be administered

- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1).

Psoriasis
Flixabi is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen ultra-violet A (PUVA) (see section 5.1).

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 30 March 2012, 19 July 2012 and 16 December 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Flixabi has been given a Marketing Authorisation in Republic of Korea on 4 December 2015.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Jens Heisterberg

- The application was received by the EMA on 3 March 2015.
- The procedure started on 25 March 2015.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2015. PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 22 June 2015.
- During the meeting on 6-9 July 2015, the PRAC adopted the PRAC assessment Overview and Advice.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 October 2015.
- The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:

  - A GCP inspection at two clinical investigational sites in Bosnia and Herzegovina and one sponsor site in Korea between 21-24 July 2015, 27-30 July 2015 and 31 August-4 September 2015, respectively. The report of the inspection carried out was issued on 8 October 2015.

- The Rapporteurs circulated the Joint Assessment Report /PRAC Rapporteur assessment report on the applicant's responses to the List of Questions to all CHMP members on 24 November 2015.
- During the meeting on 30 November-3 December 2015, the PRAC adopted the PRAC assessment Overview and Advice.
- During the CHMP meeting on 17 December 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 4 February 2016.
- During the CHMP meeting on 24 February 2016, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 25 February 2016, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 2 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of outstanding issues to all CHMP members on 16 March 2016.
- During the meeting on 29 March - 1 April 2016, 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 Flixabi.

2. Scientific discussion

2.1. Introduction

Problem statement

This centralised marketing authorisation application concerns the Biotech medicinal product Flixabi 100 mg powder for concentrate for solution for infusion.

The reference medicinal product is Remicade, 100 mg, powder for concentrate for solution for infusion, which was first authorised in the community on 13th August 1999. The active substance is the tumour necrosis factor-α (TNF-α) inhibitor infliximab.

About the product

Flixabi is a medicinal product containing infliximab, a chimeric human immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to human tumour necrosis factor alpha (TNF-α). Flixabi is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.

Flixabi is presented as powder for concentrate for solution for infusion containing 100 mg of infliximab as active substance.

Mechanism of Action

TNFα is a multipotent cytokine that occurs in monomeric and trimeric soluble and transmembrane forms. It is mainly produced by macrophages, as well as by a broad variety of other cell types including lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts and neural tissue. TNFα exhibits a wide spectrum of activity, including coordinating host immune and inflammatory response to infectious, malignant and autoimmune conditions. Indeed, large amounts of TNFα have been shown to be released in response to liposaccharide, other bacterial components, and interleukin-1 (IL-1). Whereas initial TNFα expression in response to infection or injury is beneficial, sustained or excessive expression has been identified in several chronic inflammatory autoimmune disorders such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, psoriatic arthritis (PsA), Crohn's disease (CD), and ulcerative colitis (UC).

TNFα causes its biological effects by binding to the TNF receptor, of which two types have been identified: a 55 kDa protein (p55, TNF-R1) and a 75 kDa protein (p75, TNF-R2). TNF-R1 is expressed in most tissues and can be fully activated by both the membrane-bound and soluble trimeric forms of TNF, whereas TNF-R2 is found only in cells of the immune system.

Infliximab, is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNFα. Infliximab prevents TNFα receptor activation by binding to TNFα, thereby neutralizing the biological activity of TNFα.

Type of Application and aspects on development

This Marketing Authorisation 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.

The clinical development programme of SB2 has specifically considered the EU guidelines for similar biological medicinal products and also indication-specific guidelines (see list below).

1. "Guideline on similar biological medicinal products" (CHMP/437/04 , CHMP/437/04 Rev 1) [including interim draft version];
2. "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues" (EMEA/CHMP/BWP/49348/2005);
3. "Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 , EMEA/CHMP/BMWP/42832/2005 Rev. 1);
4. "Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins" (CHMP/EWP/89249/2004);

5. “Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins” (EMEA/CHMP/BMWP/14327/2006).

2.2. Quality aspects

2.2.1. Introduction

Flixabi has been developed as a biosimilar medicinal product to the reference product Remicade (infliximab).

The finished product is presented as powder for concentrate for solution for infusion containing 100 mg of infliximab as active substance.

Other ingredients are: sucrose, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate as described in Section 6.1 of the SmPC.

The product is available in Type 1 glass vial with a rubber stopper and aluminium crimp protected by a plastic cap, as described in section 6.5 of the SmPC. Each vial contains 100 mg of infliximab and after reconstitution each ml contains 10 mg of infliximab.

2.2.2. Active Substance

General information

Flixabi (infliximab) is a chimeric human/mouse monoclonal IgG1 antibody, consisting of four polypeptide chains, connected by disulphide bonds and with one N-linked glycosylation site located at asparagine (Asn) 300 on each heavy chain. There are no O-linked glycosylation sites.

Structural characterization was performed to confirm the primary structure of infliximab with respect to its amino acid sequence and post-translational modification by a combination of different analysis including: molecular weight determination, amino acid sequencing, peptide mapping, N-glycan profile elucidation.

Infliximab neutralises the biological activities of tumour necrosis factor alpha (TNF-α) by binding with high affinity to the soluble and transmembrane forms of TNF-α, which are located on the outer membranes of T cells and similar immune cells. This inhibits or prevents effective binding of TNF-α with its receptors. In addition, infliximab has the capability of lysing cells involved in the inflammatory process. In detail, the antigen-binding fragment (Fab) domain of infliximab specifically binds to TNF-α. Direct binding of the Fab domain to cells results in signal cascades inducing apoptosis. Binding of the crystallisable fragment (Fc) domain to the complement component C1q complex and Fc receptors leads to cell lysis by complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC). Therefore investigation of potential differences across the relevant structural elements of infliximab will be important in the determination of biosimilarity.

Manufacture, characterisation and process controls

Flixabi active substance (AS) is manufactured, packaged, stability and quality-control tested in accordance with good manufacturing practice (GMP).

Description of the manufacturing process and process controls

Flixabi AS manufacturing process has been adequately described and is considered acceptable. The host cell line used in Flixabi manufacturing is the Chinese hamster ovary (CHO) cell line instead of SP2/0 cells, which are used by the reference product. This is acceptable because the CHO cell line is widely used for the manufacture of biotherapeutics. Overall the manufacturing process represents a standard process for the manufacture of monoclonal antibodies consisting of inoculation, cell culture expansion, production in bioreactor, harvest of the cell culture fluid (CCF), purification and dispensing.

The upstream process is described in sufficient detail. Performance Parameters (In-process Controls or In-process Tests) as provided in the documentation are considered acceptable. For the control of the Flixabi AS manufacturing process, the process controls are divided into controlled parameters (process inputs) and performance parameters (process outputs). For the outputs, in-process controls and in-process tests have been defined. In the narrative process description detailed information about the input parameters are provided.

The downstream purification process is described in sufficient detail. Performance Parameters (In-process Controls or In-process Tests) and control (or input) parameters as provided in the documentation are considered acceptable.

The container closure system has been adequately described. Extractable studies were performed to demonstrate compatibility of Flixabi AS with the container closure system.

Control of Materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Lists of compendial and non-compendial raw and starting materials are provided. For all these materials, identity tests are performed and certificates of analysis (CoA) from the suppliers are verified in the context of monograph or supplier specifications. The expression system is described in sufficient detail presenting the full coverage amino acid and DNA sequences. A two tiered cell banking system is used and sufficient information is provided regarding testing of MCB and WCB and release of future WCB. Cell bank testing was performed according to ICH Q5A(R1), ICH Q5B and ICH Q5D. When the generation of a new WCB is required, the replacement WCB is manufactured under good manufacturing practice according to the same process as for the original WCB. The limit of in-vitro cell age of the Flixabi cell substrate was determined based on the data from the genetic and phenotypic stability tests The data further confirmed that the defined Quality Attributes (QA) were met in the AS produced from the cells at the proposed end of production.

Control of critical steps and intermediates

The design and control of the AS manufacturing process follows a combined traditional and enhanced development approach. Acceptable information has been provided on the control strategy which was considered acceptable. The controlled parameters (process inputs) and performance parameters (process outputs) applied

are listed together with their associated action limits and, where applicable, the in-process specifications. Risk assessments have been carried out throughout the product development life cycle in order to ensure manufacturing consistency and hence clinical performance. The methodology employed for product risk assessment and determination of Flixabi CQAs was a modified risk ranking and filtering, in which the potential impact on potency, efficacy, and/or safety of the product, and certainty were factored into determining the degrees of risk. The data indicate that the chosen operating ranges guarantee the quality target product profile of Flixabi.

Process validation

Process consistency validation of Flixabi AS manufacturing process encompassing the full scale commercial batches has been successfully completed. All KCPs, CCPs, IPCs, and CIPTs were maintained within the action limits. There were no manufacturing deviations or major protocol exceptions, however minor exceptions were observed. These minor exceptions do not impact the overall conclusion of the studies. In addition, in-process measurements were also collected during the process consistency validation studies to assess process performance and procedural consistency. The results were consistent among batches. Overall batches fulfilled the validation acceptance criteria demonstrating that the final manufacturing process was performed consistently and effectively for commercial manufacturing of Flixabi AS. Impurity clearance was validated both by using direct measurements of process impurities in the manufacturing-scale intermediates for the PVR batches, and supported by using laboratory scale-down models. The clearance studies demonstrate that the manufacturing process consistently and effectively clears the following impurities including host cell DNA, host cell protein (HCP), etc to below detectable levels or otherwise acceptable levels .

Manufacturing process development

Flixabi AS manufacturing process has undergone some optimisation during development. The changes introduced are adequately described. Although only minor impact on the quality attributes was anticipated, the Applicant completed comprehensive comparability exercises. The results submitted provide convincing evidence for comparability between the pilot and the clinical, as well as the clinical and the PVR material.

Characterisation

Flixabi has been developed as a similar biological medicinal product to Remicade. The characterisation of Flixabi included a comprehensive battery of physicochemical and biological tests using sensitive and orthogonal state-of-the-art qualified analytical methods in order to elucidate the primary, secondary, and higher-order structure, post-translational modifications, glycosylation, charge variants, purity/impurities, and quantity and biological properties.

As for the process related impurities (including HCP and host cell DNA), clearance validation studies have been performed to demonstrate that the Flixabi manufacturing process provides adequate clearance of such impurities.

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.

Although the CHMP considers the specification adequate to control AS/FP recommendations are made to revisit the ranges based on additional manufacturing experience.

Analytical methods

Analytical validation has been conducted in accordance with guideline ICH Q2(R1). The validation reports are provided. The overall summary shows that the analytical methods are considered appropriately validated.

Batch analysis

The batch results of Flixabi AS batches manufactured at the proposed commercial scale in the GMP manufacturing facility of Biogen, Hillerød, Denmark and small scale pilot batches of Flixabi AS indicate that the manufacturing process is robust. All acceptance criteria were met.

Reference materials

The primary reference standard (PRS) was prepared from Flixabi AS batch. Qualification of PRS was performed against the interim reference standard (IRS) and involved QC tests as well as characterisation tests on the primary structure, quantity, identity, purity, biological activity, purity and impurities primary structure, carbohydrate and process-related impurities. A working reference standard (WRS) will be prepared for QC and stability testing of commercial batches, for physicochemical and/or biological assays, as well as for use in the transfer/validation of analytical methods. It will be qualified against the PRS according to an approved protocol.

Stability

The Applicant restricted the shelf-life for Flixabi AS based on the long-term stability results from batches. The results from all these studies demonstrate that there are no significant changes in the quality of Flixabi active substance under the long-term, intermediate and accelerated storage conditions. The parameters tested for stability / shelf life are the same as for release.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Flixabi is developed as biosimilar product to Remicade. The formulation was chosen in order to maintain the quality of Flixabi AS (infliximab), as well as the similarity of Flixabi finished product (FP) with the reference product. The only difference in the excipients used is the hydration form of dibasic sodium phosphate, which is

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

not expected to impact product quality.
Flixabi FP is a powder for concentrate for solution for infusion, which does not contain preservatives.

The product is available in Type 1 glass vial with a rubber stopper and aluminium crimp protected by a plastic cap, as described in section 6.5 of the SmPC. Each vial contains 100 mg of infliximab and after reconstitution each ml contains 10 mg of infliximab.

The excipients used in the manufacture of Flixabi FP are of compendial quality and controlled in compliance with the tests and acceptance criteria of compendial monographs.

The suitability of the formulation has been assessed by in-use stability studies as well as in formulation robustness studies. Therefore, no dedicated compatibility studies have been conducted.

The manufacturing process for the proposed commercial formulation was developed and optimized based on the experience from pilot, clinical and proposed commercial scales. The comparability between the clinical batches and the process validation run batches has been provided.

Manufacture of the product and process controls

Manufacturing and Packaging, QC release testing (sterility), and stability testing take place at Patheon Italia S.p.A. The Flixabi FP manufacturing process involves thawing of the AS, pooling, homogenisation, lyophilisation, sterile filtration, aseptic filling, capping and visual inspection. A narrative description of the manufacturing process is provided including conditions applied and ranges for manufacturing parameters of the respective process steps. Process validation of Flixabi FP manufacturing process has been completed through successful manufacturing of PVR batches. The process validation results demonstrate that the manufacturing process consistently provides product that meets its pre-defined acceptance criteria and product quality attributes. No deviations occurred that would have impacted the validation status of the manufacturing process.

The primary packaging material for Flixabi FP consists of a sterilised and de-pyrogenated Type I glass vial, stoppered with a sterilised bromobutyl rubber stopper and sealed with an aluminium crimping cap. The glass vial is Ph. Eur. grade Type I borosoilicate. The bromobutyl rubber is in accordance with Ph. Eur. Extractables and leachable studies were performed to demonstrate compatibility of Flixabi FP with the container closure system.

Product specification

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

Although the CHMP considers the specification adequate to control AS/FP recommendations are made to revisit the ranges based on additional manufacturing experience.

Analytical methods

Analytical methods specific for the FP are briefly described. For compendial methods the applicant refers to the corresponding Ph. Eur. monographs. The suitability of compendial methods was verified for their use. This is considered sufficient.

Batch analysis

All results from clinical to PVR batches are within the proposed commercial specification.

Reference materials

The Reference Standards used in the release and stability testing of Flixabi FP are the same as those used for the release and stability testing of Flixabi AS.

Stability of the product

The proposed 24 months shelf-life of Flixabi FP based on the 24 months long-term stability data of the three clinical batches is acceptable.

In use stability studies indicate that the Flixabi is stable during reconstitution and storage at 5ºC and 25ºC for 24 h. Supply chain simulation supports allowances for time out of refrigeration, as required for manufacturing, handling, inspection, labelling, packaging activities, distribution, and non-routine excursions. Photostability studies indicate that no impact on Flixabi FP is expected if Flixabi FP is exposed to ambient light during the manufacturing, labelling, packaging and distribution process.

In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Adventitious agents

The CHO cells used for production have been screened sufficiently for adventitious gents. The tests performed failed to demonstrate the presence of any viral contaminant in the MCB with the exception of retroviral particles which are well known to be present. However, this is acceptable and in line with ICH Q5A since the virus reduction capacity for this type of viral particles has been demonstrated to exceed widely the particle load in cell culture fluid which is required to produce a dose for treatment.

The virus reduction capacity of the down-stream purification process has been adequately investigated using appropriate model viruses. The process includes several steps for inactivation/removal of enveloped and non-enveloped viruses. Robust inactivation/removal of enveloped viruses has been indicated.

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated. The fermentation process is in a serum-free medium. No other animal-derived risk materials are used.

Biosimilarity

The biosimilarity of Flixabi clinical and PVR batches to Remicade from the European Union (EU), United States of America (US) and Korea (KR) markets was assessed using a range of state-of-the-art orthogonal analytical tests. Prior to side-by-side characterisation studies, characterisation was performed on batches representative of EU Remicade. The analytical data from the characterisation studies of EU Remicade was used to establish the similarity ranges. The similarity ranges were used for the determination of similarity between Flixabi and Remicade for the critical quality attributes (CQAs). For the non-CQAs, analytical data between Flixabi and Remicade were compared in a side-by-side manner. The similarity ranges for the CQAs were established upon statistical analysis of up to multiple batches of EU Remicade. The statistical analysis was based on the tolerance

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

interval . As the use of tolerance interval-based similarity range in certain cases may result in broad biosimilarity ranges allowing differences between Flixabi and Remicade, upon request the applicant additionally reassessed all quality attributes using a Min/Max approach (see below). Overall the data indicate that Flixabi can be considered similar to EU Remicade in terms of MW, AA sequence, N-terminal sequence, C-terminal sequence after digestion with Lys-C, peptide map, disulphide bond pattern, free thiol group content, methionine oxidation, and Asn deamidation. Analysis of C-terminal sequence was performed because heterogeneity is common for C-terminal lysine in IgG. The relative content of C-terminus with Lys for Flixabi was much lower than that of EU Remicade. The difference in relative contents of C-terminal Lys was explained by the use of CHO cells as host cells instead of SP2/0 cells, which are used for the reference product. It is agreed that the heterogeneity of C-terminal residues is a characteristic of therapeutic monoclonal antibodies (mAbs) and that C-terminal Lys variation does not impact PK profiles. Literature is available indicating that there is no relationship between the presence of C-terminal Lys and the biological activity of the Fc part of the molecule. TNF-α binding results showed that C-terminal Lys of the heavy chain did not impact TNF-α binding activity. Finally the C-terminal Lys is cleaved by the carboxypeptidase enzyme as it enters the blood stream. It is therefore concluded that although differences exist between Flixabi and EU Remicade this has no clinical impact.

With respect to biophysical properties determined by far and near-UV circular dichroism (CD), intrinsic and extrinsic fluorescence, Fourier transform infrared (FTIR), hydrogen/deuterium exchange mass spectrometry (HDX/MS), differential scanning calorimetry (DSC), size exclusion chromatography coupled to multi angle laser light scattering (SEC/MALLS), sedimentation velocity-analytical ultracentrifugation (SV-AUC), dynamic light scattering (DLS), extinction coefficient, and micro-flow imaging (MFI) Flixabi was considered similar to EU Remicade. Sedimentation velocity analytical ultracentrifugation (SV-AUC) was used as an orthogonal method to SEC/MALLS to investigate the monomer content, the presence of aggregates and fragments, and the MW of the main molecular species in a protein solution.

N-glycan profiles of Flixabi and EU Remicade are categorised into several groups according to structural compositions. %Afucose level of Flixabi was slightly higher than that of the upper limit of the similarity range. However, in the subsequent assessment via Min/Max approach, the results for %Afucose glycans were found between the Min/Max of EU Remicade (see below). %Charged glycan level in Flixabi was lower than that in EU Remicade. Justification was provided supporting that the difference in %Charged level between Flixabi and EU Remicade is not considered to have any impact in relation to safety/efficacy or immunogenicity. The other N-glycan species where within the similarity range.

Similarity between Flixabi and EU Remicade has been demonstrated regarding the FcγRIa, FcγRIIa, FcγRIIIb and FcRn binding activity. FcγRIIb and FcγRIIIa binding is slightly higher in Flixabi compared to Remicade and the Min/Max value. The slightly higher FcγRIIb and FcγRIIIa binding did, however, not translate into any difference in the relevant biological activity and is therefore concluded to be without impact on safety/efficacy.

The ADCC assay was performed using a stable mouse cell line that overexpresses human membrane TNF-α on the cell surface as target cells, and a human natural killer cell line expressing CD16 as effector cells. This assay system is considered sensitive in order to detect potential differences between Flixabi and EU Remicade. ADCC activity of Flixabi was within the similarity range and the Min/Max. Additional biological assays were performed to further justify the observed binding difference of FcγRIIIa using various conditions, and to evaluate the in vitro inflammatory bowel diseases (IBD) model in order to support extrapolation of indication. These additional biological assays include: TNF-β binding, transmembrane TNF-α binding, ADCC using peripheral blood mononuclear cells (PBMC), FcγRIIIa binding assay (158 F/F type), FcγRIIIa binding using NK cells from PBMC,

FcγRIIIb binding using neutrophils, evaluation of regulatory macrophage function, cytokine release activity, and inhibitory activity of apoptosis in vitro IBD model. Results of the Transmembrane TNF-α Binding Assay showed no statistically significant difference in transmembrane TNF-α binding activity between Flixabi and EU Remicade. The additional assays performed under more physiological conditions were conducted in order to demonstrate that the differences observed in glycosylation pattern, FcγR binding and ADCC activity using engineered cell line as effector cells are not relevant for the clinical outcome. The data indeed indicate that under these conditions the differences are diminished.

As mentioned above, all quality attributes were additionally assessed using a Min/Max approach. The assessment results for only 6 quality attributes were different compared to the results from the tolerant interval-based similarity range. The results for %Afucose glycans and FcRn binding were found between the Min/Max of EU Remicade, and thus additional discussion was not required. Four attributes (%HM and %Charged glycans, C1q binding, and %IgG in CE-SDS (Non-reducing)) were outside the Min/Max of EU Remicade. Additional justifications were presented for these attributes supporting that although outside the Min/Max level of EU Remicade, these quality attributes will not have negative impact neither on the safety/efficacy nor on the immunogenicity.

