CADTH

CADTH COMMON DRUG REVIEW

Common Drug Review Biosimilar Submission

INFLIXIMAB (Renflexis)

Merck Canada

Indications:

Rheumatoid Arthritis (Adult), Ankylosing Spondylitis, Crohn's Disease (Adult, Pediatric), Fistulizing Crohn's Disease (Adult), Ulcerative Colitis (Adult, Pediatric), Psoriatic Arthritis, Plaque Psoriasis (Adult)

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

ACE	Arthritis Consumer Experts
ACR 20	American College of Rheumatology 20% response criteria
ACR 50	American College of Rheumatology 50% response criteria
ACR 70	American College of Rheumatology 70% response criteria
ACR-N	American College of Rheumatology N Index
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
AUC	area under the curve
AST	aspartate aminotransferase
AUC_{inf}	area under the curve from time zero to infinity
AUC_{last}	area under the curve from time zero to the last quantifiable concentration
CD	Crohn's disease
CDC	complement-dependent cytotoxicity
CDR	CADTH Common Drug Review
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum concentration
CRP	C-reactive protein
C_{trough}	trough plasma concentration
DAS 28	Disease Activity Score 28
DMARD	disease-modifying antirheumatic drug
DP	drug product
DS	drug substance
EMA	European Medicines Agency
EU	European Union
EULAR	European League Against Rheumatism
Ex-FAS	extended full analysis set
Ex-SAF	extended safety set
FAS	full analysis set
Fc	fragment crystallisable
FcγR	fragment crystallizable gamma receptor
FcRn	neonatal fragment crystallizable receptor
GM	geometric mean
HAQ	Health Assessment Questionnaire

HAQ-DI	Health Assessment Questionnaire – Disability Index
IBD	inflammatory bowel disease
IP	investigational product
IRR	infusion-related reaction
JSN	joint space narrowing
LSM	least squares mean
MoA	mechanism of action
mTSS	modified Total Sharp Score
MTX	methotrexate
NAb	neutralizing antibody
NK	natural killer
NOC	Notice of Compliance
NSAID	nonsteroidal anti-inflammatory drug
PBMC	peripheral blood monocyte
PK	pharmacokinetic
PPS	per-protocol set
PsA	psoriatic arthritis
PsO	plaque psoriasis
QTcF	QT Interval Corrected According to Fridericia's Formula
RA	rheumatoid arthritis
RAN	randomized set
Re-RAN	re-randomized set
SAE	serious adverse event
SAF	safety set
SAWP	Scientific Advice Working Party
TB	tuberculosis
T_{max}	time to C_{max}
tmTNF	transmembrane tumour necrosis factor
TNF	tumour necrosis factor
UC	ulcerative colitis
V_z	Volume of distribution during the terminal phase
VAS	visual analogue scale

Drug	Infliximab (Renflexis; SB2)
Indication	Use in combination with methotrexate for the reduction in signs and symptoms, inhibition of the progression of structural damage and improvement in physical function in adult patients with moderately to severely active rheumatoid arthritis. The reduction of signs and symptoms and improvement in physical function in patients with active ankylosing spondylitis who have responded inadequately, or are intolerant to, conventional therapies. Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to a corticosteroid and/or aminosalicylate. Renflexis can be used alone or in combination with conventional therapy. Reduction of signs and symptoms and induction and maintenance of clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy (corticosteroid and/or aminosalicylate and/or an immunosuppressant). The safety and efficacy of Renflexis is not established in patients less than 9 years of age. Treatment of fistulizing Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment. Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). Reduction of signs and symptoms, induction and maintenance of clinical remission, and induction of mucosal healing in pediatric patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). The safety and efficacy of Renflexis have not been established in patients less than 6 years of age. Reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with psoriatic arthritis. Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, Renflexis should be used after phototherapy has been shown to be ineffective or inappropriate. When assessing the severity of psoriasis, the physician should consider the extent of involvement, location of lesions, response to previous treatments, and impact of disease on the patient's quality of life.
Reimbursement Request	Merck is requesting that SB2 be listed in accordance with the Health Canada–approved indications for the treatment of rheumatoid arthritis (adult), ankylosing spondylitis, Crohn's disease (adult and pediatric), fistulizing Crohn's disease (adult), ulcerative colitis (adult and pediatric), psoriatic arthritis and plaque psoriasis (adult), for use in patients for whom infliximab is considered to be the most appropriate treatment option. [redacted] • [redacted].
Manufacturer	Samsung Bioepis Co., Ltd. (distributed by Merck Canada)

Executive Summary

Approach to the Review

The CADTH Common Drug Review (CDR) approach to reviewing SB2 followed the *CDR Procedure and Submission Guidelines for Subsequent Entry Biologics* (March 2014). The CDR team reviewed the information provided by the manufacturer regarding product information, indications under review, the manufacturer's requested listing criteria, biosimilarity, extrapolation, and cost. Published and grey literature sources were also searched for additional relevant materials. Reviewers provided a critical appraisal of the clinical evidence, a discussion of extrapolation, and an evaluation of cost.

Product Information

SB2 is a biosimilar to the reference infliximab product, Remicade. On December 1, 2017, Health Canada approved Renflexis for the following indications:

- Use in combination with methotrexate (MTX) for the reduction in signs and symptoms, inhibition of the progression of structural damage, and improvement in physical function in adult patients with moderately to severely active rheumatoid arthritis (RA).
- Reduction of signs and symptoms and improvement in physical function in patients with active ankylosing spondylitis (AS) who have responded inadequately, or are intolerant to, conventional therapies.
- Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction of corticosteroid use in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to a corticosteroid and/or aminosalicylate. Renflexis can be used alone or in combination with conventional therapy.
- Reduction of signs and symptoms and induction and maintenance of clinical remission in pediatric patients with moderately to severely active CD who have had an inadequate response to conventional therapy (corticosteroid and/or aminosalicylate and/or an immunosuppressant). The safety and efficacy of Renflexis is not established in patients less than nine years of age.
- Treatment of fistulizing CD in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.
- Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).
- Reduction of signs and symptoms, induction and maintenance of clinical remission, and induction of mucosal healing in pediatric patients with moderately to severely active UC who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). The safety and efficacy of Renflexis have not been established in patients less than six years of age.
- Reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with psoriatic arthritis (PsA).

- Treatment of adult patients with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy. For patients with chronic moderate PsO, Renflexis should be used after phototherapy has been shown to be ineffective or inappropriate.

The manufacturer is requesting reimbursement for the following Health Canada–approved indications:

- Treatment of RA (adult), AS, CD (adult and pediatric), fistulizing CD (adult), UC (adult and pediatric), PsA, and PsO (adult) in patients for whom infliximab is considered to be the most appropriate treatment option

In addition, the manufacturer is requesting reimbursement for:

[redacted]

Clinical Evidence

The manufacturer submitted two studies to support the use of infliximab biosimilar SB2 for RA, AS, CD (adult and pediatric), fistulizing CD, UC (adult and pediatric), PsA, and PsO.

In a phase I, randomized, three-arm, single-blind study (Study SB2-G11-NHV*)*, SB2 was compared with EU-Remicade and US-Remicade reference products for pharmacokinetic (PK), safety, and immunogenicity outcomes among 159 healthy patients. A single dose of 5 mg/kg SB2 (N = 53), EU-Remicade (N = 53), or US-Remicade (N = 53) was infused intravenously over 120 minutes and patients were followed for 10 weeks. The primary outcomes were areas under the curve (AUC_{inf}, AUC_{last}) and maximum serum concentration (C_{max}); if the 90% confidence interval (CI) of the geometric mean (GM) was within the equivalence margin of 80% to 125%, SB2 was deemed pharmacokinetically equivalent to the reference products. Secondary outcomes were other PK parameters (e.g., T_{max}, k_{el}, V_z), safety (i.e., adverse events [AEs], vital signs, lab tests, ECG, and physical examination), and immunogenicity (i.e., anti-drug antibodies [ADA] and neutralizing antibodies [NAb]). The PKs of SB2 were equivalent to EU-Remicade and US-Remicade, as all parameters were within the pre-specified equivalence margin of 80% to 125%. When the PK analyses were stratified based on ADA-positive and -negative status, the results remained within the equivalence margin.

A phase III, randomized, double-blind, multinational trial (Study SB2-G31-RA*)* was conducted to evaluate the efficacy, safety, immunogenicity, and PKs of SB2 compared with EU-Remicade in 584 patients with moderate to severe RA despite MTX therapy. Patients were administered SB2 or EU-Remicade at doses of 3 mg/kg IV at weeks 0, 2, and 6, and then every eight weeks thereafter, and received MTX 10 mg/week to 25 mg/week and folic acid 5 mg/week to 10 mg/week. The primary end point was the American College of Rheumatology 20% response criteria (ACR 20) at week 30; equivalence was based on the 95% CI of the treatment difference lying within a margin of ± 15%. Secondary outcomes included ACR 50, ACR 70, the Disease Activity Score 28 (DAS 28), the European League Against Rheumatism (EULAR) response, incidence of AEs and serious adverse events (SAEs), clinical lab tests, vital signs, immunogenicity, and PKs. A total of 584 patients were randomized, 291 to SB2 and 293 to EU-Remicade. SB2 was equivalent to EU-Remicade with respect to ACR 20 at week 30. The treatments were also similar on secondary efficacy

outcomes, such as ACR 20 at week 54, ACR 50 at weeks 30 and 54, and ACR 70 at weeks 30 and 54.

The initial study lasted 54 weeks and was followed by a 24-week, double-blind transition study in which patients from the EU-Remicade group were again randomized to either switch to SB2 or remain on Remicade. The transition study included 396 patients (67.8%), 201 from the SB2 group (SB2/SB2) and 195 from the EU-Remicade group, 94 of whom were randomized to switch to SB2 (Remicade/SB2) and 101 to remain on Remicade (Remicade/Remicade). Although primary and secondary outcomes were similar after the transition phase (*P* values not provided), in a post hoc analysis that examined ACR 20 over the entire 78-week period, response patterns showed greater fluctuation for Remicade/SB2 and Remicade/Remicade than for SB2/SB2, which the manufacturer attributed to smaller sample sizes among the former two groups.

In both the phase I and phase III trials, numerical differences in some safety end points were observed (i.e., phase I study: higher percentage of treatment-emergent adverse events [TEAEs] in the SB2 group; phase III study: higher percentage with alanine aminotransferase [ALT] increase in SB2 group and higher percentage with latent tuberculosis [TB] in the switch group), although the small sample size and/or small number of events render these results inconclusive. There were also some numerical differences in ADA formation in the phase I and III trials. These differences in ADA were recognized by the FDA and the European Medicines Agency (EMA); however, both organizations deemed that they were not clinically relevant based on the totality of evidence. Further evaluation of SB2 immunogenicity compared with Remicade will occur in a planned two-year prospective, observational cohort study in patients with AS and CD (part of the Risk Management Plan of the Committee for Medicinal Products for Human Use).

Extrapolation

Extrapolation from RA to AS, PsO, PsA, CD, and UC may be reasonable given the role of tumour necrosis factor (TNF) alpha in all indications and demonstrated similarities between SB2 and Remicade in structural characteristics, physiochemical properties, fragment antigen-binding (Fab), and fragment crystallizable (Fc) biological properties, non-clinical evidence in animal models, and clinical evidence in healthy patients and patients with RA. The patterns of use of immunosuppressant therapies and dosing requirements do differ among the indications. The FDA approved SB2 for AS, PsA, PsO, adult and pediatric CD, and adult UC (pediatric UC is protected by orphan drug exclusivity that expires September 23, 2018). The EMA also approved SB2 for AS, PsA, PsO, adult and pediatric CD, and adult and pediatric UC (under trade name Flixabi). Health Canada recently granted a Notice of Compliance (NOC) to Renflexis for RA, AS, CD (adult and pediatric patients over nine years of age), fistulizing CD, UC (adult and pediatric patients over six years of age), PsA, and PsO.

Cost Comparison

At the submitted price, the annual drug acquisition cost of SB2 is 47% less than Remicade and equivalent to Inflectra across all indications when using Ontario list prices as references. Manufacturer sponsorship of treatment costs, price differences across CDR-participating drug plans, demand and feasibility of biosimilar switching, and treatment market share further influence cost considerations.

Potential Place in Therapy[1]

The infliximab reference product has been widely used for all proposed indications for more than 10 years. For rheumatologic diseases specifically, anti-TNF drugs have been the first biologic of choice after disease-modifying antirheumatic drugs (DMARDs) for RA and PsA, and after NSAIDs (nonsteroidal anti-inflammatory drugs) for AS, most often in conjunction with MTX or another DMARD if MTX is contraindicated. In rheumatology, the subcutaneous biologic drugs (and recently the Janus kinase inhibitors) are a more frequent choice than the IV medications. This is not the case in some of the other proposed indications, such as the more frequent use of infliximab for inflammatory bowel diseases (IBDs).

Adult and pediatric patients with IBD currently have a number of unmet medical needs. While anti-TNF drugs are excellent for inducing clinical remission in adult and pediatric patients with CD and active inflammation, these patients still often go on to develop fibrostenotic disease.[1] There are no medications available to treat CD strictures; these patients require surgery or endoscopic dilation. Patients with UC do not all respond to existing therapies; many go on to require colectomy. According to a clinical expert consulted by CDR for this review, anti-TNF therapies vedolizumab and ustekinumab are delivered intravenously or by injection, making them uncomfortable, especially for younger patients. All have worrisome side effects, including the risk of significant infection. These three classes of therapy are also extremely expensive, making them inaccessible to some patients and causing a significant financial burden for others. SB2 does not offer a novel mechanism of action, so it may address the financial concern simply by introducing more competition into the market. However, SB2 will not fulfill any other currently unmet needs of IBD patients.

