



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for infliximab

Proprietary Product Name: Renflexis

Sponsor: Samsung Bioepis AU Pty Ltd

October 2017

TGA Health Safety
Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
ACR20	American College of Rheumatology response \geq 20% improvement
ACR50	American College of Rheumatology response \geq 50% improvement
ACR70	American College of Rheumatology response \geq 70% improvement
ACSOM	Advisory Committee on the Safety of Medicines
ADA	Anti-drug antibody
ADCC	Antibody dependent cell mediated cytotoxicity
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
AUC _{inf}	Area under the curve from time zero to infinity
AUC _{last}	Area under the curve up to last measurable concentration
CCF	Cell culture fluid
CDC	Complement-dependent cytotoxicity
CEX	Cation Exchange chromatography
CI	Confidence interval
C _{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
CRP	C-reactive protein
CT-P13	Remsima/Flixceli/Inflectra (infliximab biosimilar)
DAS28	28-joint Disease Activity Score
DHCP	Dear Healthcare Professional
DMARD	Disease-modifying anti-rheumatic drug
ECCO	European Crohn's and Colitis Organisation
ECG	Electrocardiograph

Abbreviation	Meaning
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full analysis set
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HC	Heavy chain
HCP	Healthcare Professional
HMW	High molecular weight
IBD	Inflammatory bowel disease
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IL-	Interleukin-
IV	Intravenous
kDa	kilodalton
LC	Light chain
mAb	monoclonal antibody
MFDS	Ministry of Food and Drug Safety
mTSS	modified total Sharp score
MTX	Methotrexate
NK	Natural killer
PAC	Patient Alert Card
PBMC	peripheral blood mononuclear cells

Abbreviation	Meaning
PI	Product Information
PK	Pharmacokinetic
PPS1	Per-protocol set 1
PPS2	Per-protocol set 2
PSUR	Periodic Safety Update Report
PT	Preferred Term
QFG	QuantiFERON Gold test
RMP	Risk management plan
SAE	Serious adverse events
SB2	Renflexis (infliximab)
SD	Standard deviation
SmPC	Summary of Product Characteristics
$t_{1/2}$	Half life
T_{max}	Time to maximum plasma concentration
$tmTNF\alpha$	Transmembrane tumour necrosis factor alpha
$TNF\alpha$	Tumour necrosis factor alpha
$TNF\beta$	Lymphotoxin alpha
US	United States

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biosimilar medicine
<i>Decision:</i>	Approved
<i>Date of decision:</i>	18 November 2016
<i>Date of entry onto ARTG</i>	28 November 2016
<i>Active ingredient:</i>	Infliximab
<i>Product name:</i>	Renflexis
<i>Sponsor's name and address:</i>	Samsung Bioepis AU Pty Ltd Level 16/201 Elizabeth Street, Sydney NSW 2000
<i>Dose form:</i>	Powder for injection
<i>Strength:</i>	100 mg
<i>Container:</i>	Type I glass vial
<i>Pack size:</i>	Pack of one vial
<i>Approved therapeutic use:</i>	<p><i>Renflexis is indicated for the treatment of:</i></p> <p><i>Rheumatoid Arthritis in adults</i></p> <p><i>Renflexis, in combination with methotrexate, is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in:</i></p> <ul style="list-style-type: none">- <i>patients with active disease despite treatment with methotrexate</i>- <i>patients with active disease who have not previously received methotrexate.</i> <p><i>Renflexis should be given in combination with methotrexate. Efficacy and safety in Rheumatoid Arthritis have been demonstrated only in combination with methotrexate.</i></p> <p><i>Ankylosing Spondylitis</i></p> <p><i>Renflexis is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.</i></p> <p><i>Psoriatic arthritis</i></p> <p><i>Renflexis is indicated for the treatment of the signs and symptoms, as well as for the improvement in physical function in adult patients with active and progressive psoriatic arthritis who have responded inadequately to disease-modifying anti-rheumatic drug</i></p>

(DMARD) therapy.

Renflexis may be administered in combination with methotrexate.

Psoriasis

Renflexis is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.

Crohn's Disease in Adults and in Children and adolescents (6 to 17 years)

Renflexis is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

Refractory Fistulising Crohn's Disease

Renflexis is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years)

Renflexis is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy

<i>Route of administration:</i>	Intravenous infusion
<i>Dosage:</i>	Varies with indication, please see the PI (Attachment 1) for further details
<i>ARTG number:</i>	260410

Product background

This AusPAR describes the application by the sponsor to register Renflexis infliximab 100 mg powder for injection. Renflexis is a biosimilar version of the drug infliximab previously approved under the product name Remicade.

In this submission, similarity to Remicade (the reference medicinal product for infliximab) is claimed. The application for Renflexis, also known as SB2, is requesting approval of the same seven indications currently approved for Remicade in Australia as found in the Remicade Product Information (PI). These are:

'Renflexis is indicated for the treatment of:

Rheumatoid Arthritis in adults

Renflexis, in combination with methotrexate, is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in:

- *patients with active disease despite treatment with methotrexate*

- *patients with active disease who have not previously received methotrexate.*

Renflexis should be given in combination with methotrexate. Efficacy and safety in Rheumatoid Arthritis have been demonstrated only in combination with methotrexate.

Ankylosing Spondylitis

Renflexis is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.

Psoriatic arthritis

Renflexis is indicated for the treatment of the signs and symptoms, as well as for the improvement in physical function in adult patients with active and progressive psoriatic arthritis who have responded inadequately to disease-modifying anti-rheumatic drug (DMARD) therapy.

Renflexis may be administered in combination with methotrexate.

Psoriasis

Renflexis is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.

Crohn's Disease in Adults and in Children and adolescents (6 to 17 years)

Renflexis is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

Refractory Fistulising Crohn's Disease

Renflexis is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years)

Renflexis is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy.'

The sponsor is proposing one strength of 100 mg lyophilised powder in a single use glass vial for registration (same as Remicade) and the same dosing instructions as Remicade.

The proposed PI is essentially the same as per Remicade except for additional comparability data.

The submission is clinically supported by a single Phase III study comparing the efficacy and safety of Renflexis with Remicade in rheumatoid arthritis patients for 54 weeks (with a double blind extension period to 78 weeks that included a one way switch from Remicade to Renflexis) and a single dose Phase I study providing pharmacokinetic (PK) and safety data in healthy volunteers. The development program for Renflexis was guided by the European Medicines Agency (EMA) and United States (US) Food and Drug Administration (FDA) requirements for biosimilar medicines.

The reference drug, Remicade, used in the pivotal Phase III study, was sourced from the European Union (EU) and a bridging comparability exercise was undertaken with the Australian registered Remicade. The PK study compared Renflexis with EU and US sourced Remicade.

Infliximab itself is a chimeric human-murine immunoglobulin G (IgG) monoclonal antibody produced by recombinant DNA technology. Infliximab binds to human tumour necrosis factor alpha (TNF α), a pro-inflammatory and immunoregulatory cytokine found in synovial tissues and fluid and in interstitial inflammatory cells around joints in patients with rheumatoid arthritis. TNF α exists in soluble and transmembrane forms which activate cell-bound TNF receptors. Infliximab neutralises the biological activity of TNF α by binding with high affinity to the soluble and transmembrane forms of TNF α and inhibits binding of TNF α with its receptors. Neutralisation of soluble TNF α is thought to play an important role in reducing inflammation in rheumatoid arthritis, psoriatic arthritis, and psoriasis. In inflammatory bowel disease, inhibition of transmembrane TNF α and Fc γ receptor-mediated functions may also be important. It does not bind to lymphotoxin alpha (TNF β).

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 28 November 2016.

At the time the TGA considered this application, similar applications had been approved or were under consideration in other countries or regions as listed in Table 1, below.

Table 1. International regulatory status

Country/ region	Submission date	Status	Indications (approved or requested)
EU (EMA)	March 2015	Approved (May 2016)	<i>Adults:</i> RA, AS, PsA, Psoriasis, CD, and UC <i>Paediatrics:</i> CD and UC (both 6 to 17 years)
Republic of Korea (MFDS)	March 2015	Approved (December 2015)	<i>Adults:</i> RA, AS, PsA, Psoriasis, CD, and UC <i>Paediatrics:</i> CD and UC (both 6 to 17 years)
USA (FDA)	March 2016	Approved April 2017	<i>Adults:</i> RA, AS, PsA, Psoriasis, CD, and UC <i>Paediatrics:</i> CD (6 years of age and older)

Note: EU = European Union; EMA = European Medicines Agency; MFDS = Ministry of Food and Drug Safety; USA = United States of America; FDA = Food and Drug Administration; RA = rheumatoid arthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis, CD = Crohn's disease; UC = ulcerative colitis

Renflexis has not been previously considered by the TGA but Remicade was first approved for rheumatoid arthritis in the US in 1998, in the EU in 1999 and in Australia in 2000. The first biosimilar of infliximab, Remsima/Inflectra, was approved in the EU in 2013, in Australia in 2015 and in the USA in 2016.

Renflexis has been approved in Europe (May 2016) under the name Flixabi for the same indications as Remicade in Europe. It was also approved in the US in April 2017. The approved indications in Europe are as follows:

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.

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.

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).'

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Drug substance (active ingredient)

Infliximab (SB2) is a chimeric human/mouse monoclonal antibody (mAb), which is typically a 'Y' shaped large glycoprotein consisting of four polypeptide chains (two identical heavy chains (HC) and two identical light chains (LC)), connected by disulphide bonds. Each chain presents constant and variable regions whereby in both chains, the variable region is murine whereas the constant region is of human origin (IgG1 and human *kappa* origins for the HC and LC, respectively).

The molecular weight of SB2 is approximately 149 kilodalton (kDa) in glycosylated form. There is 1 N-linked glycosylation site is located at asparagine 300 on each HC. There are no O-linked glycosylation sites.

Drug substance manufacture

The SB2 drug substance manufacturing process involves cell culture expansion, production in a bioreactor, harvest of the cell culture fluid (CCF), purification and dispensing, resulting in highly purified SB2 drug substance.

All drug substance manufacturing steps are validated.

Stability

Stability data have been generated under real time and accelerated conditions.

Drug product

The finished drug product is as 100 mg of a white powder in a glass vial for intravenous (IV) injection.

Drug product manufacture

The drug product manufacturing process involves thawing of the formulated drug substance, mixing, bioburden reduction filtration, pooling, sterile filtration, filling lyophilisation and stoppering. A detailed description of the drug product manufacturing process has been provided.

All drug product manufacturing steps are validated.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data showed that the product is not photostable¹ (storage conditions will be reviewed at a later date).

The proposed shelf life of 24² months when it is stored 5°C ± 3°C is acceptable.

In-use stability data have also been submitted.

Biopharmaceutics

Bioavailability data are not required as the product is administered intravenously.

Biosimilarity

During the development of Renflexis, EU Remicade was used as the main reference product to demonstrate biosimilarity in terms of quality and nonclinical comparability exercise. Additional bridging comparability study was performed between the EU and Australian Remicade to present EU Remicade as a representative of the Australian registered product (Australian Remicade).

Extensive characterisation studies involving comparison of primary, secondary and tertiary structures, physicochemical properties and biological activities showed that SB2 and EU Remicade are generally similar. However, several differences have been noted as highlighted below:

- SB2 was found to possess a lower C-terminal Lys content and a higher C-terminal α-amidated Pro content. Heterogeneity of C-terminal residues is a characteristic of therapeutic monoclonal antibodies (mAb) and C-terminal Lys variation does not impact PK profiles, biological activity of the protein nor TNFα binding activity. Likewise, α-amidation of Pro is a well-known and widely occurring modification in Chinese hamster ovary cells and is known to possess no influence on the effector function and antigen binding affinity of antibodies.
- Minor differences were found in Met oxidation and deamidation profile of SB2 compared to EU Remicade. However, SB2 and EU Remicade showed similar FcRn binding activities, which indicates that the difference in Met oxidation was not significant. Moreover, the Cation Exchange chromatography (CEX) acidic fractions including deamidation showed similar FcγRIIIa or TNFα activities, which indicates that the difference in deamidation levels were not significant.
- Glycan studies results showed that while the major N-glycan structures were similar between SB2 and EU, %Afucose was higher in SB2 but antibody dependent cell

¹ Product is protected from light when in carton.

² An extension from 24 to 30 months for the drug product was approved on 11 July 2017.

mediated cytotoxicity (ADCC) assay, which is known to be associated with afucosylated glycans, were similar between SB2 and Remicade.

- The charge variants content of SB2 was outside the similarity range. However, SAR studies performed using charge variants showed that all variants possessed comparable biological activities with respect to TNF α and Fc γ RIIIa binding.
- Capillary electrophoresis–sodium dodecyl sulphate under reducing conditions showed that the heavy chain content (% non-glycosylated HC) of SB2 was slightly lower than that of EU Remicade. However this difference was predicted not to have a physiological effect
- Size exclusion chromatography results showed that SB2 had a slightly higher high molecular weight (HMW) impurity level compared to EU Remicade. The HMW impurities were identified as a dimer by sedimentation velocity-analytical ultracentrifugation analysis. However, the difference was considered too small to possess a physiological effect. Moreover, analysis results from circular dichroism, differential scanning calorimetry and sedimentation velocity-analytical ultracentrifugation analysis showed that the high order structures were similar between SB2 and EU Remicade.
- A slight increase in deuterium uptake of the peptide containing the glycosylation site was observed for SB2 compared to EU Remicade. This difference resulted from the presence of different sialic acids in EU Remicade, which may be caused by the use of a different host cell line. However, this difference was not considered to be significant, as the difference was only present for this peptide and existed in a relatively small amount.
- Fc receptors, Fc γ RIIb and Fc γ RIIIa (V/V type) binding assay results were slightly outside the similarity range. However, the ADCC results, which are associated with Fc γ RIIb and Fc γ RIIIa activities, were considered similar, since the results of SB2 were within the similarity range. Additionally, the results in Fc γ RIIIa (F/F type) binding were similar between SB2 and Remicade. Thus, the differences in Fc γ RIIb and Fc γ RIIIa binding activities were not considered to be significant. Overall, the Fc-related biological activities were considered to be similar between SB2 and EU Remicade, as confirmed by other biological assays showing similarity between the two products.

It is not unexpected to note the above minor physicochemical differences between SB2 and Remicade due to the use of different cell substrates for production, cell culture and purification conditions. However, the in vitro biological activities have been shown to be generally similar. It is not clear whether these differences in quality attributes have any clinical implication. Hence, it is imperative that the two products should be shown to display similar clinical efficacy and safety, including immunogenicity, in clinical studies as required by TGA-adopted EMA guideline EMEA/CHMP/BMWP/42832/2005.³

Quality summary and conclusions

There is no objection on quality grounds to the approval of Renflexis whose details are recorded above.

While there is no objection to the registration of Renflexis on quality grounds, there are differences in the quality characteristics of the active substance, infliximab.

As discussed in the 'Biosimilarity' section above, there are differences in the physicochemical characteristics of infliximab in Renflexis when compared to Remicade

³ EMEA/CHMP/BMWP/42832/2005 Rev 1: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.

due to the use of different cell substrates for production, cell culture and purification conditions. However, it is not clear whether these differences in quality attributes have any clinical implication. The clinical Delegate needs to ensure that these differences do not adversely impact on the efficacy and safety of the product in the clinical evaluation.

The quality evaluator recommends conditions of registration regarding batch release testing and compliance with certified product details.

Proposed conditions of registration for the Clinical Delegate

1. It is a condition of registration that all batches of Renflexis imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. It is a condition of registration that each batch of Renflexis imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

The sponsor must supply:

- a. Certificates of Analysis of all active ingredient (drug substance) and final product.
- b. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
- c. Evidence of the maintenance of registered storage conditions during transport to Australia.
- d. 3 to 5 vials of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

III. Nonclinical findings

Introduction

Data presented in the nonclinical dossier were in general accordance with the relevant guideline on nonclinical issues for biosimilar monoclonal antibodies.⁴ Submitted studies included an in vivo pharmacology study (transgenic mouse model of arthritis that overexpresses human TNF α) and two pharmacokinetic studies (transgenic mice: single and repeat dose, and rats: repeat dose). The sponsor used EU, US (and also Korean for the in vitro studies) sourced Remicade as comparators in the nonclinical studies. None of the studies were Good Laboratory Practice (GLP) compliant which is acceptable as none were pivotal safety studies.

The sponsor also conducted comparative in vitro pharmacology studies which are included in quality dossier (regional information: biosimilarity) and are to be commented on further by the quality evaluator. Because the in vitro studies used EU and US sourced Remicade as comparators, the sponsor conducted bridging studies in which quality and biological attributes of the Australian Remicade product were found to be similar to the

⁴ EMA/CHMP/BMWP/403543/2010 Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP); Date: 30 May 2012

comparators used in the pharmacology studies. Toxicity testing with the Renflexis formulation was not conducted on grounds of there being no relevant animal models available, since infliximab is only active against human or chimpanzee TNF α and toxicity characterisation in chimpanzees is both unethical and unfeasible. In correspondences with the EMA it was agreed that conduct of toxicity testing in a non-responsive species (such as rat) would be of limited utility and was therefore not recommended.⁵ Furthermore, in line with the guideline EMA/CHMP/BMWP/403543/2010 the sponsor did not conduct safety pharmacology, reproductive toxicity, genotoxicity, carcinogenicity or local tolerance studies.

Overall, the quality of the nonclinical dossier is considered adequate and the study designs used are sufficient for providing nonclinical characterisation of biosimilar infliximab.

Pharmacology

Primary pharmacology

The pharmacology of infliximab has been well characterised as part of its original assessment to register Remicade, thus the objective of the submitted pharmacology studies was to demonstrate comparable pharmacology of Renflexis infliximab to the comparator Remicade.