Although the relative percentage of HMW is low (< 1.0%) in both SB2 and EU Remicade, the %HMW level of SB2 was out of the established similarity range. The applicant provided data from other approved biosimilars in order to provide assurance that the difference observed in the HMW analysed by SEC is considered unlikely to have an impact on immunogenicity.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and this leads to the conclusion that the product will have a satisfactory and uniform performance in clinical use.

Although the CHMP considers the specification adequate to control AS/FP recommendations are made for submission of further batch data to revisit the ranges based on additional manufacturing experience.

With regard to the biosimilarity on quality grounds of Flixabi vs. Remicade, comprehensive and state-of-the-art characterisation has taken place covering all relevant structural, physicochemical and biological features of infliximab. Minor differences were observed in glycosylation pattern (%Afucose, %High Mannose, %charged variants). This is not unexpected given that different cell lines are used for Remicade and Flixabi. For %HMW level and binding to various Fcγ Receptors and subsequent biological function such as ADCC minor differences were observed as well. The Applicant has carried out a thorough investigation to support that these changes do not have any clinical relevant impact, primarily with Fc-effector function assays including: TNF-β binding, transmembrane TNF-α binding, ADCC using peripheral blood mononuclear cells (PBMC), FcγRIIIa binding assay (158 F/F type), FcγRIIIa binding using NK cells from PBMC, FcγRIIIb binding using neutrophils, evaluation of regulatory macrophage function, cytokine release activity, and inhibitory activity of apoptosis in vitro IBD model. In light of a higher incidence of anti-drug antibody (ADA) in Flixabi compared to Remicade, a major objection was raised to request the applicant to provide further reassurance that the observed minor differences in quality attributes did not affect clinical safety and efficacy, as well as to provide data from additional batches of Flixabi. In addition, as the use of tolerance interval-based similarity range might result in broad biosimilarity

ranges allowing certain differences between Flixabi and Remicade, the applicant was requested to additionally reassess all quality attributes using a Min/Max approach.

The impact of the differences on the immunogenicity of Flixabi was discussed in depth by the applicant. A comprehensive reassessment of quality attributes with a similarity range and by the Min/Max approach, in the context of higher ADA incidence in Flixabi, was presented. From the results of the assessment, it was concluded that the differences in quality attributes discussed above (including differences observed in %Afucose level of Flixabi, FcγRIIb Binding, FcγRIIIa Binding, and %Charged glycan), are unlikely to induce higher ADA incidence in Flixabi treatment group. In addition, results from HMW analysis on other infliximab biosimilars and correlation with ADA incidence collected from literature showed that there is no evidence to support the association between the slight difference in HMW level and a higher ADA incidence in Flixabi. Results from an antibody array, performed to determine the combined effect of multiple quality attributes on the structural changes, showed that there were no differences in epitopes or antibody recognition sites between Flixabi and Remicade. Lastly, results from extractables and leachables studies showed that the impurities detected were not considered to be associated with immunogenicity.

Overall the data presented support biosimilarity on quality grounds.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

Overall the current dataset is sufficient to conclude that Flixabi can be considered biosimilar to EU Remicade at the quality level.

2.2.6. Recommendations 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 points for investigation (see specification sections).

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical programme for Flixabi (also referred to as SB2 throughout this Report), included a series of *in vitro* studies and an *in vivo* efficacy study to demonstrate pharmacodynamic (PD) similarity between Flixabi and Remicade. Single and repeat dose pharmacokinetic (PK) studies in Sprague Dawley (SD) rats and the Tg197 mouse model of arthritis, and the evaluation of potential anti-drug antibody (ADA) formation were also performed to demonstrate PK and immunogenic similarities between Flixabi and Remicade.

All the non-clinical studies submitted in support of the similarity between SB2 and Remicade were conducted under non-GLP conditions.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro pharmacodynamics

The *in vitro* studies submitted to demonstrate similarity between Flixabi and Remicade are detailed in **Table 1**.

Table 1. Summary of the Flixabi *in vitro* pharmacodynamic studies

Type of Study		Results
Fab-related biological activities	TNF-α binding assay	TNF-α (soluble) binding activity of SB2 was similar to that of Remicade®.
	TNF-β binding assay	SB2 and Remicade® showed a significant lack of TNF-β (LTα3) binding activity.
	tmTNF-α binding assay	tmTNF-α binding activity of SB2 was similar to that of Remicade®.
	TNF-α neutralisation assay	Inhibitory activity of SB2 on the signal pathway was similar to that of Remicade®.
	Apoptosis assay	Apoptosis activity of SB2 was similar to that of Remicade®.
	Inhibitory activity on apoptosis in an *in vitro* IBD model	Inhibitory activity of SB2 on apoptosis was similar to that of Remicade®, which may support the extrapolation of indications to inflammatory bowel disease (IBD).
	Cytokine release activity in an *in vitro* IBD model	Cytokine IL-8 release suppression activity of SB2 was similar to that of Remicade®, which may support the extrapolation of indications to IBD.
Fc-related biological activities	FcγRIa binding assay	FcγRIa binding activity of SB2 was similar to that of Remicade®.
	FcγRIIa binding assay	FcγRIIa binding activity of SB2 was similar to that of Remicade®.
	FcγRIIIa binding assay (V/V type)	FcγRIIIa binding activity of SB2 was slightly higher than that of Remicade®, but not biologically significant as these differences did not affect ADCC activity. ADCC activity of SB2 was within the similarity range.
	FcγRIIIa binding assay (F/F type)	FcγRIIIa (F158 allotype) binding activity of SB2 was similar to that of Remicade®.
	FcγRIIIa binding assay using NK cells from PBMCs	Binding activity of SB2 to FcγRIIIa on natural killer (NK) cells of peripheral blood mononuclear cells (PBMCs) was similar to that of Remicade®.
	FcγRIIb binding assay	FcγRIIb binding activity of SB2 was slightly higher than that of Remicade®, but not significant as these differences were within assay

Type of Study		Results
		variability and did not affect ADCC activity. ADCC activity of SB2 was within the similarity range.
	FcγRIIIb binding assay	FcγRIIIb binding activity of SB2 was similar to that of Remicade®.
	FcγRIIIb binding assay using neutrophils	FcγRIIIb binding activity of SB2 using neutrophils was similar to that of Remicade®.
	ADCC assay using engineered NK cell line	ADCC activity (effector cell: engineered NK cell line) of SB2 was similar to that of Remicade®.
	ADCC assay using healthy donor PBMCs	ADCC activity (effector cell: healthy donor PBMCs) of SB2 was similar to that of Remicade®, which may support similarity in more representative condition of *in vivo* situation.
	C1q binding assay	C1q binding activity of SB2 was similar to that of Remicade®.
	CDC assay	CDC activity of SB2 was similar to that of Remicade®.
	FcRn binding assay	FcRn binding activity of SB2 was slightly higher than that of Remicade®, but not significant as these differences were within assay variability and were not translated into PK difference according to the PK results from the Phase I clinical study.
	Evaluation of regulatory macrophage induction function	Regulatory macrophage induction function of SB2 was similar to that of Remicade®, which may support the extrapolation of indications to IBD.

Biosimilarity range was established by the mean values obtained in each assay for EU Remicade± κSD. The results of the *in vitro* studies were within the similarity range (data not shown), with the exception of FcγRIIIa (V/V type), FcγRIIb, and FcRn binding assays.

In these assays the binding activities of some batches of SB2 were found to be slightly higher than the upper limit of the similarity range. More specifically, the binding activity for FcγRIIIa of SB2 relative to the bioassay standard ranged from 114 to 141%, and that of EU Remicade ranged from 77 to 108% (biosimilarity range 70-126%). for FcγRIIb the binding activity for SB2 ranged between 105-120%, compared to 99-104% for EU Remicade. For FcRn, the values for SB2 and EU Remicade ranged between 105-120% and 88-105% respectively (similarity range: 82-117%).

Tg197 transgenic mouse model of arthritis

In vivo efficacy of SB2 and EU Remicade was assessed in a study using Tg197 transgenic mouse model of arthritis (Study no BMC319). US Remicade was also used throughout the global development plan for SB2 but comparisons between US Remicade and SB2 were not considered by the CHMP for the establishment of biosimilarity.

The Tg197 model is a transgenic mouse overexpressing human TNF-α resulting in spontaneous development of arthritis closely resembling human RA pathology. In this model, mice develop chronic polyarthritis, dependent on the ectopic overexpression of bio-active human TNF-α, with 100% incidence at 4 - 7 weeks of age.

Nine groups of Tg197 mice, each consisting of 7 males and 4 females, received either SB2, EU Remicade, or US Remicade twice weekly for 7 weeks which was administered intraperitoneally at dose levels of 1, 3, and 10 mg/kg. One additional group of transgenic mice was sacrificed just prior to the first dose administration and was used as control for the histopathological status of the disease upon the initiation of treatment.

The efficacy of SB2 and Remicade was assessed by changes in arthritic scores and histopathological scores (**Table 2**). No statistically significant differences were observed in the body weights of treated animals throughout the study (data not shown).

Table 2. Percentage of inhibition of Arthritic Pathology and histopathological scores in Study no BMC319

Dose	% Inhibition of Arthritic Scores Compared to Control Untreated Mice			% Inhibition of Histopathological Scores Compared to Control Untreated Mice		
	SB2	EU Remicade®	US Remicade®	SB2	EU Remicade®	US Remicade®
1 mg/kg	44.5 ± 2.7[a]	47.7 ± 3.2	31.0 ± 4.8	2.5 ± 3.6	6.0 ± 4.7	0.9 ± 4
	$p < 0.00001$[b]			$p = 0.7928$[b]		
3 mg/kg	72.3 ± 4.7	76.8 ± 4.5	65.8 ± 3.4	50.5 ± 5.5	45.8 ± 7.3	37.9 ± 6.9
	$p < 0.00001$[b]			$p < 0.00001$[b]		
10 mg/kg	85.2 ± 3.7	85.8 ± 3.4	91.6 ± 2.2	67.1 ± 4	72.1 ± 3.1	78.7 ± 3.9
	$p < 0.00001$[b]			$p < 0.00001$[b]		

[a] Mean ± SEM of % difference between the mean value of the vehicle treated group and the individual value of each test article treated group.
[b] The statistical analysis shown compares arthritic scores or histopathological scores to the untreated mouse group.
Main PD animals consist of 4 males and 4 females. Additional 3 males were assigned to each test article (SB2) or reference articles (EU Remicade® and US Remicade®) for PK analysis, but data from the 3 males were also evaluated for the therapeutic efficacy together.

Secondary pharmacodynamic studies

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

Safety pharmacology programme

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

Pharmacodynamic drug interactions

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

2.3.3. Pharmacokinetics

Two single-dose PK studies and a repeated-dose PK study were submitted in order to demonstrate similarity between SB2 and Remicade.

A single dose PK study was performed in SD rats. Although the rat is not a relevant species for infliximab, it was reported from the literatures (Wallace and Rees 1980, McCarthy, Yoong et al. 2000) that the clearance mechanism of infliximab in rat is relevant. Another PK study involving infliximab in rats (Yang, Shenoy et al. 2003) has also supported the utility of rat model. A single dose and a repeated dose PK studies were performed in Tg197 mice.

Methods of analysis

The serum and plasma samples from all PK studies were analysed using enzyme-linked immunosorbent assay (ELISA) to quantify the levels of infliximab. ADA was also assessed in the repeated dose study using ELISA.

In order to evaluate the PK in SD rats following a single administration, concentrations of infliximab in rat serum were determined by ELISA. The range of quantitation was 25-500 ng/mL in undiluted serum.

In order to evaluate the PK in Tg197 mice following single or repeated administration, concentrations of infliximab in mouse plasma were determined by ELISA. The range of quantitation was 5-250 ng/m.

In order to evaluate immunogenicity in Tg197 mice following repeated administration, anti-infliximab antibodies in mouse serum were detected using ELISA. The determination of ADA was possible in the presence of infliximab in range of 97.7-390.6 ng/mL.

Single dose PK study in SD rats (Study No 13-RK-349N)

A single dose PK study was performed in SD rats. Each group of 6 male rats was treated with 1, 3 and 10 mg/kg of either SB2, EU Remicade or US Remicade. Blood samples were collected at 0, 0.08, 0.5, 2, 6, 24, 48, 72, 120, 168, 336, 504 hours after single dose administration. The results of the study are presented in **Figure 1** and **Table 3**.

Figure 1. Mean serum concentration of SB2, EU and US Remicade after single dose intravenous administration in rats in Study No 13-RK-349N

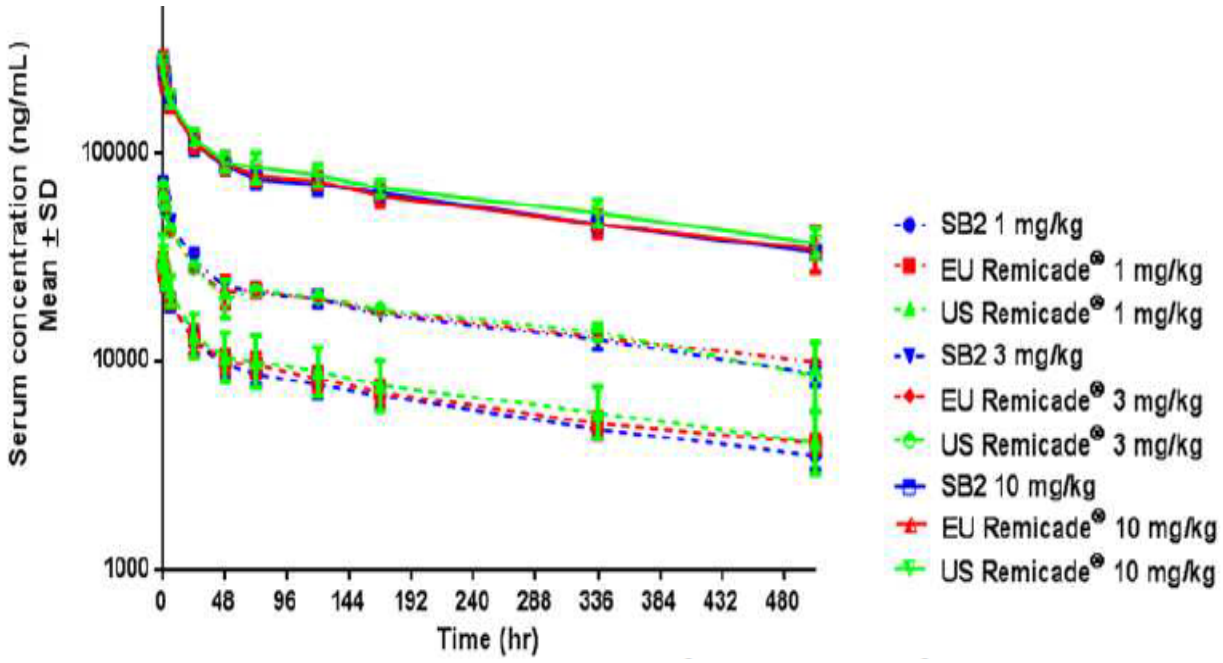


Table 3. Pharmacokinetic parameters for SB2, EU and US Remicade after single dose intravenous administration in rats in Study No 13-RK-349N

Dose	Group	Treatment	-	AUC_{last} (ng·hr/mL)		C_{max} (ng/mL)		T_{max} (hr)[a]
1 mg/kg	G3	SB2	Mean	3280148	$p = 0.4703$	29803	$p = 0.1383$	0.08
			SD	358295		2982		N/A
	G6	EU Remicade®	Mean	3476193		29232		0.29
			SD	363974		3625		N/A
	G9	US Remicade®	Mean	3753149		34484		0.08
			SD	1115673		6635		N/A
3 mg/kg	G2	SB2	Mean	8317074	$p = 0.9191$	69722	$p = 0.9511$	0.08
			SD	590218		6012		N/A
	G5	EU Remicade®	Mean	8422871		69858		0.08
			SD	522228		2989		N/A
	G8	US Remicade®	Mean	8463806		68984		0.08
			SD	771078		5834		N/A
10 mg/kg	G1	SB2	Mean	30693252	$p = 0.2912$	269111	$p = 0.7107$	0.08
			SD	2526432		24409		N/A
	G4	EU Remicade®	Mean	30867300		280924		0.08
			SD	3205474		27108		N/A
	G7	US Remicade®	Mean	33434032		274701		0.08
			SD	3867263		21648		N/A

[a] Median T_{max} values were presented.
Significance: p-value < 0.05. To assess the differences among SB2, EU Remicade®, and US Remicade®, the PK parameter estimates (C_{max} and AUC_{last}) were subjected to one-way analysis of variance (ANOVA).

Single Dose PK Study in Tg197 Transgenic Mouse Model of Arthritis (Study No BMC320A)

Pharmacokinetic parameters following single dose of SB2 was studied in part A of Study No BMC320. Each group of 3 male Tg197 mice was treated with 1, 3 and 10 mg/kg of SB2, EU Remicade or US Remicade. Blood samples were collected after single dose administration. Pharmacokinetic parameters and mean plasma concentrations from this study are summarised in **Figure 2** and **Table 4**.

Figure 2. Mean serum concentration of SB2, EU and US Remicade after single dose intraperitoneal administration in Tg197 transgenic mice in Study BMC320

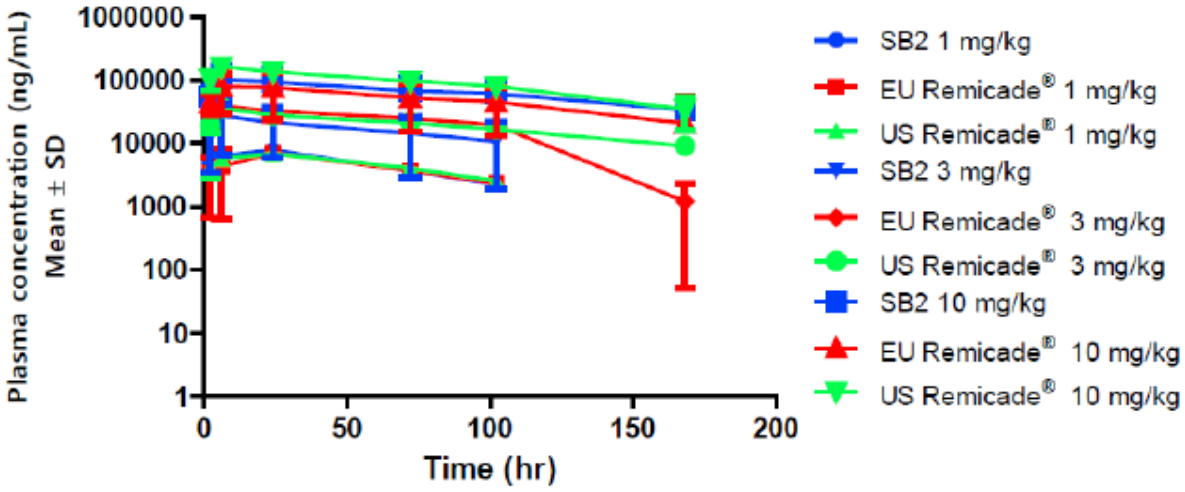


Figure 2.6.4.3-2. Mean Plasma Concentration of SB2, EU Remicade®, and US Remicade® after Single Dose Intraperitoneal Administration in Tg197 Transgenic Mice

Table 4. Mean pharmacokinetic parameters following administration of SB2, EU and US Remicade in Study BMC320

Dose	Group	Treatment	-	AUC_{last} (ng·hr/mL)		C_{max} (ng/mL)		T_{max} (hr)[a]
1 mg/kg	G3	SB2	Mean	526655	$p = 0.8877$	7868	$p = 0.4269$	24
			SD	43018		491		N/A
	G6[b]	EU Remicade®	Mean	503392		7130		24
			SD	506		252		N/A
	G9	US Remicade®	Mean	505599		6942		24
			SD	86348		1204		N/A
3 mg/kg	G2	SB2	Mean	1792254	$p = 0.1637$	27556	$p = 0.5346$	6
			SD	1345237		20758		N/A
	G5	EU Remicade®	Mean	3279971		39403		6
			SD	66562		7221		N/A
	G8	US Remicade®	Mean	2767978		36801		6
			SD	505535		4241		N/A
10 mg/kg	G1	SB2	Mean	10683196	$p = 0.5015$	105332	$p = 0.2828$	6
			SD	7218883		62997		N/A
	G4	EU Remicade®	Mean	8580792		81554		6
			SD	6618152		51657		N/A
	G7[c]	US Remicade®	Mean	15666870		167036		6
			SD	941233		19369		N/A

[a] Median T_{max} values were presented.
[b] Due to administration error, one animal per group was not included in the analysis.
Significance: p-value < 0.05. To assess the differences among SB2, EU Remicade®, and US Remicade®, the pharmacokinetic parameter estimates (C_{max} and AUC_{last}) were subjected to one-way analysis of variance (ANOVA).

Repeated Dose PK Study in Tg197 Transgenic Mouse Model of Arthritis (Study No BCM320B)

Pharmacokinetic parameters following repeated dosing was studied in part B of Study No BMC320. Each group of 3 male Tg197 mice was treated with 1, 3 and 10 mg/kg of SB2, EU Remicade, or US Remicade twice weekly for 7 weeks. Blood samples were collected at 2, 6, 24, and 72 hours after the last administration. Results from this study are presented in **Figure 3** and **Table 5**. The data from 1 mg/kg treated group were not included in PK parameter analysis due to ADA formation in all animals. For 3 mg/kg treated group, some animals showed ADA formation and data from one mouse in the SB2 group at 72 hr was lost due to an unscheduled death.