SB2 might be appropriate for anti–TNF-naive adult IBD patients who have failed traditional therapy or who have features at presentation predictive of a severe course. SB2 is also likely to be appropriate for anti–TNF-naive pediatric IBD patients in the same situations, although pediatric data on biosimilars are lacking. IBD patients who have antibody-mediated secondary loss of response to another anti-TNF drug (not Remicade) may also benefit from SB2. However, switching a patient with adult or pediatric IBD who is well on Remicade to SB2 is not currently supported by high-quality data specific to the IBD population.[2] According to a clinical expert consulted by CDR for this review, switching could pose risks to the patient, including AEs such as infusion reactions, possibly related to anti-infliximab antibody development. Switching back to Remicade in the future may be impossible because of subsequent anti-Remicade antibody development. Similarly, for rheumatology, SB2 would be an appropriate medical choice for any biologic-naive or biologic-experienced patient who would receive the reference product. Although there is evolving clinical evidence that might in the future support switching the patient from the reference product, non-medical switching has not been commonly observed with the first biosimilar of infliximab (Inflectra). The uncertainty of response and safety, the availability of a location to administer this IV drug, and the lack of acknowledgement of the interchangeability by health authorities would suggest that switching from originator infliximab to biosimilar should be undertaken only after extensive discussion between the patient and medical team.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusion

SB2 is the second proposed biosimilar of Remicade that has received market authorization in Canada. The clinical data for SB2 consist of two studies: a phase I PK study in healthy patients and a phase III efficacy and safety trial in patients with RA. The PK profile of SB2 was shown to be equivalent to its reference products. Equivalence in efficacy up to 54 weeks was demonstrated in patients with RA based on an equivalence margin of ± 15%. In both the phase I and phase III trials, numerical differences in some safety end points and immunogenicity were observed; however, the clinical interpretation of these results is uncertain given the small sample size and small number of events. There is evidence from a 24-week, double-blind, transition-extension study that suggests efficacy outcomes remain similar after switching from Remicade to SB2. The use of efficacy and safety data from the phase III trial in patients with RA to support market authorization for all other indications may be reasonable given: (a) the role of TNF alpha in all indications; and (b) demonstrated similarities between SB2 and Remicade in structural characteristics, physiochemical properties, Fab- and Fc- biological properties, non-clinical evidence in animal models, and clinical evidence in healthy patients and patients with RA.

Product Information

Overview of the Biosimilar Product

Characteristics	Manufacturer-Provided Details			
	SB2	**Canadian-Remicade**	**EU-Remicade**	**US-Remicade**
Brand name:	*SB2*	*Remicade*		
Non-proprietary name:	Infliximab			
Manufacturer:	Samsung Bioepis Co., Ltd. (distributed by Merck Canada)	Janssen Inc., Toronto	*Manufacturer of the DS:* Janssen Biologics B.V., Leiden, Netherlands Janssen Biotech Inc., Malvern, Pennsylvania *Manufacturer responsible for batch release:* Janssen Biologics B.V., Leiden, The Netherlands	*Manufactured by:* Janssen Biotech, Inc. Horsham, PA
Strength(s):	100 mg/vial			
Dosage form:	Lyophilized powder for solution			
Route of administration:	Intravenous infusion			
Drug Identification Number(s):	Not available; pre-NOC submission	02244016	Not applicable	
Therapeutic classification:	Biological Response Modifier			
Excipients	• 500 mg sucrose; • 0.5 mg polysorbate 80; • 5.55 mg monobasic sodium phosphate monohydrate; • 2.60 mg dibasic sodium phosphate heptahydrate; • No preservatives	• 500 mg sucrose; • 0.5 mg polysorbate 80; • 2.2 mg monobasic sodium phosphate, monohydrate; • 6.1 mg dibasic sodium phosphate, dehydrate; • No preservatives	• Sucrose • Polysorbate 80 • Monobasic sodium phosphate • Dibasic sodium phosphate	• 500 mg sucrose; • 0.5 mg polysorbate 80; • 2.2 mg monobasic sodium phosphate monohydrate; • 6.1 mg dibasic sodium phosphate, dehydrate; • No preservatives
Impurities[a]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	Manufacturer-Provided Details			
	SB2	Canadian-Remicade	EU-Remicade	US-Remicade
	[redacted]			

DP: drug product; EU: European Union; HMW: high molecular weight; NOC: Notice of Compliance; PVR: process validation run; US: United States

[a] Include both product and process-related impurities.

[b] Test method for HCP and HCD are CHO-specific (Remicade is produced in SP2/0 cells)

[redacted]

Source: SB2 and Remicade product monographs (Canada); Remicade Summary of Product Characteristics (EU); Remicade Label Information (US); Common Technical Document (CTD) 2.3.R; data on file with Saumsung Bioepis

Pharmaceutical form: SB2 and Remicade: Powder for Solution, Sterile, Lyophilized, 100 mg /vial

Pharmaceutical composition: Each vial of SB2 DP contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 5.55 mg monobasic sodium phosphate monohydrate and 2.60 mg dibasic sodium phosphate heptahydrate. Each vial of Remicade DP contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate and 6.1 mg dibasic sodium phosphate, dihydrate. Both products do no contain preservatives. As for Remicade*, the vial stopper for SB2 is free of natural rubber latex. Details on the function of each component in SB2 DP formulation is provided in Section 3.2.P.2.1 Components of the Drug Product (available at request).

Although minor differences in excipients exist between the SB2 and Remicade drug products, results from both comparative analytical analyses (using drug products), clinical trials in healthy volunteers and rheumatoid arthritis (RA) patients suggested biosimilar monoclonal antibodies as well as a lack of meaningful differences between the two products in terms of overall pharmacokinetics (PK), safety, and efficacy.

Dosage form: both SB2 and Remicade are supplied as a sterile white lyophilized powder for intravenous infusion.

Strength: both SB2 and Remicade are supplied as 100 mg vials to be reconstituted with 10 mL sterile water for injection, USP. For both products, the total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection USP.

Route of administration: both SB2 and Remicade are administered via intravenous infusion.

Purity and impurities:
As excipients are added during the purification process of SB2 DS production and no additional excipients added during the manufacture of SB2 DP, the impurities present or potentially present in the finished product are the same as those identified and controlled in the DS, which is discussed below.

Impurities that are present or potentially present in the SB2 DS manufactured using the proposed commercial manufacturing process are divided into product-related impurities, process-related impurities and contaminants. All impurities have been evaluated.

Process-related impurities

The process-related impurities include host cell protein (HCP), host cell DNA (HCD), [redacted]

[redacted]. Levels of these impurities were tested as an in-process control to test for process consistency up to PVR batches. In addition, impurities clearance validation has been conducted and the results of this validation study demonstrated that the SB2 purification process was capable of significantly removing these impurities from the SB2 DS (see Section 3.2.S.2.5.5 Impurity Clearance). The results of this study demonstrated that levels of all process-related impurities were sufficiently low, and are expected to pose no safety risk to patients.

Product-related impurities

[redacted].

As the formulation of SB2 DS and SB2 DP is identical, the characterization data generated with DS and DP are considered equally valid for comparison.

A summary of the results of SB2 DP purity and impurity (3 batches) are provided in the table below.

Parameter	Test	Acceptance criteria	Results range		
			SB2	EU-Remicade	US-Remicade
SB2 Drug Product PVR Batches					
High molecular weight variants[a]	SEC	% HMW impurities ≤ [redacted]	[redacted]	[redacted]	[redacted]
Molecular fragments[b]	CE-SDS (non-reducing)	[redacted]	[redacted]	[redacted]	[redacted]
Charged variants[c]	icIEF	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]

PVR: process validation run; CE-SDS: capillary electrophoresis-sodium dodecyl sulphate; SEC: size-exclusion chromatography; HMW: high molecular weight

Source: data on file with Samsung Bioepis

[a]DP release test results; comparative biosimilarity study results are only available for SB2 DP and EU-Remicade [redacted]

[b]DP release test results; comparative biosimilarity study results are only available for SB2 DP and EU-Remicade [redacted]

[c]DP release test results

Overview of the Reference Product

Infliximab is a purified, recombinant DNA-derived, chimeric human-mouse IgG monoclonal antibody (MAb) that binds to and neutralizes human tumour necrosis factor-alpha (TNF-α) with high affinity. Infliximab contains murine heavy (H) and light (L) chain variable regions (V_H and V_L, respectively) and human H and L chain constant regions (C_H and C_L, respectively). Infliximab consists of 1328 amino acids.

The reference product described in this submission is Remicade (infliximab; sterile lyophilized powder for solution) (1). Remicade is currently authorized for sale and marketing in Canada in a 100 mg/vial format (DIN: 02244016).

It should be noted that the batches of Remicade used in the SB2-G31-RA trial (rheumatoid arthritis; RA) were sourced from the EU and those used in the SB2-G11-NHV trial (health volunteers) were sourced from the EU and the US (CTD 2.3.R, section 2.3.R.5.1.).

Justification for the Use of a Non-Canadian Sourced Reference Drug

During development of SB2, EU-Remicade was used as the main reference drug. Linkage in corporate entities and formulation between Canadian and EU-Remicade has been demonstrated and that Canadian and EU-sourced Remicade were shown to have identical corporate entities in manufacturing and distribution (see section *1.1 Overview of the Biosimilar Product* above). Based on the above, EU-Remicade may be used as a reference drug for the SB2 NDS, and no additional comparability studies using Canadian-sourced Remicade is deemed necessary (CTD 2.3.R, section 2.3.R.5.2). Comparative results against US-Remicade served as supportive information only.

	Reference Status	Physicochemical & Functional Studies	Phase I Study	Phase III Study
EU-Remicade	Accepted Non-Canadian Reference	Yes	Yes	Yes
US-Remicade	Supportive	Yes	Yes	No

In Canada, Remicade (infliximab) is indicated for:

- use in combination with methotrexate for the reduction in signs and symptoms, inhibition of the progression of structural damage and improvement in physical function in adult patients with moderately to severely active **rheumatoid arthritis**.
- the reduction of signs and symptoms and improvement in physical function in patients with active **ankylosing spondylitis** who have responded inadequately, or are intolerant to, conventional therapies.
- reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in **adult** patients with moderately to severely active **Crohn's disease** who have had an inadequate response to a corticosteroid and/or aminosalicylate. REMICADE can be used alone or in combination with conventional therapy.
- reduction of signs and symptoms and induction and maintenance of clinical remission in **pediatric** patients with moderately to severely active **Crohn's disease** who have had an inadequate response to conventional therapy (corticosteroid and/or aminosalicylate and/or an immunosuppressant). The safety and efficacy of REMICADE is not established in patients less than 9 years of age.
- treatment of **fistulising Crohn's disease**, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.
- reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in **adult** patients with moderately to severely active **ulcerative colitis** who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).
- reduction of signs and symptoms, induction and maintenance of clinical remission, and induction of mucosal healing in **pediatric** patients with moderately to severely active **ulcerative colitis** who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). The safety and efficacy of REMICADE have not been established in patients less than 6 years of age.

- reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with **psoriatic arthritis**.
- treatment of adult patients with chronic moderate to severe **plaque psoriasis** who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, REMICADE should be used after phototherapy has been shown to be ineffective or inappropriate. When assessing the severity of psoriasis, the physician should consider the extent of involvement, location of lesions, response to previous treatments, and impact of disease on the patient's quality of life.

Indications

Health Canada-Approved Indications

Indication(s)	Clinical Trial Data
Not applicable; pre-Notice of Compliance (NOC) submission	Not applicable

Proposed Indications under Review by Health Canada

Proposed Indication(s)	Anticipated Date of NOC
use in combination with methotrexate for the reduction in signs and symptoms, inhibition of the progression of structural damage and improvement in physical function in adult patients with moderately to severely active rheumatoid arthritis.	December, 2017
the reduction of signs and symptoms and improvement in physical function in patients with active ankylosing spondylitis who have responded inadequately, or are intolerant to, conventional therapies.	December, 2017
reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to a corticosteroid and/or aminosalicylate. SB2 can be used alone or in combination with conventional therapy.	December, 2017
reduction of signs and symptoms and induction and maintenance of clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy (corticosteroid and/or aminosalicylate and/or an immunosuppressant). The safety and efficacy of SB2 is not established in patients less than 9 years of age.	December, 2017
treatment of fistulising Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.	December, 2017
reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).	December, 2017
reduction of signs and symptoms, induction and maintenance of clinical remission, and induction of mucosal healing in pediatric patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). The safety and efficacy of SB2 have not been established in patients less than 6 years of age.	December, 2017
reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with psoriatic arthritis.	December, 2017
treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, SB2 should be used after phototherapy has been shown to be ineffective or inappropriate. When assessing the severity of psoriasis, the physician should consider the extent of involvement, location of lesions, response to previous treatments, and impact of disease on the patient's quality of life.	December, 2017

Manufacturer's Requested Listing Criteria

Requested Listing Criteria

Requested Listing Criteria for Indications to be Reviewed by the CADTH Common Drug Review
Merck is requesting that SB2 be listed in accordance with the Health Canada–approved indications for the treatment of rheumatoid arthritis (adult), ankylosing spondylitis, Crohn's disease (adult and pediatric), fistulising Crohn's disease (adult), ulcerative colitis (adult and pediatric), psoriatic arthritis and plaque psoriasis (adult), for use in patients for whom infliximab is considered to be the most appropriate treatment option. [redacted]: • [redacted]. • [redacted].