Infliximab is an anti-TNF α antibody that inhibits binding of soluble and membrane-bound TNF α to its cell surface receptors through its Fab fragment functions. It also has an Fc domain which enables it to interact with Fc receptors and perform immune functions associated with these receptors.

In vitro comparability studies between Renflexis and EU or US sourced Remicade showed a number of qualitative similarities in biological activities, which included:

- binding affinity for human soluble and transmembrane TNF α but not for TNF β
- neutralisation of TNF α and suppression of cytokine IL-8 release
- induction/inhibition of apoptosis
- binding affinity for Fc γ RI, Fc γ RIIa, Fc γ RIIb, Fc γ RIIIa (F/F allotype), C1q
- induction of complement-dependent cytotoxicity (CDC), ADCC and recruitment/induction of regulatory macrophages

Subtle differences were noted in that Renflexis exhibited slightly higher binding affinity for Fc γ RIIb, Fc γ RIIIa (V/V allotype) and FcRn receptors compared to Remicade. With regard to Fc γ RIIIa binding, exploration of functional consequences found ADCC activity was also slightly higher with Renflexis but only when the NK92-CD16 cell line was used as a source of natural killer (NK) effector cells. However, the extent of cell lysis (a measure of ADCC activity) was comparable between IFX formulations when peripheral blood mononuclear cells (PBMCs), a more physiologically relevant source of NK cells, were used. The quality evaluator will comment further on the adequacy of these investigations. Nevertheless from a nonclinical perspective, the slightly higher affinity exhibited by Renflexis for Fc γ RIIIa and the potential for enhanced ADCC activity is not anticipated to have adverse implications to the efficacy of Renflexis, particularly since ADCC activity might be considered advantageous for inflammatory bowel disease (IBD) indications.⁶

⁵ EMA/CHMP/SAWP/70331/2012. Scientific Advice: Infliximab (SAIT102). European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP); Date: 16 February 2012

⁶ Moroi R, et al. FCGR3A-158 polymorphism influences the biological response to infliximab in Crohn's disease through affecting the ADCC activity. 2005; Immunogenetics. 65, 265–271.

Tissue cross-reactivity studies for Renflexis were not provided; however, these studies are limited in their ability to discriminate subtleties between homologous products and both the International Conference on Harmonisation (ICH) and EMA guidance recommend against these.⁷⁸

For in vivo demonstration of comparability, anti-inflammatory activity of Renflexis was assessed against EU and US sourced Remicade in a mouse model of arthritis (Tg197 mouse). Briefly, groups of mice received twice weekly infliximab doses (or vehicle) for a 7 week period and were assessed for clinical changes that denoted anti-inflammatory activity (in vivo arthritic scores, clinical signs, histological assessment of ankle joints). All infliximab formulations showed similar dose-dependent attenuation of inflammation over the 7 week period relative to untreated vehicle control mice. Although nonclinical demonstration of comparable efficacy was provided in only one of the sought-after indications, this is acceptable as in vitro investigations did not indicate inferior affinities or efficacies by Renflexis compared to EU and US sourced Remicade and thus, is not expected to differ in its pharmacological activity for other indications.

Pharmacokinetics

PK parameters of Renflexis and EU and US sourced Remicade were determined in single dose studies in transgenic mice (intraperitoneal route) and SD rats (intravenous route), and in one repeat dose study in mice. Three doses of infliximab were tested for all studies and the repeat dose study also included data on anti-drug antibody (ADA) development by infliximab formulations. Studies used male animals only, which the sponsor justified by asserting that the objectives of the studies were to determine comparability and not gender differences. Although it is unknown whether qualitative differences (such as glycosylation patterns) could result in different effects in males and females, because in vitro studies did not find overall differences in biological activities of infliximab formulations, the lack of testing in female animals is not considered to be a critical omission.

Parameters for single dosing indicated comparable absorption profiles for all infliximab formulations in both rodent species. Maximum plasma concentrations (C_{max}) and time to peak (T_{max}) were similar for all infliximab formulations. As well, plasma levels of infliximab over time (AUC) were within similar ranges at each tested dose. For the repeat dose study using Tg197 mice, PK parameters could not be determined for the 1 mg/kg dose groups for any of the formulations because of development of ADAs against infliximab in all animals. Incidence of ADA development was similar for all infliximab formulations. Pharmacokinetic data was only collected from the last day of dosing, and so the possibility of accumulation was not investigated; however, as a biological active, Renflexis is not anticipated to exhibit differences in disposition that have not already been identified with the innovator. With regard to comparable PK parameters, at 3 and 10 mg/kg doses and in animals that did not develop ADAs, C_{max} , T_{max} and AUC values were comparable between the different infliximab formulations. Clinical plasma kinetic parameters [not shown in this document] appear to support bioequivalence of Renflexis.

⁷ EMA/CHMP/ICH/731268/1998 ICH guideline S6(R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals, Step 5. June 2011

⁸ ICH S6(R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals, International Conference on Harmonisation (ICH) tripartite guideline. ICH technical requirements for registration of pharmaceuticals for human use; Date: 16 July 1997; current Step 4 version: June 2011

Toxicology

As discussed above, toxicity testing was not conducted on the Renflexis formulation since conducting such studies in non-responsive species (such as rodents) would be of limited predictive value and as such is not recommended by EMA guidance.

Local tolerance

Local tolerance of Renflexis was not assessed, which is acceptable as per guideline recommendation that advises against their use unless different or new excipients are used.

Paediatric use

Renflexis, like Remicade, has a number of paediatric indications (Crohn's disease and ulcerative colitis), but there were no new nonclinical studies in juvenile animals, which is acceptable.

Nonclinical summary and conclusions

- The scope of the nonclinical dossier was in general accordance with guidelines on nonclinical assessment of biological medicines (ICH S6; EMA/CHMP/BMWP.403543/2010). Data consisted of comparative studies on the pharmacology and pharmacokinetics of Renflexis against EU, US (and on occasion Korean) sourced Remicade. Bridging studies showed that Australian sourced Remicade was similar to the other comparators.
- Pharmacological activity of Renflexis was generally comparable to that of Remicade under in vitro conditions. Some subtle differences were noted for some of the tested parameters (higher binding affinities for some Fc-receptor related targets) but these differences did not extend to effects on biological responses in vivo. Under in vivo conditions, Renflexis and Remicade produced similar dose-dependent attenuation of inflammation in a mouse model of arthritis (Tg197 mice) over a 7 week period compared with untreated vehicle controls.
- The pharmacokinetic profile of Renflexis indicated similar absorption to the Remicade comparators under single and repeat dose study conditions in rodents. In the repeat dose study, ADAs developed at the end of the 7 week dosing period but the incidence of ADA development was similar for all infliximab formulations. Clinical plasma kinetic measurements indicated bioequivalence between the infliximab formulations.
- Overall, no major deficiencies were identified in the nonclinical dossier. Provided that the quality evaluator accepts the conclusions made about the quality aspects of Renflexis then there are no nonclinical objections to registration.
- Amendments to the draft PI were also recommended.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Rheumatoid arthritis is a chronic disorder associated with synovial inflammation, fatigue, malaise, morning stiffness, reduced physical functioning and reduced quality of life. More severe disease may be associated with joint destruction, rheumatoid nodules, lung disease and cardiovascular complications. The prevalence of rheumatoid arthritis is approximately 0.5% to 1% and it occurs more commonly in women. Without treatment, it may progress to cause severe joint deformities with loss of mobility and the ability to perform simple activities of daily living. Pain relief is provided most commonly but non-steroidal anti-inflammatory drugs (NSAIDs) which are effective but do not modify the underlying disease process. Disease-modifying anti-rheumatic drugs (DMARDs) reduce disease progression and joint damage. The most commonly used DMARD is methotrexate (MTX), but other agents such as leflunomide, injectable gold, sulfasalazine and hydrochloroquine have proved effective. However, the benefits of DMARDs are often delayed in onset and their use is limited by side-effects.

In the last 20 years, biological therapies such as monoclonal antibodies to several targets in the inflammatory chain have been developed and are now in widespread use. Infliximab (Remicade), adalimumab, certolizumab and golimumab belong to a class of TNF α inhibitors approved for use in RA and other inflammatory conditions such as psoriasis, psoriatic arthritis, ankylosing spondylitis and inflammatory bowel disease. They have proved effective although their use is limited by immunogenicity and loss of effectiveness in a significant proportion of patients with long-term use. They are generally well tolerated but there is a significant risk of hypersensitivity reactions and serious infections, including opportunistic infections and reactivation of latent TB.

TNF α is produced mainly by macrophages and is known to trigger the release of multiple pro-inflammatory factors. Elevated TNF α levels are found in synovial tissues and fluid and in interstitial inflammatory cells around joints in patients with RA. It exists in soluble and transmembrane forms which activate cell-bound TNF receptors, TNFR1 found in most tissues and TNFR2 found only on inflammatory cells. Neutralisation of soluble TNF α is thought to play an important role in reducing inflammation in rheumatoid arthritis, psoriatic arthritis, and psoriasis. In IBD, inhibition of transmembrane TNF α and Fc γ receptor-mediated functions may also be important. These potential differences in mechanism of action must be considered when comparing the safety and efficacy of TNF α inhibitors in patients with rheumatological and IBD indications. Infliximab is a chimeric human-mouse monoclonal antibody which binds with high affinity to both soluble and transmembrane forms of TNF α . It reduces the levels of TNF α and other markers of inflammation including interleukin (IL)-6 and C-reactive protein (CRP).

The TNF α inhibitor Remicade was first approved for rheumatoid arthritis in the US in 1998, in the EU in 1999 and in Australia in 2000. Three large, placebo-controlled, pivotal studies of Remicade have been conducted in patients with RA (the Studies ATTRACT, ASPIRE and START) and these are summarised in the Remicade PI. In each study, the combination of infliximab + MTX was significantly superior to placebo + MTX for response criteria including ACR20, ACR50 and ACR70⁹. In START study, the primary endpoint was safety and there was a statistically significant increase in serious infections in the infliximab + MTX group. Efficacy in other rheumatologic indications and in IBD has also been demonstrated in a series of clinical studies also summarised in the Remicade PI.

⁹ The ACR is reported as percentage improvement, comparing disease activity at two discrete time points. ACR20, ACR50 and ACR70 denotes a \geq 20%, 50% and 70% improvement respectively.

The first infliximab biosimilar CT-P13 (Remsima/Flixceli/Inflectra) was approved by the EMA in September 2013 for all indications for which Remicade is approved, using the same dosage and administration. Similar approval was given by the TGA for rheumatoid arthritis and all indications in August 2015 and it is currently under review by the FDA. CT-P13 has an equivalent PK profile to Remicade in patients with ankylosing spondylitis and equivalent efficacy in patients with rheumatoid arthritis. A summary of the CT-P13 clinical development program is reviewed in detail by McKeague, 2014.¹⁰ In the pivotal study, the CI for the treatment difference for ACR20 responses at Week 30 fell within the pre-defined $\pm 15\%$ to limits in patients with rheumatoid arthritis also receiving MTX. CT-P13 had comparable tolerability to Remicade. The immunological response was also similar with ADAs detected in 52.3% of the CT-P13 group and 49.5% of the Remicade group at Week 54.

Renflexis has been developed by the sponsor as a similar biological product to Remicade. It is expected to have a similar profile to Remicade for efficacy, safety, PK and immunogenicity in patients with RA and other inflammatory diseases.

Guidance

For an overview of the guidance available for this submission please see the relevant section in Attachment 2, and also the Delegate's Overall benefit-risk assessment later in this document.

Contents of the clinical dossier

The Renflexis submission contains the following clinical information:

- 1 clinical pharmacology study provided bioequivalence pharmacokinetic data. No pharmacodynamic data were submitted.
- 1 population PK analysis was included in the pivotal efficacy study.
- 1 pivotal efficacy/safety study (Study SB2-G31-RA)
- A Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

No dose-finding studies were submitted. No other efficacy/safety studies were submitted. No pooled analyses were submitted.

Paediatric data

The submission did not include paediatric data. The sponsor does not have a paediatric development plan but proposes to include paediatric indications as per the reference product.

Good clinical practice

Both studies were conducted according to the principles of ICH Good Clinical Practice (GCP).

¹⁰ McKeague K. A review of CT-P13: an infliximab biosimilar. *BioDrugs* 2014; 28(3):313-321

Pharmacokinetics

Studies providing pharmacokinetic data

A single pharmacokinetic study, Study SB2-G11-NHV was submitted and summarised. It was a conventional, single dose, equivalence study comparing SB2 with EU and US sourced Remicade in normal healthy subjects. A limited population PK study in the pivotal efficacy Study SB2-G31-RA was performed in a 50% sample of enrolled patients.

Evaluator's conclusions on pharmacokinetics

The PK profiles of SB2 and the reference product may be considered comparable for all parameters tested.

PK equivalence has been demonstrated between SB2 and Remicade sourced from the EU or US. As discussed (please see Attachment 2) the AUC and C_{max} 90% confidence intervals (CI) fell comfortably within the accepted 80% to 125% limits for PK equivalence. The TGA could accept batch testing to show equivalence between EU sourced Remicade and the registered Australian product but this is yet to be determined. No repeat dose data were obtained in healthy subjects. However, a limited PK population study was performed as part of the pivotal Phase III study in RA patients. Steady state was achieved between Weeks 14 and 22 and there were no differences in trough serum infliximab concentrations between the SB2 and EU Remicade groups at any time during the first 30 weeks of treatment.

The infliximab 5 mg/kg single dose study in healthy subjects was adopted following consultation with the EMA and FDA. The 5 mg/kg dose was selected as it represents the maximum usual therapeutic dose of Remicade for most indications (with the exception of inflammatory bowel disease for which 10 mg/kg may be used). A 5 mg/kg single-dose study can be considered acceptable and there are no concerns about potentially greater differences at higher doses. The PK profile of infliximab has been extensively characterised in previous studies. Kavanaugh (2000) showed proportional increases in C_{max} and AUC for single infusions of infliximab at doses of 5, 10, or 20 mg/kg in a 40 week study in rheumatoid arthritis patients.¹¹ The AUC/dose, clearance, volume of distribution, mean residence time and terminal half-life were comparable for the three doses. There was no accumulation with repeated infusions with comparable median serum infliximab concentrations at Weeks 20, 28 and 36. The Remicade PI documents equivalent linear exposure in patients with rheumatoid arthritis given 5 mg/kg and 10 mg and 5 mg/kg in patients with Crohn's disease. A review by Nesterov (2005) has identified published PK data for infliximab in patients with Crohn's disease, psoriasis and rheumatoid arthritis.¹² Although most of the data are published as abstracts, there is no evidence for meaningful differences in infliximab PK in other indications. Although PK testing has not been performed in patients with Crohn's disease at a dose of 10 mg/kg, the available evidence suggests that exposure will be linear and comparable to patients with rheumatoid arthritis. Potential differences related to soluble and transmembrane inhibition are unlikely to affect this assumption. No additional PK studies were performed as they are not required for a biosimilar (EMA/CHMP/BMWP/403543/2010). Previous Remicade studies have not shown meaningful differences in infliximab PK related to age, race or gender.

¹¹ Kavanaugh AE, et al. Chimeric Anti-tumor Necrosis Factor- α monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. *J Rheumatol* 2000; 27:841-50

¹² Nesterov I. Clinical pharmacokinetics of TNF antagonists: how do they differ? *Semin Arthritis Rheum* 2005; 34(5 Supp11):12-18

Pharmacodynamics

No studies were submitted.

Dosage selection for the pivotal studies

Infliximab dosages were based on the Remicade EU Summary of Product Characteristics (SmPC).

Efficacy

Studies providing efficacy data

One pivotal efficacy/safety study (Study SB2-G31-RA) was submitted.

Evaluator's conclusions on efficacy

Study SB2-G31-RA convincingly demonstrates equivalence between SB2 and Remicade based on achieving the primary endpoint of ACR20 responses and multiple secondary endpoints including ACR50, ACR70, European League Against Rheumatism (EULAR) score and the 28-joint Disease Activity Score (DAS28).¹³

The study was designed according to EMA guidelines and adopted after consultation with the EMA and FDA. The study population was representative of patients with moderate to severe rheumatoid arthritis who were unresponsive to MTX. Most patients were female (80.1%) with a mean age of 52.1 years and the mean duration of rheumatoid arthritis was approximately 6 years. Observer bias was minimised by the randomised and double-blind design. Compliance rates were high and overall 86.5% of patients completed the 30 week treatment period for the primary analysis.

The study achieved the primary objective of equivalence of SB2 and Remicade. At Week 30 in the Per protocol set 1 (PPS1), the mean difference in ACR20 response rates was -1.88% (95% CI: -10.26, 6.51) which fell entirely within the predefined equivalence margin of $\pm 15\%$. A range of sensitivity analyses at Weeks 30 and 54 confirmed the primary analysis. In addition, there were comparable outcomes at Weeks 30 and 54 for secondary endpoints including ACR50, ACR70, DAS28 and EULAR scores. Progression of radiographic structural damage was also comparable in the two treatment groups. Response rates were significantly higher in patients who did not develop ADAs during the treatment period, compared with those who did develop ADAs. However, subgroup analyses showed no interactions based on age, gender, baseline CRP, or geographical region. Mean serum trough infliximab concentrations of both study drugs were comparable.

The equivalence margins of $\pm 15\%$ for the 95% CI for the primary endpoint are clinically appropriate and have been accepted by the EU and FDA. The secondary endpoints confirmed the primary analysis and there was no suggestion of lack of equivalence for any individual parameter. The study endpoints for rheumatoid arthritis have been universally adopted by professional bodies, including the American College of Rheumatology and regulatory authorities including the EMA and FDA. In particular, ACR20 response rates are generally accepted as a valid primary endpoint for trials in rheumatoid arthritis patients. Two year data are preferred to detect changes in progressive radiological joint damage.