Figure 3. Mean plasma concentration of SB2, EU and US Remicade in repeat dose PK Study BMC320

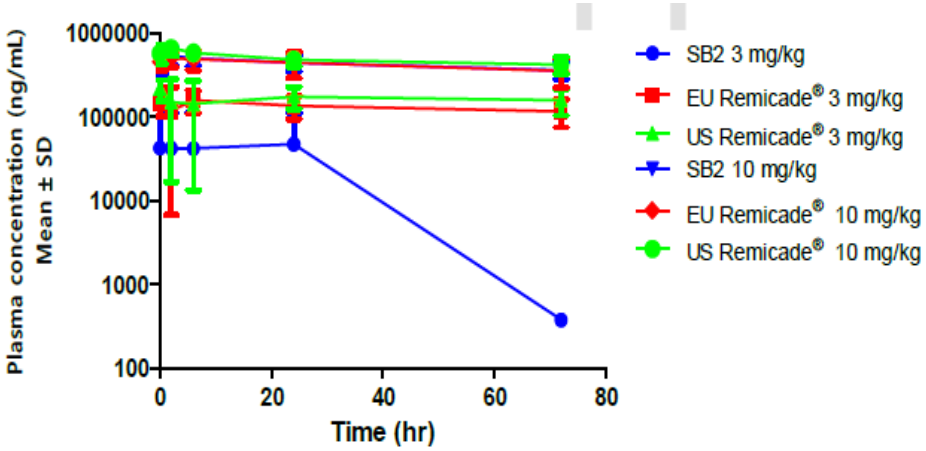


Figure 5. Mean Plasma Concentration for SB2, EU Remicade®, and US Remicade® in Repeat Dose PK Study

Table 5. Mean pharmacokinetic parameters repeat dose PK Study BMC320 after administration of 10 mg/kg of infliximab

Group No.	Treatment	-	AUC_{last} (ng•hr/mL)		C_{max} (ng/mL)		T_{max} (h)[d]
G3	SB2	Mean	31081667	$p = 0.760$	540504	$p = 0.345$	2
		SD	6700408		126292		N/A
G6	EU Remicade®	Mean	30751614		507225		2
		SD	10123799		116119		N/A
G9	US Remicade®	Mean	35129608		661234		2
		SD	6256618		129974		N/A

Immunogenicity Assessment in Repeated Dose PK Study in Tg197 Transgenic Mouse Model of Arthritis (Study no BMC320)

Immunogenicity of SB2 was evaluated as part of the repeated dose PK study in the Tg197 transgenic mouse model (Study No BMC320B). In the study, the levels of anti-infliximab antibodies in the serum of Tg197 mice that received repeated administrations twice a week for 7 weeks were analysed at the end of the dosing period using ELISA.

Anti-infliximab antibodies were detected in all animals treated with 1 mg/kg, whereas in the 3 mg/kg group, 2 of 3 animals treated with SB2 and 1 of 3 animals treated with Remicade developed ADA. In the 10 mg/kg group, ADA was not detected in any animal.

2.3.4. Toxicology

In accordance with Scientific Advice received for this Application toxicology studies were not submitted as there are no relevant animal models available to evaluate the toxicity of infliximab. In addition in accordance with EMA guidelines (EMA/CHMP/BMWP/403543/2010, EMEA/CHMP/BMWP/42832/2005), studies regarding genotoxicity, carcinogenicity, reproductive & developmental toxicity, and local tolerance were not submitted.

2.3.5. Ecotoxicity / environmental risk assessment

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

2.3.6. Discussion on non-clinical aspects

None of the nonclinical studies submitted were performed according to GLP. This was considered acceptable, as only PD and PK studies were conducted, and no pivotal safety or toxicity studies were performed.

In line with the EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 Rev. 1) and "Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues" (EMEA/CHMP/BMWP/403543/2010) further studies regarding pharmacology, pharmacokinetics, genotoxicity, reproduction toxicology and carcinogenicity were not submitted.

Infliximab plasma levels were determined by ELISA assays. The range of quantitation was 25-500 ng/mL and 5-250 ng/mL for the rat and mouse assay respectively and the sensitivity of the methods was considered sufficient.

The *in vitro* studies submitted with this application supported biosimilarity between SB2 and Remicade as all results were within the similarity range, with the exception of FcγRIIIa (V/V type), FcγRIIb, and FcRn binding assays. However, the difference was within assay variability for FcγRIIb and FcRn binding assays, and binding activity differences in FcγRIIIa (V/V type) and FcγRIIb were not translated into ADCC activity since the ADCC activity of SB2 was within the similarity range. FcRn is known to internalise antibodies into cellular endosomes to protect antibodies from proteolysis and thus plays a role in prolonging half-life of serum IgG. Nevertheless, despite the small deviations outside the similarity margin in FcRn binding activity, these were not translated into PK differences (See Section 2.4.2).

The results of the murine Tg197 model of Rheumatoid Arthritis study showed that SB2 is highly similar to Remicade in its ability to inhibit, in a dose dependent manner, the arthritic pathology and histopathology of these mice. The effects of the 1, 3 and 10 mg/kg dose regimens of SB2 were similar to the same dose regimens of Remicade.

The results of the single dose study in SD rats showed that SB2 and EU Remicade have a similar PK behaviour. There were no significant differences in the maximum observed concentration at Tmax (Cmax) and area under the concentration-time curve from time zero to the last quantifiable concentration (AUC last) among SB2 and EU Remicade.

The PK profiles of SB2 and EU Remicade were similar in Tg197 transgenic mice after repeated administration of 10 mg/kg. The similarity of PK profiles between SB2 and Remicade in 1 and 3 mg/kg group could not be adequately evaluated due to ADA development and missing values.

Formation of ADA was similar in the 1 mg/kg treatment groups following repeated dosing. In the 3 mg/kg 2 animals in the SB2 treated group showed ADA, whereas only 1 animal each in the EU and US Remicade treated groups was positive for ADA. However, as only 3 animals were included in each group, it is not possible to ascertain if there is any differences in antigenicity of SB2 and Remicade, due to the low number of animals included.

2.3.7. Conclusion on the non-clinical aspects

The provided non-clinical comparability exercise testing strategy was considered as appropriate. Relevant regulatory guidelines and scientific advice were taken into consideration.

The overall results of the in vitro Fab and Fc related binding assays demonstrated similarity between Flixabi and Remicade. Similar pharmacokinetic parameters were also observed in the single dose rat study, as well as in the single and repeat dose Tg197 mice study.

Comparative pharmacodynamics and pharmacokinetic data demonstrated biosimilarity between Flixabi and the reference product Remicade.

Overall, the non-clinical data provided by the Applicant was considered acceptable by the CHMP to support the application for SB2.

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	Study Objectives	Design	Study Population	Primary Endpoints
SB2-G11-NHV Phase I (Germany) Healthy subjects	Comparative PK, safety, tolerability, immunogenicity To investigate and compare the PK profiles of SB2 and EU-Remicade in healthy subjects.	Randomised, single-blind, three-arm, parallel group, single-dose study; Total duration: 10 weeks Single dose *i.v.* infusion of 5 mg/kg either SB2, EU- or US-Remicade	159 healthy subjects (53/arm)	AUCinf

SB2-G31-RA Phase III (UK,Czech Republic, Bulgaria, Lithuania, Latvia, Poland, Romania, Bosnia, Ukraine, Korea, India, Mexico, Philippines) RA subjects	Safety, efficacy, immunogenicity, and PK To demonstrate the equivalence of SB2 to EU-Remicade at Week 30, in terms of the ACR20 response rate in subjects with moderate to severe RA despite methotrexate (MTX) therapy	Randomised, double-blind, parallel group, multicentre study; Total duration: 78 weeks Randomised, Double- Blind period: 54 weeks *i.v.* infusions of 3 mg/kg SB2 or EU-Remicade at Weeks 0, 2, 6 and then every 8 weeks until Week 46. After Week 30 dose increments by 1.5 mg/kg per visit up to 7.5 mg/kg allowed if the subject`s RA symptoms are not well controlled by the existing dose. Transition-Extension period: 24 weeks *i.v.* infusions of 3 to 7.5 mg/kg SB2 or EU Remicade® every 8 weeks at Weeks 54, 62 and 70.	584 RA subjects (291 for SB2, 293 for EU-Remicade)	Efficacy: ACR20 at Week 30 PK: Ctrough

2.4.2. Pharmacokinetics

Study SB2-G11-NHV

This was a randomised, single-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics, safety, tolerability, and immunogenicity of three formulations of infliximab (SB2, EU sourced Remicade and US sourced Remicade) in healthy subjects.

The primary objective was to investigate and compare the PK profiles between SB2 and EU Remicade in healthy subjects;

The secondary objective was to investigate the safety, tolerability and immunogenicity of SB2 and EU Remicade in healthy subjects.

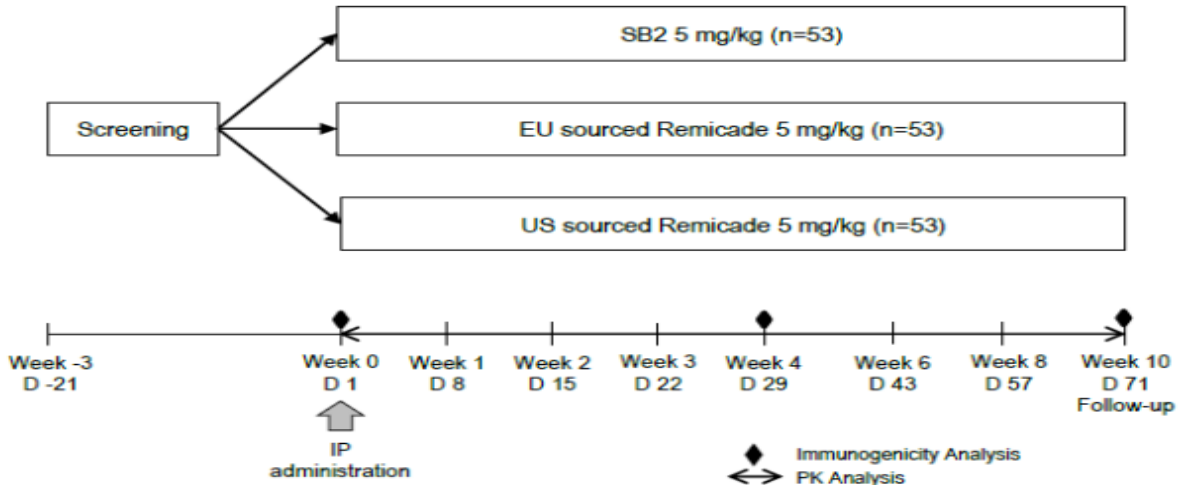
The primary PK endpoint was the area under the concentration-time curve (AUC) from time zero to infinity (AUCinf).

Secondary PK endpoints were AUClast, Cmax, time to Cmax (Tmax), terminal rate constant (kel), volume of distribution during the terminal phase (Vz), terminal half-life (t½), total body clearance (CL) and AUC

extrapolated from last time having a measurable concentration to infinity as a percentage of total AUC (%AUCextrap) were also included as secondary PK endpoints.

The design of the study is illustrated in **Figure 4**.

Figure 4. Design of Study SB2-G11-NHV



Sample size was calculated to reject the null hypothesis that the AUC-ratio of test vs. reference was below 0.8 or above 1.25.

A total of 319 subjects were screened, of which 159 subjects were randomised, 53 per arm, all of whom were included in the safety set. The demographic characteristics were balanced between the sequences in each part (data not shown).

Results

Table 6. Disposition of subjects (SB2-G11-NHV)

Treatment	SB2	EU sourced Remicade®	US sourced Remicade®	Total
Number (%) of subjects	n (%)	n (%)	n (%)	n (%)
Randomised	53 (100.0)	53 (100.0)	53 (100.0)	159 (100.0)
Completed	53 (100.0)	53 (100.0)	53 (100.0)	159 (100.0)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Percentages were based on the number of randomised subjects.

Table 7. Summary of protocol deviations by treatment in Study SB2-G11-NHV

Treatment	SB2 N=53	EU sourced Remicade® N=53	US sourced Remicade® N=53	Total N=159
Number (%) of subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any protocol deviations	14 (26.4)	14 (26.4)	17 (32.1)	45 (28.3)
Major protocol deviation	2 (3.8)	0 (0.0)	0 (0.0)	2 (1.3)
Concomitant medication	2 (3.8)	0 (0.0)	0 (0.0)	2 (1.3)
Minor protocol deviation	14 (26.4)	14 (26.4)	17 (32.1)	45 (28.3)
Time window deviation for PK blood sampling	8 (15.1)	7 (13.2)	9 (17.0)	24 (15.1)
Study procedures	7 (13.2)	7 (13.2)	12 (22.6)	26 (16.4)
Incorrect treatment or dose	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.6)

N = number of subjects in the safety set.
Percentages were based on the number of subjects in the safety set.

The PK parameters of the investigated products in this study are shown in **Table 8**.

Table 8. Summary of PK parameters in Study SB2-G11-NHV

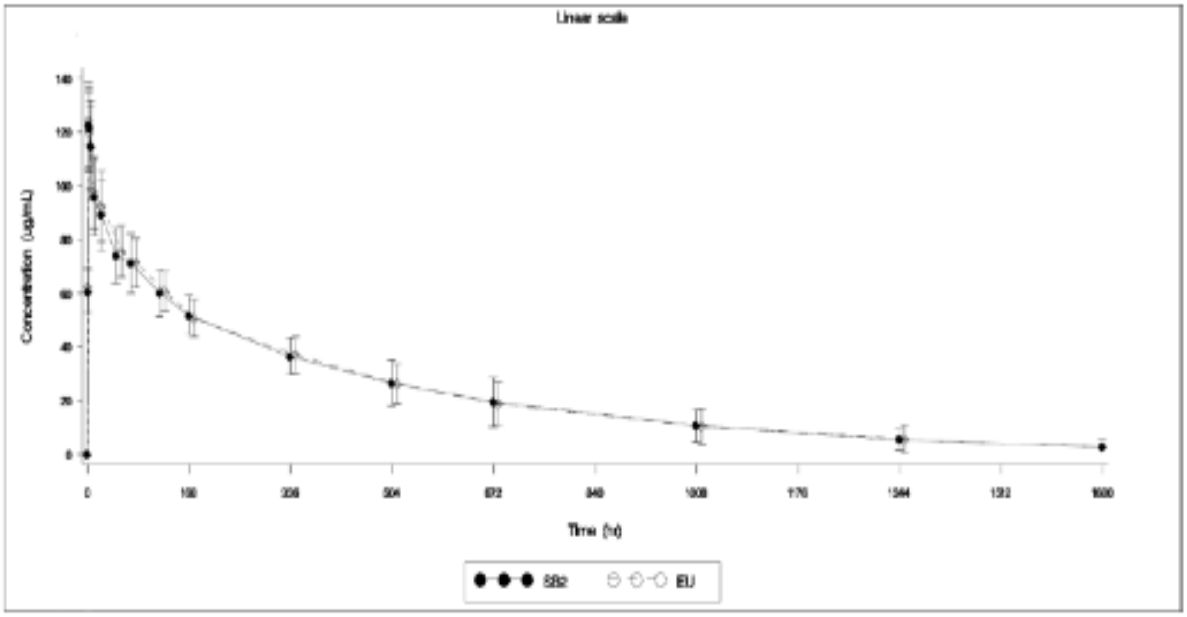
PK Parameter	Statistics	SB2 N=51	EU Remicade® N=53
AUC_{inf} (h·µg/mL)	n	51	53
	Mean	38702.8145	39359.7493
	SD	11113.62172	12332.41615
AUC_{last} (h·µg/mL)	n	51	53
	Mean	36862.4180	37022.3524
	SD	9132.75342	9398.42182
C_{max} (µg/mL)	n	51	53
	Mean	126.9975	126.2377
	SD	16.89586	17.88151
T_{max} (h)	n	51	53
	Mean	2.9294	2.5824
	SD	1.11529	0.95950
V_z (mL)	n	51	53
	Mean	4586.6308	4846.4691
	SD	1583.28395	1286.70908
k_{el} (1/h)	n	51	53
	Mean	0.0031	0.0026
	SD	0.00279	0.00141
$t_{½}$ (h)	n	51	53
	Mean	324.0859	339.4503
	SD	148.70388	155.43045
CL (mL/h)	n	51	53
	Mean	10.8980	11.0550
	SD	3.17422	3.04419
$\%AUC_{extrap}$ (%)	n	51	53
	Mean	3.8475	4.5713
	SD	3.93668	5.00777

N = number of subjects in the PK population; n = number of subjects who contributed to summary statistics. Two subjects were excluded from the PK population due to major protocol deviations

Mean serum concentration-time profiles reached maximum exposure between 2 and 6 hours post start of infusion with a median Tmax of approximately 3 hours for SB2 and US sourced Remicade and of approximately 2 hours for EU sourced Remicade.

Mean serum concentrations versus nominal times on linear scale (bottom graph) of SB2 and EU sourced Remicade are shown in **Figure 5**.

Figure 5. The mean serum concentration versus nominal time curves on linear scale for in SB2-G11-NHV



The ANOVA results (using the loge-transformed values of each PK parameters as dependent variables) of AUCinf, AUClast and Cmax for the comparison of SB2 and EU sourced Remicade in the PK population are reported in **Table 9**.

Table 9. ANOVA for PK parameters AUCinf, AUClast and Cmax comparing SB2 to EU sourced Remicade (PK population) in SB2-G11-NHV

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{Inf} (µg·h/mL)	SB2	51	51	37162.228	0.986	0.897; 1.083
	EU sourced Remicade®	53	53	37704.901		
AUC_{last} (µg·h/mL)	SB2	51	51	35701.831	0.994	0.915; 1.079
	EU sourced Remicade®	53	53	35929.929		
C_{max} (µg/mL)	SB2	51	51	125.923	1.007	0.964; 1.052
	EU sourced Remicade®	53	53	125.053		

A: SB2, B: EU sourced Remicade; LSMean = least squares mean; CI = confidence interval; N = number of subjects in PK population; n = number of subjects who contributed to analysis

Immunogenicity Evaluation

Post-dose Anti-drug Antibody (ADA) positive subjects were defined as those having positive ADA results either on Day 29 or Day 71 (**Table 10**).

Table 10. Incidence of anti-drug antibodies and neutralising antibodies to infliximab at each time point (safety set)

Parameter	Time point	Result	SB2 N=53 n/n' (%)	EU sourced Remicade® N=53 n/n' (%)	US sourced Remicade® N=53 n/n' (%)	Total N=159 n/n' (%)
Anti-drug antibodies (ADA)	Day 1 pre-dose	Positive	0/53 (0.0)	0/53 (0.0)	0/53 (0.0)	0/159 (0.0)
		Negative	53/53 (100.0)	53/53 (100.0)	53/53 (100.0)	159/159 (100.0)
	Day 29	Positive	2/53 (3.8)	0/53 (0.0)	1/53 (1.9)	3/159 (1.9)
		Negative	51/53 (96.2)	53/53 (100.0)	52/53 (98.1)	156/159 (98.1)
	Day 71	Positive	25/53 (47.2)	20/53 (37.7)	20/53 (37.7)	65/159 (40.9)
		Negative	28/53 (52.8)	33/53 (62.3)	33/53 (62.3)	94/159 (59.1)
	Post-dose	Positive	25/53 (47.2)	20/53 (37.7)	20/53 (37.7)	65/159 (40.9)
Neutralising antibodies (NAb)	Day 1 pre-dose	Positive	0/0	0/0	0/0	0/0
		Negative	0/0	0/0	0/0	0/0
	Day 29	Positive	1/2 (50.0)	0/0	0/1 (0.0)	1/3 (33.3)
		Negative	1/2 (50.0)	0/0	1/1 (100.0)	2/3 (66.7)
	Day 71	Positive	14/25 (56.0)	14/20 (70.0)	7/20 (35.0)	35/65 (53.8)
		Negative	11/25 (44.0)	6/20 (30.0)	13/20 (65.0)	30/65 (46.2)

N = number of subjects in the safety set; n' = number of subjects with available assessment results at each time point. Percentages for ADA result were based on the number of subjects with available ADA results at each time point (except post-dose).

The effects of ADA status on PK parameters are summarized in **Table 11**.