Rationale for Requested Listing Criteria

The rationale for the above requested listing criteria is based on the principle of biosimilarity, which has been demonstrated between SB2 and the currently reimbursed reference product Remicade.

First, an NOC for SB2 is expected from Health Canada for all indications no later than the anticipated date of December 4, 2017:

- SB2 has demonstrated **comparable safety and efficacy profile** to the reference product Remicade in RA patients in the pivotal efficacy study SB2-G31-RA (described in detail in section 4.2.1 below). Briefly, SB2 was demonstrated to be therapeutically similar to Remicade (both groups received concurrent methotrexate [MTX]), as determined by the similar primary endpoint of American College of Rheumatology 20% (ACR20) response at week 30 (SB2 vs. Remicade; per-protocol set 1: 64.1% vs. 66.0%, 95% confidence interval (CI): −10.26% to 6.51%; full-analysis set: 55.0% vs. 59.0%, 95% CI: −10.88% to 4.97%) which was within pre-defined equivalence margin of ±15%). In addition, all other efficacy and safety endpoints were similar between both products.
- SB2 elicited **generally similar levels of immunogenicity** as Remicade in both RA subjects and healthy volunteers. Slightly numerically higher number of subjects in the SB2 group compared to the Remicade groups in both studies developed immunogenicity but the difference was not significant and did not translate into comparative differences in terms of pharmacokinetics, clinical safety and efficacy.
- SB2 has **demonstrated PK similarity** to Remicade in both RA subjects and healthy volunteers:
    - The 90% CIs of the ratios (SB2/Remicade) of the geometric means were all contained within the regulatory agency-accepted equivalence margin for all key PK outcomes (study SB2-G11-NHV).
    - The evaluated doses of 3 mg/kg (starting dose in RA subjects, up to 7.5 mg/kg) and 5 mg/kg (healthy volunteers) in the trials are the most commonly used dosages across all anticipated SB2 indications.
- SB2 has shown **similar physicochemical properties and biological activities** to Remicade as demonstrated by the results from an extensive series of analytical and *in vitro* assays (2). Minor differences in the glycan structure did not translate into differences in physiologically relevant *in vitro* activity assays (i.e., FcγRIIIa binding in natural-killer [NK] cells from peripheral blood monocytes (PBMCs) and antibody-dependent cell-mediated cytotoxicity (ADCC) activity in human PMBCs).

- The mechanism underlying disease pathogenesis across all indications involve TNF-α, and the action of infliximab in disease modulation involves interaction with soluble TNF-α, transmembrane TNF-α, ADCC, and/or complement-dependent cytotoxicity (CDC) (see details in section 6). These activities of infliximab have been demonstrated to be similar between SB2 and Remicade as stated above.

Second, results from the *transition-extension* period of the Phase III trial in RA patients demonstrated that:

i. At week 78, SB2 had similar efficacy and safety profiles as Remicade

ii. RA subjects that were switched (re-randomized) to receive SB2 (after 54 weeks of Remicade treatment during the *randomized, double-blind* period) had similar safety, efficacy, and immunogenicity profiles as those subjects who were re-randomized to continue on Remicade up to 78 weeks, as well as to those who received SB2 for 78-weeks.

Third, the minor differences in formulation between SB2 and Remicade did not have impact on the comparative stability of SB2 vs. Remicade and had no apparent impact on the similarity between the two products in terms of analytical characteristics, as well as clinical pharmacology, safety, and efficacy.

Fourth, the SB2 that was used in the clinical studies were manufactured using the same process and location as the SB2 intended for the Canadian market. [redacted].

Fifth, the demonstration of SB2 as a biosimilar of Remicade was recognized by the European Medicines Agency (EMA) as detailed in the Committee for Medicinal Products for Human Use (CHMP)'s Assessment Report for Flixabi (EU trade name) (3), US Food and Drug Administration (FDA)'s approval for Renflexis (US trade name) (4), and Australia TGA's registration of Renflexis (5) for the following indications:

- Rheumatoid arthritis (Adult RA)
- Ankylosing spondylitis (AS)
- Adult Crohn's disease (Adult CD)
- Pediatric Crohn's disease (Pediatric CD)
- Fistulising Crohn's disease (Adult Fistulising CD)
- Adult ulcerative colitis (Adult UC)
- Pediatric ulcerative colitis (Pediatric UC) (not licensed in the US due to patent protection)
- Psoriatic arthritis (PsA)
- Plaque psoriasis (Adult PsO)

Sixth, the requested indications of SB2 are identical to those of the reference medicinal product, Remicade, for which the drug has been extensively characterized pharmacologically (6, 7). There is also nearly 18 years of clinical experience from both an efficacy and safety standpoint (1).

Based on the above, SB2 is also expected to have similar safety and efficacy as Remicade in all of the requested indications.

From the Canadian health technology assessment perspective, infliximab has been previously recommended by the CDR for the indications of RA, AS, PsO, PsA, CD, Fistulising CD, and UC (8-10).

Therefore, the therapeutic value of infliximab for the treatment of these indications has been recognized and supported by CADTH.

From the Canadian reimbursement perspective, infliximab (Remicade) is currently reimbursed by all CDR-participating drug plans across the country for the majority of all Health Canada-approved indications (with exceptions, see *Appendix 2*). As Inflectra (another infliximab biosimilar) is also currently reimbursed (the infliximab to be approved for infliximab-naïve patients), consequently, we anticipate that SB2 will receive generally similar listing decisions as Inflectra from these CDR-participating drug plans, assuming that the Canadian Drug Expert Committee issues a positive recommendation for SB2.

Seventh, the EMA has stated in its recent report *Biosimilars in the EU – Information guide for healthcare professionals* (11):

"The evidence acquired over 10 years of clinical experience shows that biosimilars approved through EMA can be used as safely and effectively in all their approved indications as other biological medicines."

"Over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicines."

Therefore, based on the totality of evidence, i.e.:

i. demonstrated biosimilarity in terms of physicochemical characteristics and *in vitro* activities between SB2 and Remicade;
ii. similar PK profile between SB2 and Remicade in healthy volunteers and RA patients;
iii. similar safety (in RA subjects and healthy volunteers), efficacy (in RA subjects), and immunogenicity (in RA subjects and healthy volunteers) profiles between SB2 and Remicade; and
iv. demonstrated safety and efficacy of SB2 in patients who previously received Remicade based on the 78-week *transition-extension* period results;
v. anticipated NOC for all requested indications by Health Canada as a biosimilar;
vi. marketing authorization by the EMA for all indications, US licensing for all indications (except pediatric UC), and Australian PBAC recommendation for all indications, the requested listing criteria for SB2 are reasonable and justified.

Biosimilarity

Quality Information

The SB2 DS is manufactured at a large scale Biogen manufacturing facility located in Hillerød, Denmark and the DP is manufactured by Patheon in Italy in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. SB2 was characterized using appropriate techniques as described in the ICH guideline Q6B. The study involved determination of the physicochemical properties, biological activity, potency, purity, impurities and quantity of SB2 using state-of-the-art orthogonal analytical methods to confirm the similarity in quality to Remicade, to ensure that the safety and efficacy profiles of SB2 would be similar to the reference product. Similarity ranges were set for the similarity study based on data from the characterization of up to 37 batches of the reference EU-Remicade. Since the preparation of the CTDs for Health Canada submission, additional batches were further tested and results are published by Hong et al. (2). The similarity range was set by statistical analysis based on the tolerance interval (mean ± *k* [k-factor] x standard deviation [SD] using two-tiered tolerance limit) with the given set of available data points (12) (CTD 2.3.R, section 2.3.R.5.1). In addition, as the use of tolerance interval-based similarity range in certain cases may result in broad biosimilarity ranges allowing differences between SB2 and Remicade, all quality attributes were reassessed using a Min/Max approach (3). Results presented below are based on similarity exercises conducted between SB2 and Remicade. The formulation of SB2 DS and SB2 DP is identical, as such, characterization data generated with DS and DP are considered equally valid for inclusion in this section.

The primary structures of SB2 and Remicade were determined and confirmed to be identical by a series of assays. Other structural characterizations were also conducted. C-terminal lysine variant analyses indicated the variants existed for both SB2 and Remicade but were considered to be clinically inconsequential since the terminal lysines are cleaved as it enters the blood stream (Table 1). With regards to the glycosylation, both infliximabs are N-glycosylated only at Asn300. Minor differences in glycosylation profile existed but these differences **did not translate into differences in various *in vitro* binding or functional activities** (Table 2). A series of other physiochemical studies (chromatographic, electrophoretic, and biophysical analytical assays) were conducted and results also demonstrated **SB2 and Remicade have similar higher-order structures** (Table 1). Results of the key assays are summarized below; detailed descriptions of these assays and all other relevant assays can be found in (Table 42) in Appendix 1 and CTD Modules 2.3.R and 2.3.S.

Table 1: Summary of select physicochemical and biophysical test methods for similarity of SB2 and Remicade (IFN)

Test Method(s)	Summary of Results	Reference(s)
Structural Characterization and Confirmation: Primary Structure		CTD 2.3.R, section 2.3.R.5.3.1 CTD 2.3.S, section 2.3.S.3.1.1
• Full sequencing	• Amino acid sequence of SB2 was identical to that of EU-IFN	
• N-terminal sequence analysis	• 2 forms of N-terminal peptide in the heavy chain and 1 form of N-terminal peptide in the light chain were identified • Their relative levels were similar between SB2 and EU-IFN • The heavy and light chain N-terminal sequences of SB2 were similar to those of EU-IFN	

Test Method(s)	Summary of Results	Reference(s)
Structural Characterization and Confirmation: Primary Structure		CTD 2.3.R, section 2.3.R.5.3.1 CTD 2.3.S, section 2.3.S.3.1.1
• C-terminal sequence analysis	• One form of the light chain at C-terminus was identified, whereas three different forms of the HC at C-terminus were commonly identified. • With the exception of a single form in HC (presented only in SB2 due to the use of a specific cell line, but considered insignificant), it was concluded that the C-terminal sequence of SB2 was identical to the expected sequence.	
• Disulphide bond	• The disulphide bonds were analysed using (liquid chromatography-electrospray ionisation-mass spectrometry/mass spectrometry) LC-ESI-MS/MS • **Results showed that the disulphide linkage patterns was similar between SB2 and EU-IFN**	
• C-terminal Lysine (Lys) variant analysis	• The relative level of the Lys variant in SB2 was lower than that in EU-IFN indicating that most of the Lys on the C-terminus of SB2 was found cleaved. • The heterogeneity of C-terminal residues is a characteristic of therapeutic mAbs and C-terminal lysine variation that is known not to impact pharmacokinetic profiles and the biological activity of the fragment crystallisable (Fc) fusion protein. • In addition, the C-terminal lysine does not possess any physiological effect as it is cleaved by carboxypeptidase as it enters the blood. • Results from the TNF-α binding functional assay showed that C-terminal Lys variants had no influence on TNF-α binding activity. **Therefore, the difference in C-terminal Lys content was not considered significant.**	
Structural Characterization and Confirmation: Carbohydrate Structure/Glycan Profile (Physicochemical)		CTD 2.3.R, section 2.3.R.5.3.2 CTD 2.3.S, section 2.3.S.3.1.2
• N-glycan Profile	• N-glycan profiles differed slightly between SB2 and EU-IFN • The afucosylated glycans (%Afucose) content in SB2 was higher than EU-IFN • However, in the subsequent Min/Max assessment, the %Afucose results were found to be between the Min/Max of EU-IFN (3). • Afucosylated glycan level in therapeutic proteins is associated with FcγRIIIa binding activity and antigen-dependent cell-mediated cytotoxicity (ADCC). The FcγRIIIa binding and ADCC activities were similar between SB2 and EU-IFN. • Thus, the difference in %Afucose between SB2 and EU-IFN was not considered significant. • Charged glycan (%Charged) level in SB2 was lower than that of EU-IFN but was within the similarity range. • All other glycans were within the similiarity range.	
Physicochemical Properties: Electrophoretic Patterns		CTD 2.3.R, section 2.3.R.5.3.4 CTD 2.3.S, section 2.3.S.3.1.4
• Charge Heterogeneities by Imaged Capillary Isoelectric Focusing (icIEF)	• icIEF was used to determine the relative contents of charge variants in SB2 and EU-IFN. • SB2 possessed a lower content of main peak and a higher content of basic variants compared to those of EU-IFN; however, SAR studies performed using cation-exchange chromatography (CEX)-fractionated peaks showed that the charge variant content did not affect TNF-α and FcγRIIIa binding activities. • **These results therefore indicated that the difference in charge variants did not translate into differences in the biological activity of SB2 and were not considered significant.**	
Physicochemical Properties: Biophysical		CTD 2.3.R, section 2.3.R.5.3.5 CTD 2.3.S, section 2.3.S.3.1.5
• Far-ultraviolet (UV) circular dichroism (CD) Spectroscopy	• Far-UV analysis is a rapid analysis method for assessing secondary structure and folding, and also protein interactions. • Results showed good overlap in the far-UV plots between SB2 and EU-IFN. • **SB2 and EU-IFN were considered similar in terms of far-UV CD spectroscopic profiles.**	
• Near UV CD Spectroscopy	• Near-UV analysis measures the tertiary structure of proteins. • **SB2 and EU-IFN were considered similar in terms of near-UV CD spectroscopic profiles.**	
• Fourier Transform Infrared Spectroscopy (FTIR)	• FTIR was used to analyze the secondary structure of SB2 and EU-IFN • The spectra observed for SB2 and EU-IFN were similar • Therefore, the FTIR spectra of SB2 were considered to be similar to those of EU-IFN	
• Differential	• The shapes of the thermal scans for SB2 and EU-IFN were similar.	