¹³ The ACR (American College of Rheumatology) Response Criteria is a standard criteria to measure the effectiveness of various arthritis medications or treatments in clinical trials for Rheumatoid Arthritis. The ACR is reported as percentage improvement, comparing disease activity at two discrete time points. ACR20, ACR50 and ACR70 denotes a $\geq 20\%$, 50% and 70% improvement respectively.

Only one year data are available in Study SB2-G31-RA but there are no obvious trends to suggest different treatment effects. In the ATTRACT study, only 8% of patients developed ADAs but approximately half of rheumatoid arthritis patients can be expected to develop ADAs after one year based on other studies. In Study SB2-G31-RA at Week 54, the proportions of patients with positive ADA results in the SB2 and Remicade groups were 62.4% and 57.5%, respectively ($p = 0.27$). The presence of ADAs reduced efficacy in both groups but the differences between treatments were not statistically significant.

The study design, baseline demographics and disease characteristics were comparable to the ATTRACT study, and also to the PLANETRA study which compared the efficacy, safety and immunogenicity of Remsima and Remicade in a total of 606 patients.¹⁴ The study duration and endpoints were comparable and the same equivalence limits of $\pm 15\%$ for the 95% CI for ACR20 response were applied. In the PP population, ACR20 responses in the Remsima and Remicade groups were 73.4% and 69.7%, respectively, comparable to response rates achieved by both treatment groups in Study SB2-G31-RA. Key secondary efficacy endpoints were also comparable and no significant differences were observed for any parameter. In the PLANETRA study at Week 30, ADAs were detected in 48.4% and 48.2% of the Remsima and Remicade groups, respectively.

RA is generally accepted as a valid clinical model for assessing TNF α inhibitors by regulatory authorities. The choice of RA as opposed to other inflammatory diseases has been criticised because RA lacks sufficiently sensitive and measurable markers of response. However, markers used in RA have proved sufficiently sensitive to detect statistically and clinically significant treatment differences compared with placebo in multiple studies. RA is the most common relevant indication and there is a wide body of literature to support its use, particularly in Remicade efficacy studies.

If approval for SB2 is given, a significant proportion of RA and other patients in Australia can be expected to switch from Remicade to SB2. It should be made a condition of approval that the switch data from the transition-extension period to Week 78 of SB2-G31-RA be reviewed for both efficacy and safety (see Attachment 2, Clinical Questions). The converse switch from SB2 to Remicade is unlikely. However, this is not addressed in the transition-extension study and the sponsor should provide a justification for not doing so (see Clinical Questions). The proposed PI addresses the question of switching under 'Precautions'. Prescribers are cautioned that SB2 is not a generic Remicade and that switching should occur only under the supervision of an appropriate specialist. This statement is adequate but switch data should be added from the transition-extension study as they are presumably now available. With this exception, no further clinical studies or data are required.

Extrapolation of indications

Two important EU guidelines on similar biological medicinal products address nonclinical and clinical issues when considering bioequivalence.^{3,4} Nonclinical issues include in vitro studies such as receptor binding studies, cell based assays, binding to Fc gamma receptors, and Fab and Fc-associated functions relevant to mechanisms of action. In vivo studies include relevant PK/PD effects and nonclinical toxicity. Clinical studies should include comparative PK studies of the reference and similar products; and at least one efficacy and safety study. PD markers should be relevant to the therapeutic effects of the product, and comparative PK/PD studies may also be required. The clinical studies should fully explore immunogenicity. If comparability is established, extrapolation to other indications may be justified based on the overall quality of the data.

¹⁴ Yoo DH, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013; 72:1613-1620

A review by Weise (2014) notes that extrapolation of data is an established scientific and regulatory principle which has been exercised for many years for more than twenty biosimilar products.¹⁵ Clinical data are typically generated using appropriate comparability studies in one indication and extrapolated to the other indications. In only one case has a regulatory authority required additional clinical studies in other approved indications (a recent exception by Health Canada for an IBD indication). Acceptable data include comparable efficacy, safety and immunogenicity in a selected indication. To merit extrapolation, the mechanism of action should be carefully assessed, particularly if it involves multiple receptors or binding sites. If structure and functions, PK/PD effects and efficacy can be shown to be comparable for the biosimilar and the reference product, adverse drug reactions can also be expected at similar frequencies. However, similar immunogenicity cannot be assumed and comparability requires additional clinical confirmation.

Weise (2014) provided scientific advice to the EMA for the approval of the first biosimilar infliximab (Remsima) for which Remicade was the reference product. As noted in this review, the mechanism of infliximab is similar in rheumatological indications and in psoriasis, with binding to both soluble and membrane-bound TNF α . However, the Fc-region of infliximab is thought to contribute to the potential mechanisms associated with IBD (ADCC or CDC). Nonetheless, extrapolation was granted by the EMA based on the following arguments:

- Extensive analytical testing showed similar physicochemical and structural characteristics for Remsima compared with Remicade with only small differences in the proportion of isoforms.
- Despite the potential role of ADCC and CDC in IBD, the main mode of action in all therapeutic indications is binding to the soluble and/or membrane-bound TNF α .
- There was similar inhibition of the direct effects of TNF α on epithelial cells which play an important role in Crohn's disease.
- Induction of regulatory macrophages is a putative mode of action of infliximab in IBD. The biosimilar and reference products showed similar induction.
- A large PK study in ankylosing spondylitis patients displayed bioequivalence between the test and reference products.
- Equivalent efficacy and comparable safety and immunogenicity were demonstrated in a large, randomised study of patients in rheumatoid arthritis.

These views in relation to IBD have been challenged by bodies such as ECCO.¹⁶ In its position paper on biosimilars, ECCO proposes caution based on concerns including:

- Subtle differences in molecular structure may cause profound differences in clinical efficacy or immunogenicity.
- Rules applied to the production of generic chemical medicines cannot be transferred to biosimilars.
- Different biological and biosimilar medicines targeting the same molecule are neither identical in efficacy nor toxicity, even in the same clinical entity.

¹⁵ Weise M, et al. Biosimilars: the science of extrapolation. *Blood* 2014; 124(22):3191-3196

¹⁶ Danese S, et al. Governing Board and Operational Board of ECCO. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). *J Crohn's Colitis* 2013; 7(7):586-589

- A biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the reference biological has been shown to be safe and effective.
- Specific evidence obtained in patients with IBD should be required to establish efficacy and safety for this specific indication, because experience with currently licensed biological medicines has already shown that clinical efficacy in IBD cannot be predicted by effectiveness in other indications, such as rheumatoid arthritis (an unreferenced statement).
- Post-marketing collection of data is necessary to confirm safety and identifying any increase in frequency of predictable adverse events.
- Switching products should only be made with the knowledge and approval of the patient and prescriber.

No comparator studies of a biosimilar infliximab have been performed in indications other than RA and there is no direct clinical evidence to support the arguments of regulators or sceptics. Bodies such as ECCO recommend comparative clinical trials in IBD patients in the interest of caution. On the other hand, regulatory authorities will accept extrapolation based on a balance of probabilities that efficacy and safety will be comparable. The TGA recently approved Remsima infliximab for all indications (ARTG date: 27 November 2015). Health Canada is a notable exception as it has recently approved Remsima for rheumatological indications but rejected extrapolation to IBD.

The sponsor has submitted a justification for extrapolation based on the following arguments:

1. The mechanism of action of infliximab requires high affinity binding to both soluble and transmembrane TNF α , which occur in varying elevated concentrations in tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis and psoriasis (Lin, 2008).^{17,18} This high affinity binding has been demonstrated for SB2.
2. According to the scientific advice soluble TNF α is important in the pathogenesis of ankylosing spondylitis, psoriatic arthritis and plaque psoriasis); and membrane bound TNF α is important in paediatric and adult CD and UC as discussed above.
3. Nonclinical characterisation studies have shown similar structural, physicochemical and biological properties to Remicade. Multiple in vitro assays have explored the effects of SB2 and Remicade. These included: transmembrane tumor necrosis factor alpha (tmTNF α) binding assays, Fc receptor binding assays, CDC assays, ADCC assays and apoptosis assays (including IBD models). Overall, the results for SB2 were comparable to Remicade.
4. Although the SB2 PK profile has not been tested in doses > 5 mg/kg, infliximab has been tested in doses up to 20 mg/kg. Exposure is linear with no accumulation after multiple administrations. Although doses of up to 10 mg/kg may be required in CD patients, the frequency of administration is the same. No significant PK differences have been reported in patients with rheumatoid arthritis, ankylosing spondylitis, psoriasis and adult and paediatric Crohn's disease.^{12,19}

In the evaluators' opinion, sufficient justification has been provided to recommend extrapolation of efficacy endpoints to all other indications including IBD. The PK study,

¹⁷ Wong M, et al. TNF α blockade in human diseases: mechanisms and future directions. Clin Immunol 2008; 126:121-136

¹⁸ Lin J, et al. TNF α blockade in human diseases: an overview of efficacy and safety. Clin Immunol 2008; 126(1):13-30

¹⁹ Klotz U, et al. Clinical pharmacokinetics and use of infliximab. Clin Pharmacokinet 2007; 46(8):645-660

Study SB2-G11-NHV, showed comparability between SB2 and Remicade for all key parameters within the accepted 80 to 125% limits for the 90% CI. In the pivotal Study SB2-G31-RA in RA patients, the primary endpoint for bioequivalence was met based on ACR20 responses at Week 30. The treatment difference of -1.88% (95% CI: -10.26, 6.51) was comfortably within the predefined $\pm 15\%$ equivalence limits. Immunogenicity incidences at Week 54 were higher than those observed in similar studies; however, immunogenicity was comparable in SB2 and Remicade patients.

Based on the overall data, SB2 and Remicade are comparable and extrapolation to all indications is justified if appropriate post-marketing surveillance is ensured. However, this opinion is dependent on a positive evaluation of the in vitro data supporting comparability.

Safety

Studies providing safety data

1 pivotal efficacy study (Study SB2-G31-RA) along with 1 clinical pharmacology study (Study SB2-G11-NHV) were submitted.

Patient exposure

In Study SB2-G31-RA, mean (standard deviation (SD)) exposure to study drug was 282.2 (91.02) days in the SB2 group and 287.8 (81.68) days in the Remicade group. At Week 30, 65.2% and 65.5% of the respective groups were receiving a dose of 3 mg/kg, 19.7% and 22.9% respectively were receiving 4.5 mg/kg. In the SB2 group at Week 46, 50.7%, 17.2% and 10.7% were respectively receiving 3.0 mg/kg, 4.5 mg/kg and 6.0 mg/kg. In the Remicade group at Week 46, 50.2%, 21.2%, 5.8% and 1.7% were respectively receiving 3.0 mg/kg, 4.5 mg/kg, 6.0 mg/kg and 7.5 mg/kg. Exposure ≥ 323 days occurred in 180 and 181 patients in the SB2 and Remicade groups, respectively.

Exposure was sufficient to show comparability with the known overall safety profile of infliximab. However, the number of patients was not sufficient to detect statistically significant or clinically important differences between the biosimilar and reference products.

Safety issues with the potential for major regulatory impact

Serious skin reactions

No safety signals were detected. No serious skin reactions were reported with the exception of two SAEs of urticarial in the Remicade group.

Unwanted immunological events

The incidences of ADAs, NABs and infusion-related reactions are evaluated in Section Laboratory tests above. The incidence of ADAs was comparable in each treatment group.

A full overview of safety issues with the potential for major regulatory impact is available in Attachment 2.

Post-marketing data

Not applicable, no post-marketing data exists for this submission.

Evaluator's conclusions on safety

The assessment of clinical safety is based on Study SB2-G31-RA which included 583 patients (290 SB2, 293 Remicade). The mean duration of exposure was 282.2 days and 287.8 days in the respective groups. The incidences of adverse events (AE) up to Week 54 were comparable in the SB2 (61.7%) and Remicade (65.2%) groups and most events were of mild or moderate severity. Severe AEs were reported in 8.6% and 6.8% of the respective groups and serious adverse events (SAE) were reported in 10.0% of the SB2 group and 10.6% of the Remicade group. The most commonly reported SAEs by Preferred Term (PT) were rheumatoid arthritis (1% versus 1%) and pneumonia (1% versus 0.7%). Only one death was recorded (left ventricular failure) and this was not considered drug related. Discontinuations because of adverse events were reported in approximately 10% of each treatment group. Overall, the most commonly reported AEs by PT were latent TB (6.9%), nasopharyngitis (6.5%), alanine transaminase (ALT) increased (5.5%), rheumatoid arthritis (5.3%), headache (5.0%), upper respiratory tract infections (3.9%), aspartate transaminase (AST) increased (3.8%), bronchitis (3.8%), back pain (3.1%), arthralgia (2.7%) and pneumonia (2.6%). The incidence of AEs was comparable in subgroups defined by ADA status, age and gender. AEs of special interest (serious infections, TB, malignancies, congestive cardiac failure and infusion-related reactions) were also comparable in each treatment group. Infusion-related reactions were reported in 5.9% and 5.1% of the SB2 and Remicade groups, respectively. QuantiFERON Gold seroconversions from negative to positive occurred in 7 to 8% of the treatment groups. Treatment emergent ADAs (nearly all neutralising) were detected in approximately 60% of patients, with no significant differences between treatment groups.

The pattern and severity of adverse events in SB2-G31-RA were comparable to the PLANETRA study. In PLANETRA at Week 30, AEs had been reported in 60.1% and 60.8% of patients in the Remsima and Remicade groups, respectively. Most events were mild to moderate and SAEs were reported in 10.0% and 7.0% of the respective groups. The most commonly reported events considered drug related were latent TB and increased hepatic transaminases. Infusion reactions were reported in 6.6% and 8.3% of patients, respectively. In ADA+ patients, 6.7% and 13.3% of patients, respectively, reported infusion reactions, compared with 4.2% and 2.8%, respectively in ADA- patients.

The safety profiles of SB2 and Remicade were comparable with no notable differences between treatment groups. The pattern of adverse events is consistent with that demonstrated in the comparative study of Remsima versus Remicade. It is also consistent with the Remicade PI and other published studies. No new safety signals related to SB2 infliximab have been identified.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of Renflexis (SB2) in the proposed usage are:

- Equivalent PK to Remicade in single dose studies in healthy subjects.
- Equivalent to Remicade for efficacy, safety and immunogenicity in patients with rheumatoid arthritis.
- Extrapolation to other rheumatological indications including IBD.

First round assessment of risks

The risks of Renflexis (SB2) in the proposed usage are:

- No unique risks have been identified compared with Remicade.
- Risks related to loss of efficacy, new safety signals and immunogenicity may emerge with long-term use in larger patient numbers.
- Dangers related to switching between SB2, Remicade and other infliximab biosimilars have not yet been quantified.
- Some authorities and professional bodies do not accept extrapolation to patients with IBD.

First round assessment of benefit-risk balance

The benefit-risk balance of Renflexis given the proposed usage, is favourable. Acceptable equivalence to the reference product in patients with rheumatoid arthritis has been demonstrated based on criteria outlined in the relevant guidelines published by the EMA and TGA. Extrapolation to other rheumatological indications and to IBD are permitted within the regulatory framework if the balance of probabilities is favourable based on equivalent PK, PD, efficacy, safety and immunogenicity. In the view of the EMA, equivalence was demonstrated, and the balance of probabilities was considered favourable for the first infliximab biosimilar Remsima, and more recently for Renflexis. Based on the same criteria, the TGA has also recently approved Remsima for all indications including IBD.

As discussed above (see Clinical evaluator's conclusions on efficacy), TNF α is elevated in rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and ulcerative colitis. Inhibition of soluble TNF α receptors is important in the rheumatological indications, but transmembrane receptor inhibition is also important in IBD patients. Other mediating processes such as reverse signalling, apoptosis, ADCC, and CDC may also be important. Differing mechanisms of action related to TNF α inhibition may distinguish the rheumatological and IBD indications. However, a series of nonclinical studies have shown comparable effects for SB2 and Remicade. Moreover, although CD patients may require higher doses of infliximab, PK studies of up to 20 mg/kg have shown linear kinetics with no evidence of accumulation. Studies of SB2 doses > 5 mg/kg have not been performed with SB2 but there is no reason to expect PK differences at higher doses in Crohn's disease patients.

Renflexis has comparable effects to Remicade in in vitro and in vivo assays, comparable PK in healthy subjects, comparable efficacy and safety in rheumatoid arthritis patients, and similar immunogenicity. On the balance of probabilities, the overall evidence supports equivalence, and extrapolation to other rheumatological conditions and IBD is appropriate.

The risks associated with switching between Renflexis, Remicade and other biosimilars are largely unknown. They should be assessed with analysis of transition-extension data in Study SB2-G31-RA and by appropriate post-marketing pharmacovigilance, particularly in patients with IBD. Switching should be undertaken only by specialists in the appropriate therapeutic areas.

First Round Recommendation Regarding Authorisation

Approval is recommended for the proposed indications (conditional to satisfactory responses to clinical questions and a positive evaluation of the quality data).

Second Round Evaluation of clinical data submitted in response to questions

For details of the evaluator's questions, sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

No change to the first round assessment.

Second round assessment of risks

No change to the first round assessment.

Second round assessment of benefit-risk balance

No change to the first round assessment. The benefit-risk balance remains positive.

Second round recommendation regarding authorisation

Approval is recommended for the proposed indications.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk management plan (RMP) as follows: EU-RMP Version 2.0 (dated 20 August 2015, data lock point 27 March 2015) and Australian Specific Annex (ASA) Version 1.0 (dated 1 September 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 2.