Table 11. ANOVA for PK parameters AUCinf, AUClast and Cmax comparing SB2 to EU sourced Remicade (PK population) in subjects with and without Anti-drug Antibodies in SB2-G11-NHV

ADA status	PK Parameter	Treatment	N	n	Geometric LSMean	Ratio of SB2/EU Remicade®	
						LSMean ratio	90% CI of Ratio
ADA negative	AUC_{inf} (µg·h/mL)	SB2	51	28	43546.870		
		EU Remicade®	53	33	42985.426	1.013	0.911 - 1.127
		US Remicade®	53	33	42728.588	1.019	0.927 - 1.120
	AUC_{last} (µg·h/mL)	SB2	51	28	40931.784		
		EU Remicade®	53	33	40035.985	1.022	0.936 - 1.117
		US Remicade®	53	33	40282.152	1.016	0.936 - 1.103
	C_{max} (µg/mL)	SB2	51	28	128.256		
		EU Remicade®	53	33	125.805	1.019	0.957 - 1.086
		US Remicade®	53	33	128.305	1.000	0.938 - 1.066
ADA positive	AUC_{inf} (µg·h/mL)	SB2	51	23	30639.242		
		EU Remicade®	53	20	30372.052	1.009	0.902 - 1.128
		US Remicade®	53	20	31265.300	0.980	0.867 - 1.107
	AUC_{last} (µg·h/mL)	SB2	51	23	30228.302		
		EU Remicade®	53	20	30054.949	1.006	0.902 - 1.122
		US Remicade®	53	20	30792.351	0.982	0.873 - 1.104
	C_{max} (µg/mL)	SB2	51	23	123.140		
		EU Remicade®	53	20	123.822	0.994	0.938 - 1.054
		US Remicade®	53	20	127.074	0.969	0.910 - 1.032

Study SB2-G31-RA

This was a randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, PK and immunogenicity of SB2 compared with Remicade in subjects with moderate to severe RA despite MTX therapy. See Section 2.5 for full details.

The PK evaluation of SB2 compared to Remicade was one of the secondary objectives of the study. Of the 583 subjects that comprised the Full Analysis Set, 325 were analysed for PK parameters. Insufficient samples were available for assessment of 54 week data, but analysis up to week 30 was possible.

Concentration of infliximab at baseline and prior to dosing at Weeks 2, 6, 14, 22 and 30 (Ctrough) are summarised in **Table 12**.

Table 12. Summary of Serum Trough Concentration (µg/mL) SB2-G31-RA (PK population)

Time-point	Statistics	SB2 N=165	Remicade® N=160
Week 0	n	160	149
	Mean (SD)	0.000 (0.0000)	0.000 (0.0000)
	CV%	NC	NC
	Min, Max	0.00, 0.00	0.00, 0.00
Week 2	n	161	156
	Mean (SD)	17.965 (8.6612)	16.954 (6.0218)
	CV%	48.2125	35.5191
	Min, Max	0.00, 90.08	0.00, 34.79
Week 6	n	155	153
	Mean (SD)	13.374 (11.1216)	12.039 (7.1710)
	CV%	83.1586	59.5654
	Min, Max	0.00, 73.32	0.00, 35.87
Week 14	n	153	143
	Mean (SD)	3.593 (6.0938)	3.380 (3.6535)
	CV%	169.6090	108.0864
	Min, Max	0.00, 54.66	0.00, 23.24
Week 22	n	146	147
	Mean (SD)	3.538 (10.6475)	2.390 (2.6090)
	CV%	300.9453	109.1630
	Min, Max	0.00, 110.54	0.00, 12.90
Week 30	n	139	143
	Mean (SD)	1.915 (2.8055)	2.224 (4.7326)
	CV%	146.5085	212.7572
	Min, Max	0.00, 19.33	0.00, 50.71

CV% = coefficient of variation; Max = maximum; Min = minimum; NC = not calculated; SD = standard deviation

The serum trough concentration results from this study were compared to those observed in other infliximab trials, e.g. the ATTRACT and PLANETRA studies (Maini, St Clair et al. 1999; Yoo, Hrycaj et al. 2013, **Figure 6**).

Figure 6. Mean and standard deviation of infliximab serum trough concentrations from different clinical studies

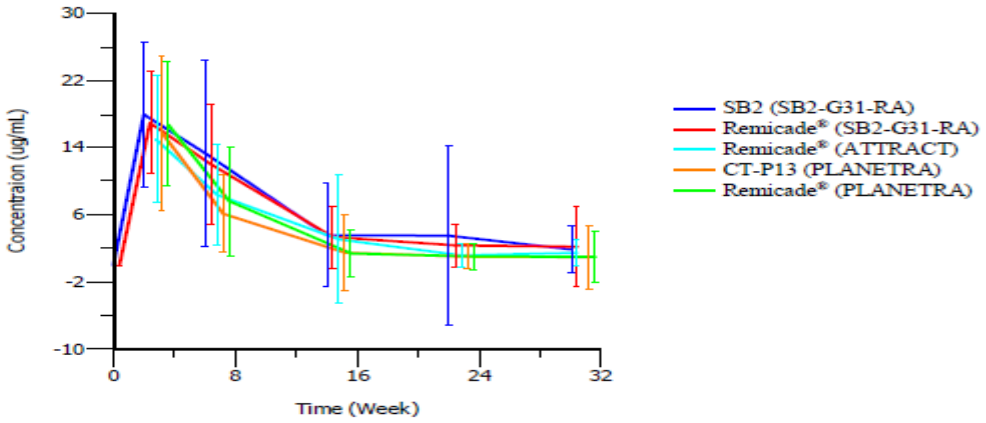


Figure 1. Mean and SD of Infliximab Serum Trough Concentration from Different Clinical Studies.
[illegible] mentioned clinical studies were measured at the same timepoint. For the convenience of the Agency's assessment, the measured timepoint in each study was slightly adjusted for the clear display of SD.

Immunogenicity evaluation

Blood samples were taken at each visit to determine the incidence of ADA.

ADA were detected in serum samples using a bridging, double antigen format assay specific for the antibodies to infliximab. Serum samples in which ADA were detected would be reflexed to a NAb assay to evaluate the effect of the ADA on the biological activity of infliximab. Specifically, the effects of ADA on the ability of infliximab to provide competitive inhibition of TNF-α were measured.

The overall ADA result was defined as positive if the subject had at least 1 positive ADA result up to that time-point regardless of the ADA test result at Baseline.

Table 13. Incidence of Anti-drug antibodies and neutralising antibodies to infliximab, in Study SB2-G31-RA (safety set)

		SB2 N=290			Remicade® N=293			Total N=583		
Timepoint	Parameter	n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 0	ADA	290	5	(1.7)	293	7	(2.4)	583	12	(2.1)
	Nab	5	0	(0.0)	7	0	(0.0)	12	0	(0.0)
Week 2	ADA	286	10	(3.5)	291	14	(4.8)	577	24	(4.2)
	Nab	10	4	(40.0)	14	4	(28.6)	24	8	(33.3)
Week 6	ADA	282	21	(7.4)	286	16	(5.6)	568	37	(6.5)
	Nab	21	11	(52.4)	16	7	(43.8)	37	18	(48.6)
Week 14	ADA	274	73	(26.6)	280	63	(22.5)	554	136	(24.5)
	Nab	73	70	(95.9)	63	60	(95.2)	136	130	(95.6)
Week 22	ADA	268	121	(45.1)	273	108	(39.6)	541	229	(42.3)
	Nab	121	113	(93.4)	108	96	(88.9)	229	209	(91.3)
Week 30	ADA	251	133	(53.0)	264	116	(43.9)	515	249	(48.3)
	Nab	133	129	(97.0)	116	109	(94.0)	249	238	(95.6)
Week 30 overall	ADA	287	158	(55.1)	292	145	(49.7)	579	303	(52.3)
	Nab	158	146	(92.4)	145	130	(89.7)	303	276	(91.1)
Week 38	ADA	243	123	(50.6)	255	115	(45.1)	498	238	(47.8)
	Nab	123	114	(92.7)	115	103	(89.6)	238	217	(91.2)
Week 46	ADA	237	121	(51.1)	231	99	(42.9)	468	220	(47.0)
	Nab	121	113	(93.4)	99	87	(87.9)	220	200	(90.9)
Week 54	ADA	223	118	(52.9)	222	89	(40.1)	445	207	(46.5)
	Nab	118	99	(83.9)	89	78	(87.6)	207	177	(85.5)
Week 54 overall	ADA	287	179	(62.4)	292	168	(57.5)	579	347	(59.9)
	Nab	179	166	(92.7)	168	147	(87.5)	347	313	(90.2)

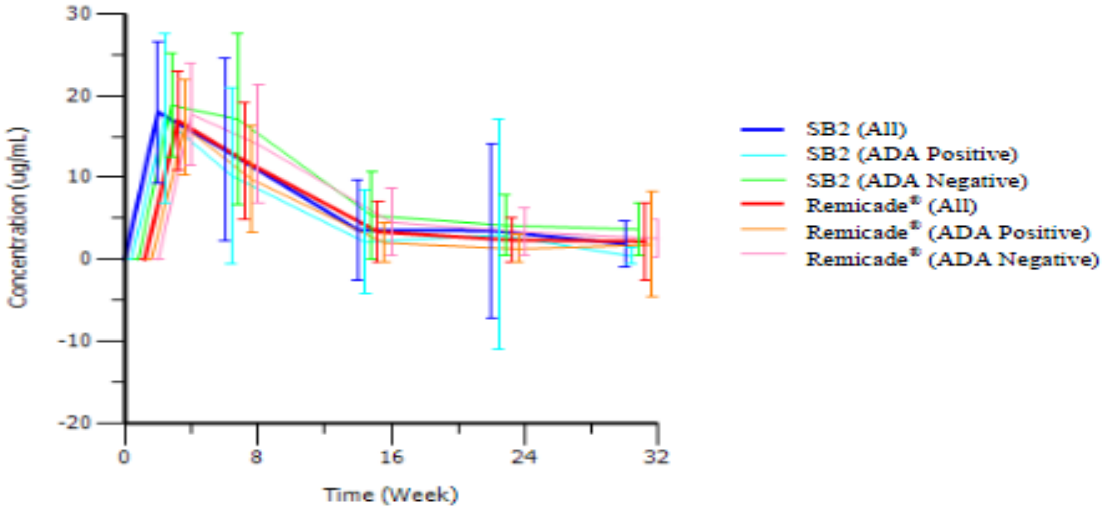
ADA = anti-drug antibody, NAb = neutralising antibody; n': number of subjects with available ADA/NAb results against SB2 at each timepoint
ADA was determined as positive if at least 1 ADA positive result was obtained up to the timepoint regardless of the ADA result at Week 0.
Percentages were based on n'.

As some patients tested positive for ADA at baseline, the Applicant submitted a re-analysis to exclude these patients.

When excluding the patients with ADA-positive result at baseline, the patients with overall seroconverted ADA-result are 54.4% in the SB2 treatment group vs. 48.4% in the EU Remicade group.

Summary statistics of trough concentration at each time point by treatment and overall ADA up to Week 30 are provided in **Figure 7**.

Figure 7. Mean and SD of trough concentrations of SB2 and EU Remicade by overall ADA up to Week 30 in Study SB2-G31-RA



The clearance and half-life, in Study SB2-G11-NHV are presented in **Table 14**.

Table 14. Clearance and half-life of SB2 and EU Remicade by overall ADA status in Study SB2-G11-NHV

PK Parameter	ADA	SB2	EU Remicade®
CL (mL/h)	All	10.9±3.2	11.1±3.0
	Negative	9.4±2.0	9.5±2.5
	Positive	12.7±3.4	13.6±2.0
$t_{1/2}$ (h)	All	324.1±148.7	339.5±155.4
	Negative	411.0±116.3	420.6±133.1
	Positive	218.3±111.1	205.5±77.2

Absorption

No bioavailability studies were submitted for SB2.

Distribution

Volume of distribution during the terminal phase was estimated in healthy volunteers (SB2-G11-NHV) to be 4.59 litres (SB2) and 4.85 litres (EU Remicade).

Elimination

The mean terminal $t_{1/2}$ in healthy male volunteers was estimated to be about 324h for SB2 compared to 339 h for EU Remicade (SB2-G11-NHV).

Dose proportionality and time dependencies

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

Special populations

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

Pharmacokinetic interaction studies

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

2.4.3. Pharmacodynamics

Infliximab binds to and inhibits the functional activity of TNF-α which may exist as a soluble or a transmembrane form (sTNF-α and tmTNF-α, respectively). The primary mechanism of action of infliximab appears to be a complex formation with TNF-α, decreasing its availability and consequently reducing its ability to induce inflammatory effects.

The clinical development programme aimed to demonstrate the similarity between SB2 and the reference product Remicade and therefore in accordance with the EMA guideline (EMEA/CHMP/BMWP/42832/2005 Rev. 1) further clinical studies on the pharmacodynamics of SB2 were not conducted.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic properties of SB2 were investigated in two clinical studies, one in healthy volunteers (Study SB2-G11-NHV) and in patients with Rheumatoid Arthritis (RA, Study SB2-G31-RA).

In study SB2-G11-NHV, the primary objective was to show the similarity in the PK profiles in healthy volunteers (male and female) between SB2 and EU Remicade and the equivalence in exposure. Biosimilarity was demonstrated with ratios between SB2 and EU Remicade for AUCinf, AUClast, and Cmax close to one and 90% CI within the pre-specified margins of 0.8-1.25.

There was a difference of 9.5% more ADA positive patients at day 71 and post dose assessment in the SB2 group compared to the EU sourced Remicade group. However, more ADA positive patients treated with EU sourced Remicade developed neutralising antibodies compared to SB2 treated patients (70% versus 56%). Nevertheless the absolute difference in number of patients developing antibodies between the treatment arms is quite small. Importantly the significance of these differences appears to be limited as they did not have a marked impact on the PK comparability between studied treatments.

In study SB2-G31-RA, the PK characteristics of the SB2 group was compared to EU sourced Remicade by determining the trough (pre-dose) concentrations from week 0 to week 30.

The overall trough concentrations were similar at each time-point between the 2 treatment groups. The serum trough concentrations showed high inter-subject variability especially post-week 6, with coefficient of variation (CV) above 50%. However, high variability of serum trough concentrations is an expected pharmacokinetic characteristic in infliximab-treated patients. For example, in the ATTRACT and PLANETRA studies which were conducted using the same dosing regimen with RA patients as the SB2-G31-RA study, the high inter-subject variability of serum trough concentrations was also observed with CV higher than 50% at most of the time points in those trials.

The higher incidence of ADA was also observed in SB2-G31-RA for subjects treated with SB2 compared to the Remicade treated subjects. The impact of this on the PK properties was evaluated based on comparison of results in ADA positive and ADA negative patients between the two treatment groups.

For subjects with overall post-dose positive ADA results up to Week 30, mean trough concentration between the 2 treatment groups were comparable up to Week 14. However, the mean SB2 trough concentration levels were highly variable after Week 14 groups. For subjects with overall post-dose negative ADA results up to Week 30, the mean SB2 trough concentrations were higher compared to the EU Remicade treatment group at all time points. The differences in the mean values were most likely due to the considerable inter-subject variability in both studied groups. Importantly, the clearance and half-life data were comparable between SB2 and EU Remicade subjects for all, ADA positive and ADA negative groups.

2.4.5. Conclusions on clinical pharmacology

Results from Study SB2-G11-NHV and supportive evidence from Study SB2-G31-RA demonstrated similarity between Flixabi (SB2) and Remicade.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose-response studies were submitted. As this application relates to a biosimilar product, there is no requirement for dose-response studies. The proposed dosing regimens for SB2 are identical to those approved for Remicade.

2.5.2. Main study

Study SB2-G31-RA

A randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of SB2 compared to Remicade in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy.

Methods

Study Participants

Main Inclusion Criteria

- Male or female aged 18-75 years old.
- Had been diagnosed as having RA according to the revised 1987 ACR criteria for at least 6 months prior to Screening.
- Had moderate to severe active disease despite MTX therapy defined as:
    - 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.
    - Either erythrocyte sedimentation rate (ESR; Westergren) ≥ 28 mm/h or serum C-reactive protein (CRP) ≥ 1.0 mg/dL at Screening.
- Had been treated with MTX for at least 6 months prior to randomisation and be on a stable dose of MTX 10-25 mg/week given orally or parenterally for at least 4 weeks prior to Screening.
- Female subjects who were not pregnant or nursing at Screening and who were not planning to become pregnant from Screening until 6 months after the last dose of investigational product (IP).

Main exclusion Criteria

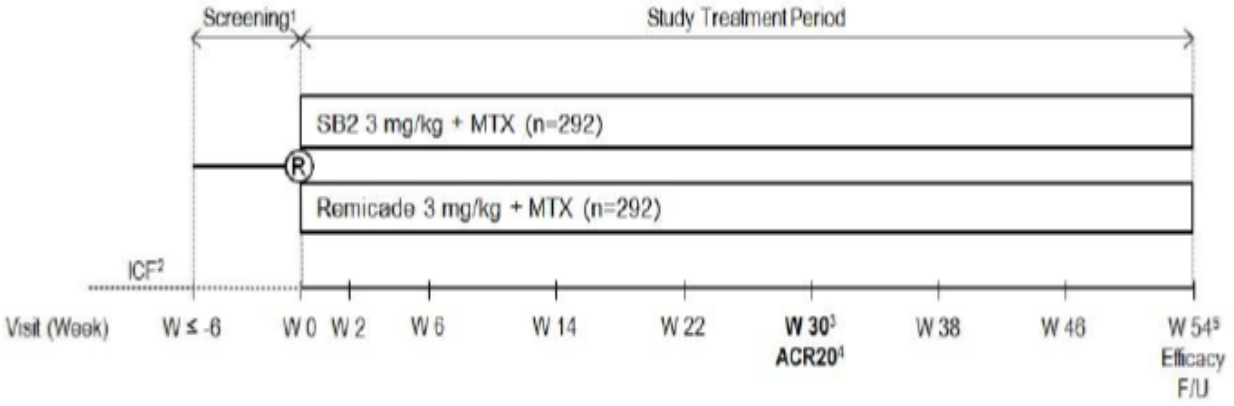
- Had been treated previously with any biological agents including any tumour necrosis factor inhibitor.
- Had a known hypersensitivity to human immunoglobulin proteins or other components of SB2 or Remicade.
- Had abnormal renal or hepatic function
- Had a positive serological test for hepatitis B virus (HBV) or hepatitis C virus (HCV) or had a known history of infection with human immunodeficiency virus.
- Had a current diagnosis of active tuberculosis (TB).
- Had had a serious infection or had been treated with i.v. antibiotics for an infection within 8 weeks or oral antibiotics within 2 weeks prior to Randomisation.
- Had a history of an infected joint prosthesis which had not been removed or replaced.
- Other inflammatory or rheumatic diseases.

Treatments

The study design is presented in **Figure 8**.

At Week 0, eligible subjects were randomised in a 1:1 ratio to receive either SB2 or EU Remicade. Each subject was administered infliximab via a 2 hour i.v. infusion, at Weeks 0, 2 and 6 and then every 8 weeks up to Week 46. The dose level of Investigational Product (IP) was maintained at 3 mg/kg up to Week 22.

Figure 8. Graphical design of Study SB2-G31-RA



From Week 30, the dose level could be increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by the existing dose.

In addition, each subject also took a stable dose of oral or parenteral MTX (10-25 mg weekly) and was required to take folic acid 5-10 mg weekly while taking MTX.

Transition-Extension Period Weeks 54 to 78

This period of the study was a randomised, double-blind, Transition-Extension period to investigate safety, tolerability, immunogenicity and efficacy of SB2 in subjects with RA who transitioned from the EU Remicade treatment group compared with subjects who maintained EU Remicade treatment (data currently not available).

Objectives

Primary objectives:

The primary objective of this study was to demonstrate the equivalence of SB2 to Remicade at Week 30, in terms of American College of Rheumatology 20% response criteria (ACR20) response rate in subjects with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) therapy.

Secondary objectives:

Secondary objectives related to the PK and immunogenicity of SB2 and EU Remicade were as follows:

- To evaluate the PK of SB2 compared to EU Remicade in subjects with moderate to severe RA despite methotrexate (MTX) therapy.
- To evaluate the immunogenicity of SB2 compared to EU Remicade in subjects with moderate to severe RA despite MTX therapy.

Outcomes / endpoints

The primary endpoint was the ACR20 response rate at Week 30.

Secondary efficacy endpoints included:

- The ACR20 response at Week 54
- The ACR 50% response criteria (ACR50) and ACR 70% response criteria (ACR70) response at Week 30 and Week 54
- The numeric index of the ACR response (ACR-N) at Week 30 and Week 54
- The disease activity score based on a 28 joint count (DAS28 score) at Week 30 and Week 54

The ACR20 response indicated:

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

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

• At least a 20% improvement from Baseline in at least 3 of the following 5 criteria:
  - Subject pain assessment using a 100 mm visual analogue scale (VAS)
  - Subject global assessment using a 100 mm VAS
  - Physician global assessment using a 100 mm VAS

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

The DAS28 score was calculated using the following equation (four-variable equation):
DAS28 = 0.56 × √(tender 28 joint count) + 0.28 × √(swollen 28 joint count) + 0.70 × ln(ESR) + 0.014 × general health.

Sample size

The ACR20 responses from selected studies with regards to the study population and treatment regimen were used for the equivalence margin and sample size calculation and are summarised in **Table 18**.