Test Method(s)	Summary of Results	Reference(s)
Structural Characterization and Confirmation: Primary Structure		CTD 2.3.R, section 2.3.R.5.3.1 CTD 2.3.S, section 2.3.S.3.1.1
Scanning Calorimetry (DSC)	• The two main thermal transitions (as measured in SB2) were T_{m1}, 69.5°C and T_{m2}, 84.0°C. • Results also indicated that all T_m values were similar within 2 SD of the mean. • **Therefore, SB2 was considered similar to EU-IFN in terms of thermal stability profiles.**	
Purity/Impurities	• See Process-Related Impurities in section 1.1 Overview of the Biosimilar Product above	CTD 2.3.P, section 2.3.P.5.5 CTD 2.3.S, section 2.3.S.3.2

A comprehensive number of comparative *in vitro* studies were also conducted to evaluate the functional similarity between SB2 and Remicade. The relevant assays were qualified and closely associated with the mode of action of infliximab (e.g., TNF-α binding). Fc-related binding and functional activities were assessed as well. An overview of the *in vitro* studies conducted is given in Table 2.

The binding activity of SB2 to fragment crystallizable gamma receptors (FcγRIa, FcγRIIa, FcγRIIIb) and neonatal fragment crystallizable receptor (FcRn) were all within similarity ranges and Min/Max values. However, for FcγRIIb and FcγRIIIa, the binding is slightly higher in SB2 compared to Remicade (Min/Max value). The binding to FcγRIIb and FcγRIIIa is known to be associated with ADCC activity (13). Subsequent studies evaluating FcγRIIIa binding in NK cells from PBMCs from healthy donors, as well as ADCC activity in mouse cell line over-expressing human transmembrane tumour necrosis factor (tmTNF-α), human NK cell line over-expressing CD16 (FcγRIIIa/b), and PBMCs from healthy donors showed that SB2 and Remicade had similarly level of binding and biological activity.

Additional biological assays were performed to further justify the observed binding difference of FcγRIIIa as well as to evaluate the *in vitro* inflammatory bowel diseases (IBD – including Crohn's disease and ulcerative colitis) model in order to support extrapolation of indication. These assays included: FcγRIIIa binding assay (158 F/F type), TNF-β binding, FcγRIIIb binding using neutrophils, evaluation of regulatory macrophage function, cytokine release activity, and inhibitory activity of apoptosis *in vitro* IBD model.

Results of the tmTNF-α binding assay showed no statistically significant difference between SB2 and EU-Remicade. The additional assays performed under more physiological conditions were conducted in order to demonstrate that the differences observed in glycosylation pattern, FcγR binding and ADCC activity using engineered cell line as effector cells are not relevant for the clinical outcome. The data indeed indicate that under these conditions the differences are diminished.

In summary, the overall results of the *in vitro* assays associated with the mechanism of action of infliximab demonstrated similarity between SB2 and Remicade. Detailed descriptions of these assays and all other relevant assays can be found in Table 43 in Appendix 1, as well as CTD Modules 2.3.R and 2.3.S.

Table 2: Summary of select studies comparing biological activities between SB2 and Remicade (IFN)

Test Method(s)	Summary of Results	Reference(s)
Biological Characterization: Fab-Related Binding Assays		CTD 2.3.R, section 2.3.R.5.3.7 CTD 2.3.S, section 2.3.S.3.1.6
• TNF-α Binding Assay	TNF-α binding activity of SB2 was within the similarity range (85-111%).	
• TNF-α Neutralization	The relative potency of SB2 was within the similarity range (84-116%).	
Fc-Related Biological Activities and Additional Biological Assays		CTD 2.3.R, sections 2.3.R.5.3.8 & 9 CTD 2.3.S, sections 2.3.S.3.1.7 & 8
• FcγRIIb Binding Assay	• FcγRIIb binding activity of SB2 was within the similarity range (78-116%) except for five batches. • The binding values were also slight higher than the Min/Max value (3). • However, no significant difference was observed in orthogonal method (binding affinity measurement by SPR) and the binding activity of SB2 was within the similarity range of the US-IFN. • Also, since results from the ADCC assay were within the similarity range, it was considered that the FcγRIIb binding activity between SB2 and EU-IFN was similar.	
• FcγRIIIa Binding Assay (158 V/V Form)	• FcγRIIIa binding activity of SB2 was within the similarity range (69-127%) except for five batches. • The binding values were also slight higher than the Min/Max value (3). • Despite this difference, the deviation was as minimal as 4-15%, and did not translate into difference in the relevant biological activity. • Specifically, results of ADCC, which is closely related to FcγRIIIa, was within similarity range. • There was also no significant difference observed in orthogonal method (binding affinity measurement by SPR). • Finally, there was no signification difference in physiologically more relevant assay condition (NK cell binding assay). • Therefore, the FcγRIIIa binding activity between SB2 and EU-IFN was considered to be similar.	
• tmTNF-α Binding Assay	The *p*-value of the *t*-test analysis demonstrated that there was no difference between the tmTNF-α binding activity of SB2 compared to EU-IFN.	
• ADCC	There was no statistical difference between the ADCC activities of SB2 compared to EU-IFN in PBMCs from healthy donors, consistent with results using NK92-CD16 cells.	
• CDC	The complement-dependent cytotoxicity (CDC) activity of SB2 was within the similarity range (79-120%). Therefore, CDC activity between SB2 and EU-IFN was considered similar	

Pivotal Clinical Studies

Introduction

The drug development process for SB2 has been designed to replicate Remicade. As such, an extensive biosimilarity and similarity exercise has been performed to demonstrate that SB2 and the reference medicinal product Remicade correspond in terms of quality, safety and efficacy; of which has aligned with the respective EU and Health Canada guidances. In addition to multiple jurisdiction-specific guidelines, the applicant requested scientific advice (SA) from the EMA/Scientific Advice Working Party (SAWP) (EMA/CHMP/SAWP/70331/2012; request for clarification [EMA/221989/2012]; follow-up SA [EMA/CHMP/SAWP/451470/2012]). Furthermore, the applicant consulted with the US Food and Drug Administration (FDA) on the overall product development requirements in a pre-Investigational New Drug meeting (US FDA Meeting Minutes PIND 113461, 2012). Overall, the clinical development programme was designed taking into consideration the SA received by EMA and the FDA. See CTD 2.5, section 2.5.1.2 for details.

Overview of Studies (CTD 2.5, section 1.1)

As outlined in EU guidance (EMEA/CHMP/BMWP/42832/2005; EMA/CHMP/BMWP/403543/2010) (14, 15) and Health Canada guidance (Guidance for Sponsors: Information and Submission Requirements) (16, 17), clinical evidence on similarity needs to be provided in respect to the efficacy of the biosimilar product as well as to safety and PK.

Based on the positive quality similarity results and the *in vitro* and *in vivo* non-clinical study results, a clinical Phase I study was conducted to compare the PK, safety/tolerability, and immunogenicity in order to demonstrate similarity between SB2 and Remicade (Study SB2-G11-NHV). This was followed by a clinical Phase III study in RA patients to demonstrate similarity in efficacy, safety/tolerability, immunogenicity, and patient PK profiles between SB2 and Remicade (Study SB2-G31-RA).

Study SB2-G11-NHV was a randomized, single-blind, three-arm, parallel group, single-dose study to compare the PK, safety/tolerability and immunogenicity of three formulations of infliximab (SB2, EU-Remicade and US-Remicade) in healthy subjects. Study methodology, in particular dosing (single administration of 5 mg/kg), and choice of study population (healthy subjects) were in agreement with EMA SA and the study was conducted in accordance with EMA recommendations (refer to EMA/CHMP/SAWP/70331/2012). For the acceptability of use of healthy volunteers in this study, please refer to section *Acceptability of Healthy Volunteers as a Sensitive PK Population* below.

Study SB2-G31-RA was a pivotal Phase III, randomized, double-blind, parallel-group, multicentre study designed to evaluate the efficacy, safety/tolerability and immunogenicity of SB2 compared to EU-Remicade in subjects with moderate to severe RA despite MTX therapy up to 54 weeks. In addition, the steady-state PK (trough plasma concentration [C_{trough}]) of SB2 and EU-Remicade was evaluated. Study SB2-G31-RA also contained a randomized, double-blind, transition-extension period that was conducted from Week 54 to Week 78 (additional 24 weeks). The *transition-extension* period was added to the protocol after the initiation of the study and was designed to evaluate the long-term safety, tolerability, immunogenicity and efficacy of SB2 and EU-Remicade in patients with RA previously treated with EU-Remicade (i.e. subjects completing the 54-week of the Remicade were re-randomized on a 1:1 ratio to receive either SB2 or EU-Remicade). Those who received SB2 in the 54-week period continued to receive SB2 in the transition period. As of this submission, the study, up to Week 78, has been completed with full data available in the form of Clinical Study Report (78-week CSR). However, the CTDs included in this submission only contained data up to 54 weeks (which was included in the Health Canada filing). For the acceptability of use of RA patients in this study, please refer to section *Acceptability of RA Subjects as a Sensitive Disease Population* below.

Acceptability of Healthy Volunteers as a Sensitive PK Population

In accordance with guideline EMA/CHMP/BMWP/403543/2010, healthy subjects were selected as the appropriate population for demonstrating equivalence in a comparative single-dose study as this population showed well tolerability and is considered more homogeneous and hence more sensitive as compared to patient populations. This was endorsed by EMA SA (EMA/CHMP/SAWP/70331/2012).

Acceptability of RA Subjects as a Sensitive Disease Population

In addition to being an indication (i.e. RA) for which CDR evaluation is being requested for, in order to demonstrate similarity in efficacy between SB2 and Remicade, and following EU guidance (in particular EMEA/CHMP/BMWP/42832/2005; EMA/CHMP/BMWP/403543/2010 (14, 15)), the clinical Phase III study SB2-G31-RA was conducted in a study population appropriate for demonstrating biosimilarity and was designed sensitive enough for detecting potential differences between SB2 and Remicade. Study SB2-G31-RA was not aimed at demonstrating efficacy *per se*, since efficacy in the respective therapeutic indications has already been established with Remicade. The purpose was to investigate similarity between SB2 and Remicade, assessed according to an equivalence approach. Among the therapeutic indications, RA has been studied most thoroughly, with validated and reasonably sensitive methods to study the disease activity of RA available. The selected dose reflects the clinically effective and approved dose of EU-Remicade. The study methodology was aligned to recommendations of the EMA SA in terms of treatment regimen, study endpoints and patient population (EMA/CHMP/SAWP/70331/2012; EMA/CHMP/SAWP/451470/2012). See CTD 2.5, section 2.5.1.2 for information.

In addition to the above, as detailed in the *Rationale for the Equivalence Margins Used* below, the pivotal trials conducted in Remicade demonstrated a large ACR20 response with Remicade over placebo. This suggests that with an appropriate endpoint, RA subjects possess the sensitivity to detect differences between treatments.

Study Name	Design	Objectives	Population
State the study name	Provide a brief description of the study design	State the study objectives	Therapeutic area and key characteristics
SB2-G31-RA	**Pivotal, Randomized, Double-blind** (*Randomized, Double-blind*) Period Pivotal Phase III, safety/efficacy, double blind, active-controlled, parallel assignment, multicentre RCT *Transition-Extension* Period Double blind, randomized, active-controlled, parallel assignment, multicentre	*Randomized, Double-blind* Period To compare the efficacy, safety, immunogenicity, and steady-state pharmacokinetics of SB2 with reference product infliximab (IFN; Remicade) in patients with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) therapy. *Transition-Extension* Period To evaluate the safety, tolerability, immunogenicity and efficacy in subjects with RA who transitioned to SB2 from EU-Remicade compared to subjects who maintained EU-Remicade from the randomized, double-blind period	The therapeutic area is rheumatology. Patients with moderate to severe rheumatoid arthritis (RA) despite MTX therapy; Diagnosed according to revised 1987 ACR criteria, on stable MTX therapy *Randomized, Double-blind* Period Key characteristics: the average age was 52.1 years old. The majority of patients were female (80.1%) and white (86.6%). *Transition-Extension* Period Key characteristics: the average age was 52.0 years old. The majority of patients were female (79.3%) and white (90.4%).
SB2-G11-NHV	Pivotal Phase I, PK, single-blind, parallel group, single-dose, randomized study	To demonstrate PK equivalence between SB2 and EU sourced Remicade, between SB2 and US sourced Remicade, and between EU-Remicade and US-Remicade. Safety, tolerability, and immunogenicity were investigated as secondary objectives.	Study was conducted in healthy subjects but the intended therapeutic area is rheumatology, dermatology, and gastroenterology. Key characteristics: the average age ranged between 39.4 – 40.7 years old. The majority of patients were males (92.5 – 96.2%) and white (96.2 – 98.1%).