Table 2. Ongoing safety concerns provided by the sponsor in the RMP submission

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

Summary of safety concerns	
	<p>Demyelinating disorders</p> <p>Lymphoma (excluding HSTCL)</p> <p>Hepatobiliary events</p> <p>HSTCL</p> <p>Intestinal or perianal abscess (in Crohn's disease)</p> <p>Serious infusion reactions during a re-induction regimen following disease flare</p> <p>Sarcoidosis/sarcoid-like reactions</p> <p>Paediatric malignancy</p> <p>Leukaemia</p> <p>Acute hypersensitivity reaction (including anaphylactic shock)</p> <p>Melanoma</p> <p>Merkel cell carcinoma</p>
Important potential risks	<p>Malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma)</p> <p>Colon carcinoma/dysplasia (in ulcerative colitis)</p> <p>Skin cancer (excluding melanoma and Merkel cell carcinoma)</p> <p>Exposure during pregnancy</p> <p>Infusion reaction associated with shortened infusion duration (in rheumatoid arthritis)</p>
Missing information	<p>Long-term safety in adults patients with ulcerative colitis, psoriatic arthritis or psoriasis</p> <p>Long-term safety in children with Crohn's disease and ulcerative colitis</p> <p>Long-term safety in children</p> <p>Safety in very young children (< 6 years)</p> <p>Use of infliximab during lactation</p>

Pharmacovigilance plan

The sponsor proposes additional pharmacovigilance activities. The additional pharmacovigilance activities are summarised below:

- Study SB2-G31-RA
 - A randomised, double blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, PK and immunogenicity of SB2 compared to Remicade in subjects with moderate to severe rheumatoid arthritis despite MTX therapy.

- BSRBR-RA (category 3)
 - An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice.
- ARTIS (category 3)
 - A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in rheumatoid arthritis, juvenile idiopathic arthritis, and other rheumatic disease patients treated with infliximab
- UK IBD (category 3)
 - Facilitate continuous improvement in IBD patient care and access to care across the UK
 - Improve understanding of long-term outcomes for IBD patients
 - Support IBD research
- RABBIT (category 3)
 - A prospective, observation 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 rheumatoid arthritis and compare this to a cohort of rheumatoid arthritis patients who are treated with non-biologic DMARDs.
- Spanish Registry of Adverse Events of Biological Therapies (BIOBADASER)
 - To identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, and to estimate the frequency of their occurrence
 - To identify unexpected adverse events
 - To identify relevant adverse events that occur following the suspension of the treatment
 - To estimate the relative risk of occurrence of adverse events with biological therapies in patients with rheumatoid arthritis compared to those not exposed to these treatments
 - To identify risk factors for suffering adverse reactions with these treatments
 - To evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of treatment.

Risk minimisation activities

The sponsor is proposing additional risk minimisation activities.

The sponsor provides the following information with regard to the educational materials for health care providers (HCPs):

[The sponsor] will develop and implement an additional risk minimisation plan aimed at minimising the risk of serious, potentially preventable morbidity and mortality which may be associated with the treatment of SB2. Also, these measures aim to encourage adverse event reporting and product traceability. Key elements of the proposed additional risk minimisation measures are listed below.

1. Expected Trainees

Health care professionals (HCPs)

2. Education Materials

[The sponsor] will adopt an educational approach similar to the activities in place for the reference product. The following comprehensive educational curriculum will be developed to assist in training and educating HCPs before the prescription of the drug:

- *The educational curriculum for all indications is intended to ensure that HCPs are aware of the risk of serious and potentially life-threatening adverse reactions, including TB and other infections, and to provide guidance on appropriate screening and selection of patients.*
- *The educational curriculum for the indications paediatric Crohn's disease and paediatric ulcerative colitis is intended to ensure that HCPs are aware of the following:*
 - *The risk of opportunistic infections and tuberculosis (TB) in patients treated with SB2.*
 - *The need to assess the risk of TB in patients prior to treating with SB2.*
 - *The risk of acute infusion related reactions and delayed hypersensitivity reactions.*
 - *The risk of lymphoma and other malignancies.*
 - *The patient alert card, which is to be given to patients using SB2.*
 - *That children may be at increased risk of developing infections and the need for immunisations to be up to date.*
- *For traceability purposes, HCPs will also be educated of the importance of recording both the brand name and batch number of the product each patient receives.*
- *Core educational materials are subject to modification in various country-specific contexts.*
- *Educational materials will be constantly updated for further improvements.'*

'For additional risk minimisation, the format to be adopted will be similar to that of the reference product Remicade. The Patient Alert Card (PAC) is not applicable in Australia, but educational programs will be provided, with separate review and approval by the TGA.'

Reconciliation of issues outlined in the RMP report

Table 3 summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the TGA's evaluation of the sponsor's responses.

Table 3. Reconciliation of issues outlined in the first round RMP evaluation

Sponsor's response to Round 1 recommendations with RMP evaluator's comment
<p><i>TGA recommendation 1:</i> Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA consolidated request for further information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.</p>

Sponsor's response to Round 1 recommendations with RMP evaluator's comment

Sponsor's response: No safety considerations have been raised in the nonclinical and clinical evaluation reports. The questions regarding clinical efficacy are not considered to be associated with safety issues. The sponsor is providing the 78-Week clinical study report describing safety, efficacy and immunogenicity endpoints to cover the transition-extension period of Study SB2-G31-RA to Week 78, from which the sponsor has not found any new safety concerns.

RMP evaluator comment: The sponsor's response is acceptable

TGA recommendation 2: It is recommended that the following should be added as Safety Concerns/Missing Information items and become part of the risk management plan: Bowel stenosis (in Crohn's disease) (or a similar term to the same effect) should be added as an Important Potential Risk.

Sponsor's response: Bowel stenosis (in Crohn's disease) (or a similar term to the same effect) was requested to be excluded from the Renflexis EU RMP in PRAC Rapporteur Risk Management Plan Assessment Report. Although the rationale for this request was not provided by the PRAC, the sponsor understands that this is in order to be in line with the safety concerns of the reference product. This is supported by the fact that the same deletion had been made to the RMP of Remsima, another biosimilar to Remicade, which was included in information published on the EMA website on October 30, 2015 (EMA/PRAC/722174/2015).

The sponsor respectfully proposes that bowel stenosis should not be included as an important potential risk since the reference product Remicade does not define it as a safety concern in the EU RMP and the sponsor does not have any reasonable company data to categorise bowel stenosis as an important potential risk.

RMP evaluator comment: Bowel stenosis, stricture or obstruction in Crohn's disease was removed from the EU-RMP for the innovator product (Remicade) in 2013. Considering this, the sponsor's position is supported.

TGA recommendation 3: The sponsor should state how the additional pharmacovigilance activities in the pharmacovigilance plan that may use infliximab products other than Renflexis will capture which infliximab preparation is used (that is Remicade, Renflexis, or another product).

Sponsor's response: The sponsor plans to collect relevant safety information through five European registry programs: BSRBR-RA, ARTIS, UK IBD, RABBIT, and BIOBADASER. The registries capture clinical data using brand names, and data relating only to Flixabi (the brand name of Renflexis in the European countries) will be provided to the sponsor, following the confidential agreement between participating stakeholders in the registries, including other pharmaceutical companies.

RMP Evaluator comment: The sponsor's response adequately addresses the concerns regarding the registries and is acceptable

TGA recommendation 4: The following additional risk minimisation activity items are required: Dosing/infusion schedule card (for patients); Educational brochure (for

Sponsor's response to Round 1 recommendations with RMP evaluator's comment
health professionals); Prescriber checklist (as an aid for the prescriber); A Dear Healthcare Professional Letter (containing the following information: biosimilar status; main adverse events (infections (including sepsis, tuberculosis and opportunistic infections), malignancy (for example lymphoma), and immunogenicity); contraindications; reference to PI).
<p><i>Sponsor's response:</i> the drafts of the following risk minimisation activity items are provided as separate attachments in PDF format. These include:</p> <ul style="list-style-type: none"> • Dosing/infusion schedule card: 3 types of schedule cards for Dermatology, Gastroenterology and Rheumatology areas • Educational brochure: product overview for HCP with important clinical information • Prescriber checklist: checklist of topics specific to the administration of Renflexis that can be used to assess patient prior to their infusion • A Dear Healthcare Professional Letter: reminder of essential information regarding Renflexis treatment.
<p><i>RMP evaluator comment:</i> The draft educational risk minimisation items have been reviewed. A distribution plan has also been provided for the material. The sponsor's approach is acceptable.</p>
<p>TGA recommendation 5: For this submission, the sponsor should provide the TGA with the following details for agreement: All draft Australian education materials; and a clear distribution plan for Australia.</p>
<p><i>Sponsor's response:</i> Draft material and distribution plan were provided, see above.</p>
<p><i>RMP evaluator comment:</i> The sponsor's response is acceptable (see above).</p>
<p>TGA recommendation 6: In the 'Description' section, the PI should contain a statement that Renflexis is a biosimilar to the reference product Remicade (or a statement to that effect), despite the existing similar statement in the 'Precautions' section.</p>
<p><i>Sponsor's response:</i> The sponsor has adopted the recommendation and included the statement in the 'Description' section of the PI, subject to the agreement of the Delegate.</p>
<p><i>RMP evaluator comment:</i> The sponsor's response is acceptable, pending the Delegate's consideration</p>
<p>TGA recommendation 7: In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicines information document be revised to accommodate the changes made to the product information document.</p>
<p><i>Sponsor's response:</i> The sponsor has revised the draft consumer medicines information (CMI) document reflecting the update in the product information document, subject to</p>

Sponsor's response to Round 1 recommendations with RMP evaluator's comment

the agreement of the Delegate.

RMP evaluator comment: The sponsor's response is acceptable.

Summary of recommendations

There are no outstanding issues in relation to the RMP for this submission.

Advisory Committee on the Safety of Medicines (ACSOM) advice was not sought for this submission.

The suggested wording for conditions of registration are as follows:

- Implement EU-RMP Version 3.0 (dated 1 April 2016, DLP 27 April 2015) with Australian Specific Annex Version 2.0 (dated 18 May 2016) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

This submission is to register a biosimilar version of infliximab (Remicade) under the product name Renflexis which was developed by Samsung Bioepis. In this submission, similarity to Remicade (the reference medicinal product) is claimed. The application for Renflexis, also known as SB2, is requesting approval of the same seven indications currently approved for Remicade in Australia.

This submission also includes advice (Addendum) from the clinical unit at the TGA that manages the IBD and psoriasis indications.

The TGA has produced a specific guideline in relation to biosimilar medicines along with the adoption of numerous EU guidelines that explains the background to biosimilars and regulatory aspects. The TGA published guideline is called 'Evaluation of biosimilars' which was published on 30 July 2013 and was updated in December 2015. This guideline notes that a biosimilar medicine is a version of an already registered biological medicine that:

- Has a demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on comprehensive comparability studies.
- Before a biosimilar medicine can be registered in Australia, a number of laboratory and clinical studies need to be performed to demonstrate the comparability (biosimilarity) of the new biosimilar to the reference biological medicine already registered in Australia.
- The TGA has adopted a number of European guidelines that outline the quality, nonclinical and clinical data requirements specific to biosimilar medicines; and the ICH guideline on the assessment of comparability.
- For a biosimilar to be registered in Australia, the reference medicine must be a biological medicine that has been registered in Australia based on full quality, safety

and efficacy data and the Australian reference medicine must have been marketed in Australia for a substantial period and have a volume of marketed use so that there is likely to be a substantial body of acceptable data regarding the safety and efficacy for the approved indications. However it may be possible for the sponsor to compare the biosimilar in certain clinical studies and in vivo nonclinical studies to a medicine not registered in Australia in which case the reference medicine must be approved for general marketing by a regulatory authority with similar scientific and regulatory standards as the TGA (for example the EMA or US FDA) and a bridging study must be provided to demonstrate that the comparability studies are relevant to the Australian reference medicine.

- To justify extrapolated indications based on Section 6 of the adopted EU guideline.
- To have a clearly distinguishable tradename from all other products and the active ingredient is to use the same name as the reference's active ingredient without a specific biosimilar identifier suffix. The World Health Organization are considering a naming convention for the active ingredients of all biological medicines, including biosimilars.
- The inclusion of comparative clinical trial information in the PI along with a clear distinction of the clinical trial information generated on the reference medicine.
- There may be post-registration requirements and all biosimilars must have an RMP.

There are a number of specific EU guideline adopted by the TGA relevant to this submission, besides the general guidelines:

- CPMP/EWP/556/95 Rev 1: Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis. Effective: 29 January 2007
- EMEA/CHMP/EWP/438/04: Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis. Effective: 5 February 2008
- CPMP/EWP/4891/03: Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis. Effective: 23 February 2010
- CHMP/EWP/2454/02: Guideline on clinical investigation of medicinal products indicated for the treatment of Psoriasis. Effective: 28 July 2005
- CPMP/EWP/2284/99 Rev. 1: Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease. Effective: 25 February 2009
- CHMP/EWP/18463/2006: Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis. Effective: 8 April 2009
- CHMP/437/04/Rev 1: Guideline on Similar Biological Medicinal Products. Effective: 25 May 2015
- EMA/CHMP/BMWP/86289/2010: Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. Effective: 1 June 2014
- EMA/CHMP/BMWP/403543/2010: Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. Effective: 17 August 2015

Quality

The quality evaluator has recommended approval on quality grounds and has recommended batch release testing as a condition of registration. However there were some differences in the physicochemical characteristics of infliximab in Renflexis when

compared with Remicade due to the use of different cell substrates for production, cell culture and purification conditions. It was not clear whether these differences in quality attributes have any clinical implications. The sponsor used the EU sourced Remicade as the reference product in the clinical study, therefore a bridging comparability study was undertaken to compare EU and Australian sourced Remicade. The structural, physicochemical and biological activity properties of Renflexis and EU Remicade were studied and a detailed comparison in the primary quality evaluation report. Based on all the comparison studies, Renflexis and EU Remicade are generally similar (and a bridging comparability study between EU Remicade and Australian Remicade showed comparability in terms of primary structure, physicochemical properties and biological activities), however some differences were noted (see Quality findings, Biosimilarity above)

Sufficient evidence has been provided to demonstrate that the risks related to the presence of adventitious agents (virus, prions and mycoplasma) in the manufacturing of Renflexis have been controlled to an acceptable level. Container safety was deemed acceptable and there were no objections from a microbiological perspective or bacterial endotoxin testing. A shelf life of 24 months²⁰ when stored at 5°C ± 3°C was supported by the data. The PI, CMI and labels from a quality perspective were accepted by the evaluator.

Nonclinical

The nonclinical evaluator had no objections to the registration of Renflexis providing the quality aspects were acceptable to the quality evaluator.

The nonclinical dossier contained comparative studies on pharmacology and pharmacokinetics against EU and US sourced Remicade and bridging studies showed that Australian-sourced Remicade was similar to other comparators. The scope of the nonclinical program was in general accordance with the EU guideline on nonclinical assessment of biosimilars of monoclonal antibodies. Pharmacological activity of Renflexis was generally comparable to that of Remicade under in vitro conditions. Some subtle differences were noted for some of the tested parameters (such as higher binding affinities for some Fc-receptor related targets) but these differences did not extend to effects on biological responses in vivo. Under in vivo conditions, Renflexis and Remicade produced similar dose-dependent attenuation of inflammation in a mouse model of arthritis (Tg197 mice) over a 7 week period compared with untreated vehicle controls. The PK profile of Renflexis indicated similar absorption to the Remicade comparators under single and repeat dose study conditions in rodents. In the repeat dose study, ADAs developed at the end of the 7 week dosing period but the incidence of ADA development was similar for all infliximab formulations. Clinical plasma kinetic measurements indicated bioequivalence between the infliximab formulations. The lack of toxicity testing, local tolerance and juvenile animal studies was acceptable.

In vitro comparability studies between Renflexis and EU or US sourced Remicade showed a number of qualitative similarities in biological activities, which included: binding affinity for human soluble and transmembrane TNF α but not for TNF β , neutralisation of TNF α and suppression of cytokine IL-8 release, induction/inhibition of apoptosis, binding affinity for Fc γ RI, Fc γ RIIa, Fc γ RIIb, Fc γ RIIIa (F/F allotype), C1q and induction of CDC, ADCC and recruitment/induction of regulatory macrophages. Subtle differences were noted in that Renflexis exhibited slightly higher binding affinity for Fc γ RIIb, Fc γ RIIIa (V/V allotype) and FcRn receptors compared to Remicade. With regard to Fc γ RIIIa binding, exploration of functional consequences found ADCC activity was also slightly higher with Renflexis but only when the NK92-CD16 cell line was used as a source of NK effector cells. However, the

²⁰ An extension from 24 to 30 months for the drug product was approved on 11 July 2017.

extent of cell lysis (a measure of ADCC activity) was comparable between infliximab formulations when PBMCs, a more physiologically relevant source of NK cells, were used. Nevertheless, from a nonclinical perspective, the slightly higher affinity exhibited by Renflexis for FcγRIIIa and the potential for enhanced ADCC activity was not anticipated to have adverse implications to the efficacy of Renflexis.

Clinical

Pharmacokinetics

The clinical dossier presented 2 studies for demonstrating similarity in PK characteristics between Renflexis and Remicade. The Phase I study (Study SB2-G11-NHV) in healthy volunteers was considered the primary PK study for demonstrating similarity, and the population PK sub-study of the Phase III study (Study SB2-G31-RA) provided supporting evidence.