Table 15. ACR20 Responses in Pivotal Studies with Remicade

	3 mg/kg Remicade®[a]	Placebo	Absolute difference Remicade® – placebo (%)	Time measurement	DMARD
	ACR20 response events/total (%)	ACR20 response events/total (%)			
Westhovens (2006)	199/343 (58%)	87/341 (25.5%)	33%	22 weeks	MTX
Maini (1999)	44/86 (51%)	17/88 (19%)	32%	30 weeks	MTX
Abe (2006)	30/49 (61.2%)	11/47 (23.4%)	38%	14 weeks	MTX
Overall	273/478 (57%)	115/476 (24%)	33%		

[a] All references include ACR20 response from both Remicade® 3 mg/kg.

A random-effects meta-analysis of the selected studies estimated a risk difference of 0.3293 with a 90% CI [0.2801, 0.3785]. To preserve at least 50% of the effect of Remicade over and above placebo, an equivalence limit of 15% was used for the primary analysis.

Assuming a 20% dropout rate, a sample size of 292 per treatment group (overall sample size of 584) would allow 233 completed subjects in each group, and the observed two-sided 95.0% CI would be expected to lie within the equivalence margin with 82% power.

Randomisation

Subjects were randomised using an Interactive Web Response System (IWRS) or the Interactive Voice Response System (IVRS) to either SB2 or Remicade in a 1:1 ratio.

Blinding (masking)

This was a double-blind trial and subjects, investigators, joint assessors and other study personnel were to remain blinded throughout the entire treatment period.

Statistical methods

The following analysis data sets were defined:

- Full Analysis Set [FAS]: all randomised subjects;
- Per-protocol Set 1 [PPS1]: all FAS subjects who completed the week 30 visit and adhered (from baseline to week 30) within the range of 80–120% for both the expected number of IP administrations and the expected sum of MTX doses without any pre-defined major protocol deviations (PDs) that affected the efficacy assessment;
- Safety Set [SAF]: all subjects who received at least 1 dose of double-blind study treatment; subjects were analysed as treated;
- Pharmacokinetic Population [PK population]: all subjects in the SAF who had at least 1 post-dose PK sample collected
- Per-protocol Set 2[PPS2]: all FAS subjects who completed the Week 54 visit and had an adherence (from Baseline to Week 54) within the range of 80-120% for both the expected number of IP administrations and the expected sum of MTX doses without any major protocol deviations that affected the efficacy assessment.

The primary efficacy analysis was done on the PPS1 without any missing data imputation.

A non-parametric randomised based analysis of covariance approach [Koch, 1998] was used to estimate the 95% CIs of the treatment difference of ACR20 response rate, controlling for 'region' as a factor and baseline CRP value as a covariate.

The primary efficacy analysis was repeated for the FAS imputing week 30 ACR20 responses for subjects who discontinued before week 30 to explore the robustness of the results. The following missing data imputation methods were applied:

- Complete case analysis: exclusion of subjects with missing data at week 30.
- Non-responder analysis: subjects with missing ACR20 response at week 30 imputed as ACR20 non-responders
- Pattern mixture analysis using multiple imputations except for subjects who withdrew from the study with the primary reason of lack of efficacy or AE (who were considered as non-responder).

As a sensitivity analysis to the non-parametric method for the primary analysis, an analysis of covariance (ANCOVA) with treatment group and region as a factors and Baseline CRP value as covariate was performed for the PPS1.

The same approach as for the primary endpoint (ACR20) was used to analyse ACR50/ACR70 at week 30 using PPS1. For analyses with FAS, subjects with missing values were treated as non-responders.

An analysis of variance (ANOVA) model with treatment group and region as factors was applied to test the treatment difference of SB2 versus Remicade for continuous secondary efficacy variables (e.g. ACR-N at week 30, change from baseline in DAS28 at week 30, change from baseline in mTSS). The least square mean difference (LSMean), standard error (SE) and two-sided 95% CI for the treatment difference were reported for FAS. To assess equivalence in the change from Baseline of DAS28, the two-sided 95% CI of the difference in DAS28 score between SB2 and Remicade was compared to the equivalence margin of [−0.6, 0.6].

Results

Participant flow

Of the 584 patients randomised to treatment, up to Week 54, 124 (21.2%) subjects had withdrawn from the study: 60 subjects (20.6%) from the SB2 treatment group and 64 subjects (21.8%) from the Remicade treatment group. In both treatment groups, the most common reasons for withdrawal were withdrawal of consent for 49 subjects (8.4%) and AEs in 48 subjects (8.2%). Patient disposition is shown in **Table 19**.

Table 16. Disposition of subjects in Study SB2-G31-RA.

	SB2	Remicade®	Total
	n (%)	n (%)	n (%)
Screened			805
Screening failures			221
Reasons for screening failures			
Does not meet inclusion criteria			43 (19.5)
Does meet exclusion criteria			140 (63.3)
Withdrew consent			35 (15.8)
Other			15 (6.8)
Randomised	291	293	584
Completed Week 30 of treatment	246 (84.5)	259 (88.4)	505 (86.5)
Withdrew before Week 30	45 (15.5)	34 (11.6)	79 (13.5)
Reason for withdrawal			
Adverse event	21 (7.2)	10 (3.4)	31 (5.3)
Protocol deviation	1 (0.3)	3 (1.0)	4 (0.7)
Lack of efficacy	5 (1.7)	5 (1.7)	10 (1.7)
Subject lost to follow-up	0 (0.0)	1 (0.3)	1 (0.2)
Investigator Discretion	1 (0.3)	3 (1.0)	4 (0.7)
Withdrew consent	17 (5.8)	12 (4.1)	29 (5.0)
Completed Week 54 of treatment	227 (78.0)	225 (76.8)	452 (77.4)
Withdrew before Week 54	60 (20.6)	64 (21.8)	124 (21.2)
Reason for withdrawal			
Adverse event	27 (9.3)	21 (7.2)	48 (8.2)
Protocol deviation	1 (0.3)	5 (1.7)	6 (1.0)
Lack of efficacy	5 (1.7)	6 (2.0)	11 (1.9)
Subject lost to follow-up	0 (0.0)	1 (0.3)	1 (0.2)
Pregnancy	0 (0.0)	1 (0.3)	1 (0.2)
Investigator Discretion	4 (1.4)	4 (1.4)	8 (1.4)
Withdrew consent	23 (7.9)	26 (8.9)	49 (8.4)
Subjects from Eastern Ukraine sites without disposition information available*	4 (1.4)	4 (1.4)	8 (1.4)

Recruitment

The study was initiated in August 2013 and the week 54 cut-off date was in March 2015. The study is ongoing. A total of 73 study centres across 11 countries worldwide enrolled patients.

Conduct of the study

The protocol was amended 4 times mainly to better align the study with the SmPCs of Remicade and methotrexate.

A total of 41 (7.0%) subjects were excluded from PPS1 due to major protocol deviations (**Table 20**). The most common major protocol deviation that led to exclusion from PPS1 were concomitant medication criteria (10 [3.4%] subjects in the SB2 treatment group and 8 [2.7%) subjects in the Remicade treatment group) and eligibility and entry criteria (6 [2.1%] subjects and 9 [3.1%] subjects, respectively).

Table 17. Summary of major protocol deviations in Study SB2-G31-RA by treatment group (Randomised set)

	SB2		Remicade®		Total	
	N=291		N=293		N=584	
Subjects with protocol deviation	n (%)		n (%)		n (%)	
With at least 1 major protocol deviation	60	(20.6)	59	(20.1)	119	(20.4)
Subjects excluded from PPS1 as a result of major protocol deviation[a]	22	(7.6)	19	(6.5)	41	(7.0)
Concomitant medication criteria	10	(3.4)	8	(2.7)	18	(3.1)
Eligibility and entry criteria	6	(2.1)	9	(3.1)	15	(2.6)
IP compliance	1	(0.3)	1	(0.3)	2	(0.3)
Study procedure criteria	7	(2.4)	1	(0.3)	8	(1.4)
Other subjects with major protocol deviations	28	(9.6)	34	(11.6)	62	(10.6)
IP compliance	13	(4.5)	18	(6.1)	31	(5.3)
Study procedure criteria	12	(4.1)	17	(5.8)	29	(5.0)
Eligibility and entry criteria	4	(1.4)	3	(1.0)	7	(1.2)

[a] Subjects may have more than one protocol deviation, therefore the sum of the individual protocol deviation subgroups may be greater than the total number of patients excluded from PPS1

Baseline data

Baseline demographic, disease and rheumatoid disease activity characteristics are summarised in **Tables 21**, **22** and **23** respectively.

Table 18. Demographic Characteristics in Study SB2-G31-RA (Randomised set)

	SB2		Remicade®		Total	
	N=291		N=293		N=584	
Age (years)						
Mean (SD)	51.6	(11.92)	52.6	(11.74)	52.1	(11.83)
Age group n (%)						
< 65 years	251	(86.3)	248	(84.6)	499	(85.4)
≥ 65 years	40	(13.7)	45	(15.4)	85	(14.6)
Gender n (%)						
Male	59	(20.3)	57	(19.5)	116	(19.9)
Female	232	(79.7)	236	(80.5)	468	(80.1)
Race, n (%)						
White	252	(86.6)	254	(86.7)	506	(86.6)
American Indian or Alaskan Native	0	(0.0)	0	(0.0)	0	(0.0)
Asian	37	(12.7)	39	(13.3)	76	(13.0)
Black or African American	0	(0.0)	0	(0.0)	0	(0.0)
Native Hawaiian or other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)
Other	2	(0.7)	0	(0.0)	2	(0.3)
Ethnicity n (%)						
Hispanic or Latino	5	(1.7)	3	(1.0)	8	(1.4)
Chinese	0	(0.0)	0	(0.0)	0	(0.0)
Indian (Indian subcontinent)	1	(0.3)	1	(0.3)	2	(0.3)
Japanese	0	(0.0)	0	(0.0)	0	(0.0)
Mixed ethnicity	1	(0.3)	0	(0.0)	1	(0.2)
Other	284	(97.6)	289	(98.6)	573	(98.1)
Height (cm)						
Mean (SD)	164.58	(9.278)	164.79	(8.569)	164.69	(8.922)
Weight (kg)						
Mean (SD)	72.27	(15.812)	71.92	(16.513)	72.10	(16.155)
BMI (kg/m^2)						
Mean (SD)	26.62	(5.252)	26.49	(5.973)	26.56	(5.621)

Table 19. Baseline Disease Characteristics in Study SB2-G31-RA (Randomised set)

	SB2	Remicade®	Total
	N=291	N=293	N=584
Disease duration (years)			
Mean (SD)	6.31 (5.863)	6.56 (5.972)	6.44 (5.914)
Min, Max	0.5, 31.5	0.5, 32.4	0.5, 32.4
Duration of MTX use (months)			
Mean (SD)	53.05 (49.537)	48.44 (45.600)	50.74 (47.618)
Min, Max	6.1, 262.6	3.7, 220.3	3.7, 262.6
Weekly dose of MTX at Baseline (mg)			
Mean (SD)	14.71 (4.229)	14.68 (4.099)	14.69 (4.161)
Min, Max	10.0, 25.0	10.0, 25.0	10.0, 25.0

Table 20. Baseline Rheumatoid Disease Characteristics in Study SB2-G31-RA

	SB2	Remicade®	Total
	N=290	N=293	N=583
Swollen joint count (0-66)			
Mean (SD)	14.6 (7.84)	14.9 (7.69)	14.8 (7.76)
Min, Max	4, 48	3, 41	3, 48
Tender joint count (0-68)			
Mean (SD)	23.7 (12.30)	24.0 (12.22)	23.8 (12.25)
Min, Max	7, 66	6, 66	6, 66
Physician global assessment VAS (0-100 mm)			
Mean (SD)	61.7 (15.55)	61.8 (15.79)	61.8 (15.66)
Min, Max	19, 98	18, 100	18, 100
Subject global assessment VAS (0-100 mm)			
Mean (SD)	62.8 (17.50)	62.7 (18.66)	62.8 (18.08)
Min, Max	17, 100	7, 100	7, 100
Subject pain assessment VAS (0-100 mm)			
Mean (SD)	61.2 (18.58)	63.3 (19.97)[a]	62.3 (19.30)[b]
Min, Max	13, 100	15, 100	13, 100
HAQ-DI (0-3)			
Mean (SD)	1.4720 (0.61994)	1.5444 (0.58103)	1.5084 (0.60128)
Min, Max	0.000, 3.000	0.000, 2.875	0.000, 3.000
C-reactive protein (mg/L)			
Mean (SD)	12.4 (18.68)	13.7 (19.15)	13.0 (18.91)
Min, Max	1, 153	1, 125	1, 153
C-reactive protein n(%)[c]			
n	291	293	584
< 10 mg/L	185 (63.6)	182 (62.1)	367 (62.8)
≥ 10 mg/L	106 (36.4)	111 (37.9)	217 (37.2)
Erythrocyte sedimentation rate (mm/h)			
Mean (SD)	44.6 (19.19)	46.7 (22.33)	45.7 (20.84)
Min, Max	3, 120	10, 138	3, 138
Rheumatoid factor n(%)[c]			
n	291	293	584
Positive	215 (73.9)	208 (71.0)	423 (72.4)
Negative	76 (26.1)	84 (28.7)	160 (27.4)
Missing	0 (0.0)	1 (0.3)	1 (0.2)

[a] n = 292; [b] n = 582; [c] Randomised set

Prior and Concomitant Medication

A similar proportion of subjects in the SB2 and Remicade treatment groups (37.6% and 44.4% of subjects, respectively) had taken medications which started and stopped prior to the study (i.e., prior medication), and the majority of subjects received concomitant medications during the study (95.9% and 94.9% of subjects, respectively).

The most frequently reported prior medications by ATC class were glucocorticoids, which were used by 43 (14.8%) subjects in the SB2 treatment group and 53 (18.1%) subjects in the Remicade treatment group. Glucocorticoids were also taken as a concomitant medication by more than half of the subjects during the study (201(69.3%) subjects in the SB2 treatment group and 205 (70.0%) subjects in the Remicade treatment group).

Numbers analysed

Table 21. Data sets analysed in Study SB2-G31-RA

	SB2		Remicade®		Total	
	n (%)		n (%)		n (%)	
Randomised set	291		293		584	
Full analysis set	290	(99.7)	293	(100.0)	583	(99.8)
Safety set	290	(99.7)	293	(100.0)	583	(99.8)
Per-protocol set 1	231	(79.4)	247	(84.3)	478	(81.8)
Per-protocol set 2	202	(69.4)	208	(71.0)	410	(70.2)
Pharmacokinetic population	165	(56.7)	160	(54.6)	325	(55.7)

Percentages were based on the number of randomised subjects.

One Subject, from the SB2 group, was excluded from the FAS and SAF because the subject withdrew before the first infusion was administered (due to not meeting inclusion/exclusion criteria).

Outcomes and estimation

Primary endpoint

The primary analysis of ACR20 response with the number of subjects who achieved ACR20 response at Week 30 for the PPS1 is presented in **Table 25**.

Table 22. Primary Analysis of ACR20 Response Rate at Week 30 in Study SB2-G31-RA, PPS1

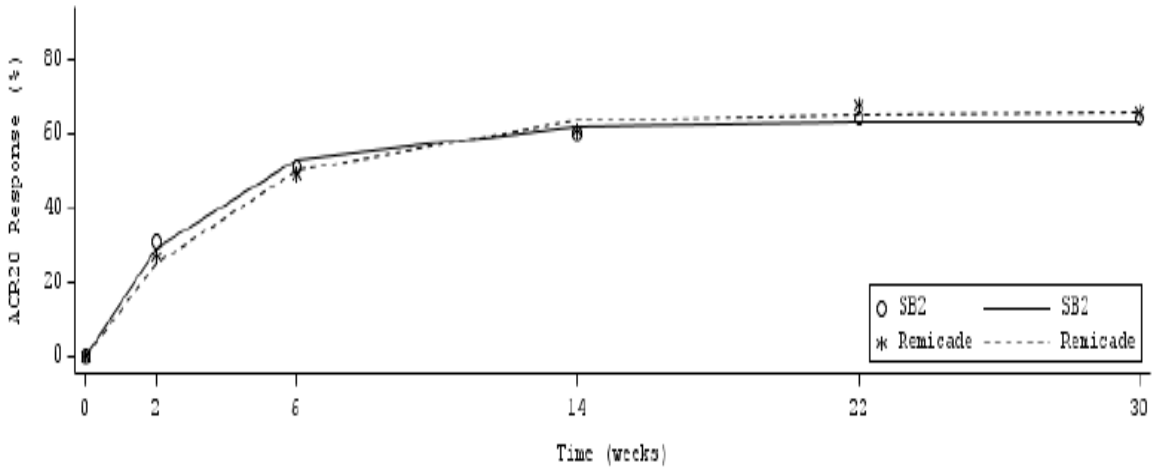
Treatment	n/n'	(%)	Adjusted Difference Rate	95% CI
SB2 (N=231)	148/231	(64.1)	−1.88%	(−10.26%, 6.51%)
EU Remicade® (N=247)	163/247	(66.0)		

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

Supportive Analysis of Primary Efficacy Analysis

The time-response curves of SB2 and Remicade up to Week 30 showing the ACR20 response over time were estimated to be equivalent and supported the robustness of the primary efficacy analysis. The time-response graphs for the ACR20 response for the PPS1 are presented in **Figure 9.**

Figure 9. The time-response graph for ACR20 response for the PPS1 in Study SB2-G31-RA, PPS1



Sensitivity Analysis of Primary Efficacy Variable

To explore the robustness of the ACR20 responses for the PPS1, the same analysis was performed for the FAS (**Table 26**).

Table 23. Analysis of ACR20 Response Rate at Week 30 in Study SB2-G31-RA; Non-responder Analysis (Full Analysis Set)

Treatment	n/n'	(%)	Adjusted Difference Rate	95% CI
SB2 (N=290)	161/290	(55.5)	−2.95%	(−10.88%, 4.97%)
Remicade® (N=293)	173/293	(59.0)		

CI = confidence interval; N = number of subjects in the full analysis set1; n' = number of subjects with available assessment results; n = number of responders
Subjects with missing ACR20 response at Week 30 were considered as ACR20 non-responders at Week 30.

The sensitivity analysis using ANCOVA (adjusting for baseline CRP and region) is shown in **Table 27**.

Table 24. Analysis of Covariance for ACR20 response at week 30 in Study SB2-G31-RA, PPS1

ACR response	Timepoint	Treatment	Responder n' n (%)	Adjusted Difference (SB2 - Remicade) Rate (SE)	95% CI
ACR20	Week 30	SB2 (N=231)	231 148 (64.1)	-1.87% (4.285%)	(-10.30%, 6.55%)
		Remicade (N=247)	247 163 (66.0)		

Secondary endpoints

ACR20 Response at Week 54

The analysis of ACR20 response rate at Week 54 for the FAS is presented in **Table 28.**

Table 25. Analysis of ACR 20 Response rate at week 54 in in Study SB2-G31-RA Non-responder analysis (FAS)

Treatment	n/n'	(%)	Adjusted Difference Rate	95% CI
SB2 (N=290)	147/290	(50.7)	–1.15%	(–9.16%, 6.86%)
Remicade® (N=293)	154/293	(52.6)		

CI = confidence interval; N = number of subjects in the full analysis set; n' = number of subjects with an assessment; n = number of responders.
Subjects with missing ACR20 response at Week 54 were considered as non-responders at Week 54.

ACR50 and ACR70 Response at Week 30 and Week 54

Table 26. Analysis of ACR50 and ACR70 Response Rates at Week 30 and Week 54 in Study SB2-G31-RA; Non-responder Analysis (FAS)

Timepoint	ACR response	Treatment	n/n'	(%)	Adjusted Difference Rate	95% CI
Week 30	ACR50	SB2 (N=290)	89/290	(30.7)	−2.53%	(−10.07%, 5.00%)
		Remicade® (N=293)	99/293	(33.8)		
	ACR70	SB2 (N=290)	45/290	(15.5)	−1.08%	(−7.06%, 4.91%)
		Remicade® (N=293)	50/293	(17.1)		
Week 54	ACR50	SB2 (N=290)	93/290	(32.1)	3.07	(−4.26%, 10.40%)
		Remicade® (N=293)	87/293	(29.7)		
	ACR70	SB2 (N=290)	53/290	(18.3)	1.10%	(−5.08, 7.28%)
		Remicade® (N=293)	52/293	(17.7)		

CI = confidence interval; N = number of subjects in the full analysis set; n' = number of subjects with an assessment; n = number of responders
Subjects with missing ACR50 or ACR70 response at Week 30 and/or Week 54 were treated considered as ACR50 or ACR70 non-responders at Week 30 and/or Week 54.

ACR-N at Week 30 and Week 54

The mean ACR-N at Week 30 was similar in both treatments with 36.63% in the SB2 treatment group and 37.81% in the Remicade treatment group. The mean ACR-N at Week 54 was 38.82% for the SB2 treatment group and 39.77% for the Remicade treatment group.

DAS28 Score at Week 30 and Week 54

The mean change in DAS28 score from Baseline to Week 30 was 2.3275 in the SB2 treatment group and 2.3309 in the Remicade treatment group. The mean change in DAS28 score from Baseline to Week 54 was 2.4219 in the SB2 treatment group and 2.4735 in the Remicade treatment group.

An ANCOVA (adjusted for Baseline DAS28 and region) for the change from Baseline in DAS28 score at Week 30 and Week 54 for the FAS is shown in **Table 30**.