RCT: randomized controlled trial

SB2-G31-RA

Study Characteristics

Brief description of the study

This study was divided into a randomized, double-blind period and a transition-extension period. This randomized, double-blind period was a parallel group, multicentre clinical study designed to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of SB2 (infliximab biosimilar) compared to EU-Remicade (innovator) in subjects with moderate to severe RA despite MTX therapy. The primary endpoint was ACR20 at Week 30, through which therapeutic similarity was concluded between SB2 and EU-Remicade if the 95% CI of the adjusted treatment difference was entirely contained within the equivalence margin of −15% to 15%. Additional efficacy, safety, PK, and immunogenicity outcomes were also assessed. The transition-extension period was conducted from Week 54 to Week 78. In this period, subjects treated with SB2 in the main period (up to Week 54) maintained SB2 treatment; subjects treated with EU-Remicade in the main period were re-randomized 1:1 to receive either SB2 or EU-Remicade. Long-term safety, tolerability, immunogenicity, and efficacy were evaluated.

Characteristics		Details for SB2-G31-RA
Study Design	**Objective**	Pivotal efficacy and safety study
	Blinding	Double-blind (Patients, Investigators, joint assessors and other study staff)
	Study period	2013-08 to 2015-08
	Study centers	73 centres in 11 countries from Europe and Asia
	Design	Equivalence
Study Population	**Randomized (N)**	**Randomized, Double-blind Period:** 584 **Transition-extension Period:** 395

	Inclusion criteria	**Randomized, Double-blind Period:**
		• Male or female aged 18–75 years at the time of signing the informed consent form (ICF).
		• Had been diagnosed as having RA according to the revised 1987 ACR criteria for at least 6 months prior to Screening.
		• Had moderate to severe active disease despite MTX therapy defined as:
		  ○ More than or equal to 6 swollen joints and more than or equal to 6 tender joints (from the 66/68 joint count system) at Screening and Randomization.
		  ○ Either erythrocyte sedimentation rate (erythrocyte sedimentation rate [ESR]; Westergren) ≥ 28 mm/h or serum C-reactive protein (CRP) ≥ 1.0 mg/dL at Screening.
		• Had been treated with MTX for at least 6 months prior to Randomization and be on a stable dose of MTX 10–25 mg/week given orally or parenterally for at least 4 weeks prior to Screening.
		• Female subjects who were not pregnant or nursing at Screening and who were not planning to become pregnant from Screening until 6 months after the last dose of investigational product (IP).
		
		Transition-Extension Period:
		• Had been enrolled and completed the scheduled Week 54 visit of the randomized, double blind period of the SB2-G31-RA study.
		• In the opinion of the Investigator, subjects who may have benefited from continuing IP treatment (either SB2 or Remicade), understood the implications of taking part in the study and were willing to participate in the transition-extension period.
		Female subjects who were not pregnant or nursing and who were not planning to become pregnant until 6 months after the last dose of IP.

	Exclusion criteria	**Randomized, Double-blind Period:** • Had been treated previously with any biological agents including any tumour necrosis factor inhibitor. • Had a known hypersensitivity to human immunoglobulin proteins or other components of Remicade or SB2.

Characteristics		Details for SB2-G31-RA
		• Had abnormal renal or hepatic function at Screening defined as the following: a. Serum creatinine ≥ 2 × the upper limit of normal (ULN). b. Serum alanine transaminase or aspartate transaminase ≥ 2 × ULN. • Had abnormal haematological parameters at Screening defined as the following: a. Haemoglobin < 8.0 g/dL. b. White blood cell count < 3.5×10^3 cells/μL (< 3.5×10^9 cells/L). c. Neutrophil count < 1.5×10^3 cells/μL. d. Platelet count < 100×10^3 cells/μL. e. Lymphocyte count < 800 cells/μL. • Had a positive serological test for hepatitis B (HBV) or hepatitis C (HCV) or had a known history of infection with human immunodeficiency virus. • Had a current diagnosis of active tuberculosis (TB). • Had a serious infection (such as sepsis, abscess, opportunistic infections or invasive fungal infection including histoplasmosis) or had been treated with intravenous (IV) antibiotics for an infection within 8 weeks or oral antibiotics within 2 weeks prior to Randomization. Non-significant infections did not need to be considered exclusionary at the discretion of the Investigator. • Had a history of an infected joint prosthesis, which had not been removed or replaced. • Had any of the following conditions: ○ Other inflammatory or rheumatic diseases. ○ History of any malignancy within the previous 5 years prior to Screening. ○ History of lymphoproliferative disease including lymphoma. ○ History of congestive heart failure (New York Heart Association Class III/IV) or unstable angina. ○ Physical incapacitation (ACR functional Class IV or wheelchair-/bed-bound). ○ History of demyelinating disorders (such as multiple sclerosis or Guillain-Barré syndrome). **Transition-extension Period:** • Had been withdrawn from the SB2-G31-RA study for any reason. • Had any significant medical conditions, such as an occurrence of a serious adverse event (SAE) or intolerance of SB2 or Remicade during the randomized, double-blind period of the SB2-G31-RA study which may have rendered the subject unsuitable to participate in the transition-extension period, at the discretion of the Investigator. • Planned to participate in another study with an IP during the transition extension period. Had been taking or planned to take any biological agents except SB2 and Remicade during the transition-extension period.
Drugs	**Intervention**	• SB2, 3 mg/kg, infused intravenously over 2 h, at week 0, week 2, week 6, and then every 8 weeks until week 46 (last dose prior to Week 54; for the *randomized, double-blind* period) or Week 70 (last dose prior to Week 78; for the *transition-extension* period). • Dose increases could occur from week 30 by 1.5 mg/kg per visit, up to a total of 7.5 mg/kg. MTX was given as an oral or parenteral weekly dose of 10–25 mg/week with folic acid of 5–10 mg/ week.
	Comparator(s)	• EU-sourced Remicade, 3 mg/kg, infused intravenously over 2 h, at week 0, week 2, week 6, and then every 8 weeks until week 46 (last dose prior to Week 54; for the *randomized, double-blind* period) or Week 70 (last dose prior to Week 78; for the *transition-extension* period). • Dose increases could occur from week 30 by 1.5 mg/kg per visit, up to a total of 7.5 mg/kg. MTX was given as an oral or parenteral weekly dose of 10–25 mg/week with folic acid of 5–10 mg/ week.

Characteristics		Details for SB2-G31-RA
Duration	**Treatment**	**Randomized, Double-blind Period:** • 46 weeks of active treatment (last dose prior to Week 54) **Transition-extension Period:** 16 weeks of active treatment (last dose prior to Week 78)
	Follow-up	Not applicable
Outcomes	**Primary End Point(s)**	ACR20 response at week 30 in the per-protocol set 1 (PPS1).
	Other End Points	**Randomized, Double-blind Period:** • ACR20 response at week 54 • ACR 50% response criteria (ACR50) and ACR 70% response criteria (ACR70) response at Week 30 and Week 54 • The numeric index of the ACR response (ACR-N) at Week 30 and Week 54 • The area under the curve (AUC) of ACR-N up to Week 30 • The disease activity score based on a 28 joint count (DAS28 score) at Week 30 and Week 54 • The European League Against Rheumatism (EULAR) response at Week 30 and Week 54 • The AUC of the change in DAS28 from Baseline up to Week 30 • Major clinical response (ACR70 response for 6 consecutive months) at Week 54 • Change from Baseline in modified Total Sharp Score (mTSS) at Week 54 • Adverse events/serious adverse events • Clinical laboratory abnormalities • Vital signs abnormalities • Immunogenicity • Pharmacokinetic endpoints **Transition-extension Period:** • ACR20, ACR50 and ACR70 response • Continuous ACR-N • The change in DAS28 from Week 0 • The EULAR response • Adverse events/serious adverse events • Clinical laboratory abnormalities • Vital signs abnormalities • Immunogenicity

Characteristics		Details for SB2-G31-RA
Notes	**Publications**	**Randomized, Double-blind Period:** • Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, Baranauskaite A, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76(1):58-64. (18) *(Please note that this publication is based on the 30-week CSR, and not the 54-week CSR provided in this submission).* • Smolen JS, Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, et al. Comparing biosimilar SB2 with reference infliximab after 54 weeks of a double-blind trial: clinical, structural and safety results. Rheumatology. 2017. (19) • Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, Baranauskaite A, et al. A Randomized, Double-Blind, Phase III Study Comparing SB2, an Infliximab Biosimilar, to the Infliximab Reference Product (Remicade) in Patients with Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy: 54-Week Results [abstract]. Arthritis Rheumatol. 2015;67(suppl 10). (20) • Choe J-Y, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, Baranauskaite A, et al. SAT0152 A Randomised, Double-Blind, Phase III Study Comparing SB2, An Infliximab Biosimilar, To the Infliximab Reference Product (Remicade) in Patients with Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy. Annals of the Rheumatic Diseases. 2015;74(Suppl 2):706-7. (21) • Choe J-Y, Smolen JS, Keystone E, Genovese MC, Choi J, Rho YH. THU0140 Efficacy and Safety Analysis by Overall anti-Drug Antibody Results Up To Week 30 in Patients with Rheumatoid Arthritis Treated with Sb2 (An Infliximab Biosimilar) or Infliximab Reference Product in Phase III Study. Ann Rheum Dis. 2016;75(Suppl 2):232. (22) • Durez P, Mysler E, Smolen JS, Choe J-Y, Choi J, Rho YH. THU0149 The 54-Week Results of Interferon-γ Release Assay in A Phase III Study Comparing SB2, An Infliximab Biosimilar, To Infliximab Reference Product in Patients with Rheumatoid Arthritis. Ann Rheum Dis. 2016;75(Suppl 2):235-6. (23) • Choe JY, Smolen J, Keystone E, Genovese MC, Lee C, Rho YH, et al. Efficacy and safety analysis by overall anti-drug antibody result up to week 30 in patients with rheumatoid arthritis treated with SB2 (an infliximab biosimilar) or reference infliximab in a phase III study. J Rheumatol. 2017;44(6). (24) **Transition-extension Period:** • Smolen JS, Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, et al. Similar Safety and Immunogenicity and Sustained Efficacy after Transition to SB2 (An Infliximab Biosimilar) Vs Ongoing Reference Infliximab (Remicade) in Patients with Rheumatoid Arthritis: Results of Phase III Transition Study [abstract]. Arthritis Rheumatol. 2016;68(suppl 10). (25) • Smolen JS, Choe J-Y, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, et al. FRI0162 Similar Safety and Immunogenicity and Sustained Efficacy after Transition To SB2 (An Infliximab Biosimilar) vs Ongoing Infliximab Reference Product in Patients with Rheumatoid Arthritis: Results of Phase III Transition Study. Ann Rheum Dis. 2016;75(Suppl 2):488. (26) NCT01936181

Intervention and Comparators

Interventions Employed (e.g., dose, route and frequency of administration, duration, etc.)

- SB2 (infliximab biosimilar) or EU-Remicade, 3 mg/kg, infused intravenously over 2 h, at Weeks 0, 2, 6, and then every 8 weeks until Week 46 (for the *randomized, double-blind* period) or Week 70 (for the *transition-extension* period).
- Dose increases could occur from Week 30 by 1.5 mg/kg per visit, up to a total of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms are not well controlled by the existing dose. If adequate response is achieved, subjects continued on the selected dose.

Reference Products Used

- All batches of the reference product, Remicade, used in the trial, were sourced from the EU.

Placebos and Controls (if applicable)

- An active comparator was used in this trial; therefore no placebo was used.

Concomitant Medications

- To prevent infusion related reactions (IRRs), pre-medications such as corticosteroids, antihistamines or paracetamol were allowed per investigator discretion.
- MTX was given as an oral or parenteral weekly dose of 10–25 mg/week with folic acid of 5–10 mg/ week.
- Non-steroidal anti-inflammatory drugs and corticosteroids (≤10 mg prednisolone) were allowed if taken for a stable dose for 4 weeks before randomization.

Outcomes (Key Efficacy and Safety)

ACR20: The primary endpoint was the ACR20 response at Week 30 in the PPS1, through which equivalence (as per study protocol definition) was to be established if the 95% CI of the adjusted treatment difference between SB2 and Remicade was entirely contained within the equivalence margin of −15% to 15%.

The ACR20 response indicated:

- At least a 20% improvement from baseline in swollen joint count (66 joint count)
- At least a 20% improvement from baseline in tender joint count (68 joint count)
- At least a 20% improvement from baseline in at least three of the following five criteria:
  - Subject pain assessment using a 100 mm visual analogue scale (VAS)
  - Subject global assessment using a 100 mm VAS
  - Physician global assessment using a 100 mm VAS
  - Subjects assessment of disability using the Health Assessment Questionnaire - Disability Index (HAQ-DI)
  - Acute phase reactant level (C-reactive protein [CRP]) (27).

ACR20 time-response model up to 30 weeks: estimated separate time-response curves for each treatment group over the time course of the study.