The first study was a single dose, randomised, single blind, three arm, parallel group, Phase I study conducted in 159 healthy subjects at a single centre comparing Renflexis, EU Remicade and US Remicade. Infliximab was given by IV infusion at a dose of 5 mg/kg over a period of 2 hours with IV hydrocortisone (100 mg), oral paracetamol (1000 mg) and oral loratadine (10 mg) as prophylaxis against infusion reactions. A conventional cross-over design was not possible because of the long half-life of infliximab and the risks of immunogenicity in healthy subjects. PK variables (area under the curve from time zero to infinity (AUC_{inf}) area under the curve up to last measurable concentration (AUC_{last}) and C_{max} using 0.8 to 1.25 confidence limits) were measured to compare Renflexis with EU and US sourced infliximab and to compare EU and US sourced Remicade. Similarity was demonstrated as follows:

- Renflexis and EU Remicade were comparable (ratio) for:
 - AUC_{inf} (0.986, 90%CI 0.897 to 1.083)
 - AUC_{last} (0.994, 90%CI 0.915 to 1.079)
 - C_{max} (1.007, 90%CI 0.964 to 1.052)
 - T_{max} and $t_{1/2}$ were similar
 - Renflexis and US Remicade were comparable
 - EU Remicade and US Remicade were also comparable.

ADA development showed a higher rate on Renflexis than EU or US sourced Remicade (47.2%, 37.7% and 37.7% in the Renflexis, EU-Remicade and US Remicade groups, respectively). Volume of distribution and mean terminal $t_{1/2}$ were comparable (4.59 L versus 4.85 L and 324 h versus 339 h respectively).

The second study was a sub-study of the Phase III clinical study in rheumatoid arthritis. This sub-study was conducted in 309 patients (160 Renflexis and 149 EU Remicade) who provided baseline and trough levels at 2, 6, 14, 22 and 30 weeks. Steady state concentrations for Renflexis and Remicade were achieved between Weeks 14 to 22 of therapy. Mean serum trough concentrations of infliximab were comparable between Renflexis (ranging from 3.593 µg/mL at Week 14 to 1.915 µg/mL at Week 30) and EU Remicade (ranging from 3.380 µg/mL at Week 14 to 2.224 µg/mL at Week 30). Both formulations of infliximab exhibited high variability with the co-efficient of variation (%) ranging up to 300% for Renflexis and 213% for EU sourced Remicade. The evaluator noted that mean trough concentrations were comparable between treatment groups in ADA- and ADA+ patients at Week 30.

Pharmacodynamics

This submission did not contain any specific pharmacodynamic data which is acceptable.

Efficacy

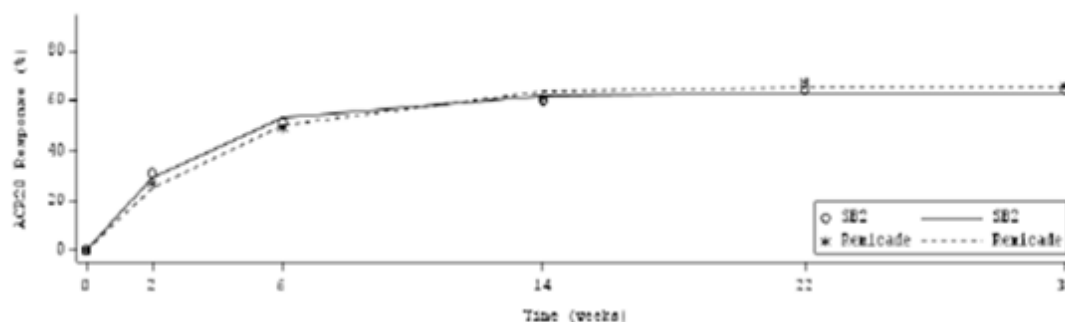
The dose selected for the pivotal study was based on the approved dose used in the Remicade PI.

Study SB2-G31-RA

This study was a 54 week, multinational, multicentre, randomised, double-blind, parallel-group, comparative equivalence trial of 3 mg/kg IV infusion of Renflexis versus EU Remicade in 584 patients with moderate to severe rheumatoid arthritis, despite MTX treatment, at Weeks 0, 2 and 6 and then every 8 weeks until the final dose at Week 46. The rheumatoid arthritis indication was selected after consultation with the EMA and FDA. Patients who had a suboptimal response to therapy at Week 30 had the option to increase the dose of study drug by 1.5 mg/kg increments to a maximum dose of 7.5 mg/kg. MTX at a dose of 10 to 25 mg weekly and folic acid were taken during the study. The study had 82% power and an equivalence margin of $\pm 15\%$. To declare equivalence between the 2 treatment groups, the 2-sided 95% CI of the difference of the two populations should be contained within $\pm 15\%$. Study completion to week 54 was 77.4%. At week 54, 21.2% of patients (20.6% Renflexis, 21.8% Remicade) had withdrawn from the study, most commonly due to withdrawal of consent (7.9% versus 8.9%) and adverse events (9.3% versus 7.2%). Protocol deviations occurred in 20.4% of subjects but were similarly matched across treatments. At baseline, both groups had comparable demographic and disease characteristics (mean 52 years, 80% female, 87% White, mean 6.4 years of rheumatoid arthritis, mean 14.7 mg of MTX at baseline with a mean 51 months prior use, mean 23.8 tender joints, mean 14.8 swollen joints, mean 13.0 mg/L CRP, mean 45.7 mm/h erythrocyte sedimentation rate (ESR), 72.4% Rheumatoid factor positive).

The primary efficacy outcome using the validated ACR20 response at Week 30, per protocol analysis, demonstrated equivalence at 64.1% for Renflexis and 66.0% for Remicade (treatment difference of -1.88% , 95% CI: -10.26% to 6.51%); that is, within the pre-specified equivalence margins. The full analysis set cohort demonstrated similar findings (55.5% for Renflexis and 59.0% for Remicade, -2.95% , 95% CI: -10.88% , 4.97%). A time-response curve demonstrated a close fit for ACR20 response, as shown below in Figure 1.

Figure 1. Study SB2-G31-RA, Time-response model for ACR20 response up to Week 30 (Per protocol set 1)



ACR20 responses at Week 30 (using the PPS1 cohort) were equivalent between the two treatment groups for baseline CRP reading (≥ 10 mg/L versus < 10 mg/L), region (EU versus non-EU), age (< 65 years versus ≥ 65 years) and gender. In the Renflexis group, mean CRP was 11.7 mg/L at baseline and 8.8 mg/L at Week 54. In the Remicade group,

mean CRP was 12.9 mg/L at baseline and 8.3 mg/L at Week 54. In the Renflexis group, mean Health Assessment Questionnaire Disability Index (HAQ-DI) score was 1.46 at baseline and 0.99 at Week 54. In the Remicade group, mean HAQ-DI was 1.51 at baseline and 0.98 at Week 54. Secondary efficacy endpoints comparing Renflexis to Remicade (treatment difference) were supportive:

- ACR20 at Week 54 (PPS2): 65.3% versus 69.2% (-3.07%, 95%CI -12.00%, 5.86%)
- ACR20 at Week 54 (FAS): 50.7% versus 52.6% (-1.15%, 95%CI -9.16%, 6.86%)
- ACR50 at Week 30 (PPS1): 35.5% versus 38.1% (-2.13%, 95%CI -10.69%, 6.43%)
- ACR70 at Week 30 (PPS1): 18.2% versus 19.0% (-0.25%, 95%CI -7.26%, 6.75%)
- ACR50 at Week 54 (PPS2): 41.6% versus 38.9% (3.43%, 95%CI -5.74%, 12.6%)
- ACR70 at Week 54 (PPS2): 22.3% versus 24.0% (-1.07%, 95%CI -9.12%, 6.98%)
- DAS28 score at Week 30: 2.411 versus 2.367 (0.044, 95%CI -0.186, 0.274)
- DAS28 score at Week 54: 2.469 versus 2.472 (-0.004, 95%CI -0.246, 0.239)
- EULAR at Week 30: good was 25.7% versus 25.7%, moderate was 58.1% versus 54.7%
- EULAR at Week 54: good was 31.7% versus 27.9%, moderate was 48.5% versus 55.4%
- Major Clinical Response (ACR70 for 6 months) at week 54: 7.9% versus 6.5%
- Change from baseline in the modified total Sharp score (mTSS) at Week 54 (FAS): 0.38 units versus 0.37. Change in joint erosions was 0.14 versus -0.03 and change in joint space narrowing was 0.24 versus 0.40.

The ACR20 response rate at Week 30 was lower in the ADA+ subgroup than in the ADA- subgroup, however, the response rates were comparable in the Renflexis and Remicade groups irrespective of the ADA status (see Table 4, below). The differences were within the equivalence margins of $\pm 15\%$ and there was no significant interaction between treatment and overall ADA status. At Week 30 and Week 54, ACR50 and ACR70 response rates in ADA- and ADA+ subgroups were similar.

Table 4. ANCOVA for ACR20 Response at Week 30 by 30-week ADA result and treatment (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%)	0.989
	Remicade (N=126)	126 74 (58.7)			
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.

- A double blind extension phase of an additional 24 weeks was undertaken in which patients receiving Renflexis continued on treatment (n = 201) and Remicade patients in the initial phase were re-randomised to continue on Remicade (n = 101) or transition to Renflexis (n = 94). About 93.4% completed 78 weeks of therapy. At Week 78, the rate of ACR20 response was 68.3% in the continuing Renflexis group (65.7% at Week 54 in this group) and 63.5% in patients who switched from Remicade to Renflexis (71.3% at Week 54 in this group) as shown below in Table 5. ACR50 and 70 showed a similar response.

Table 5. Study SB2-G31-RA ACR, response rates by visit from Week 54 to Week 78

ACR Response	Timepoint	SB2		Remicade®			
				SB2		Remicade®	
		n/n'	(%)	n/n'	(%)	n/n'	(%)
ACR20	Week 54	132/201	(65.7)	67/94	(71.3)	70/101	(69.3)
	Week 62	129/193	(66.8)	68/94	(72.3)	67/101	(66.3)
	Week 70	118/180	(65.6)	61/88	(69.3)	68/98	(69.4)
	Week 78	123/180	(68.3)	54/85	(63.5)	64/93	(68.8)
ACR50	Week 54	87/201	(43.3)	39/94	(41.5)	40/101	(39.6)
	Week 62	79/193	(40.9)	42/94	(44.7)	42/101	(41.6)
	Week 70	78/180	(43.3)	36/88	(40.9)	43/98	(43.9)
	Week 78	73/180	(40.6)	32/85	(37.6)	44/93	(47.3)
ACR70	Week 54	49/201	(24.4)	25/94	(26.6)	23/101	(22.8)
	Week 62	41/193	(21.2)	22/94	(23.4)	21/101	(20.8)
	Week 70	46/180	(25.6)	18/88	(20.5)	25/98	(25.5)
	Week 78	46/180	(25.6)	19/85	(22.4)	29/93	(31.2)

n' = number of subjects with an available assessment; n = number of responders

Safety

The mean exposure to Renflexis was 282 days with 180 patients exposed for ≥ 323 days. At Week 46, 50.7%, 17.2% and 10.7% respectively were receiving 3.0 mg/kg, 4.5 mg/kg and 6.0 mg/kg compared to 50.2%, 21.2%, 5.8% and 1.7% respectively were receiving 3.0 mg/kg, 4.5 mg/kg, 6.0 mg/kg and 7.5 mg/kg on Remicade. AEs were reported by 61.7% and 65.2% of patients in the Renflexis and Remicade groups. Comparing Renflexis with Remicade, AEs reported most commonly by class (as shown in Table 6, below) were infections and infestations (29.3% versus 37.5%), musculoskeletal and connective tissue disorders (13.1% versus 13.3%), investigations (14.8% versus 10.6%), gastrointestinal disorders (9.7% versus 10.9%), skin and subcutaneous tissue disorders (9.7% versus 10.6%) and nervous system disorders (9.0% versus 10.2%). The most common events are listed below and of note were latent TB (6.6% versus 7.2%), ALT increased (7.9% versus 3.1%), rheumatoid arthritis (6.9% versus 3.8%) and AST increased (4.1% versus 3.4%). Adverse drug reactions (Treatment-related adverse events) overall were similar between groups (24.1% and 23.5%) but differences were seen in infections (6.6% versus 9.2%) and investigations (7.2% versus 1.7%) with ALT increased (4.5% versus 0.7%), AST increased (3.1% versus 0.7%) and latent TB (1.4% versus 2.4%). Acute infusion reactions occurred in 5.9% versus 5.1% with most reactions being mild or moderate and all patients recovered. There were two events of hypersensitivity and one anaphylactic reaction on Renflexis compared with one event of urticaria and one event of anaphylactic shock on Remicade. All of the serious infusion-related reactions occurred in ADA+ patients. A similar proportion of patients had AEs by age and gender.

Table 6. Most common adverse events (≥ 2% incidence) by Preferred Term in Study SB2-G31-RA (Safety set)

Treatment	SB2		Remicade®		Total	
	N=290		N=293		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.

One death, considered unrelated, was reported in the Remicade group. AEs leading to discontinuation were 10.3% versus 8.2% and SAEs were 10.0% versus 10.6% with serious infections and infestations (4.1% versus 2.4%) being most common (pneumonia 1.0% versus 0.7%). In the Renflexis group, there were 3 SAEs due to pneumonia versus 2 cases in the Remicade group. Neoplasms were reported in 4 patients on Renflexis versus 1 on Remicade. A total of 18 subjects (6.2%) in the Renflexis group and 25 subjects (8.5%) in the Remicade arm had a positive QuantiFERON Gold test (QFG) at Baseline. Overall, 12.5% and 14.2% of the respective groups had a post-screening positive QFG test at some point in the treatment period and 7.5% versus 7.8% of patients had a shift in QFG test from negative at baseline to positive by Week 54. Active TB was reported in one case (0.3%) in the Renflexis group (tuberculous pleurisy) and in one case (0.3%) in the Remicade group (pulmonary TB). None of the patients with latent TB (that is, QFG+) at screening developed active TB during the study following TB prophylaxis treatment. Elevated ALT occurred in 11.9% versus 9.4% at Week 54 (AST was 12.4% versus 9.0%). There were no possible Hy's law cases. Elevated serum creatinine was 2.2% versus 5.4%. There were no notable differences in biochemistry or haematology (increased neutrophils was 2.8% versus 1.4%). Electrocardiograph (ECG) and vital sign changes were mostly similar.

Positive ADA results were reported in 62.4% versus 57.5% ($p = 0.27$) and neutralising antibodies were detected in 92.7% versus 87.5% of the respective groups. In ADA-patients up to Week 54, AEs were reported in 60.2% versus 72.6% respectively. In ADA+ patients up to Week 54, AEs were reported in 62.6% versus 60.1% respectively. The incidence of serious TEAEs up to Week 54 by ADA status was comparable between the groups.

In the extension phase, AEs were reported in 40.3% of continuing Renflexis patients versus 36.2% in the switched patients and 35.6% in the patients who stayed on Remicade. Treatment related AEs and AEs leading to discontinuation were similar across groups. Comparing those who stayed on Renflexis with those who stayed on Remicade, infusion related AEs were 3.5% versus 2.0%, serious AEs were 3.5% versus 3.0% and latent TB was 5.5% versus 4.0%. There were no deaths. At Week 78, ADAs were detected in 53.6% of the Renflexis group versus 50.5% of the Remicade group, and the majority of these antibodies were neutralising (91.3% versus 88.2% respectively).

After switching from Remicade to Renflexis at Week 54, SAEs were higher on Renflexis (6.4%) than in those continuing to receive Remicade (3.0%), as shown below in Table 7. There were numerical differences in AEs reported by PT although the pattern of events in each group was mostly comparable. Infusion related reactions (3.2% versus 2.0%), increased ALT (4.3% versus 1.0%), AST (4.3% versus 2.0%) and latent TB (7.4% versus 4.0%) were slightly more common in the switch group than those who stayed on Remicade. However, interpretation is confounded by low event numbers in each group. At Week 78, ADAs were detected in 45.7% of the switch group versus 50.5% of the Remicade group, and the majority of these antibodies were neutralising (88.4% versus 88.2% respectively).

Table 7. SB2-G31-RA AEs by PT reported in the transition period

Treatment	SB2			Remicade®						Total					
	N=201			Overall		SB2		Remicade®		N=396					
				n	(%)	E	n	(%)	E				n	(%)	E
Preferred term	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E			
TEAEs	81	(40.3)	147	70	(35.9)	138	34	(36.2)	65	36	(35.6)	73	151	(38.1)	285
Latent tuberculosis	11	(5.5)	14	11	(5.6)	13	7	(7.4)	9	4	(4.0)	4	22	(5.6)	27
Nasopharyngitis	11	(5.5)	11	6	(3.1)	7	2	(2.1)	2	4	(4.0)	5	17	(4.3)	18
Rheumatoid arthritis	7	(3.5)	8	6	(3.1)	7	2	(2.1)	2	4	(4.0)	5	13	(3.3)	15
ALT increased	5	(2.5)	5	5	(2.6)	5	4	(4.3)	4	1	(1.0)	1	10	(2.5)	10
AST increased	4	(2.0)	4	6	(3.1)	6	4	(4.3)	4	2	(2.0)	2	10	(2.5)	10
Upper respiratory tract infection	1	(0.5)	1	8	(4.1)	10	3	(3.2)	3	5	(5.0)	7	9	(2.3)	11
Bronchitis	5	(2.5)	5	3	(1.5)	3	1	(1.1)	1	2	(2.0)	2	8	(2.0)	8
Pharyngitis	1	(0.5)	1	2	(1.0)	2	2	(2.1)	2	0	(0.0)	0	3	(0.8)	3
Tonsillitis	0	(0.0)	0	3	(1.5)	4	2	(2.1)	3	1	(1.0)	1	3	(0.8)	4
Headache	1	(0.5)	1	2	(1.0)	2	2	(2.1)	2	0	(0.0)	0	3	(0.8)	3
Antinuclear antibody positive	0	(0.0)	0	2	(1.0)	2	0	(0.0)	0	2	(2.0)	2	2	(0.5)	2

ALT = alanine aminotransferase; AST = aspartate aminotransferase; E = frequency of treatment-emergent adverse events; TEAE = treatment-emergent adverse event

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 extended safety set.