Table 27. Analysis of Covariance for change in DAS28 Score at week 30 and week 54 in Study SB2-G31-RA, FAS

Timepoint	Treatment	n'	LSMean	Difference mean	95% CI
Week 30	SB2 (N=290)	253	2.411	0.044	(−0.186, 0.274)
	Remicade® (N=293)	265	2.367		
Week 54	SB2 (N=290)	227	2.469	−0.004	(−0.246, 0.239)
	Remicade® (N=293)	222	2.472		

CI = confidence interval; LSMean = Least-Squares Mean; N = number of subjects in the full analysis set; n' = number of subjects with an assessment

Ancillary analyses

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

ADAs

The ANCOVA (adjusted for Baseline CRP and region) for ACR20 response rates at Week 30 by 30-week overall ADA status for the PPS1 are presented in **Table 31.**

Table 28. Analysis of Covariance for ACR20 response rates at Week 30 by 30-week overall ADA status in Study SB2-G31-RA, PPS1

30-week ADA Result	Treatment	Responder n'	n	(%)	Adjusted Difference Rate (SE)	95% CI	P value
Positive	SB2 (N=127)	127	72	(56.7)	−0.88% (5.966%)	(−12.63%, 10.87%)	
	Remicade (N=126)	126	74	(58.7)			0.989
Negative	SB2 (N=104)	104	76	(73.1)	−1.57% (5.914%)	(−13.23%, 10.08%)	
	Remicade (N=121)	121	89	(73.6)			

ACR = American College of Rheumatology; ADA = anti-drug antibodies; ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects in the per-protocol set 1; n' = number of subjects with available assessment results; n = number of responders; SE = standard error
The p- value is for the interaction term.

The ACR20, ACR50 and ACR70 response rates by 30-week (PPS1) and 54-week (PPS2) overall ADA status in are summarised in **Tables 32** and **33** respectively**.**

Table 29. ACR20, ACR50 and ACR70 response rates at Week 30 by up to 30-week overall ADA status in Study SB2-G31-RA, PPS1

ACR Response	ADA Result	SB2		EU Remicade®	
		n'	n (%)	n'	n (%)
ACR20	**OVERALL[a]**	**231**	**148 (64.1%)**	**247**	**163 (66.0%)**
	NEGATIVE	104	76 (73.1%)	121	89 (73.6%)
	POSITIVE	127	72 (56.7%)	126	74 (58.7%)
ACR50	**OVERALL[a]**	**231**	**82 (35.5%)**	**247**	**94 (38.1%)**
	NEGATIVE	104	46 (44.2%)	121	54 (44.6%)
	POSITIVE	127	36 (28.3%)	126	40 (31.7%)
ACR70	**OVERALL[a]**	**231**	**42 (18.2%)**	**247**	**47 (19.0%)**
	NEGATIVE	104	27 (26.0%)	121	25 (20.7%)
	POSITIVE	127	15 (11.8%)	126	22 (17.5%)

n'= number of subjects with available assessment results

[a] subjects in PPS1 with ACR results at Week 30.

Table 30. ACR20, ACR50 and ACR70 response rates at Week 54 by up to 54-week overall ADA status in Study SB2-G31-RA, PPS2

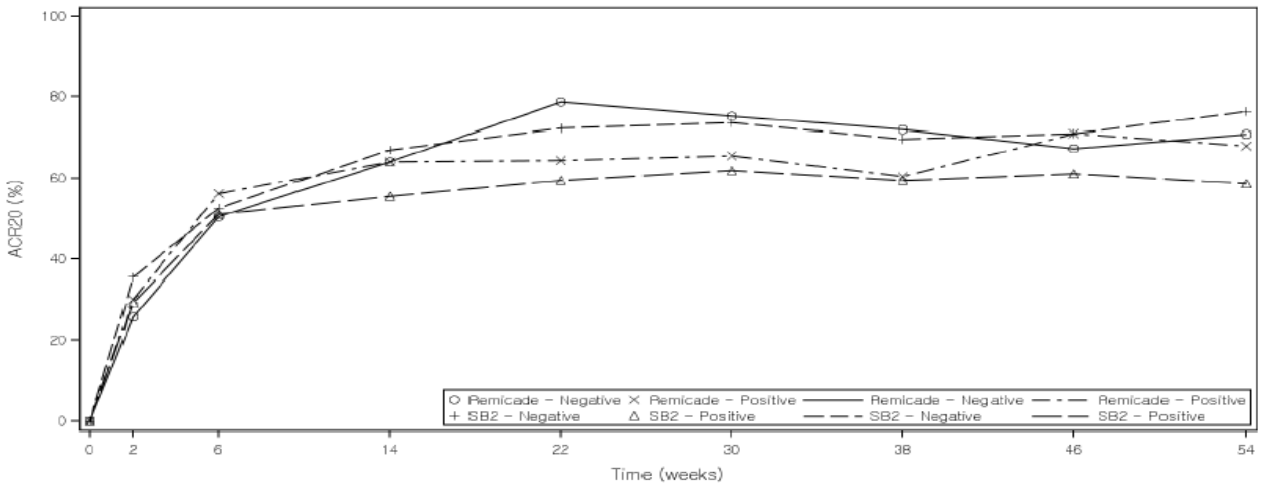
ACR Response	ADA Result	SB2		EU Remicade®	
		n'	n (%)	n'	n (%)
ACR20	**OVERALL[a]**	**202**	**132 (65.3%)**	**208**	**144 (69.2%)**
	NEGATIVE	76	58 (76.3%)	89	63 (70.8%)
	POSITIVE	126	74 (58.7%)	119	81 (68.1%)
ACR50	**OVERALL[a]**	**202**	**84 (41.6%)**	**208**	**81 (38.9%)**
	NEGATIVE	76	41 (53.9%)	89	40 (44.9%)
	POSITIVE	126	43 (34.1%)	119	41 (34.5%)
ACR70	**OVERALL[a]**	**202**	**45 (22.3%)**	**208**	**50 (24.0%)**
	NEGATIVE	76	23 (30.3%)	89	21 (23.6%)
	POSITIVE	126	22 (17.5%)	119	29 (24.4%)

n'= number of subjects with available assessment results

[a] subjects in PPS2 with ACR results at Week 54

The ACR20 response curves for the per-protocol set 2 (PPS2) up to Week 54 by ADA status are shown in **Figure 10.** Similar response curves were observed for ACR50 and 70 (data not shown).

Figure 10. ACR 20 response curves by ADA status at each time-point in Study SB2-G31-RA, PPS2



Dose increase

The number patients who had their dose increased during the study were numerically lower in the SB2 treatment group compared to the EU Remicade treatment group (57 vs. 67 at Week 30, 77 vs. 83 at Week 38, 81 vs. 84 at Week 46, SB2 vs. EU Remicade respectively).

An analysis of patients which increased their dose by up to Week 30 ADA status is presented in **Table 34**.

Table 31. Dose increase pattern by up to Week 30 ADA status in each visit (safety set) in Study SB2-G31-RA

			SB2		EU Remicade®	
Visit	**ADA Result**	**Dose**	**N**	**n (%)**	**N**	**n (%)**
Overall*	NEGATIVE	Increased	129	33 (25.6%)	147	42 (28.6%)
	POSITIVE	Increased	158	55 (34.8%)	145	56 (38.6%)
Week 30	NEGATIVE	3	109	90 (82.6%)	129	97 (75.2%)
		4.5	109	19 (17.4%)	129	32 (24.8%)
		Total Increased	109	19 (17.4%)	129	32 (24.8%)
	POSITIVE	3	136	98 (72.1%)	130	95 (73.1%)
		4.5	136	38 (27.9%)	130	35 (26.9%)
		Total Increased	136	38 (27.9%)	130	35 (26.9%)

			SB2		EU Remicade®	
Visit	ADA Result	Dose	N	n (%)	N	n (%)
Week 38	NEGATIVE	3	106	77 (72.6%)	125	89 (71.2%)
		4.5	106	26 (24.5%)	125	30 (24.0%)
		6	106	3 (2.8%)	125	6 (4.8%)
		Total Increased	106	29 (27.4%)	125	36 (28.8%)
	POSITIVE	3	132	84 (63.6%)	120	73 (60.8%)
		4.5	132	40 (30.3%)	120	41 (34.2%)
		6	132	8 (6.1%)	120	6 (5.0%)
		Total Increased	132	48 (36.4%)	120	47 (39.2%)
Week 46	NEGATIVE	3	104	72 (69.2%)	120	83 (69.2%)
		4.5	104	19 (18.3%)	120	28 (23.3%)
		6	104	13 (12.5%)	120	8 (6.7%)
		7.5	104	0 (0.0%)	120	1 (0.8%)
		Total Increased	104	32 (30.8%)	120	37 (30.8%)
	POSITIVE	3	124	75 (60.5%)	111	64 (57.7%)
		4.5	124	31 (25.0%)	111	34 (30.6%)
		6	124	18 (14.5%)	111	9 (8.1%)
		7.5	124	0 (0.0%)	111	4 (3.6%)
		Total Increased	124	49 (39.5%)	111	47 (42.3%)

Efficacy parameters were analysed by ever or never dose increase. The ACR20 response rates in PPS2 by visit are presented in **Table 35**.

Similar trends were observed for the ACR50 and ACR70 response rates in PPS2 (data not shown).

Table 32. ACR20 response rates by dose increment in PPS2 in Study SB2-G31-RA

ACR20 (PPS2)		SB2			EU Remicade®			Total		
Dose Increase	Visit	N	n	%	N	n	%	N	n	%
No	Week 30	152	115	75.7	160	128	80.0	312	243	77.9
	Week 38	134	105	78.4	137	106	77.4	271	211	77.9
	Week 46	127	99	78.0	127	99	78.0	254	198	78.0
	Week 54	127	93	73.2	129	103	79.8	256	196	76.6
Yes	Week 30	50	19	38.0	48	17	35.4	98	36	36.7
	Week 38	68	23	33.8	71	30	42.3	139	53	38.1
	Week 46	75	32	42.7	79	44	55.7	154	76	49.4
	Week 54	75	39	52.0	79	41	51.9	154	80	51.9

PPS2: per-protocol set 2; Based on Listing 16.2.6-1.3, Listing 16.2.3-1.1 and Listing 16.2.9-1.7 (54-week CSR).
Dose increased subjects were cumulatively included in each visit category (i.e. once the dose was increased in a certain visit time the subject was counted as dose increased from that time point to the end).
N: patients who had a dose information

Similar trends were observed for the ACR50 and ACR70 response rates in PPS2 (data not shown).

CRP levels

Of the 83 subjects whose baseline CRP level was ≥ 10 mg/L in the SB2 treatment group, 57 subjects (68.7%) achieved an ACR20 response at Week 30. Of the 90 subjects whose baseline CRP level was ≥ 10 mg/L in the Remicade treatment group, 62 subjects (68.9%) achieved an ACR20 response at Week 30. The adjusted treatment difference and its 95% CI in ACR20 response rate at Week 30 within subjects whose baseline CRP level was ≥ 10 mg/L was 1.09 (- 13.02%, 15.19%).

Of the 148 subjects in the SB2 treatment group whose baseline CRP level was < 10 mg/L, 91 subjects (61.5%) achieved an ACR20 response at Week 30. Of the 157 subjects in the Remicade treatment group whose baseline CRP level was < 10 mg/L, 101 subjects (64.3%) achieved an ACR20 response at Week 30. The adjusted treatment difference and its 95% CI in ACR20 response rate at Week 30 within subjects whose baseline CRP level was < 10 mg/L was -2.91% (- 13.65%, 7.82%).

Demographics

There was no statistically significant interaction in ACR20 response rate at Week 30 between treatment and region, age group or gender.

Summary of main study

The following table summarise the efficacy results from the main study 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 33. Summary of Efficacy for trial SB2-G31-RA

Title: A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB2 Compared to Remicade in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy			
Study identifier	SB2-G31-RA		
Design	Randomised, double-blind, active-controlled multicenter study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		54 weeks not applicable 24 weeks
Hypothesis	Equivalence; equivalence margin for the difference in ACR20 responder at week 30: [-15%, 15%]		
Treatments groups	SB2		SB2 iv 3mg/kg, weeks 0,2,6 and then q8w until week 46, randomized: n = 291
	Remicade		Remicade iv 3mg/kg, weeks 0,2,6 and then q8w until week 46, randomized: n = 293
Endpoints and definitions	Primary endpoint	ACR20	ACR20 response at week 30
	Secondary	ACR50	ACR50 response at week 30
	Secondary	ACR70	ACR70 response at week 30
	Secondary	DAS28	Change in DAS28 score at week 30
Database lock	Date not reported		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Per Protocol Set week 30			
Descriptive statistics and estimate variability	Treatment group	SB2	Remicade	
	Number of subject	231	247	
	ACR20 at week 30 (Response rate)	64.1%	66.0%	
	ACR50 at week 30 (Response rate)	35.5%	38.1%	
	ACR70 at week 30 (Response rate)	18.2%	19.0%	
Effect estimate per comparison	Primary endpoint ACR20 at week 30	Comparison groups	SB2 - Remicade	
		Difference in response	-1.88%	
		95%-CI	(-10.26%, 6.51%)	
		P-value	N/A	
	Secondary endpoint ACR50 at week 30	Comparison groups	SB2 - Remicade	
		Difference in response	-2.13%	
		95%-CI	(-10.69%, 6.43%)	
		P-value	N/A	
	Secondary endpoint ACR70 at week 30	Comparison groups	SB2 - Remicade	
		Difference in response	-0.25%	
		95%-CI	(-7.26%, 6.75%)	
		P-value	N/A	
Analysis description	**Secondary analysis**			
Analysis population and time point description	Full Analysis Set week 30			
Descriptive statistics and estimate variability	Treatment group	SB2	Remicade	
	Number of subject	290	293	
	ACR20 at week 30 (Response rate)	55.5%	59.0%	
	ACR50 at week 30 (Response rate)	30.7%	33.8%	
	ACR70 at week 30 (Response rate)	15.5%	17.1%	
Effect estimate per comparison	Primary endpoint ACR20* at week 30	Comparison groups	SB2 - Remicade	
		Difference in response	-2.95%	

		95%-CI	(-10.88%, 4.97%)
		P-value	N/A
	Secondary endpoint ACR50* at week 30	Comparison groups	SB2 - Remicade
		Difference in response	-2.53%
		95%-CI	(-10.07%, 5.00%)
		P-value	N/A
	Secondary endpoint ACR70* at week 30	Comparison groups	SB2 - Remicade
		Difference in response	-1.08%
		95%-CI	(-7.06%, 4.91%)
		P-value	N/A
	Secondary endpoint Change in DAS28 at week 30	Comparison groups	SB2 – Remicade
		Adjusted mean difference	0.044
		95%-CI	(-0.186, 0.274)
		P-value	N/A
Notes	*subjects with missing values imputed as non-responder		

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

Not applicable.

Supportive studies

No supportive efficacy trials were performed.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The main study SB2-G31-RA, was a randomised, double-blind, parallel-group, multicentre study in 584 patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Study SB2-G31-RA evaluated the equivalence of the biosimilar SB2 and the reference product EU-Remicade, in terms of ACR20 response after 30 weeks treatment. The randomised, double-blind study period was 54 weeks with an extension period up to 78 weeks, where patients on EU-Remicade were randomised to receive either SB2 or EU-Remicade. Data up to 54 weeks has been presented with this application. The study design and the choice of patient population were overall in compliance with scientific advice given and fulfil the criteria for the evaluation of the biosimilarity.

The primary endpoint, the ACR20 (American College of Rheumatology) response at week 30 is an appropriate endpoint for detecting potential differences between the investigational product and the reference product and is therefore considered acceptable. A number of appropriate secondary endpoints were evaluated, including: ACR20 at week 54, ACR50 and ACR70 at week 30 and 54, numeric index of the ACR response (ACR-N) at week 30 and 54. Overall the endpoints used were appropriate and acceptable in order to detect potential differences between SB2 and EU-Remicade. The equivalence margin was based on a meta-analysis of three studies in RA patients using the endpoint ACR20. An equivalence margin of 15% had been discussed as acceptable in a prior

scientific advice and can be justified statistically as it ensures superiority to historical placebo.

No substantial amendments were made to the study protocol after study start. 84.5% SB2 patients and 88.4% EU-Remicade patients completed 30 weeks treatment. Baseline characteristics including RA disease activity in SB2 and EU-Remicade patients were comparable.

Efficacy data and additional analyses

Primary efficacy results in the per protocol group indicate that the ACR20 response rate at Week 30 was equivalent in the SB2 and Remicade treatment groups. The proportion of subjects achieving ACR20 response at Week 30 was 64.1% (148/231) and 66.0% (163/247) in the SB2 and Remicade treatment groups, respectively. Furthermore, the ACR20 response rate at Week 30 in the full analysis set was 55.5% (161/290) for SB2 and 59.0 % (173/293) for Remicade with an adjusted difference rate of -2.95% and CI (-10.88%, 4.97%).

Sensitivity analyses involving several methods of imputation for the full analysis set and an analysis of variance (ANOVA) adjusting for baseline CRP and region, support the primary efficacy analysis.

The adjusted difference rate in ACR 50 and 70 response rate at Week 30 in the full analysis set were -2.53% and -1.08%, respectively.. AUC of ACR-N up to Week 30, and DAS28 Score at Week 30 also confirmed similarity. Of particular importance is the comparison of efficacy as measured by change in DAS28 score at Week 30, which may provide greater sensitivity as it is a continuous variable. The difference between SB2 and EU Remicade was 0.044 (−0.186, 0.274) and was also entirely contained within the pre-defined equivalence margin of [−0.6. 0.6].

The ACR20 response rate at Week 54 for the FAS was 50.7% (147/290) in the SB2 treatment group and52.6% (154/293) in the Remicade treatment group. The adjusted treatment difference and its 95% CI in ACR20 response rate at Week 54 in FAS was -1.15% (−9.16%, 6.86%), which therefore also showed that the ACR20 response rate of SB2 was similar to Remicade at Week 54.
Similar differences in the results between SB2 and EU Remicade patients were observed with the more stringent ACR50 and ACR70.

Efficacy by ADA status

When analysing efficacy parameters by ADA status, the efficacy endpoints results were still similar between the two treatment groups in both ADA sub-groups at Week 30 and Week 54 in PPS and FAS.

The ACR response rates at Week 30 by up to W30 ADA status were similar between the SB2 and the EU Remicade treatment groups. (ACR20 in PPS with positive ADA up to W30: 56.7% in SB2, 58.7% in EU Remicade) The same result was shown in patients with up to W30 ADA negative. Therefore, despite the numerically higher rate of ADA in the SB2 group these do not appear to have a clinically relevant effect.

Among the patients who had up to Week 54 ADA positive, the results of ACR20/50/70 response rates at Week 54 were similar between the SB2 and the EU Remicade treatment groups. The same result was shown in patients who had up to Week 54 ADA negative. When analysing the time-response graphs for the ACR20, ACR50 and ACR70 response by up to Week 54 ADA status, the results still showed similarity between the two treatment groups in both ADA subgroups. The CHMP noted that the interpretation of the results of the subgroup analysis by ADA status, can only be considered supportive of the primary analysis as it is inherently limited by the decreased power of the analysis due to the smaller number of subjects in each subgroup.

Dose increase and impact of ADA

Dose increased patients were comparable in the SB2 treatment group compared to the EU Remicade treatment group. Among ADA positive patients (up to W30 ADA), the proportion of ever dose increased patients was also comparable; 55/158 (34.8%) vs. 56/145 (38.6%) in the SB2 and the EU Remicade treatment groups.

For PPS2, the ACR20 response rates for those who had a dose increase were 38.0% vs. 35.4% at Week 30 and 52.0% vs. 51.9% at Week 54. From these findings, the baseline efficacy at Week 30 as well as the overall improvement of efficacy after dose increase was considered to be comparable between the two treatment groups.

The similar trend was observed for the ACR50 and ACR70 response rates in PPS2.

2.5.4. Conclusions on the clinical efficacy

The main efficacy study SB2-G31-RA conducted in RA patients provided robust evidence of equivalence between Flixabi and Remicade based on ACR20 response at Week 30, the primary endpoint, and this was supported by secondary efficacy parameters and sensitivity analyses.

The numerically higher rate of ADA that was observed in subjects treated with SB2 compared to EU-Remicade did not result in any meaningful differences in efficacy. Significantly, the number of subjects which required a dose increase was similar between the two treatment arms, and was not impacted by ADA status which provides further evidence of similarity in terms of efficacy.

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

Therefore these results demonstrate equivalence in efficacy between the proposed biosimilar Flixabi and the reference product Remicade.

2.6. Clinical safety

The safety data base consisted of two studies, the phase III study in patients with RA and the phase I PK study in healthy volunteers. The safety results from the phase I PK study have been described in Section 2.4.2 of this report, and are considered supportive in characterising the short term safety profile of SB2.