ACR20, ACR50, ACR70: ACR20 at Week 54, ACR50 at Weeks 30 and 54; and ACR70 at Weeks 30 and 54

ACR-N at Weeks 30 and 54**:** The ACR-N provides a single number that characterizes the percentage of improvement from baseline that a patient has experienced in analogy to ACR20, ACR50, and ACR70 responses. Thus, patients with an ACR-N of 20 just meet but do not exceed criteria for an ACR20 response, patients with an ACR-N of 50 just meet criteria for an ACR50 response, and patients with an ACR-N of 70 meet but do not exceed criteria for an ACR70 response. To generalize, a patient with an ACR-N of X (e.g., 38) means that the patient has achieved an improvement of at least X% (e.g., 38%) in tender and swollen joints and an improvement of at least X% (e.g., 38%) in 3 of the 5 other parameters (28).

AUC of ACR-N up to week 30

DAS28 at Weeks 30 and 54: The DAS28 score was calculated using the following equation (four-variable equation):

- DAS28 = 0.56 × √(tender 28 joint count) + 0.28 × √(swollen 28 joint count) + 0.70 × ln(ESR) + 0.014 × general health.
- General health was subject global assessment using a 100 mm VAS (29-31).
- To claim the equivalence in the change from Baseline of DAS28, the two-sided 95% CI of the difference in DAS28 score between SB2 and EU-Remicade was compared to the equivalence margin of [−0.6, 0.6], which was taken from the definition of EULAR response. The EULAR response was defined as no response when the improvement of DAS28 from Baseline was less than or equal to 0.6 regardless of Baseline DAS28 score.

AUC of Changes in DAS28 from baseline up to Week 30, which was Base - Value

EULAR response criteria at Weeks 30 and 54:

The EULAR response was based upon the DAS28 score. Subjects were classified as having either a good, moderate or no response based on the following (32):

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

HAQ-DI at baseline, Weeks 30 and 54**:** The HAQ-DI assesses physical function of the subject. Specifically, it assesses the degree of difficulty a person has had in accomplishing tasks in eight functional areas (1. dressing and grooming; 2. arising; 3. eating; 4. walking; 5. hygiene; 6. reach; 7. grip; and 8. common daily activities) over the previous 7 days, taking into account any aids or help required. Each question asks on a scale ranging from 0 to 3 if the categories can be performed without any difficulty (scale 0) up to cannot be done at all (scale 3) (33, 34).

mTSS change from baseline to Week 54: mTSS is calculated from joint erosion score plus joint space narrowing score (35). The joint erosion score is a summary of erosion severity in 32 joints of the hands and 12 joints of the feet. Each joint is scored, according to the surface area involved, from 0 to 5, with 0 indicating no erosion, 1 indicating discrete erosions, 2 to 3 indicating larger erosions according to surface area involved, 4 indicating erosions extending over middle of the bone and 5 indicating extensive loss of bone from more than one half of the articulating bone. Because each side of a foot joint is graded on this scale, the maximum joint erosion score for a foot joint is 10. Thus, the maximal joint erosion score is 280. The JSN score summarizes the severity of JSN in 30 joints of the hands and 12 joints of the feet. Assessment of JSN, including subluxation, is scored from 0 to 4, with 0 indicating normal, 1 indicating focal or doubtful, 2 indicating generalized, less than 50% of the original joint space, 3 indicating generalized, more than 50% of the original joint space or subluxation and 4 indicating bony ankylosis or complete luxation. The score for JSN ranges from 0 to 120 in the hands and from 0 to 48 in the feet. Thus, the maximal JSN score is 168 and the worst possible mTSS is 448.

Immunogenicity: Blood samples for determination of immunogenicity were collected at baseline and Weeks 2, 6, 14, 22, 30, 38, 46 and 54. Anti-drug antibodies (ADAs) were measured using validated electrochemiluminescence immunoassays and neutralizing antibodies were measured using a competitive ligand-binding assay.

A single assay format with labelled versions of the biosimilar candidate SB2 was used for both clinical studies to minimize bioanalytical bias associated with inter-assay variability and the possibilities of inconstant false-positive / false-negative results due to labelling of multiple antigens (to minimize preparing biotinylated and sulfo versions of both SB2 and Remicade)

Safety: All reported terms for AEs were coded using the Medical Dictionary for Regulatory Activities (MedRA). A treatment-emergent AE (TEAE) was defined as any AE with an onset date on or after the date of the first administration of IP until Week 54, an ET visit, or the follow-up telephone (where subjects were withdrawn prior to Week 54). AEs with increased severity during the treatment period were considered as TEAEs whether already present during the pre-treatment period or not. Pre-existing AEs before the treatment period with no increase in severity during the treatment period were not considered as TEAEs. Laboratory data, data from other tests (e.g., vital signs, twelve-lead electrocardiogram [ECG], etc.) were also recorded.

Statistical Analyses

Statistics Protocol for Equivalence Testing

Primary Efficacy Endpoint (ACR20 at Week 30)

The null hypothesis tested for the primary efficacy analysis was that either (1) SB2 is inferior to Remicade or (2) SB2 is superior to Remicade based on a pre-specified equivalence margin. The two-sided 95% confidence interval (CI) of the difference in ACR20 response rate between SB2 and Remicade was computed and compared to the equivalence margin of [−15%, 15%]. The primary efficacy analysis for ACR20 response was performed for the PPS1. No missing data was imputed for the PPS1. The 95% CIs of the treatment difference in terms of ACR20 response rate applied a non-parametric analysis that controls for region as a factor and Baseline CRP value as a covariate.

As a sensitivity analysis, the primary efficacy analysis was repeated for the Full Analysis Set (FAS) using imputed ACR20 responses for those subjects who discontinued before Week 30/Week 54 to explore the robustness of the results from PPS1/PPS2. The detailed missing data imputation methods included: available data, non-responder, and pattern mixture analyses.

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

Supportive Analysis of Primary Efficacy Analysis: Time-Response Model

The time-response model estimated the separate time-response curves for each treatment group over the time course of the study; and was used as a supportive analysis to the primary assessment of equivalence. The 2-norm measured squared differences across all time points for the 2 treatment groups. The equivalence between the 2 treatments was declared if the 95% CI for the 2-norm of the difference in time-response functions was less than the pre-specified equivalence margin of 61.80.

Change from Baseline in DAS28

An ANCOVA model of change from Baseline in DAS28 at Week 30 with treatment group and region (pooled centre) as factors and the Baseline DAS28 value as a covariate was

used to test the treatment difference of SB2 versus Remicade. The least-squares means (LS Means), SE and two-sided 95% CI for the treatment difference were reported for the FAS. To claim the equivalence in the change from Baseline of DAS28, the two-sided 95% CI of the difference in DAS28 score between SB2 and Remicade was compared to the equivalence margin of [−0.6, 0.6].

Rationale for the Equivalence Margins Used

ACR20 at Week 30

The ACR20 responses from selected studies with regards to study population and treatment regimen were used for the equivalence margin and sample size calculation (Table 3).

Table 3: ACR20 Responses in Pivotal Studies in Remicade

	ACR20 Response Events/Total (%)		Absolute difference Remicade – Placebo (%)	Time Measurement	DMARD
	Remicade[a]	Placebo			
Westhovens (2006) (36)	199/343 (58%)	87/341 (25.5%)	33%	22 weeks	MTX
Maini (1999) (37)	44/86 (51%)	17/88 (19%)	32%	30 weeks	MTX
Abe (2006) (38)	30/49 (61.2%)	11/47 (23.4%)	38%	14 weeks	MTX
Overall	273/478 (57%)	115/476 (24%)	33%		

ACR20: American College of Rheumatology 20% response criteria; DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate.
[a] All references include ACR20 response from Remicade 3 mg/kg.
Source: CTD 2.7.3, Table 2.7.3.2-1

A random-effects meta-analysis of the selected studies estimated a risk difference of 0.3293 with a 90% CI [0.2801, 0.3785], where approximately 50% of lower limit of 90% CI is preserved on or over placebo to obtain the equivalence margin.

The equivalence margin of −15% to 15% at week 24 for ACR20 response rate was also in line with the US FDA Guidance for Industry Non-Inferiority Clinical Trials and the CHMP Guideline on the Choice of the Non-inferiority Margin and was also agreed with the regulatory agencies (39, 40).

Times Response Model

Using the time-response modelling on the historical data (41), the 95% CI for the 2-norm of the treatment difference was calculated as [123.60, 179.43]. The equivalence margin was defined as 61.80, which was half of the lower bound of the 95% CI for the treatment effect. The upper limit of 95% CI for the 2-norm between SB2 and Remicade was compared to 61.80.

Change from Baseline in DAS28

To claim the equivalence in the change from Baseline of DAS28, the two-sided 95% CI of the difference in DAS28 score between SB2 and Remicade was compared to the equivalence margin of [−0.6, 0.6], which was taken from the definition of EULAR response. The EULAR response was defined as no response when the improvement of DAS28 from Baseline was less than or equal to 0.6 regardless of Baseline DAS28 score.

Analysis Sets

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

Randomized Set [RAN]: RAN consisted of all subjects in the ENR who received a randomization number at the Randomization Visit. For analyses and displays based on RAN, subjects were classified according to the treatment they were assigned at randomization.

Re-Randomised Set [Re-RAN]: Re-RAN consisted of all subjects who provided informed consent for the transition-extension period and were re-randomised at Week 54. For analyses and displays based on Re-RAN, subjects were classified according to the treatment they were assigned at randomisation in the transition-extension period.

Full Analysis Set [FAS]: FAS consisted of all subjects who were randomized at the Randomization Visit. Following the intent-to-treat principle, subjects were analyzed according to the treatment they were assigned at Randomization. However, subjects who did not qualify for randomization and were inadvertently randomized into the study were excluded from the FAS, provided these subjects did not receive any IP during that study phase.

Extended Full Analysis Set [Ex-FAS]: Ex-FAS consisted of all subjects who were randomized to the transition-extension period at Week 54 and had taken at least 1 dose of IP during the transition extension period. Following the intent-to-treat principle, subjects were analysed according to the treatment they were assigned at re-randomization.

Per-protocol Set 1 [PPS1]: PPS1 consisted of all FAS subjects who completed the Week 30 visit and had an adherence (from Baseline to Week 30) within the range of 80–120% for both the expected number of IP administrations and the expected sum of MTX doses without any major protocol deviations that affected the efficacy assessment. The PPS1 was the primary analysis set.

Per-protocol Set 2 [PPS2]: PPS2 consisted of all FAS subjects who completed the Week 54 visit and had an adherence (from Baseline to Week 54) within the range of 80-120% for both the expected number of IP administrations and the expected sum of MTX doses without any major protocol deviations that affected the efficacy assessment.

Safety Set [SAF]: SAF consisted of all subjects who received at least 1 dose of double-blind IP during the study period. Subjects were analysed according to the treatment received. If there was any doubt whether a subject was treated or not, they were assumed as treated for the purposes of analysis.

Extended Safety Set [Ex-SAF]: Ex-SAF consisted of all subjects who received at least 1 dose of IP during the transition-extension period. Subjects were analysed according to the treatment received.

Pharmacokinetic Population [PK population]: PK population consisted of all subjects in the SAF who had at least 1 post-dose PK sample collected.

Reference Locations (e.g., sections of the Common Technical Document and/or Clinical Study Report)

- For the description of the statistics protocol for equivalence testing, please refer to CTD Module 2.7.3 (p.10-11); 78-week CSR SB2-G31-RA, sections 9.7.1.7.1 and 9.7.1.7.2

- For the description of the rationale for the equivalence margins used, please refer to CTD Module 2.7.5 (p.31-32); 78-week CSR SB2-G31-RA, sections 9.7.1.7.1, 9.7.1.7.2, and 9.7.2.
- For description of the analysis set, please refer to the 78-week CSR SB2-G31-RA, section 9.7.1.1.