The safety profile of Renflexis appeared to be similar to EU and US sourced Remicade in the PK study. Any treatment emergent adverse events occurred in 50.9%, 39.6% and 43.4% respectively. All events were of mild or moderate severity, most were mild and no subjects discontinued the study because of adverse events. The pattern of events was that expected in a healthy subject study and there were no notable differences between the treatment groups. There were no deaths. Three serious adverse events were reported in two subjects in the Renflexis group, a road traffic accident with concussion and rupture of a renal cyst and a Borrelia infection.

Clinical evaluator's recommendation

The clinical evaluator has recommended approval of Renflexis for all seven of the approved indications for Remicade. The evaluator provided the following recommendation:

'Renflexis has comparable effects to Remicade in in vitro and in vivo assays, comparable PK in healthy subjects, comparable efficacy and safety in RA patients, and similar immunogenicity. On the balance of probabilities, the overall evidence supports equivalence, and extrapolation to other rheumatological conditions and IBD is appropriate.'

Risk management plan

The TGA has accepted the EU RMP for Renflexis (infliximab), version 3.0, dated 1 April 2016 (data lock point 27 April 2015), with the ASA, version 2.0, dated 18 May 2016.

There were no outstanding issues in relation to the RMP for Renflexis. The submission was not referred to ACSOM. The important potential risk of immunogenicity will be monitored by the proposed study below, but no additional risk minimisation activities have been assigned as it was considered that the risk minimisation measures for serious infusion reactions and serum sickness address the clinical manifestations of this risk.

The proposed additional pharmacovigilance activity: 'prospective observational cohort study of SB2 in AS and CD' will observe safety, efficacy, and further characterise the important potential risk of immunogenicity in ankylosing spondylitis and Crohn's disease patients. The study milestones and protocol are yet to be finalised. These should be submitted in future updates to the ASA.

The sponsor has provided drafts of all educational material proposed in Australia. This includes the educational material for HCPs including a pre-treatment check-list and 'Dear Healthcare Professional' (DHCP) letter; and for patients a dose schedule card, education brochures for different indication groups, and desktop and mobile gated access digital patient portals. The distribution plan for dissemination of the educational materials was also provided. The risk minimisation materials omit the patient alert card proposed in the EU, and the sponsor's justification for this was accepted by the evaluator (in line with the risk minimisation measures in place for Remicade in Australia). The materials have been reviewed and the sponsor's approach to the additional risk minimisation measures was accepted.

The sponsor is also planning to collect relevant safety information through five European registry programs: BSRBR-RA, ARTIS, UK IBD, RABBIT, and BIOBADASER.

Addendum to the Delegate's overview

Background

This addendum by a second Delegate concerns only the extrapolation of indications and dose regimens for psoriasis and IBD. General background information has been provided above.

Quality evaluation

There is no objection to the registration of Renflexis on quality grounds.

While there is no objection to the registration of Renflexis on quality grounds, there are differences in the quality characteristics of the active substance, infliximab, when

compared to the innovator product, Remicade. The quality evaluator stated that the Delegate needs to ensure that these differences do not adversely impact on the efficacy and safety of the product in the clinical evaluation.

Nonclinical evaluation

The nonclinical evaluator recommended that, provided that the quality evaluator accepts the conclusions made about the quality aspects of Renflexis then there are no nonclinical objections to registration.

Overall, no major deficiencies were identified in the nonclinical dossier.

Pharmacological activity of Renflexis was generally comparable to that of Remicade under in vitro conditions. Some subtle differences were noted for some of the tested parameters (higher binding affinities for some Fc-receptor related targets) but these differences did not extend to effects on biological responses in vivo. Under in vivo conditions, Renflexis and Remicade produced similar dose-dependent attenuation of inflammation in a mouse model of arthritis (Tg197 mice) over a 7 week period compared with untreated vehicle controls.

Clinical evaluation

The clinical evaluator has recommended that all current indications for the innovator infliximab be approved for Renflexis. As noted in the clinical evaluation report there were no clinical data for the proposed psoriasis and IBD indications.

The clinical evaluator considered extrapolation of indications in Section: Efficacy Conclusions, Extrapolation of Indications of the clinical evaluation report (see Attachment 2 for further details). In that section the major recommendations of two important TGA adopted EU guidelines relevant to this submission are summarised:

- EMEA/CHMP/BMWP/42832/2005 Rev 1: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; and
- EMA/CHMP/BMWP/403543/2010: Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues.

A review paper included in the clinical evaluation data was also discussed in that section of the clinical evaluation report. That paper addressed concerns frequently raised in the medical community about the use of biosimilars in extrapolated indications. The major points in that paper were:

- In the context of biosimilars, extrapolation of efficacy and safety data from one indication to another may be considered if biosimilarity to the reference product has been shown by a comprehensive comparability program ... including safety, efficacy, and immunogenicity in a key indication that is suitable to detect potentially clinically relevant differences; and
- If the relevant mechanism of action of the active substance and the target receptor(s) involved in the tested and in the extrapolated indication(s) are the same, extrapolation is usually not problematic.

The clinical evaluator has also noted a 2013 position paper on biosimilars from the ECCO. That paper included the following statement:

'Specific evidence obtained in patients with IBD should be required to establish efficacy and safety for this specific indication, because experience with currently licensed biological medicines has already shown that clinical efficacy in IBD cannot

be predicted by effectiveness in other indications, such as rheumatoid arthritis' (an unreferenced statement in the submission).

A search of the ECCO website did not reveal the above position statement however there were numerous papers/poster presentations from members concerning biosimilar TNF α antagonists in IBD indications. It may be that the 2013 position has now been superseded. There was no current position statement regarding extrapolation on the ECCO website.

Given the above recommendations the mechanism of action of infliximab in psoriasis and IBD needs to be considered. The main area of concern has been that there may be clinically significant differences in the mechanism of action of infliximab particularly in IBD and to a lesser extent in psoriasis. Of concern, there may be a clinically significant contribution to efficacy in IBD due to either ADCC and/ or to membrane bound rather than soluble infliximab. Differences in ADCC activity were also postulated for psoriasis.

Binding to tmTNF α is listed as an additional mechanism of action of TNF antagonists in IBD. Two approved TNF antagonists, etanercept and certolizumab pegol, along with Infliximab, bind both precursor tmTNF α and soluble TNF α and block the interaction between TNF α molecules and TNF α receptors type 1, type 2 and soluble TNF α receptors; thus blocking TNF α -mediated cell signalling and inhibiting the expression of inflammatory genes.

While neither etanercept nor certolizumab pegol are registered for treatment of any indications even so, both are used in treatment of inflammatory conditions. Etanercept is derived from TNF receptor and, compared to anti-TNF monoclonal antibodies has lower avidity and less stable binding to tmTNF α . However, the clinical experience with certolizumab, which lacks an Fc domain and therefore lacks the capability of participating in ADCC or mediating other Fc dependent functions is, nonetheless, an effective IBD therapy (although not approved by TGA for these indications).

For this submission the sponsor's justification for extrapolation was based on the following arguments (extracted from the clinical evaluation report):

1. The mechanism of action of infliximab requires high affinity binding to both soluble and transmembrane TNF α , which occur in varying elevated concentrations in tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis and psoriasis.^{17,18} This high affinity binding has been demonstrated for SB2.
2. According to the Scientific Advice, soluble TNF α is important in the pathogenesis of ankylosing spondylitis, psoriatic arthritis and plaque psoriasis); and membrane bound TNF α is important in paediatric and adult CD and UC as discussed above.
3. Nonclinical characterisation studies have shown similar structural, physicochemical and biological properties to Remicade. Multiple in vitro assays have explored the effects of SB2 and Remicade. These included: tmTNF- α binding assays, Fc receptor binding assays, CDC assays, ADCC assays and apoptosis assays (including IBD models). Overall, the results for SB2 were comparable to Remicade.
4. Although the SB2 PK profile has not been tested in doses > 5 mg/kg, infliximab has been tested in doses up to 20 mg/kg. Exposure is linear with no accumulation after multiple administrations. Although doses of up to 10 mg/kg may be required in CD patients, the frequency of administration is the same. No significant PK differences have been reported in patients with RA, AS, psoriasis and adult and paediatric CD.^{12,19}

RMP

The RMP evaluator has noted that there are no outstanding issues in relation to the RMP. The advice of ACSOM was not sought for this submission.

The sponsor has proposed a 'prospective observational cohort study of SB2 in (ankylosing spondylitis) AS and (Crohn's disease) CD' to observe safety and efficacy and to further characterise the potential risk of immunogenicity in ankylosing spondylitis and Crohn's disease patients. The study milestones and protocol are yet to be finalised. The RMP evaluator has recommended these should be submitted in future updates to the ASA.

The RMP evaluator noted that the sponsor has clarified the risk minimisation activities proposed and provided drafts of all educational material proposed for use in Australia. These include educational material for healthcare professionals, including a pre-treatment check-list and DHCP letter. For patients a dose schedule card, education brochures for different indication groups, and desktop and mobile gated access digital patient portals have been proposed. The distribution plan for dissemination of the educational materials was also provided. The risk minimisation materials omit the patient alert card proposed in the EU, and the sponsor has provided justification for this (it is in line with the risk minimisation measures in place for the reference product (Remicade) in Australia. The materials have been reviewed and the sponsor's approach to the additional risk minimisation measures is acceptable.

Risk-benefit analysis

Delegate's considerations

Quality

Acceptable comparability on quality grounds was demonstrated between EU Remicade and Renflexis and between EU Remicade and Australian Remicade, however minor differences were noted. The evaluator commented that it is not unexpected to note minor physicochemical differences between Renflexis and EU Remicade due to the use of different cell substrates for production, cell culture and purification conditions. However, the in vitro biological activities have been shown to be generally similar. It is not clear whether these differences in quality attributes have any clinical implication, thus the need to consider the nonclinical and clinical data for any differences in efficacy, safety or immunogenicity.

Nonclinical

The nonclinical dossier was acceptable and the evaluator had no objections to registration. Pharmacological activity of Renflexis was generally comparable to that of Remicade under in vitro conditions. The pharmacokinetic profile of Renflexis indicated similar absorption to Remicade. Under in vivo conditions, Renflexis and Remicade produced similar dose-dependent attenuation of inflammation in a mouse model of arthritis. ADA development was similar for all infliximab formulations. Renflexis exhibited slightly higher binding affinity for FcγRIIb, FcγRIIIa (v/v allotype) and FcRn receptors compared to Remicade but the potential for enhanced ADCC activity was not anticipated to have adverse implications for efficacy.

Pharmacology

Renflexis demonstrated comparable pharmacokinetics to EU Remicade in healthy volunteers using AUC_{inf} , AUC_{last} and C_{max} in a study design that was agreed with the EMA and US FDA. In the substudy of the Phase III study in rheumatoid arthritis, similar trough infliximab concentrations were seen with steady state between Weeks 14 to 22 but there was high variability. The 5 mg/kg dose selected for the PK study was considered acceptable as it is the usual maximum dose for most indications and proportional increases in C_{max} and AUC have been shown in other studies of infliximab at higher doses. However, this data only provides PK information for one of the approved adult indications (rheumatoid arthritis). Published data in Crohn's disease, psoriasis and rheumatoid

arthritis suggested no meaningful differences in PK in other indications however this data is limited. The sponsor will be requested to comment on potential differences in pharmacokinetic profiles across indications.

No pharmacodynamic data were provided which is acceptable given the established use of infliximab and the clinical data submitted.

Efficacy

The efficacy of Renflexis is supported by a therapeutic equivalence study comparing it with EU Remicade in a rheumatoid arthritis population taking a stable dose of methotrexate. The study was designed according to EMA guidelines and adopted after consultation with the EMA and FDA. Renflexis demonstrated equivalence to Remicade for the primary endpoint and was supported by several secondary endpoints, consistent with the EU guideline on rheumatoid arthritis, up to Week 54. Response rates were significantly higher in patients who did not develop ADAs during the treatment period, compared with those who did develop ADAs but the proportions who were ADA positive and negative were similar between Renflexis and Remicade. The equivalence margin chosen in this study allowed for up to a 15% difference in efficacy but is considered to be the maximal acceptable margin and was the same margin used in other anti-TNF biosimilar studies. The selected efficacy endpoints are accepted validated measures that have been used in previous rheumatoid arthritis studies and are consistent with the EU guideline. Patients had received an average of 50.7 months of methotrexate prior to randomisation at a mean weekly dose of 14.7 mg. The use of prior MTX in the study, as well as the measures of disease activity, is consistent with the approved RA treatment indication for Remicade which is in 'patients with active disease despite treatment with methotrexate'. However, there is no data on monotherapy use. The baseline disease characteristics of the population were comparable to those reported in the ATTRACT study (Remicade) and baseline disease characteristics were also similar except the number of swollen and tender joints was higher in ATTRACT and CRP was lower in ATTRACT but the mean weekly dose of MTX was similar. These differences are not considered major given the purpose of this study is to demonstrate equivalence between Renflexis and Remicade within a study, not between studies.

Overall, Renflexis has demonstrated comparable efficacy to EU Remicade for adult patients with rheumatoid arthritis. Given that biosimilarity has been demonstrated with respect to quality aspects between Renflexis and EU Remicade and a bridging comparability study between EU Remicade and Australian Remicade showed comparability then Australian Remicade and Renflexis should have similar efficacy. The quality evaluator noted some minor quality differences between EU Remicade and Renflexis but these did not appear to effect efficacy. In addition, data from the extension study indicated maintenance of response in those who continued treatment with Renflexis up to Week 78.

Paediatric indications

The sponsor has applied for use in the paediatric population, as per the Remicade indications. In Europe, Renflexis (Flixabi) has been approved for the paediatric indications.

Safety

The safety profile of Renflexis was overall comparable to EU Remicade from the pivotal study with an adequate sample size and duration of exposure that is consistent with the EU guideline on rheumatoid arthritis. Overall, the incidence of AEs, ADRs and SAEs were similar between groups. Infection related AEs and infusion reactions occurred with a similar frequency on both treatments but slightly higher liver function tests (LFTs) and reports of RA were recorded on Renflexis. There were slightly more severe AEs and less mild AEs on Renflexis. Serious infections were also slightly higher on Renflexis. Positive

ADA results and neutralising antibodies were high in both groups but there was no significant difference between them. The immunogenicity profile of Renflexis may be different in studies where concomitant MTX is not used. No deaths were reported in the Renflexis group. Neoplasms were higher on Renflexis (4 versus 1) and this will need monitoring in the RMP and through overseas registries. There was one report of active TB in each group. The incidence of AEs was comparable in subgroups defined by ADA status, age and gender. The extension phase data did not appear to show new safety concerns for patients continuing on Renflexis to Week 78 with a similar profile to Remicade, including ADA development, but there were some differences.

Extrapolation of indications

The TGA has adopted EU guideline EMA/CHMP/BMWP/403543/2010 which discusses extrapolation of indications. The guideline notes:

'Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification. If pivotal evidence for comparability is based on PD and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then applicants should provide relevant data to support extrapolation to all claimed clinical indications. Applicants should support such extrapolations with a comprehensive discussion of available literature including the involved antigen receptor(s) and mechanism(s) of action. For example, if a reference mAb is licensed both as an immunomodulator and as an anticancer antibody, the scientific justification as regards extrapolation between the two (or more) indications is more challenging. The basis for such extrapolation forms an extensive quality and non-clinical database, including potency assay(s) and in vitro assays that cover the functionality of the molecule, supplemented by relevant clinical data as described further in this document. The possibility of extrapolating safety including immunogenicity data also requires careful consideration, and may have to involve more specific studies (see sections 5 and 7). For the mechanism of action, e.g. the depletion of immune cells, several mechanisms may play a role in the various clinical conditions. For example, ADCC appears to be more important in some indications than in others. To provide further evidence about the mechanism of action, it may also be helpful to perform a literature search to identify what is known, e.g. about potential signalling inhibition by the reference mAb that would not be covered by ADCC/CDC tests, in particular direct induction of apoptosis. This could provide more knowledge on potential read-outs that could be used to support comparability on a molecular level.'

The sponsor submitted a justification for extrapolation of indications as stated in Points 1-4 above.

Inhibition of soluble TNF α receptors is important in rheumatological indications, but transmembrane receptor inhibition is also important in IBD patients. Renflexis and Remicade showed similarity in quality aspects as well as comparable biological activities, including binding affinity for human soluble and tmTNF α , neutralisation of TNF α , binding affinity for Fc γ RI, Fc γ RIIa, Fc γ RIIb, Fc γ RIIIa (F/F allotype), C1q and induction of CDC, ADCC and recruitment/induction of regulatory macrophages. Similar clinical pharmacokinetics in healthy volunteers and similar efficacy, safety and immunogenicity between Renflexis and Remicade in rheumatoid arthritis patients were demonstrated. A common mechanism of action exists and there is a similar safety profile across the adult indications seen with the reference product. The nonclinical and clinical evaluators supported the extrapolation of indications.