Patient exposure

SB2-G31-RA

A total of 584 patients were randomised in a 1:1 ratio to receive either SB2 or EU Remicade both at 3 mg/kg via IV infusion at weeks 0, 2, 6 and then every 8 weeks until week 46. From week 30 the dose could be increased by 1.5 mg/kg up to a maximum 7.5 mg/kg. Of the 584 randomised patients, 583 received at least 1 injection of SB2 (n=290) or EU Remicade (n=293); the mean duration of exposure was 282.2 days in the SB2 and 287.8 days in the EU Remicade treatment groups respectively (**Table 37**).

Table 34. Duration of exposure to study drug (Safety Set), in Study SB2-G31-RA

Duration of exposure (days)	SB2 N=290		Remicade® N=293		Total N=583	
Statistics						
N	290		293		583	
Mean (SD)	282.2 (91.02)		287.8 (81.68)		285.0 (86.42)	
Min, Max	1, 365		1, 340		1, 365	
Exposure, n (%)						
≥ 1 day	290	(100.0)	293	(100.0)	583	(100.0)
≥ 15 days	283	(97.6)	290	(99.0)	573	(98.3)
≥ 43 days	275	(94.8)	282	(96.2)	557	(95.5)
≥ 99 days	268	(92.4)	275	(93.9)	543	(93.1)
≥ 155 days	255	(87.9)	267	(91.1)	522	(89.5)
≥ 211 days	243	(83.8)	256	(87.4)	499	(85.6)
≥ 267 days	238	(82.1)	242	(82.6)	480	(82.3)
≥ 323 days	180	(62.1)	181	(61.8)	361	(61.9)
≥ 379 days	0	(0.0)	0	(0.0)	0	(0.0)

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

Adverse events

A total of 370 (63.5%) subjects reported 1177 Treatment-emergent adverse events (TEAEs): 179 (61.7%) subjects reported 565 TEAEs in the SB2 treatment group and 191 (65.2%) subjects reported 612 TEAEs in the Remicade treatment group. The most frequently reported of these are summarised in **Table 38**.

Table 35. Number (%) of Patients with TEAEs and Number of Events by Preferred Term That Occurred in ≥ 2% of Patients in any Treatment Group (Safety Set) (Study SB2-G31-RA)

Treatment	SB2 N=290			Remicade® N=293			Total N=583		
Preferred term	**n**	**(%)**	**E**	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Any TEAEs	179	(61.7)	565	191	(65.2)	612	370	(63.5)	1177
Latent tuberculosis	19	(6.6)	19	21	(7.2)	21	40	(6.9)	40
Nasopharyngitis	18	(6.2)	23	20	(6.8)	27	38	(6.5)	50
Alanine aminotransferase increased	23	(7.9)	27	9	(3.1)	10	32	(5.5)	37
Rheumatoid arthritis	20	(6.9)	21	11	(3.8)	13	31	(5.3)	34
Headache	16	(5.5)	29	13	(4.4)	14	29	(5.0)	43
Upper respiratory tract infection	12	(4.1)	14	11	(3.8)	21	23	(3.9)	35
Aspartate aminotransferase increased	12	(4.1)	14	10	(3.4)	10	22	(3.8)	24
Bronchitis	9	(3.1)	10	13	(4.4)	15	22	(3.8)	25
Back pain	7	(2.4)	7	11	(3.8)	12	18	(3.1)	19
Arthralgia	8	(2.8)	9	8	(2.7)	10	16	(2.7)	19
Pneumonia	7	(2.4)	7	8	(2.7)	8	15	(2.6)	15
Urinary tract infection	8	(2.8)	8	6	(2.0)	6	14	(2.4)	14
Hypertension	5	(1.7)	5	9	(3.1)	9	14	(2.4)	14
Cough	6	(2.1)	7	7	(2.4)	7	13	(2.2)	14
Rash	6	(2.1)	7	6	(2.0)	7	12	(2.1)	14
Pharyngitis	5	(1.7)	6	7	(2.4)	10	12	(2.1)	16
Pyrexia	3	(1.0)	3	8	(2.7)	10	11	(1.9)	13
Abdominal pain upper	4	(1.4)	6	6	(2.0)	6	10	(1.7)	12
Dizziness	2	(0.7)	3	6	(2.0)	10	8	(1.4)	13
Dyspepsia	1	(0.3)	3	7	(2.4)	7	8	(1.4)	10

TEAE = treatment-emergent adverse event; E = frequency of treatment-emergent adverse events
Adverse events were coded by SOC and PT using the MedDRA Version 16.0 coding dictionary.
Percentages were based on the number of subjects in the safety set.

In terms of severity, the majority of the TEAEs were mild or moderate in severity, with only 8.6% of subjects in the SB2 treatment group and 6.8% of subjects in the Remicade treatment group to be reported as severe. The majority of TEAEs were considered to be unrelated to the IP. A total of 121 TEAEs were reported to be related to the IP in 70 (24.1%) subjects in the SB2 treatment group, and 129 TEAEs were related to the IP in 69 (23.5%) subjects in the Remicade treatment group (**Table 39**).

Table 36. Summary of Treatment-Emergent Adverse Events by Severity and causality (Safety Set) (Study SB2-G31-RA)

Treatment	SB2 N=290			Remicade® N=293			Total N=583		
Number of subject experiencing	n	(%)	E	n	(%)	E	n	(%)	E
TEAEs	179	(61.7)	565	191	(65.2)	612	370	(63.5)	1177
TEAE severity									
Mild	76	(26.2)	376	92	(31.4)	394	168	(28.8)	770
Moderate	78	(26.9)	153	79	(27.0)	189	157	(26.9)	342
Severe	25	(8.6)	36	20	(6.8)	29	45	(7.7)	65
TEAE causality									
Related	70	(24.1)	121	69	(23.5)	129	139	(23.8)	250
Not related	109	(37.6)	442	122	(41.6)	483	231	(39.6)	925
Unknown	0	(0.0)	2	0	(0.0)	0	0	(0.0)	2

At the PT level, the most frequently reported TEAE related to the IP were ALT increased (13 [4.5%] subjects in the SB2 treatment group and 2 [0.7%] subjects in the Remicade treatment group), AST increased (9 [3.1%] and 2 [0.7%] subjects, respectively) and latent TB (4 [1.4%] subjects and 7 [2.4%] subjects, respectively).

Adverse Events Leading to Discontinuation

A total of 62 TEAEs leading to IP discontinuation were reported in 54 (9.3%) subjects: 36 events were reported in 30 (10.3%) subjects in the SB2 treatment group and 26 events were reported in 24 (8.2%) subjects in the Remicade treatment group. The most common AEs leading to discontinuation in the respective groups were latent TB (0.7% vs 1.4%), pneumonia (1% vs 0.3%), rheumatoid arthritis (1.4% vs 0%) and hypersensitivity (1% vs 0%).

Serious adverse event / deaths / other significant events

Deaths

During the study, 1 death was reported in the Remicade treatment group. The patient died on Day 68 following a TEAE of worsening of her left ventricular heart failure. The event occurred following a preceding serious adverse event of pneumonia and was not considered to be related to the IP.

Serious adverse events

The proportion of subjects who experienced any SAEs was comparable between the 2 treatment groups. A total of 68 SAEs were reported in 60 (10.3%) of the subjects: 29 (10.0%) subjects reported 33 SAEs in the SB2 treatment group and 31 (10.6%) subjects reported 35 SAEs in the Remicade treatment group. Of these events, 10 events in the SB2 were considered related to the treatment:

• Two cases of hypersensitivity

• Three cases of pneumonia

• One case each for: anaphylactic reaction, tuberculous pleurisy, brain neoplasm, pseudo-membranous colitis and Clostridium difficile colitis while 7 treatment related were reported in the Remicade Group:

• One case each for: urticaria, major depression and psychotic disorder, fistula on foot, anaphylactic shock, pericarditis, pneumonia and ovarian cyst torsion.

Other significant events

Malignancies were reported for 2 subjects in the SB2 treatment group (1 with breast cancer, 1 with prostate cancer). No malignant neoplasms were reported in the EU Remicade treatment group.

A total of 31 cases of RA aggravation were observed up to week 54, 20 cases in patients treated with SB2 compared to 11 cases of patients treated with EU Remicade. There was a numerically higher incidence of moderate events in the EU Remicade treatment group and a higher incidence of mild and severe events in the SB2 treatment group. The incidence of serious adverse event RA aggravations was 3 subjects in the SB2 treatment group and 3 subjects in the EU Remicade treatment group.

Adverse events of special interest (AESI)

There were 16 TEAEs of special interest (serious infections and tuberculosis) reported in 16 (2.7%) subjects overall: 9 events in 9 (3.1%) subjects in the SB2 treatment group and 7 events in 7 (2.4%) subjects in the Remicade treatment group (**Table 40**).

Table 37. TEAEs of Special Interest by System Organ Class and Preferred Term (safety set) (SB2-G31-RA)

System organ class / Preferred term	SB2 N=290 n	(%)	E	Remicade N=293 n	(%)	E	Total N=583 n	(%)	E
Any AESI	9	(3.1)	9	7	(2.4)	7	16	(2.7)	16
INFECTIONS AND INFESTATIONS	9	(3.1)	9	7	(2.4)	7	16	(2.7)	16
PNEUMONIA	3	(1.0)	3	2	(0.7)	2	5	(0.9)	5
CLOSTRIDIUM DIFFICILE COLITIS	1	(0.3)	1	0	(0.0)	0	1	(0.2)	1
PNEUMONIA BACTERIAL	1	(0.3)	1	0	(0.0)	0	1	(0.2)	1
PYELONEPHRITIS	1	(0.3)	1	0	(0.0)	0	1	(0.2)	1
SOFT TISSUE INFECTION	1	(0.3)	1	0	(0.0)	0	1	(0.2)	1
TUBERCULOUS PLEURISY	1	(0.3)	1	0	(0.0)	0	1	(0.2)	1
URINARY TRACT INFECTION	1	(0.3)	1	0	(0.0)	0	1	(0.2)	1
CELLULITIS	0	(0.0)	0	1	(0.3)	1	1	(0.2)	1
DIABETIC FOOT INFECTION	0	(0.0)	0	1	(0.3)	1	1	(0.2)	1
ERYSIPELAS	0	(0.0)	0	1	(0.3)	1	1	(0.2)	1
PULMONARY TUBERCULOSIS	0	(0.0)	0	1	(0.3)	1	1	(0.2)	1
WOUND INFECTION	0	(0.0)	0	1	(0.3)	1	1	(0.2)	1

- TEAE: treatment-emergent adverse event; E: frequency of TEAEs
- Special Interest: serious infection, tuberculosis.
- Adverse events were coded to system organ class and preferred term using the MedDRA Version 16.0 coding dictionary.
- Percentages were based on the number of subjects in the Safety set.

Impact of Anti-Drug Antibodies on clinical safety

To analyse the impact of ADA on the safety profile of SB2 the Applicant provided an analysis by ADA status. The incidence by ADA status is presented in **Table 41**.

Table 38. Incidence of TEAEs by ADA status up to week 54 in Study SB2-G31-RA

Treatment	SB2			EU Remicade®		
	N	n (%)	E	N	n (%)	E
Any TEAEs						
ADA-positive	179	112 (62.6)	329	168	101 (60.1)	323
ADA-negative	108	65 (60.2)	233	124	90 (72.6)	289

N: number of subjects; E: number of events

Further analysis of the incidence of TEAE categorised by SOC groups by up to Week 54 ADA status confirmed comparable incidence of TEAE between the two treatment groups (data not shown).

The incidence of serious TEAE up to Week 54 by up to W54 ADA status was comparable between the SB2 and the EU Remicade treatment groups, as shown in **Table 42.**

Table 39. Serious TEAEs in by ADA status up to week 54 in Study SB2-G31-RA

	SB2			EU Remicade		
54-Week ADA result	N	%	E	N	%	E
Positive Any SAE	15	8.4	17	16	9.5	18
Negative Any SAE	12	11.1	14	15	12.1	17

N: number of subjects; E: number of events

RA aggravation and hypersensitivity and/or infusion related reactions by ADA status were also analysed (**Tables 43 and 44**).

Table 40. RA aggravation by treatment group and ADA status up to week 54 in Study SB2-G31-RA

Treatment group	ADA Positive	ADA Negative
SB2	12/179 (6.7%)	8/108 (7.4%)
EU Remicade®	5/168 (3.0%)	6/124 (4.8%)

Table 41. Hypersensitivity and/or infusion related reactions by treatment group and ADA status up to week 54 in Study SB2-G31-RA

54-week ADA Status	SB2 n/N (%)	EU Remicade® n/N (%)
Negative	2/108 (1.9%)	4/124 (3.2%)
Positive	17/179 (9.5%)	15/168 (8.9%)

N: number of subjects

Laboratory findings

The only marked difference between SB2 and Remicade treated patients, were the reports of increased alanine transaminase (27 events from 23 patients and 10 events from 9 patients for SB2 and the EU Remicade treatment groups, respectively). A small increase was also noted for reports of aspartate transaminase (AST) increased (14 events from 12 patients and 10 events from 10 patients were reported from SB2 and EU Remicade treatment groups, respectively). Two patients from each treatment group showed a prolonged ALT elevation, and one patient in the EU Remicade treatment group showed a prolonged AST elevation.

In order to review any effects on liver function relative to hepatobiliary dysfunctions, the adverse events in hepatobiliary system organ class were compared between the SB2 and the EU Remicade treatment groups. No numerical imbalance was observed as six AEs from five patients were reported in each treatment group.

Safety results in study SB2-G11-NHV

A total of 124 TEAEs was reported in 71 (44.7%) subjects. 50 TEAEs were reported from 27 (50.9%) subjects following SB2 administration, 36 TEAEs were reported from 21 (39.6%) subjects after EU sourced Remicade administration, and 38 TEAEs were reported from 23 (43.4%) subjects after US sourced Remicade administration. All reported TEAEs were of mild or moderate severity, with the majority of reported TEAEs being of mild severity.

The most frequent TEAEs across the 3 treatment groups were nasopharyngitis and headache. There were no marked differences between SB2 and reference IPs.
There were no deaths or discontinuation due to AEs during the study.

The overall incidence of IP-related TEAEs in was 47.2% (25/53) and 26.4% (14/53) in subjects treated with SB2 and EU Remicade, respectively. The number of IP-related TEAEs reported by more than one subject in either the SB2 or the EU Remicade treatment group is presented in **Table 45**.

Table 42. IP-related TEAEs experienced by more than 1 subject in study SB2-G11-NHV

Preferred Term	Treatment			
	SB2 (N=53)		EU Remicade® (N=53)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Nasopharyngitis	6 (11.3)	6	4 (7.5)	4
Headache	3 (5.7)	6	5 (9.4)	7
Rhinitis	3 (5.7)	3	2 (3.8)	2
Diarrhoea	2 (3.8)	2	1 (1.9)	1
Fatigue	2 (3.8)	2	0 (0.0)	0
Arthralgia	2 (3.8)	3	0 (0.0)	0

Safety in special populations

No studies in special populations were submitted.

Safety related to drug-drug interactions and other interactions

In accordance with the EMA biosimilar guideline (EMEA/CHMP/BMWP/42832/2005), no further specific studies on the potential impact of drug interactions were submitted with SB2.

Post marketing experience

No post-marketing data were submitted.

2.6.1. Discussion on clinical safety

Most available comparative safety data of Flixabi (SB2) are derived from the trial in RA (SB2-G31-RA) involving 290 patients exposed to Flixabi, out of whom 246 (84.5%) completed 30 weeks (time of primary endpoint). A comparable number of patients were exposed to EU Remicade.

Additionally 53 patients received one dose of Flixabi in a PK trial in healthy volunteers (SB2-G11-NHV) which can however contribute in the evaluation of short term safety. A higher number of IP-related TEAEs was observed in subjects treated with SB2 compared to EU Remicade. However, this imbalance could not be attributed to a specific safety concern and was due to single case reports of some events. There was no severe case of TEAE occurrence and the majority of the IP-related TEAEs were transient and self-limiting. Overall, results from this study demonstrated that the safety profile of a single dose of infliximab in healthy subjects was comparable between SB2 and EU sourced Remicade.

In the trial in the RA patients, the type and incidence of ADRs to the test and reference products appeared overall similar and in line with those expected on the basis of the Remicade SmPC.

Furthermore, the incidences of TEAEs and SAEs were comparable between SB2 and EU Remicade.

Most of the TEAEs reported were mild to moderate in intensity and the number of TEAEs that was considered to be related to IP was comparable between the SB2 and the EU Remicade treatment group.

There was a slight increased trend in the less mild (26.2% vs 31.4%) and more severe (8.6% vs 6.8%) TEAEs in the SB2 group compared to EU Remicade. However, the TEAEs that led to IP discontinuation, were balanced between the SB2 and EU Remicade Groups (30 (10.3%) vs 24 (8.2%), respectively).

When analysing the reasons for discontinuation no clear pattern or differences between the two groups could be detected. Importantly, the cases of infections, one of the most frequently reported serious risks associated with infliximab use, were evenly distributed between the two treatment groups.

With lab values, the only marked difference remaining was an increase in alanine amino transferase and to a lesser extent aspartate aminotransferase in the SB2 arm (7.9% and 3.1%) compared to the Remicade arm 4.1% and 3.4%). However, most of the liver enzyme elevations were transient, and there was no difference in prolonged enzyme elevation between the SB2 and the EU Remicade treatment groups.

Serious infections occurred in 12 (4.1%) subjects in the SB2 treatment group and 7 (2.4%) subjects in the Remicade treatment group. However the difference was considered most likely to be a chance finding given the

small overall number of cases. This was further supported by the fact that a similar number of patients developed latent tuberculosis (SB2 19 patients (6.6%) and Remicade 21 patients (7.2%) during follow up which would suggest that the level of risk between the two treatments is similar.

Malignancies were reported for 2 subjects in the SB2 treatment group (1 with breast cancer, 1 with prostate cancer). No cases of malignant neoplasms were reported in the EU Remicade treatment group. The small number of reported cases did not suggest a difference with regards to the risk of malignancy between the two treatments.

There was one death reported from the EU Remicade treatment group, which was considered not related to the IP.

A slightly (numerically) higher number of patients in the SB2 arm developed ADAs compared to those treated with EU Remicade. A sub-group analysis in ADA positive patients was performed to evaluate the impact of the observed increased immunogenicity. The incidence of TEAE was slightly lower in the SB2 treatment group than the EU Remicade treatment group (60.2% vs. 72.6%, respectively) in ADA-negative subgroup, while the incidence of TEAE was comparable (62.6% vs. 60.1%, respectively) in ADA-positive subgroup.

The incidence of serious TEAE up to Week 54 ADA status was also comparable between the SB2 and the EU Remicade treatment groups.

Hypersensitivity and infusion related reactions which are considered to be influenced by immunogenicity were specifically analysed by ADA status. ADA-positive subgroup had a higher incidence of hypersensitivity and/or infusion related reactions compared with the ADA-negative subgroup, which is consistent with the information in the Summary of Product Characteristics of Remicade. The incidence within each ADA subgroup was considered to be comparable between the two treatment groups.

The incidence of RA aggravation was more prevalent in ADA negative subgroup than ADA positive subgroup in both treatment groups (7.4 vs. 6.7%) in SB2 group; 4.8 vs. 3.0% in EU Remicade group. The incidence of RA as an TEAE was slightly higher in the SB2 treatment group than the EU Remicade treatment group in both ADA-negative and ADA-positive subgroups. This could be explained by the overall higher incidence of RA as a TEAE in the SB2 treatment group. No difference was observed between the two treatment groups in distribution of severity of RA aggravation and ADA status.

2.6.2. Conclusions on the clinical safety

The size of the safety database and duration of exposure is considered appropriate for the evaluation of the general safety profile of SB2. The safety profile was consistent with previous studies in these types of study populations of RA patients and healthy volunteers and this class of drugs.

The incidence, severity and nature of reported TEAEs did not suggest any major safety concerns. The TEAEs were generally comparable between SB2 and Remicade treatment groups; the higher incidence of anti-drug antibodies in the SB2 treated patients compared to those treated with EU Remicade and its potential impact on the safety profile of SB2 was extensively analysed but did not reveal any differences compared to Remicade.

In conclusion, the CHMP concluded that the safety profile for SB2 is acceptable and not different to that of Remicade.