Results

Baseline Characteristics

Table 4: Major Demographic and Baseline Characteristics for the Randomised, Double-blind Period for Study SB2-G31-RA (RAN)

Parameter*	SB2		EU-Remicade		Total	
	N=291		N=293		N=584	
Age (years)	51.6	(11.92)	52.6	(11.74)	52.1	(11.83)
Gender n (%)						
Male	59	(20.3)	57	(19.5)	116	(19.9)
Female	232	(79.7)	236	(80.5)	468	(80.1)
Race, n (%)						
White	252	(86.6)	254	(86.7)	506	(86.6)
Asian	37	(12.7)	39	(13.3)	76	(13.0)
Other	2	(0.7)	0	(0.0)	2	(0.3)
Ethnicity n (%)						
Hispanic or Latino	5	(1.7)	3	(1.0)	8	(1.4)
Indian (Indian subcontinent)	1	(0.3)	1	(0.3)	2	(0.3)
Mixed Ethnicity	1	(0.3)	0	(0.0)	1	(0.2)
Other	284	(97.6)	289	(98.6)	573	(98.1)
Height (cm)	164.58	(9.278)	164.79	(8.569)	164.69	(8.922)
Weight (kg)	72.27	(15.812)	71.92	(16.513)	72.10	(16.155)
BMI (kg/m^2)	26.62	(5.252)	26.49	(5.973)	26.56	(5.621)
Disease duration (years)	6.31	(5.863)	6.56	(5.972)	6.44	(5.914)
Duration of MTX use (months)	53.05	(49.537)	48.44	(45.600)	50.74	(47.618)
Weekly dose of MTX at baseline (mg)	14.71	(4.229)	14.68	(4.099)	14.69	(4.161)
Swollen joint count (0-66)**	14.6	(7.84)[a]	14.9	(7.69)	14.8	(7.76)[b]
Tender joint count (0-68)**	23.7	(12.30)[a]	24.0	(12.22)	23.8	(12.25)[b]
Physician global assessment VAS (0-100)**	61.7	(15.55)[a]	61.8	(15.79)	61.8	(15.66)[b]
Patient global assessment VAS (0-100)**	62.8	(17.50)[a]	62.7	(18.66)	62.8	(18.08)[b]
Patient pain assessment VAS (0-100)**	61.2	(18.58)[a]	63.3	(19.97)[c]	62.3	(19.30)[d]
HAQ-DI (0-3)**	1.4720	(0.61994)[a]	1.5444	(0.58103)	1.5084	(0.60128)[b]
CRP (mg/L)**	12.4	(18.68)[a]	13.7	(19.15)	13.0	(18.91)[b]
CRP n (%)	291		293		584	
≥ 10 mg/L	106	(36.4)	111	(37.9)	217	(37.2)
< 10 mg/L	185	(63.6)	182	(62.1)	367	(62.8)
ESR (mm/h)**	44.6	(19.19)[a]	46.7	(22.33)	45.7	(20.84)[b]
Rheumatoid factor n (%)	291		293		584	

Parameter*	SB2		EU-Remicade		Total	
	N=291		N=293		N=584	
Positive	215	(73.9)	208	(71.0)	423	(72.4)
Negative	76	(26.1)	84	(28.7)	160	(27.4)
Missing	0	(0.0)	1	(0.3)	1	(0.2)

BMI = Body Mass Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ-DI = health assessment questionnaire-disability index; MTX = methotrexate; SD = standard deviation; VAS = visual analogue scale

[a] N=290; [b] N=583; [c] N=292; [d] N=582

Note: [a&b] correspond to numbers from Full Analysis Set

*Except where indicated otherwise, values are presented as mean (SD)

**Full Analysis Set

Source: CTD 2.7.3, Tables 2.7.3.2-3 and 2.7.3.2-5

Table 5: Demographic Characteristics (at baseline) for the Transition-Extension Period for Study SB2-G31-RA (Re-RAN)

		Remicade			
	SB2	Overall	SB2	Remicade	Total
Parameter*	N=201	N=195	N=94	N=101	N=396
Age (years)	51.8 (12.13)	52.2 (11.08)	53.0 (10.97)	51.5 (11.19)	52.0 (11.61)
Gender n (%)					
Male	43 (21.4)	39 (20.0)	17 (18.1)	22 (21.8)	82 (20.7)
Female	158 (78.6)	156 (80.0)	77 (81.9)	79 (78.2)	314 (79.3)
Race, n (%)					
White	183 (91.0)	175 (89.7)	87 (92.6)	88 (87.1)	358 (90.4)
Asian	17 (8.5)	20 (10.3)	7 (7.4)	13 (12.9)	37 (9.3)
Other	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Ethnicity n (%)					
Hispanic or Latino	3 (1.5)	3 (1.5)	2 (2.1)	1 (1.0)	6 (1.5)
Other	198 (98.5)	192 (98.5)	92 (97.9)	100 (99.0)	390 (98.5)
Height (cm)	165.18 (9.007)	165.54 (7.732)	165.69 (8.028)	165.40 (7.483)	165.36 (8.395)
Weight (kg)	72.72 (14.671)	72.68 (16.168)	72.20 (14.869)	73.12 (17.353)	72.70 (15.407)
BMI (kg/m^2)	26.64 (5.015)	26.52 (5.822)	26.27 (5.102)	26.75 (6.436)	26.58 (5.421)
Disease duration (years)	6.30 (6.172)	6.52 (5.774)	6.30 (5.421)	6.72 (6.104)	6.41 (5.973)
Duration of MTX use (months)	51.11 (46.808)	50.92 (48.035)	49.69 (45.374)	52.07 (50.586)	51.02 (47.356)
Weekly dose of MTX at Study Baseline (mg)	14.65 (4.108)	14.76 (3.953)	14.31 (3.870)	15.17 (4.004)	14.70 (4.028)
Swollen joint count (0-66)	14.1 (6.80)	14.4 (7.35)	14.6 (7.59)	14.3 (7.16)	14.2 (7.07)
Tender joint count (0-68)	23.9 (12.20)	24.2 (11.42)	23.7 (11.29)	24.6 (11.56)	24.0 (11.81)
Physician global assessment VAS (0-100 mm)	60.8 (15.11)	62.0 (15.27)	61.9 (16.15)	62.0 (14.48)	61.4 (15.18)
Subject global assessment VAS (0-100 mm)	61.7 (17.33)	63.6 (17.72)	62.8 (18.12)	64.3 (17.41)	62.6 (17.53)
Subject pain assessment VAS (0-100 mm)	60.0 (17.94)	63.9 (19.87)	60.9 (20.42)	66.7 (19.02)	61.9 (18.99)

Parameter*	SB2	Remicade			Total
		Overall	SB2	Remicade	
	N=201	N=195	N=94	N=101	N=396
HAQ-DI (0-3)	1.4527 (0.60449)	1.5071 (0.56563)	1.5372 (0.60348)	1.4790 (0.52947)	1.4795 (0.58557)
CRP (mg/L)	12.0(19.11)	13.7 (20.28)	13.8 (21.87)	13.7 (18.80)	12.9 (19.69)
CRP, n (%)					
≥ 10 mg/L	68 (33.8)	70 (35.9)	31 (33.0)	39 (38.6)	138 (34.8)
< 10 mg/L	133 (66.2)	125 (64.1)	63 (67.0)	62 (61.4)	258 (65.2)
ESR (mm/h)	43.0 (17.52)	45.5 (21.29)	45.7 (22.97)	45.3 (19.71)	44.2 (19.48)
Rheumatoid factor, n (%)					
Positive	140 (69.7)	133 (68.2)	67 (71.3)	66 (65.3)	273 (68.9)
Negative	61 (30.3)	61 (31.3)	27 (28.7)	34 (33.7)	122 (30.8)
Missing	0 (0.0)	1 (0.5)	0 (0.0)	1 (1.0)	1 (0.3)

BMI: Body Mass Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ-DI: health assessment questionnaire-disability index; MTX: methotrexate; SD: standard deviation; VAS: visual analogue scale

Percentages were based on the number of re-randomized subjects.

Baseline is defined as the last non-missing value prior to the first study drug date in the randomised, double-blind period.

*Except where indicated otherwise, values are presented as mean (SD)

Source: CTD 2.7.3, Tables 2.7.3.2-4 and 2.7.3.2-6

Similarity/Differences

In the *randomized, double-blind* period, the demographic characteristics, baseline disease characteristics, and baseline characteristics for rheumatoid disease activity were similar and well balanced between the treatment groups with no significant differences between groups. Similarly, the demographic, disease characteristics, and rheumatoid disease activity were similar between the 3 groups at the beginning of the *transition-extension* period. The majority of patients were females and white.

Concomitant Conditions/Medications

In the *randomized, double-blind* period, a similar number of subjects in the SB2 and Remicade groups (232 [79.7%] and 243 [82.9%], respectively) had medical or surgical histories and continuing medical conditions. The most commonly reported continuing medical conditions were in the SB2 and the EU-Remicade groups were vascular disorders (104 [35.7%] and 117 [39.9%], respectively) and musculoskeletal and connective tissue disorders (113 [38.8%] and 107 [36.5%], respectively).

In the *transition-extension* period, a similar number of subjects in the SB2/SB2, Remicade/SB2 and Remicade/Remicade treatment groups (162 [80.6%], 79 [84.0%], 90 [89.1%] subjects, respectively) had medical or surgical histories and continuing medical conditions in any primary SOC. The most commonly reported continuing medical conditions in the SB2/SB2, Remicade/SB2, and Remicade/Remicade groups were musculoskeletal and connective tissue disorders (82 [40.8%], 42 [44.7%], 37 [36.6%] subjects, respectively) and vascular disorders (74 [36.8%], 37 [39.4%] and 40 [39.6%] subjects, respectively).

In the *randomized, double-blind* period, the majority of subjects received concomitant medications during the study (95.9% and 94.9% of subjects, respectively). Glucocorticoids were taken as a concomitant medication by more than half of the subjects during the study

(SB2: 201 [69.3%] subjects; EU-Remicade: 205 [70.0%] subjects). Other frequently reported concomitant medications were proton pump inhibitors (SB2: 117 [40.3%] subjects; EU-Remicade: 109 [37.2%] subjects), and anilides (SB2: 81 [27.9%] subjects; EU-Remicade: 87 [29.7%] subjects). The use of concomitant medications by ATC drug class was similar between 2 treatment groups.

In the *transition-extension* period, the majority of subjects in the SB2/SB2, Remicade/SB2 and Remicade/Remicade treatment groups received concomitant medications (94.5%, 93.6% and 94.1% of subjects, respectively). Frequently taken concomitant medications in the SB2/SB2, Remicade/SB2 and Remicade/Remicade treatment groups were glucocorticoids (140 [69.7%], 62 [66.0%], 71 [70.3%] subjects, respectively), proton pump inhibitors (76 [37.8%], 35 [37.2%], 41 [40.6%] subjects, respectively), and anilides (47 [23.4%], 21 [22.3%] and 24 [23.8%] subjects, respectively). The use of concomitant medications by ATC drug class was similar between the 3 treatment groups.

Patient Disposition

A total of 584 subjects with moderate to severe RA despite MTX therapy were randomized into the randomized, double-blind period. A total of 505 (86.5%) patients completed 30 weeks and 452 (77.4%) patients completed 54 weeks of the study. One subject withdrew from the study after randomization but before receiving the first IP and was not included in the FAS. 478 (81.8%) patients were included in PPS1 and 410 (70.2%) patients were included and analysed in the PPS2.

Prior to Week 30, 79 (13.5%) patients withdrew, with 45 (15.5%) subjects from the SB2 and 34 (11.6%) subjects from the EU-Remicade groups, respectively. In both treatment groups, the most common reasons for withdrawal were adverse events (AEs) (5.3%) and withdrawal of consent (5.0%).

Prior to Week 54, 124 (21.2%) subjects withdrew (60 [20.6%] patients from SB2 vs. 64 [21.8%] patients from the EU-Remicade treatment group; counting those withdrew prior to Week 30). In both treatment groups, the most common reasons for withdrawal were again AEs (8.2%) and withdrawal of consent (8.4%) (Table 6).

Table 6: Summary of Patient Disposition for the Randomized, Double-blind Period for Study SB2-G31-RA (ENR)

Disposition	SB2-G31-RA (*Randomized, Double-blind* Period)		
	SB2	Remicade	Total
Screened, N			805
Randomized, N	291	293	584
Completed Week 30 of treatment, N (%)	246 (84.5)	259 (88.4)	505 (86.5)
Withdrew before Week 30, N (%)	45 (15.5)	34 (11.6)	79 (13.5)
WDAEs, N (%)	21 (7.2)	10 (3.4)	31 (5.3)
Protocol deviation, N (%)	1 (0.3)	3 (1.0)	4 (0.7)
Lack of efficacy, N (%)	5 (1.7)	5 (1.7)	10 (1.7)
Subject lost to follow-up, N (%)	0 (0.0)	1 (0.3)	1 (0.2)
Investigator discretion, N (%)	1 (0.3)	3 (1.0)	4 (0.7)
Withdrew consent, N (%)	17 (5.8)	12 (4.1)	29 (5.0)
Completed Week 54 of treatment, N (%)	227 (78.0)	225 (76.8)	452 (77.4)
Withdrew before Week 54, N (%)*	60 (20.6)	64 (21.8)	124 (21.2)
WDAEs, N (%)	27 (9.3)	21 (7.2)	48 (8.2)

Disposition	SB2-G31-RA (*Randomized, Double-blind* Period)		
	SB2	Remicade	Total
Protocol deviation, N (%)	1 (0.3)	5 (1.7)	6 (1.0)
Lack of efficacy, N (%)	5 (1.7)	6 (2.0)	11 (1.9)
Subject lost to follow-up, N (%)	0 (0.0)	1 (0.3)	1 (0.2)
Pregnancy, N (%)	0 (0.0)	1 (0.3)	1 (0.2)
Investigator discretion, N (%)	4 (1.4)	4 (1.4)	8 (1.4)
Withdrew consent, N (%)	23 (7.9)	26 (8.9)	49 (8.4)
Subjects from Eastern Ukraine sites without disposition information available**	4 (1.4)	4 (1.4)	8 (1.4)
Randomized Set, N	291	293	584
Full Analysis Set, N	290	293	583
Per-Protocol Set 1, N	231	247	478
Per-Protocol Set 2, N	202	208	410
Pharmacokinetic Set, N	165	160	325
Safety, N	290	293	583

SAE = serious adverse event; WDAE = withdrawal due to adverse event

Percentages were based on the number of randomised subjects.

Percentages for the screening failure reason were based on the number of screening failures in the randomized, double-blind period and the transition-extension period. Multiple screening failure reasons were possible.

* Includes those discontinued prior to Week 30

** Data collected or updated for these Eastern Ukrainian sites after the first database lock (30-week CSR) were excluded from the analysis due to regional issues.

Source: 78-week CSR SB2-G31-RA, Tables 10-1, 11-1; CTD 2.7.3, Table 2.7.3.2-2

At Week 54, 201 subjects from the SB2 treatment group and 195 subjects from the Remicade treatment group consented into the *transition-extension* period. Of the 195 subjects who received Remicade during the *randomized, double-blind* period that consented into the *transition-extension* period, 94 subjects were re-randomized to receive SB2 (Remicade/SB2 treatment group) and 101 subjects were re-randomized to continue on Remicade (Remicade/Remicade treatment group). The 201 subjects who received SB2 during the *randomized, double-blind* period continued to receive SB2 (SB2/SB2 treatment group).