There is some controversy in the literature about whether or not RA is a sensitive clinical model for extrapolation of efficacy and safety data to other treatment indications because RA lacks sufficiently sensitive and measurable markers of response. However, endpoints in RA have been able to detect differences compared to placebo across multiple studies, RA was accepted by the EMA and FDA as being acceptable for this study, RA is the most common relevant indication and there is a wide body of literature and EU guidelines supporting the endpoints used. RA has also been used in other biosimilar equivalence studies such as the first infliximab biosimilar. Although the requested indications have several pathophysiological mechanisms, antagonism of endogenous TNF by infliximab is a common pathway of producing response.

The similarity between EU Remicade and Renflexis demonstrated in the clinical data in one indication and the justification provided to extrapolate to other indications appears to be reasonable. The clinical unit in TGA that handles gastroenterology and dermatology indications also supported the extrapolation to Crohn's disease, ulcerative colitis in adults, children and adolescents and psoriasis.

Immunogenicity

The comparative clinical study and the pharmacokinetic study indicated that the rate of ADA development was slightly higher in patients on Renflexis than Remicade (Phase III study: 62.4% versus 57.5%, $p = 0.27$). The overall rates of ADA development were also considerably higher in the phase 3 study for both Renflexis and Remicade compared to the historical data on Remicade (around 8% in rheumatoid arthritis patients treated with methotrexate) but this has been speculated to be due to potentially increased assay sensitivity. However, the evaluator notes that approximately half of rheumatoid arthritis patients can be expected to develop ADAs after one year based on other studies. The first infliximab biosimilar study of Remsima/Inflectra versus Remicade at Week 30 showed ADA development occurred in 48.4% versus 48.2% respectively which was also much higher than historical data. Any potential differences in ADA development could impact efficacy but despite small numerical differences in efficacy, these differences were not significant. The proportion of patients having an increased dose of infliximab was also similar between Renflexis and Remicade (at Week 46: 50.7% of Renflexis were on 3 mg/kg and 50.2% of Remicade were on 3 mg/kg). Examining the ACR20 responses for the Phase III study, it can be seen that the ACR20 response, regardless of treatment group was significantly lower in ADA positive patients but that the difference between Renflexis and Remicade was not significant for either ADA positive or ADA negative groups. Information from the EMA indicate that the number of patients who had an infliximab dose increase was not affected by the ADA status. Safety data also indicate that AEs that could be associated with ADA development, for example, hypersensitivity and infusion associated reactions, were not increased with Renflexis compared with Remicade. The sponsor will be monitoring immunogenicity in the post-market study in ankylosing spondylitis and Crohn's disease and the submission of this study will be a condition of registration. The sponsor should follow up this issue in the Periodic Safety Update Reports (PSUR) to discuss the potential difference in immunogenicity for patients treated with or without concomitant MTX.

MTX was used in the clinical study and it is not known if there would be differences in PK or immunogenicity without it in the other approved indications. MTX may reduce the immune response and there is published data indicating that concomitant MTX alters the immunogenicity, and potentially the pharmacokinetic profile, of anti-TNF therapy and there are lower rates of concurrent MTX use with anti-TNF therapy in inflammatory spondylitis, skin psoriasis and psoriatic arthritis. Therefore, there is potential for a different immunogenicity response when MTX is not used.

RMP

An acceptable RMP with ASA has been provided and the sponsor is planning an observational clinical study in ankylosing spondylitis and Crohn's disease to observe safety, efficacy, and further characterise the important potential risk of immunogenicity.

Overall conclusions

The quality, nonclinical and clinical evaluators have all recommended approval and an acceptable RMP/ASA has been provided. Pending further advice from the TGA's Advisory Committee on Prescription Medicines (ACPM), the Delegate considers that sufficient data and justification have been provided, consistent with adopted EU guidelines, to support the similarity of Renflexis to Australian Remicade to support the registration of Renflexis on quality, safety and efficacy grounds for all seven indications that are approved for Remicade.

Switching

The double blind extension study suggested that for the patients who switch from EU Remicade to Renflexis at Week 54 there is a slightly reduced clinical response at Week 78 (that is, 24 weeks after treatment switch) compared to those who stayed on Renflexis or Remicade. There did not appear to be new safety concerns in switched patients but there were some increased frequencies in AE rates in switching patients: SAEs (6.4% versus 3.0%), infusion related reactions (3.2% versus 2.0%), increased ALT (4.3% versus 1.0%), increased AST (4.3% versus 2.0%) and latent TB (7.4% versus 4.0%) compared to those who stayed on Remicade. ADA development was slightly less in switched patients compared to continuing Remicade patients (45.7% versus 50.5%). However, interpretation of these results is confounded by low event numbers. The clinical evaluator considered there were no meaningful differences in the pattern of AEs reported in patients switched from Remicade to Renflexis. This data is however limited, one way only and with no data available on multiple switching or switching between Renflexis and the first infliximab biosimilar (Remsima/Inflectra) or vice versa.

The clinical evaluator provided the following comment on switching: The risks associated with switching between Renflexis, Remicade and other biosimilars are largely unknown. They should be assessed with analysis of transition-extension data in Study SB2-G31-RA and by appropriate post-marketing pharmacovigilance, particularly in patients with IBD. Switching should be undertaken only by specialists in the appropriate therapeutic areas. The sponsor provided the transition-extension data as discussed above and the clinical evaluator made the following comment about switching for the PI after reviewing the data: Under the new TGA guideline, a switching precaution under medical supervision is not mandatory but should be considered on a case by case basis. In this instance, the evaluators recommend that switching should be performed under supervision. The two products are biosimilar but the molecules are not identical. While the overall comparative data are re-assuring, there is a theoretical risk of anaphylaxis during switching, though such risks have not been identified as being of particular concern with switching between anti-TNF agents.

The TGA biosimilars guideline does not require general switching precautions in the PIs of biosimilars. The infliximab PI contains precautions regarding hypersensitivity reactions and infusion reactions and will include safety data (as well as efficacy data) on switching patients compared to those who stayed on Remicade. The PI will also include data on ADA development. Since infliximab is given by intravenous infusion in a hospital or infusion centre, then a healthcare professional should be available should there be concerns with hypersensitivity or infusion reactions. All infliximab PIs state that treatment is to be administered under the supervision of specialised physicians. The evaluator notes that the data are re-assuring and that the risk of anaphylaxis during switching is theoretical. The evaluator also notes that this risk has not been identified as being a particular concern

with switching between anti-TNF drugs. The approved EU SmPC for Renflexis (Flixabi) does not contain a specific precaution on switching and the approved PI for the first infliximab biosimilar (Remsima/Inflectra) also does not contain a specific precaution regarding switching. Of note, the approved US PI for Inflectra does not contain a precaution on switching. The sponsor is proposing an observational study that will include assessment of immunogenicity and the sponsor is planning to collect safety data through five European registries.

Data deficiencies

There is no direct evidence of similarity in six of the requested indications. The effects of high ADA levels and neutralising antibodies may not emerge until further long-term data are available. Data in patient populations not concomitantly exposed to MTX is lacking.

Conditions for registration

The following are proposed as conditions of registration and the sponsor is invited to comment in the Pre-ACPM response:

1. The implementation in Australia of the EU Risk Management Plan for Renflexis (infliximab), version 3.0, dated 1 April 2016 (data lock point 27 April 2015), with the Australian Specific Annex, version 2.0, dated 18 May 2016, included with submission PM-2015-02764-1-3, and any subsequent revisions, as agreed with the TGA.
2. The following study reports must be submitted to the TGA as soon as possible after completion:
 - a. Final study report for the prospective observational cohort study of Renflexis in ankylosing spondylitis and Crohn's disease.
3. Batch Release Testing
 - a. It is a condition of registration that all batches of Renflexis imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
 - b. It is a condition of registration that each batch of Renflexis imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.
 - c. The sponsor must supply:
 - i. Certificates of Analysis of all active ingredient (drug substance) and final product.
 - ii. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
 - iii. Evidence of the maintenance of registered storage conditions during transport to Australia.
 - iv. 3 to 5 vials of each batch for testing by the TGA together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Summary of issues

The primary issues with this submission are as follows with further information in the Discussion section above:

1. The efficacy data demonstrated comparability between Renflexis and Remicade and the extension study suggested there is maintenance of clinical response.
2. The sponsor has submitted a justification to extrapolate the submitted data from adult rheumatoid arthritis patients and healthy volunteer PK data to support the registration of the other indications of ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis (including use in children and adolescents 6 to 17 years for the latter two indications).
3. The safety profiles appeared to be mostly comparable and the extension study did not appear to identify new safety concerns, but there were some differences.
4. A slightly higher rate of anti-drug antibody development was seen on Renflexis than Remicade in the two studies, but not significantly in the Phase III study. Immunogenicity may also be potentially different in indications where concomitant methotrexate is not routine.
5. The sponsor has included data in the PI on the transition-extension phase of the clinical study regarding switching patients.
6. The quality evaluator noted some minor differences between Renflexis and Remicade in the comparability analysis.

Proposed action

The Delegate had no reason to say, at this time, that the application for Renflexis should not be approved for registration, pending further advice from ACPM.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Provide an update on the status of any application in Canada.
2. Comment on the potential clinical implications of each of the differences noted in the comparability exercise between Renflexis and Remicade, as discussed above in the quality evaluation.
3. Are any further studies planned to investigate the efficacy and safety of switching patients between Remicade and Renflexis or multiple switching or between infliximab biosimilars?
4. Please discuss how the pharmacokinetic profiles compare across the requested indications for infliximab and how this data compares to the pharmacokinetic data submitted.
5. There is a potential for immunogenicity responses to be different in indications that do not normally use concomitant MTX, for example, psoriasis. What is the justification to support use in these indications? How does the sponsor intend to monitor for the potential difference in immunogenicity across the different infliximab indications, for example PSURs, post-market studies and registries.
6. Are there any differences in efficacy between Renflexis and Remicade based on ADA development and the proportion of patients requiring higher infliximab doses? What is the correlation between increasing infliximab dose and the incidence of testing positive for ADA with either Renflexis or Remicade? Are there potential differences in the rate of ADA development across the indications, with and without methotrexate use?
7. How does ACR20 response rates change over time by whether a patient had their infliximab dose increased or not?

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. What are ACPMs views on the similarity of efficacy between Renflexis and Remicade to support the indication of rheumatoid arthritis for this biosimilar infliximab?
2. What are ACPMs views on the extrapolation of the data/justification to support the other indications?
3. What are ACPMs views on the comparability of the safety profiles of Renflexis and Remicade?
4. What are ACPMs views on the development of anti-drug antibodies seen with Renflexis and Remicade?
5. What are ACPMs views on the switching data in the PI?
6. What are ACPMs views on the clinical significance of the differences noted in the module 3 comparability evaluation?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Addendum to the Delegates overview***Second Delegate's considerations***

This submission considers evidence to support registration of a biosimilar infliximab. The mechanism of action of infliximab in all its approved indications is considered to be essentially the same. Considering the mechanism of action and the demonstrated similarity of PK and clinical equivalence between the innovator product, Remicade and Renflexis it is proposed to extrapolate the indications for Remicade pertaining to psoriasis and IBD to Renflexis. The dose recommendations should also be the same.

The second Delegate notes that the dose regimen for infliximab required for IBD indications is higher than is required for the rheumatoid arthritis indication in which clinical equivalence was demonstrated, additionally the patient groups treated in IBD indications is also broader in that it includes children. The Delegate recommends that extrapolation also apply to the IBD and plaque psoriasis indications for Renflexis.

Summary of issues

This addendum seeks advice on the extrapolation of clinical data obtained in healthy volunteers in a PK study and in patients with rheumatoid arthritis in an equivalence study to support the IBD and psoriasis indications and dose regimens for Renflexis.

Equivalent efficacy and safety of Renflexis has been demonstrated only for the Rheumatoid arthritis indication in adults and it is proposed to extrapolate that data to allow for extension of efficacy and safety of Renflexis to all indications of the innovator infliximab product, including indications for use in children. Extrapolation of the dose regimens for these indications is also proposed.

Proposed action

The second Delegate had no reason to say, at this time, that the proposed extrapolation of data to include the psoriasis and IBD indications and dose regimens for Renflexis should not be approved subject to successful negotiation of the Product Information and other conditions of registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Extrapolation of the indications for Remicade, including the IBD and psoriasis indications has been proposed. Does the committee consider there are elements unique to this submission that would limit the extrapolation of data to include the psoriasis and IBD indications? If so what are these factors?
2. Does the committee consider that additional requirements should be placed post-market to support use of Renflexis in children with IBD?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Response to Question 1

The application to Canada was submitted in September 2015 and currently in the review process. The proposed indications are rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, fistulising Crohn's disease, and ulcerative colitis in adults, paediatric Crohn's disease (9 years of age and older) and paediatric ulcerative colitis (6 years of age and older).

Response to Question 2

As the agency commented, minor differences in quality attributes were observed between Renflexis and EU Remicade for the physicochemical and the biological properties. The potential implication of the differences on the clinical outcome of Renflexis was discussed in depth as follows:

- It has been reported that C-terminal Lys variants does not impact the biological activities and pharmacokinetics of monoclonal antibodies.²¹ The C-terminal Pro α -amidation is known to occur widely in Chinese hamster ovary cells but not to impact antigen-binding or effector functions of antibodies.²² Therefore, the slight differences observed were not considered to have an impact on the biological activity and to be translated into clinically meaningful difference.
- The observed difference in Met oxidation and deamidation did not have an impact on the biological activity as supported by similar FcRn binding activities between Renflexis and EU Remicade and SAR study results, respectively. Therefore, the slight differences observed were not considered to be translated into clinically meaningful difference.
- The level of %Afucose glycans was slightly higher in Renflexis than that of EU Remicade. However, ADCC activity, which is known to be affected by the %Afucose level, of Renflexis and EU Remicade was similar. Therefore, the slight difference of %Afucose were not considered to have an impact on the biological activity and to be translated into clinically meaningful difference.
- Charge variants in Renflexis and EU Remicade were evaluated. Overall, both assessments showed that Renflexis was found to possess a higher content of basic variants, compared to those of EU Remicade due to slightly higher levels of α -amidation on C-terminal proline residue. In addition, the levels of C-terminal Lys were shown to be lower in Renflexis. The impact of C-terminal variants was discussed above.

²¹ Keck R et al. Characterization of a complex glycoprotein whose variable metabolic clearance in humans is dependent on terminal N-acetylglucosamine content. *Biologicals* 36 (2008) 49

²² Brinckerhoff LH et al. Terminal modifications inhibit proteolytic degradation of an immunogenic mart-127-35 peptide: implications for peptide vaccines. *Int. J. Cancer*: 83, 326-334 (1999)

Johnson KA et al. Cation exchange-HPLC and mass spectrometry reveal C-terminal amidation of an IgG1 heavy chain. *Analytical Biochemistry* 360 (2007) 75-83

- Percentage IgG of Renflexis analysed by capillary electrophoresis–sodium dodecyl sulphate (reducing) was slightly lower than the EU similarity range, which was attributed to the higher level of non-glycosylated heavy chain (NGHC) of Renflexis. However, it is known that the absence of glycan, resulting in unmasking of the region, is not related with immunogenicity.²³ Furthermore, the results from an orthogonal analysis by capillary electrophoresis–sodium dodecyl sulphate (non-reducing) showed that percentage IgG was similar between Renflexis and EU Remicade. Therefore, the slight differences observed in %IgG by capillary electrophoresis–sodium dodecyl sulphate (reducing) were not considered to be significant and to be translated into clinically meaningful difference.
- Although the level of %HMW analysed by size exclusion was slightly higher in Renflexis than in EU Remicade, the heterogeneity of %HMW analysed by size exclusion chromatography/multiple angle laser light scattering and sedimentation velocity-analytical ultracentrifugation was comparable between Renflexis and EU Remicade. Therefore, the differences in %HMW analysed by size exclusion chromatography was not considered to be significant and to be translated into clinically meaningful difference.
- A slight increase in deuterium uptake observed for Renflexis was resulted from the presence of different sialic acids. N-acetylneuraminic acid forms were observed in Renflexis, whereas only N-glycolylneuraminic acid forms were observed in EU Remicade. These differences were caused by the different production host cells. According to a previous publication²⁴, immunogenic response occurred in the presence of higher levels of N-glycolylneuraminic acid. Therefore, the presence of different sialic acids was not considered to be significant and to be translated into clinically meaningful difference.
- The two Fc-related binding activities were assessed using two orthogonal assays. The FcγRIIb and FcγRIIIa binding affinities of Renflexis were shown to be similar to those of EU Remicade. Therefore, the differences in FcγRIIb and FcγRIIIa binding activities were not considered to be significant and to be translated into clinically meaningful difference.

Therefore, based on the assessment discussed above, the sponsor concluded that there is no difference in quality attributes which may impact clinical outcome.

Response to Question 3

The sponsor has already submitted the study results of double-blind extension (Study SB2-G31-RA) with switching data, at the time of response to further TGA questions. The results from the extension study showed that comparable efficacy was maintained after switching and there were no meaningful differences in the patterns of AEs reported in patients who switched from Remicade to Renflexis. In this regard, the sponsor does not plan any specific additional switch studies after approval to investigate the efficacy and safety of switching from Remicade to Renflexis or multiple switching, or between infliximab biosimilars, at this moment.

Response to Question 4

It is well known that infliximab has a linear PK and no major differences in infliximab PK profiles have been reported between authorised infliximab indications (including between paediatric and adult populations).

²³ Jung ST et al. Bypassing glycosylation: engineering aglycosylated full-length IgG antibodies for human therapy. *Current Opinion in Biotechnology* 2011, 22:858–867

²⁴ Hossler P et al. Review Optimal and consistent protein glycosylation in mammalian cell culture. *Glycobiology* vol. 19 no. 9 pp. 936–949, 2009

Following a single infusion of infliximab (5, 10 or 20 mg/kg) in patients with active rheumatoid arthritis, C_{max} and AUC were proportional to the given dose, whereas the derived PK parameters such as clearance and terminal elimination $t_{1/2}$ were independent of the dose.