2.7. Risk Management Plan

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

The PRAC considered that the risk management plan version 2.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP requested the addition of immunogenicity as a potential risk in the risk management plan and a category 3 study to address this concern in AS and CD patients. As a consequence, the CHMP endorsed the Risk Management Plan version 3.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	HBV reactivation CHF Opportunistic infections Serious infections including sepsis (excluding opportunistic infections and TB) TB Serum sickness (delayed hypersensitivity reactions) Haematologic reactions SLE/lupus like syndrome Demyelinating disorders Lymphoma (excluding HSTCL) Hepatobiliary events HSTCL Intestinal or perianal abscess (in CD) Serious infusion reactions during a re-induction regimen following disease flare Sarcoidosis/sarcoid-like reactions Paediatric malignancy Leukaemia Acute hypersensitivity reaction (including anaphylactic shock) Melanoma Merkel cell carcinoma BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi Cervical cancer
Important potential risks	Malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma, cervical cancer) Colon carcinoma/dysplasia (in UC) Skin cancer (excluding melanoma and Merkel cell carcinoma) Exposure during pregnancy Infusion reaction associated with shortened infusion duration Immunogenicity
Missing information	Long-term safety in adult patients with UC, PsA, or psoriasis Long-term safety in children with CD and UC

	Long-term safety in children Safety in very young children (< 6 years) Use of infliximab during lactation

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)
SB2-G31-RA	A randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, PK and immunogenicity of Flixabi compared to Remicade® in subjects with moderate to severe RA despite MTX therapy	HBV reactivation, congestive heart failure, opportunistic infections, serious infections including sepsis (excluding opportunistic infections and TB), TB, serum sickness (delayed hypersensitivity reactions), haematologic reactions, SLE /lupus like syndrome, demyelinating disorders, lymphoma (excluding HSTCL), hepatobiliary events, HSTCL, sarcoidosis/sarcoid-like reactions, leukaemia, acute hypersensitivity reaction (including anaphylactic shock), melanoma, Merkel cell carcinoma, malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma), skin cancer (excluding melanoma and Merkel cell carcinoma), exposure during pregnancy	Started	Week 30 CSR: Feb 2015 (completed) Week 54 CSR: Jul 2015 (completed) Week 78 CSR: 2016 3Q (planned)
BSRBR-RA Category 3	An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed	HBV reactivation, congestive heart failure, opportunistic infections, serious infections including sepsis (excluding opportunistic infections and TB), TB, serum	Planned for 2017 1Q	Final report planned for 2027 Annual interim reports will be submitted during

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)
	as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice.	sickness (delayed hypersensitivity reactions), haematologic reactions, SLE /lupus like syndrome, demyelinating disorders, lymphoma (excluding HSTCL), hepatobiliary events, HSTCL, serious infusion reactions during a re-induction regimen following disease flare, sarcoidosis/sarcoid-like reactions, leukaemia, acute hypersensitivity reaction (including anaphylactic shock), melanoma, Merkel cell carcinoma, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, cervical cancer, malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma, cervical cancer), skin cancer (excluding melanoma and Merkel cell carcinoma), exposure during pregnancy, infusion reaction associated with shortened infusion duration, immunogenicity, use of infliximab during lactation		the study period and until submission of the final report.
ARTIS Category 3	A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, JIA, and other	HBV reactivation, congestive heart failure, opportunistic infections, serious infections including sepsis (excluding opportunistic infections and TB), TB, serum sickness (delayed	Planned for 2017 1Q	Final report planned for 2027 Annual interim reports will be submitted during

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)
	rheumatic disease patients treated with infliximab.	hypersensitivity reactions), haematologic reactions, SLE /lupus like syndrome, demyelinating disorders, lymphoma (excluding HSTCL), hepatobiliary events, HSTCL, serious infusion reactions during a re-induction regimen following disease flare, sarcoidosis/sarcoid-like reactions, leukaemia, acute hypersensitivity reaction (including anaphylactic shock), melanoma, Merkel cell carcinoma, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, cervical cancer, malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma, cervical cancer), skin cancer (excluding melanoma and Merkel cell carcinoma), exposure during pregnancy, infusion reaction associated with shortened infusion duration, immunogenicity, long-term safety in adult patients with UC, PsA, or psoriasis, use of infliximab during lactation		the study period and until submission of the final report.
UK IBD Category 3	1. Facilitate continuous improvement in IBD patient care and access to care across the UK	HBV reactivation, congestive heart failure, opportunistic infections, serious infections including sepsis (excluding opportunistic infections	Planned for 2017 1Q	Final report planned for 2027 Annual interim

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	2. Improve understanding of long term outcomes for IBD patients from care 3. Support IBD research	and TB), TB, serum sickness (delayed hypersensitivity reactions), haematologic reactions, SLE /lupus like syndrome, demyelinating disorders, lymphoma (excluding HSTCL), hepatobiliary events, HSTCL, intestinal or perianal abscess (in CD), serious infusion reactions during a re-induction regimen following disease flare, sarcoidosis/sarcoid-like reactions, paediatric malignancy, leukaemia, acute hypersensitivity reaction (including anaphylactic shock), melanoma, Merkel cell carcinoma, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, cervical cancer, malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma, cervical cancer), colon carcinoma/dysplasia (in UC), skin cancer(excluding melanoma and Merkel cell carcinoma) , exposure during pregnancy, infusion reaction associated with shortened infusion duration, immunogenicity, long-term safety in adult patients with UC, PsA, or psoriasis, long-term safety in		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)
		children with CD and UC, long-term safety in children, use of infliximab during lactation		
RABBIT Category 3	A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs	HBV reactivation, congestive heart failure, opportunistic infections, serious infections including sepsis (excluding opportunistic infections and TB), TB, serum sickness (delayed hypersensitivity reactions), haematologic reactions, SLE /lupus like syndrome, demyelinating disorders, lymphoma (excluding HSTCL), hepatobiliary events, HSTCL, serious infusion reactions during a re-induction regimen following disease flare, sarcoidosis/sarcoid-like reactions, leukaemia, acute hypersensitivity reaction (including anaphylactic shock), melanoma, Merkel cell carcinoma, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, cervical cancer, malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma, cervical cancer), skin cancer (excluding melanoma and Merkel cell carcinoma), exposure during pregnancy, infusion reaction associated with shortened infusion	Planned for 2017 1Q	Final report planned for 2027 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)
		duration, immunogenicity, use of infliximab during lactation		
Spanish Registry of Adverse Events of Biological Therapies (BIOBADASER) 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 2. To identify unexpected adverse events 3. To identify relevant adverse events that occur following the suspension of the treatment 4. To estimate the relative risk of occurrence of adverse events with biological therapies in patients with RA compared to those not exposed to these treatments 5. To identify risk factors for suffering adverse reactions with these treatments 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	HBV reactivation, congestive heart failure, opportunistic infections, serious infections including sepsis (excluding opportunistic infections and TB), TB, serum sickness (delayed hypersensitivity reactions), haematologic reactions, SLE /lupus like syndrome, demyelinating disorders, lymphoma (excluding HSTCL), hepatobiliary events, HSTCL, serious infusion reactions during a re-induction regimen following disease flare, sarcoidosis/sarcoid-like reactions, leukaemia, acute hypersensitivity reaction (including anaphylactic shock), melanoma, Merkel cell carcinoma, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, cervical cancer, malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma, cervical cancer), skin cancer (excluding melanoma and Merkel cell carcinoma), exposure during pregnancy, infusion reaction associated with shortened infusion duration,	Planned for 2017 1Q	Final report planned for 2027 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 reasons for the interruption of the treatment	immunogenicity, long-term safety in adult patients with UC, PsA, or psoriasis, use of infliximab during lactation		
Prospective observational cohort study of Flixabi in AS and CD for 2 years (tentative title)	To observe safety, efficacy and immunogenicity of Flixabi with active comparator (Remicade®) in AS and CD	Immunogenicity Serum sickness (delayed hypersensitivity reactions) Serious infusion reactions during a re-induction regimen following disease flare Acute hypersensitivity reaction (including anaphylactic shock)	Planned	Final (to be determined) Annual interim reports will be submitted during the study period and until submission of the final report.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
HBV reactivation	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	Patient Alert Card
CHF	Proposed text in SmPC: **Section 4.3 Contraindications** **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	Patient Alert Card
Opportunistic infections	Proposed text in SmPC: **Section 4.3 Contraindications** **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	Patient Alert Card Educational materials for HCPs
Serious infections and sepsis (excluding opportunistic infections and TB)	Proposed text in SmPC: **Section 4.3 Contraindications** **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	Patient Alert Card Educational materials for HCPs
TB	Proposed text in SmPC:	Patient Alert Card

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.3 Contraindications **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	Educational materials for HCPs
Serum sickness (delayed hypersensitivity reactions)	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	Educational materials for HCPs
Haematologic reactions	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	None proposed
SLE/lupus-like syndrome	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	None proposed
Demyelinating disorders	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** S**ection 4.8 Undesirable effects**	None proposed
Lymphoma (excluding HSTCL)	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	Educational materials for HCPs
Hepatobiliary events	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	None proposed
HSTCL	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	Educational materials for HCPs
Intestinal or perianal abscess (in CD)	Proposed text in SmPC: **Section 4.3 Contraindications** **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	None proposed
Serious infusion reactions during a re-induction regimen following disease flare	Proposed text in SmPC: **Section 4.2 Posology and method of administration** **Section 4.8 Undesirable effects**	None proposed
Sarcoidosis or sarcoid-like reactions	Proposed text in SmPC: **Section 4.8 Undesirable effects**	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Paediatric malignancy	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use**	Educational materials for HCPs
Leukaemia	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	None proposed
Acute hypersensitivity reaction (including anaphylactic shock)	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	Educational materials for HCPs
Melanoma	Proposed text in SmPC: **SmPC Section 4.8 Undesirable effects**	Educational materials for HCPs
Merkel cell carcinoma	Proposed text in SmPC: **SmPC Section 4.8 Undesirable effects**	Educational materials for HCPs
BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.6 Fertility, pregnancy and lactation** **Section 4.8 Undesirable effects**	Patient alert card Educational materials for HCPs
Cervical cancer	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	None proposed
Malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma, cervical cancer)	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use**	Educational materials for HCPs
Colon carcinoma/dysplasia (in UC)	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use**	None proposed
Skin cancer (excluding melanoma and Merkel cell carcinoma)	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use**	None proposed
Exposure during pregnancy	Proposed text in SmPC: **Section 4.4 Special warnings and precautions for use** **Section 4.6 Fertility, pregnancy and lactation**	Patient Alert Card
Infusion reaction associated with	Proposed text in SmPC:	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
shortened infusion duration	**Section 4.2 Posology and method of administration**	
Immunogenicity	None proposed	None proposed
Long-term safety in adult patients with UC, PsA, or psoriasis	None proposed.	None proposed
Long-term safety in children with CD and UC	The SmPC presents available data in paediatric CD and UC patients. As soon as additional information on long-term-safety in children with CD and UC is available, it will be analysed and included in the labelling.	None proposed
Long-term safety in children	The SmPC describes that infliximab is not indicated in paediatric indications other than paediatric CD and UC because of insufficient information on safety and efficacy. As soon as additional information on long-term safety in children is available, it will be analysed and included in the labelling.	None proposed
Safety in very young children (< 6 years)	Proposed text in SmPC: **Section 4.2 Posology and method of administration**	None proposed
Use of infliximab during lactation	Proposed text in SmPC: **Section 4.6 Fertility, pregnancy and lactation**	None proposed

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Flixabi (Infliximab) is included in the additional

monitoring list as a new biological product.

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

3. Benefit-Risk Balance

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

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

Benefits

Beneficial effects

From a quality perspective the Applicant provided a comprehensive characterisation of Flixabi with respect to relevant structural, physicochemical and biological features of infliximab. Prior to side-by-side characterisation studies, characterisation was performed on multiple batches of EU Remicade to establish the similarity ranges. The physicochemical and biological properties of Flixabi are considered similar to those of Remicade. Minor differences were observed in glycosylation pattern (%Afucose, %High Mannose, %charged variants), %high molecular weight impurity level, however the applicant provided sufficient justification that these changes would have no impact on efficacy and safety when comparing Flixabi with Remicade.

From a non-clinical perspective, similarity between Flixabi and EU Remicade was considered established with regards to the FcγRIa and FcγRIIIb binding activity. Some small differences were noted in the FcγRIIa-, FcγRIIb-, and FcγRIIIa-binding activity, which was slightly higher for Flixabi compared to that of EU Remicade. Nevertheless, these differences did not translate into differences outside the similarity range in functional assays such as those measuring ADCC activity.

From a clinical perspective, available data support biosimilarity between Flixabi and Remicade based on:

- Comparable pharmacokinetic which was demonstrated in healthy volunteers, whereby the point estimate was close to unity and the 90%CI for the ratio of means of AUC_{inf} being well within the prespecified and accepted margins. Additional supportive evidence was provided from the study in RA patients.
- Primary efficacy analysis in RA which demonstrated that the ACR20 response rate at Week 30 was equivalent in the Flixabi and Remicade treatment groups. The proportion of subjects achieving ACR20 response at Week 30 was 64.1% (148/231) and 66.0% (163/247) in the Flixabi and Remicade treatment groups, respectively. The adjusted rate difference was -1.88% (95%CI -10.26; 6.51). Furthermore, the performed sensitivity analyses, analysis of secondary endpoints such as ACR 50, ACR 70, DAS28 Score at week 30 and the overall 54 week efficacy data support biosimilarity with Flixabi versus Remicade with all parameters within the pre-specified similarity margin.

Uncertainty in the knowledge about the beneficial effects

Rates of ADA positivity were 5- to 6-fold higher in the RA trial under discussion for both Remicade and Flixabi compared to the historical Remicade data reflecting the much increased sensitivity of the current assay. ADA rates were higher in the Flixabi cohort by 5-12% at the individual time points of determination (with about 50% of patients in the Flixabi cohort determined ADA positive).

Despite these numerical differences observed, there was no meaningful effect on any of the efficacy parameters analysed. Sub-group analyses did not reveal differences of clinical relevance in either ADA positive or ADA negative subjects when comparing Flixabi and Remicade cohorts. The applicant has provided evidence that a similar percentage of subjects receiving Flixabi and Remicade required higher doses of study drug irrespective of ADA status, which provides further evidence that no clinically relevant impact on efficacy was noted by treating physicians.

Risks

Unfavourable effects

Safety data were provided from the clinical studies in healthy volunteers and patients with RA. The safety data set comprised all subjects who received at least one dose of the study drug and was considered sufficient to adequately compare the safety profiles of Flixabi and Remicade.

The analysis up to week 54 conformed that the adverse event profile was comparable between Flixabi and EU-Remicade.

Uncertainty in the knowledge about the unfavourable effects

The numerically higher incidence of ADA in Flixabi treated patients was not associated with an unfavourable safety profile compared to Remicade. In particular, adverse events which are known to be associated with ADAs such as hypersensitivity and infusion-related reactions were not increased with Flixabi compared to Remicade.

Benefit-risk balance

Importance of favourable and unfavourable effects

The Applicant provided a thorough comparative exercise in terms of quality, efficacy and safety parameters in line with EU guidance to demonstrate biosimilarity between Flixabi and EU-Remicade.

Benefit-risk balance

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

As expected for a biosimilar, small differences in quality attributes were detected but sufficient evidence was provided that these do not to translate in meaningful differences in the clinical use of Flixabi. Pharmacokinetic

equivalence between Flixabi and EU-Remicade was demonstrated in healthy volunteers. Similar efficacy and safety was established in a clinical trial in patients with rheumatoid arthritis. All clinical efficacy measures, i.e. primary (ACR 20) and secondary (ACR 50, 70, DAS28) at week 30 and 54 were within the pre-specified limits. A numerical difference of ADA positivity did not translate into a relevant difference in efficacy. No differences were observed in the safety profile of Flixabi and Remicade.

Therefore, biosimilarity between Flixabi and EU Remicade has been established and the benefit-risk of Flixabi is considered positive based on the submitted data.

Discussion on the benefit-risk balance

In accordance with the EU guidelines, the development of Flixabi comprised similarity exercises with comparison of the structural characteristics, physicochemical properties and biological activities between Flixabi and Remicade, followed by in vivo similarity studies.

In vitro and *in vivo* non-clinical studies confirmed the similarity of Flixabi and Remicade in PK and in TNF-α-related PD. Considering the mode of action of infliximab, the small differences observed in these studies were not considered to have any impact on the efficacy/safety profile of Flixabi.

Furthermore, in a sensitive clinical model (RA), the efficacy and safety of Flixabi was also shown to be similar to that of Remicade.

The historically reported rates of ADA formation for Remicade have been around 8% in patients with RA treated concomitantly with MTX, the rates observed in both Remicade and Flixabi treated patients in the submitted RA trial were considerably higher (5 to 6 fold). Thus, it can be concluded that the ADA assay used for this application has a profoundly increased sensitivity. It also follows that an increased sensitivity of the laboratory determination of ADA formation and therefore an increase in "immunogenicity" per se does not necessarily translate into a clinically relevant effect. Any observed difference in ADA formation rate therefore has to be judged in the context of clinical data observed in a trial and in this instance did not translate in any meaningful differences between Flixabi and Remicade.

For indications for which pathogenesis appears to be dominated by soluble TNF-α (ankylosing spondylitis, psoriatic arthritis and plaque psoriasis) extrapolation is supported by the TNF-α binding assay and the cell-based assay (TNF-α neutralisation assay by NF-κB reporter gene).

With respect to the membrane bound TNF-α, it has been reported that at least four distinct mechanisms are involved in the inhibition of TNF-α-bearing cells by anti-TNF agents: (i) inhibition of tmTNF-α-mediated effector functions, (ii) destruction of TNF-α-bearing cells by CDC, (iii) destruction of TNF-α-bearing cells by ADCC and (iv) destruction of TNF-α-bearing cells by outside-to-inside signal (reverse signalling). Transmembrane-TNF-α binding assays, but also Fc receptor binding assays, CDC, ADCC and apoptosis assays were performed. Overall, these results showed that Flixabi is similar to the reference product in terms of tmTNF-α related activities.

It has been described that the rate of ADA positivity is amongst other factors dependent on the population, dose, dose interruptions and co-medication. However, there is no reason to believe that the ADA formation would be affected differentially by these factors for molecules that are considered highly similar such as Flixabi and Remicade. Although, it may be argued that methotrexate used in the clinical trial may have reduced the immune response, it should be noted that anti-drug antibody development is nevertheless reportedly highest in patients with rheumatoid arthritis compared to other licensed indications of Remicade.

Therefore, with the totality of evidence, the CHMP considered that it was justifiable to extrapolate the equivalent clinical efficacy and the comparable safety profile from the Flixabi study in RA patients to all of the indications where Remicade has been approved.

The applicant intends to claim the same therapeutic indications for the biosimilar Flixabi as those granted for Remicade in the EU. Even though available data demonstrate that the numerically higher rate of ADA in Flixabi treated patients compared to Remicade as measured by the assays employed do not have an effect on the safety and efficacy in patients with RA, additional long-term data will be provided through the observational study in patients with ankylosing spondylitis and Crohn's disease.

Divergent positions to the majority recommendation are appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Flixabi in the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis in adult patients and Crohn's disease and ulcerative colitis in adults and in children and adolescents aged 6 to 17 year is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Prior to launch in each Member State, the MAH shall agree the final educational material with the competent authority in that Member State, consisting of information provided to all healthcare professionals expected to prescribe the product.

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

- The risk of opportunistic infections and tuberculosis (TB) in patients treated with Flixabi.
- The need to assess the risk of TB in patients prior to treating with Flixabi.
- The risk of acute hypersensitivity reactions (including anaphylactic shock) and delayed hypersensitivity reactions.
- The risk of lymphoma, melanoma, Merkel cell carcinoma, and other malignancies.
- The risk of disseminated BCG infection after BCG vaccination of infants up to 6 months of age who were exposed in utero to infliximab.
- The patient alert card, which is to be given to patients using Flixabi.

Prescribers of Flixabi for paediatric Crohn's disease and paediatric ulcerative colitis shall additionally be made aware:

- That children may be at increased risk of developing infections and that their immunisations need to be up-to-date.

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

None.

Divergent positions to the majority recommendation are appended to this report.

APPENDIX 1

DIVERGENT POSITIONS dated 1 April 2016

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of a marketing authorisation of Flixabi as a biosimilar to Remicade and in the indications licensed to Remicade.
The reason for the divergent opinion was the following:

- Flixabi appears to be associated with a higher incidence of ADA than the originator, Remicade. It is acknowledged that it cannot be excluded that the observed difference was a chance finding or a finding associated with limitations in the immunogenicity assays that were used. However, an increased incidence was observed both in the Phase 1 and the Phase 3 studies, and it has not been substantiated that the difference was an artefact due to – for example – problems with the interpretation with the immunogenicity assays that were used.

- In the Phase 3 trial, which was conducted in patients with rheumatoid arthritis, the efficacy of Flixabi, whilst meeting the pre-specified equivalence margins, was consistently, although not universally, estimated to be lower than that of Remicade. It is not possible with reasonable certainty to exclude that the estimated reduction in efficacy of Flixabi was the result of the higher incidence of ADA. In this regard, it is noteworthy that the Phase 3 study showed that the efficacy, regardless of treatment group, was significantly lower in ADA positive patients than in ADA negative patients.

- Since the patients with rheumatoid arthritis investigated in the Phase 3 trial are treated concomitantly with immunomodulator therapy, they may exhibit less immunogenicity than patients in other infliximab-licensed indications. The consequences of any difference on ADA incidence, and consequently the impact on efficacy in these indications are unclear.

- It is considered that the uncertainties outlined above should be resolved by the Applicant before licensing.

- The proposal by the Applicant to resolve the concerns related to immunogenicity in the post-marketing setting by initiating a prospective observational cohort study in the indications of ankylosing spondylitis and Crohn's disease is considered inadequate. In addition, it is questionable to what extent a non-randomised, observational study can provide data that will effectively address the uncertainties.

In conclusion, the undersigned CHMP members consider the benefit-risk balance of Flixabi to be negative since biosimilarity to Remicade has not been established.

DIVERGENT POSITIONS dated 1 April 2016

Flixabi EMEA/H/C/004020/0000

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