In addition, during a long-term study (for 102 weeks) in patients with rheumatoid arthritis treated infliximab (3 or 10 mg/kg) every 4 or 8 weeks, the median of peak and trough concentrations of infliximab were dose-proportional and stable over time for all four regimens, which indicated no changes in PK linearity over time.²⁵

The PK linearity of infliximab was also shown in patients with Crohn's disease. Clinical studies with Crohn's disease patients who were treated with infliximab with a single dose (1 to 20 mg/kg, n = 20) and multiple doses (maintenance therapy, 5 or 10 mg/kg, n = 573) showed that the PK of infliximab is linear (whereas derived PK parameters such as clearance, $t_{1/2}$, volume of distribution at steady state, and mean residence time were independent of the dose) as observed in rheumatoid arthritis patients.

In addition to PK linearity in adult patients with rheumatoid arthritis and Crohn's disease, paediatric patients (aged 8 to 17 years) with active Crohn's disease also showed that the serum concentrations of infliximab were increased in proportion to the infused dose (1, 5 or 10 mg/kg).²⁶

Given the evidences indicating the linearity and non-time dependency of infliximab PK, the sponsor believes that once the PK equivalence was confirmed in the most sensitive populations (that is, healthy volunteers), it can be extrapolated to other indications even though these indications have different dose level and dose schedules (that is, 5 mg/kg at Weeks 0, 2, 6, and then every 8 weeks for adult Crohn's disease, paediatric Crohn's disease, adult ulcerative colitis, paediatric ulcerative colitis, plaque psoriasis and psoriatic arthritis, and 5 mg/kg at Weeks 0, 2, 6, and then every 6 to 8 weeks for ankylosing spondylitis). The most sensitive population to compare PK profiles is dependent on the homogeneity of the population. Healthy volunteers are considered to be more homogeneous (and hence more sensitive) than patients since the influence of disease related factors and concomitant medications on pharmacokinetics can be excluded.

Therefore, based on PK linearity of infliximab and demonstrated PK bioequivalence in the most sensitive populations (healthy subjects and rheumatoid arthritis patients), the sponsor concludes that PK characteristics of Renflexis as equivalent to those of Remicade can be applied to other proposed indications.

Response to Question 5

As the TGA noted, there may be a potential difference in immunogenicity response in indications that do not normally use concomitant MTX with rheumatoid arthritis indication.

On the other hand, widely differing ADA incidences have been reported across infliximab clinical studies, regardless of concomitant MTX use. These studies differed considerably in various aspects, including co-medication, timing of ADA determination and ADA assay used. Therefore, without investigating multiple patients receiving similar co-medications and using a single laboratory to determine ADA incidence, it is hard to draw definitive conclusions about the actual differences in immunogenicity across indications.

²⁵ Maini RN et al. Sustained Improvement Over Two Years in Physical Function, Structural Damage, and Signs and Symptoms Among Patients With Rheumatoid Arthritis Treated With Infliximab and Methotrexate. *Arthritis & Rheumatism* Vol. 50, No. 4, April 2004, pp 1051-1065

²⁶ Baldassano R et al. Infliximab (Remicade) Therapy in the Treatment of Pediatric Crohn's Disease. *Am J Gastroenterol* 2003;98:833- 838

Recently, three clinical trials for the biosimilar CT-P13 investigated ADAs against the biosimilar and Remicade using a similar (MSD) assay in several indications including rheumatoid arthritis and ankylosing spondylitis (the indication without any MTX treatment). In these study results, ADA incidences in rheumatoid arthritis patients receiving concomitant MTX were higher than ADA incidences observed in ankylosing spondylitis (monotherapy) and Crohn's disease at Week 14 (see Figure 2, below). At Week 54, a higher proportion of patients in the rheumatoid arthritis study developed ADAs compared to those in the ankylosing spondylitis study (see Figure 3, below). These results strongly suggest that, despite the usage of concomitant MTX, rheumatoid arthritis could be sensitive enough to measure the incidence of immunogenicity. Furthermore, these results indicate that there are no substantial differences in ADA incidence between rheumatoid arthritis and Crohn's disease.²⁷

Figure 2. ADA Incidences of CT-P13 at Week 14 in RA, AS and CD

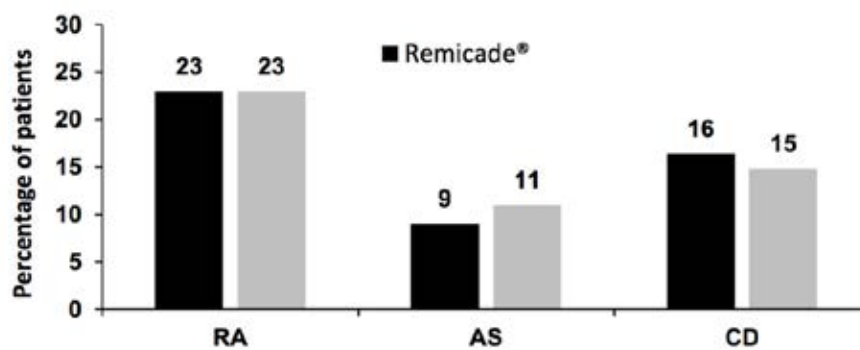
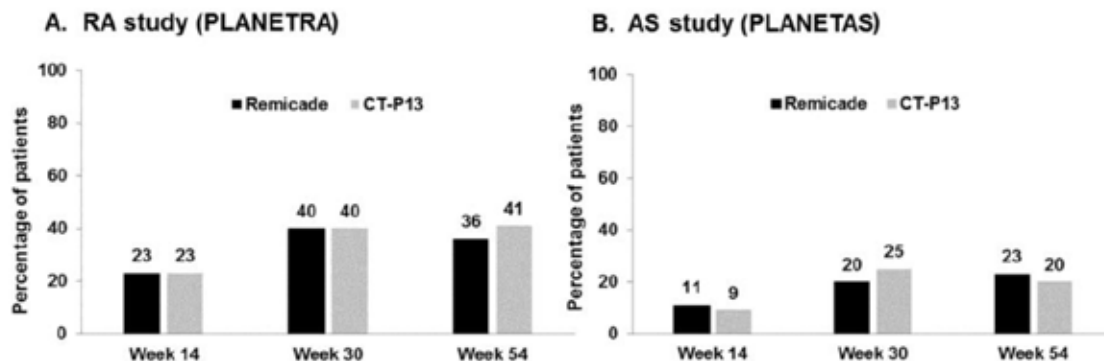


Figure 3. ADA Incidences of CT-P13 at Week up to Week 54 in RA and AS



In addition, it was shown that the majority of ADAs against infliximab recognise the murine parts in the molecule's Fab domain.²⁸ This supports the notion that the primary sequence is a key determinant for the immunogenicity of infliximab and other factors contributing to the products microheterogeneity are less likely to be a major influence on the development of ADAs. Since Renflexis has the same primary sequence with that of Remicade, the ADA against infliximab has similar characteristics. This is supported by recent evidence that ADAs against Remicade from patients in IBD cross-react with CT-P13²⁹, indicating that there are no differences in the way ADAs recognised the two products.

²⁷ Ben-Horin S et al. The immunogenicity of biosimilar infliximab: can we extrapolate the data across indications? *Expert Rev. Gastroenterol. Hepatol.* 9(S1), S27-S34 (2015)

²⁸ Ben-Horin S et al. The immunogenic part of infliximab is the F(ab₉)₂, but measuring antibodies to the intact infliximab molecule is more clinically useful. *Gut* 2011;60:41-48

²⁹ Ben-Horin S et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. *Gut* 2015;0:1-7.

Therefore, the sponsor concludes that the comparable immunogenicity observed in RA patients can be applied to all other indications.

Furthermore, the sponsor will monitor immunogenicity, which is an important potential risk, through routine and additional pharmacovigilance activities. Prospective observational cohort studies with ADA measurement in ankylosing spondylitis and Crohn's disease patient populations are planned and will be conducted, which will be another source for immunogenicity monitoring in diverse indications. AEs possibly related to immunogenicity reported to the sponsor from clinical use like infusion related reactions and loss of efficacy will also be considered and evaluated through signal management process, from which a new safety signal will be reported in PSURs.

Response to Question 6

As acknowledged by the TGA, the ACR20 response rate at Week 30 was lower in the ADA positive subgroup than in the ADA negative subgroup. However, the response rates were comparable between the Renflexis and EU Remicade treatment groups irrespective of ADA status (see Table 8, below). The differences were within the predefined equivalence margin of (-15%, 15%). Similar results were obtained when assessed the ACR50 and ACR70 response rates in ADA subgroup analysis at Week 30 and Week 54.

Table 8. ANCOVA for ACR20 response at Week 30 by 30-week ADA results and treatment (PPS1)

30-week ADA Result ^a	Treatment	Responder n'	n	(%)	Adjusted Difference Rate (SE)	95% CI	p-value
Positive	Renflexis (N=127)	127	72	(56.7)	-0.88% (5.966%)	(-12.63%, 10.87%)	0.989
	Remicade [®] (N=126)	126	74	(58.7)			
Negative	Renflexis (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 antibody; 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

^a ADA result up to Week 30

In addition, to investigate whether ADA positive at Week 30 led the dose increase in Renflexis and Remicade treatment groups in a comparable manner, the number of patients with ADA positive at Week 30 who were dose increased at any time up to Week 54 was investigated as shown below in Table 9. The proportion of dose increased patients was comparable and even slightly lower in the Renflexis treatment group compared to the EU Remicade treatment group (52/133 (39.1%) versus 51/116 (44.0%), Renflexis versus EU Remicade, respectively), which indicates that the ADA led a dose increase in the both treatment groups in a comparable manner.

Table 9. Number (%) of dose increased patients with ADA positive a Week 30

ADA Incidence	Dose Increment	Renflexis		EU Remicade [®]	
		N	n (%)	N	n (%)
ADA positive at Week 30 ^a	Dose increased	133	52 (39.1%)	116	51 (44.0%)
	Dose never increased	133	81 (60.9%)	116	54 (56.0%)

N: patients with ADA positive at Week 30; n: dose increased patients among N.

^aAt Week 30, a total of 133 patients in the Renflexis treatment group and 116 patients in the EU Remicade[®] treatment group were ADA positive. Among those, 6 patients in the Renflexis treatment group and 3 patients in the EU Remicade[®] treatment group withdrew after Week 22 and before Week 30 visits.

Furthermore, the Renflexis and the EU Remicade treatment groups showed comparable efficacy results in the dose increased and the dose never increased groups (see more detailed information on the response to Question 7).

Therefore, any notable differences in efficacy (ACR20 response rate) between Renflexis and Remicade based on ADA development and the patients who necessitate dose-increase were not found.

The potential differences in the rate of ADA development across the indications, especially with and without MTX use were discussed in the response to Question 5.

Response to Question 7

When the efficacy parameters were analysed by ever or never dose increase, the Renflexis and the EU Remicade treatment groups showed comparable efficacy results in the dose increased and the dose never increased groups (Table see 10, below).

For Per Protocol Set 2 (PPS2), the ACR20 response rates for those patients who had a dose increase were 38.0% (Renflexis) versus 35.4% (EU Remicade) at Week 30 and 52.0% (Renflexis) versus 51.9% (EU Remicade) at Week 54. For those patients who never dose increased, the ACR20 response rates were 75.7% (Renflexis) versus 80.0% (EU Remicade) at Week 30 and 73.2% (Renflexis) versus 79.8% (EU Remicade) at Week 54.

Table 10. ACR Response rates by dose increment for the PPS2

ACR20 (PPS2)		Renflexis			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 dose information

Therefore, ACR20 response rates change over time were comparable between the two treatment groups either in dose-increased group or in dose-never increased group.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) resolved to recommend to the TGA Delegate of the Secretary that: taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Renflexis lyophilised powder in a single use glass vial containing 100mg of infliximab to have an overall positive benefit-risk profile for the sponsor application indications:

'Renflexis is indicated for the treatment of:

Rheumatoid Arthritis (RA) in adults

Renflexis, in combination with methotrexate, is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in:

- *patients with active disease despite treatment with methotrexate*
- *patients with active disease who have not previously received methotrexate.*

Renflexis should be given in combination with methotrexate. Efficacy and safety in RA have been demonstrated only in combination with methotrexate.

Ankylosing Spondylitis (AS)

Renflexis is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.

Psoriatic arthritis (PsA)

Renflexis is indicated for the treatment of the signs and symptoms, as well as for the improvement in physical function in adult patients with active and progressive PsA who have responded inadequately to disease-modifying anti-rheumatic drug (DMARD) therapy.

Renflexis may be administered in combination with methotrexate.

Psoriasis (Ps)

Renflexis is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.

Crohn's Disease (CD) in Adults and in Children and adolescents (6 to 17 years)

Renflexis is indicated for the treatment of moderate to severe CD to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

Refractory Fistulising CD

Renflexis is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Ulcerative colitis (UC) in Adults and in Children and adolescents (6 to 17 years)

Renflexis is indicated for the treatment of moderately severe to severe active UC in patients who have had an inadequate response to conventional therapy.'

In making this recommendation the ACPM:

- noted that the development program for Renflexis was guided by the EMA and FDA requirements for biosimilar medicines.
- noted that the proposed indications and the proposed PI is essentially the same as for Remicade except for additional comparability data.
- noted that the quality evaluator noted some minor quality differences between EU Remicade and Renflexis but these did not appear to affect efficacy.
- noted that the nonclinical evaluator had no objections to the registration to Renflexis.
- noted that Renflexis has demonstrated comparable efficacy to EU Remicade for adult patients with rheumatoid arthritis.
- noted that the safety profile of Renflexis is comparable to EU Remicade from the pivotal study with an adequate sample size and duration of exposure that is consistent with the EU guideline on rheumatoid arthritis.
- agreed that the clinical data can be extrapolated to all proposed indications according to EU guidelines adopted by the TGA.
- noted that rate of ADA development was slightly higher in patients on Renflexis than Remicade.
- noted that although efficacy and safety did not appear to be significantly impacted by switching, numbers were too small to draw conclusions.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Monitoring immunogenicity in the post-market study in ankylosing spondylitis and Crohn's disease and the submission of study results upon completion.
- Subject to satisfactory implementation of the RMP most recently negotiated by the TGA.

Proposed PI/ CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- A statement in the PI mentioning that 'the effects of the increased level of ADA induced by Renflexis compared to Remicade beyond 78 weeks are not known'.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *What are ACPMs views on the similarity of efficacy between Renflexis and Remicade to support the indication of rheumatoid arthritis for this biosimilar infliximab?*

The ACPM finds the similarity of efficacy between Renflexis and Remicade acceptable.

2. *What are ACPMs views on the extrapolation of the data/justification to support the other indications?*

The ACPM agreed that the data presented fits the EU and TGA published guidelines as updated in 2015 for Assessment of Biosimilars.

3. *What are ACPMs views on the comparability of the safety profiles of Renflexis and Remicade?*

The ACPM agreed that the 54 week study showed no significant change in the safety profile.

4. *What are ACPMs views on the development of ADAs seen with Renflexis and Remicade?*

The ACPM noted that at least half of the patients treated with infliximab develop ADA over time. The incidence appears to be slightly higher with Renflexis. It is not clear whether it translates into a clinical effect as efficacy is comparable and it doesn't appear to be a safety signal in the short-term studies.

5. *What are ACPMs views on the switching data in the PI?*

The ACPM agreed that the PI included adequate information on the effects of switching in the Clinical Trials and Adverse Effects sections.

6. *What are ACPMs views on the clinical significance of the differences noted in the quality comparability evaluation?*

The ACPM agreed, that the chemical differences don't appear to result in clinically significant effects.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Renflexis infliximab 100 mg powder for injection vial indicated for:

'Renflexis is indicated for the treatment of:

Rheumatoid Arthritis in adults

Renflexis, in combination with methotrexate, is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in:

- *patients with active disease despite treatment with methotrexate*
- *patients with active disease who have not previously received methotrexate.*

Renflexis should be given in combination with methotrexate. Efficacy and safety in Rheumatoid Arthritis have been demonstrated only in combination with methotrexate.

Ankylosing Spondylitis

Renflexis is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.

Psoriatic arthritis

Renflexis is indicated for the treatment of the signs and symptoms, as well as for the improvement in physical function in adult patients with active and progressive psoriatic arthritis who have responded inadequately to disease-modifying anti-rheumatic drug (DMARD) therapy.

Renflexis may be administered in combination with methotrexate.

Psoriasis

Renflexis is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.

Crohn's Disease in Adults and in Children and adolescents (6 to 17 years)

Renflexis is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

Refractory Fistulising Crohn's Disease

Renflexis is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years)

Renflexis is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy'

Specific conditions of registration applying to these goods

Specific conditions of registration applying to these goods include:

1. The Renflexis EU-Risk Management Plan (RMP), version 3.0, dated 1 April 2016 (data lock point 27 April 2015), with the Australian Specific Annex version 2.0, dated 18

May 2016, included with submission PM-2015-02764-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

2. The following study reports must be submitted to the TGA as soon as possible after completion, for evaluation:
 - a. Final study report for the prospective observational cohort study of Renflexis in ankylosing spondylitis and Crohn's disease
3. Batch release testing:
 - a. It is a condition of registration that all batches of Renflexis imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
 - b. It is a condition of registration that each batch of Renflexis imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.
 - c. The sponsor must supply:
 - i. Certificates of Analysis of all active ingredient (drug substance) and final product.
 - ii. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
 - iii. Evidence of the maintenance of registered storage conditions during transport to Australia.
 - iv. 3 to 5 vials of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Attachment 1. Product Information

The PI for Renflexis approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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