Of the 396 subjects who enrolled in the *transition-extension* period, 370 (93.4%) subjects completed 78 weeks of the study. At up to Week 78, 26 (6.6%) subjects withdrew from the study (SB2/SB2: 15 [7.5%] subjects; Remicade/SB2: 6 [6.4%] subjects; Remicade/Remicade: 5 [5.0%] subjects). The most common reasons for withdrawal were withdrawal of consent (2.5%) and AEs (1.8%). The frequency of withdrawal was similar between the 3 treatment groups overall, up to Week 78 (Table 7).

Table 7: Summary of Patient Disposition for the Transition-Extension Period for Study SB2-G31-RA (ENR)

Disposition	SB2-G31-RA (*Transition-Extension* Period)				
	SB2	Remicade			Total
		Overall	SB2	Remicade	
	N (%)	N (%)	N (%)	N (%)	N (%)
Consented into *transition-extension* period	201	195			396
Screening failures	0	0			0
Re-randomized at Week 54	201 (100.0)	195 (100.0)	94 (100.0)	101 (100.0)	396 (100.0)
Completed Week 78 of treatment	186 (92.5)	184 (94.4)	88 (93.6)	96 (95.0)	370 (93.4)
Withdrew before Week 78	15 (7.5)	11 (5.6)	6 (6.4)	5 (5.0)	26 (6.6)
WDAEs, N (%)	3 (1.5)	4 (2.1)	3 (3.2)	1 (1.0)	7 (1.8)
Subject lost to follow-up, N (%)	3 (1.5)	3 (1.5)	1 (1.1)	2 (2.0)	6 (1.5)
Investigator discretion, N (%)	2 (1.0)	1 (0.5)	0 (0.0)	1 (1.0)	3 (0.8)
Withdrew consent, N (%)	7 (3.5)	3 (1.5)	2 (2.1)	1 (1.0)	10 (2.5)
Extended Full Analysis Set, N	201 (100.0)	195 (100.0)	94 (100.0)	101 (100.0)	396 (100.0)
Extended Safety Set, N	201 (100.0)	195 (100.0)	94 (100.0)	101 (100.0)	396 (100.0)

In the transition-extension period, percentages were based on the number of re-randomized subjects

Percentages for the screening failure reason were based on the number of screening failures in the randomised, double-blind period and the transition-extension period. Multiple screening failure reasons were possible.

'Completed Week 78 of treatment' and 'Withdrew before Week 78' were counted for subjects who entered the transition-extension period only.

Source: 78-week CSR SB2-G31-RA, Tables 10-1, 11-1

Efficacy Results

ACR20 at Week 30 (Primary Endpoint)

The primary endpoint of study SB2-G31-RA was the ACR20 response at Week 30, through which equivalence (as per study protocol definition) was to be established if the 95% CI for the treatment difference between SB2 and Remicade was within ±15%. Results from both the PPS1 and FAS showed similar response ACR20 response rates at Week 30 between SB2 and Remicade (PPS1: 64.1% vs. 66.0%, respectively; FAS: 55.5% vs. 59.0%, respectively). The 95% CIs of the adjusted difference rates falling within the predefined equivalence margin of ±15% for both PPS1 and FAS (-−10.26%, 6.51% and −10.88%, 4.97%, respectively) (Table 8).

Table 8: ACR20 Response Rate at Week 30 for Study SB2-R31-RA (PPS1 and FAS)

Population	n/n' (%)				Adjusted Difference Rate	95% CI
	N	SB2	N	Remicade		
PPS1	231	148/231 (64.1%)	247	163/247 (66.0%)	-1.88%	−10.26%, 6.51%
FAS[a]	290	161/290 (55.5%)	293	173/293 (59.0%)	−2.95%	−10.88%, 4.97%

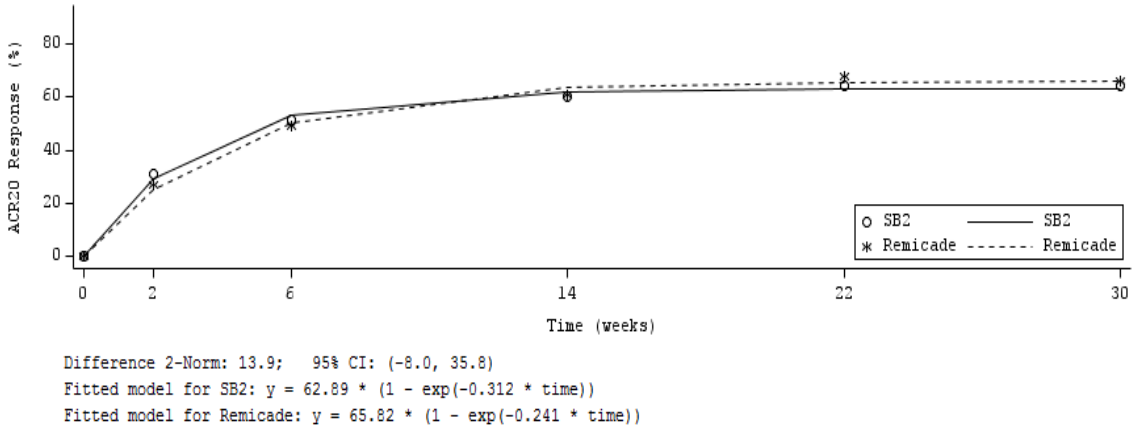
CI: confidence interval; N: number of patients in either the PPS1 or FAS; n' = number of patients with an assessment; n: number of responders

[a] For the FAS, patients with missing ACR20 at Week 30 were considered as non-responders at Week 30.

Source: CTD 2.7.3, Tables 2.7.3.2-7 and 2.7.3.2-8

To further demonstrate the robustness of the primary efficacy analysis, time-response curves for ACR20 response (PPS1) for SB2 and Remicade were constructed (41). Results showed that over the course of the first 30 weeks of treatment, the ACR20 response between SB2 and Remicade can be considered as similar (Figure 1). The 2-norm of the treatment difference (which can be viewed as the response difference between the two treatments over the time course) was 13.9 and the 95% CI of the treatment difference was (–8.0, 35.8), where the upper limit 35.8 was less than the pre-specified equivalence margin of 61.80.

Figure 1: Time-Response Model for ACR20 Response up to Week 30 (PPS1) for study SB2-G31-RA



Source: CTD 2.7.3, Fig. 2.7.3.2-3

Subgroup analyses in PPS1 showed similar proportion of ADA-negative patients achieving ACR20 response at Week 30 (adjusted treatment difference [95% CI]: −1.57% [−13.23%, 10.08%], which was within the equivalence margin of [–15%, 15%]). In the ADA-positive group, the adjusted treatment difference and its 95% CI in ACR20 response rate at Week 30 was −0.88% (−12.63%, 10.87%) which was also contained within the pre-defined equivalence margin of [−15%, 15%]. Overall, there was no significant interaction in ACR20 response rate at Week 30 between treatment and overall post-dose ADA status (p = 0.989).

In addition, there was no significant interaction in ACR20 response rate at Week 30 between treatment and Baseline CRP level in the PPS1 (*p*-value = 0.719), and there was also no statistically significant interaction between treatment and region, age group or gender at Week 30 in the PPS1. See CTD 2.7.3, section 2.7.3.2.3.2.3 for details.

Therefore, based on the primary outcome, it can be concluded that SB2 was therapeutically similar to Remicade.

Other ACR Responses

In this study, several other ACR response endpoints were also evaluated, which included ACR20 at Week 54, as well as ACR50, ACR70, and ACR-N at Weeks 30 and 54. The results for these ACR response rates are presented for both the PPS1/2 (Table 9) and the FAS (Table 10). All ACR response rates for both the PPS1/2 and the FAS at different time points were similar; with the 95% CI of the adjusted difference rates within the equivalence margin of ±15% defined for the primary endpoint. These results further supported the therapeutic similarity between SB2 and Remicade.

Table 9: ACR20, 50, and 70 Response Rates for the *Randomized, Double-blind* Period for Study SB2-G31-RA (PPS)

ACR Response	Time Point	Treatments	n/n'	%	Adjusted Difference Rate	95% CI
ACR20[a]	Week 54[b]	SB2 (N=202)	132/202	65.3	−3.07%	−12.00%, 5.86%
		Remicade (N=208)	144/208	69.2		
ACR50[c]	Week 30[d]	SB2 (N=231)	82/231	35.5	−2.13%	−10.69%, 6.43%
		Remicade (N=247)	94/247	38.1		
	Week 54[b]	SB2 (N=202)	84/202	41.6	3.43%	-5.74%, 12.60%
		Remicade (N=208)	81/208	38.9		
ACR70[e]	Week 30[d]	SB2 (N=231)	42/231	18.2	−0.25%	−7.26%, 6.75%
		Remicade (N=247)	47/247	19.0		
	Week 54[b]	SB2 (N=202)	45/202	22.3	-1.07%	-9.12%, 6.98%
		Remicade (N=208)	50/208	24.0		

CI: confidence interval; N: number of patients in the per-protocol set 1 or 2; n': number of patients with an assessment; n: number of responders.

[a] ACR20: American College of Rheumatology 20% response criteria; [b] PPS2;

[c] ACR50: American College of Rheumatology 50% response criteria; [d] PPS1

[e] ACR70: American College of Rheumatology 70% response criteria

Source: CTD 2.7.3, Tables 2.7.3.2-9, 2.7.3.2-11, 2.7.3.2-13

Table 10: ACR20, 50, and 70 Response Rates for the *Randomized, Double-blind* Period for Study SB2-G31-RA (Non-responder Analysis; FAS)

ACR Response	Time Point	Treatments	n/n'	%	Adjusted Difference Rate	95% CI
ACR20[a]	Week 54[b]	SB2 (N=290)	147/290	50.7	−1.15%	−9.16%, 6.86%
		Remicade (N=293)	154/293	52.6		
ACR50[c]	Week 30[d]	SB2 (N=290)	89/290	30.7	−2.53%	−10.07%, 5.00%
		Remicade (N=293)	99/293	33.8		
	Week 54[d]	SB2 (N=290)	93/290	32.1	3.07%	−4.26%, 10.40%
		Remicade (N=293)	87/293	29.7		
ACR70[e]	Week 30[d]	SB2 (N=290)	45/290	15.5	−1.08	−7.06%, 4.91%
		Remicade (N=293)	50/293	17.1		
	Week 54[d]	SB2 (N=290)	53/290	18.3	1.10%	−5.08%, 7.28%
		Remicade (N=293)	52/293	17.7		
ACR-N[f]	Week 30[d]	SB2 (N=290)	253[g]/290	36.6	−0.9%[h]	−6.0%, 4.2%
		Remicade (N=293)	265[g]/293	37.8		
	Week 54[d]	SB2 (N=290)	228[g]/290	38.8	−0.6%[h]	−6.1%, 5.0%
		Remicade (N=293)	225[g]/293	39.8		

CI: confidence interval; N: number of patients in the FAS; n': number of patients with an assessment; n: number of responders.

[a] ACR20: American College of Rheumatology 20% response criteria

[b] Subjects with missing ACR20 response at Week 54 were considered as non-responders at Week 54

[c] ACR50: American College of Rheumatology 50% response criteria

[d] Subjects with missing ACR50 or ACR70 were considered as ACR50 or ACR70 non-responder

[e] ACR70: American College of Rheumatology 70% response criteria

[f] ACR-N: Numeric index of the ACR response (FAS only)

[g] number of patients with an assessment

[h] treatment difference of the LS Means

Patients with missing ACR20, ACR50 or ACR70 responses at Week 30 and/or Week 54 were considered as non-responders at the corresponding week.

Source: CTD 2.7.3, Tables 2.7.3.2-10, 2.7.3.2-12, 2.7.3.2-14; 54-week CSR SB2-G31-RA, Tables 14.2-5.1, 14.2-6.1

In a sub-group analysis, the ACR50 and ACR70 responses by overall post-dose ADA result up to Week 30 for the PPS1 (54-week CSR SB2-G31-RA, Table 14.2-3.4) were similar between the SB2 and Remicade treatment groups in both the ADA-positive and ADA-negative subgroups.

The ACR20, ACR50 and ACR70 response rates by 54-week overall post-dose ADA status for the PPS2 (54-week CSR SB2-G31-RA, Tables 14.2-1.6 [ACR20] and 14.2-3.5 [ACR50 and 70]) and for the FAS (54-week CSR, Tables 14.2-1.8 [ACR20] and 14.2-3.6 [ACR50 and 70]) were generally similar between the SB2 and Remicade treatment groups among subjects who had an overall post-dose negative ADA result and those with overall post-dose positive results.

ACR20, ACR50, ACR70 Response Rates and ACR-N for the Transition-extension Period

Summaries of ACR20, ACR50 and ACR70 by visit for the Ex-FAS (available data only analysis) are provided in Table 11. The response rates were similar across the 3 groups for each of ACR20, 50, and 70 as well as for each time point. The ACR-N pattern between the transition treatment groups (Remicade/SB2 and Remicade/Remicade) as well as the SB2/SB2 treatment groups was considered to be similar.

Table 11: ACR20, 50, 70 Response Rates and ACR-N by Visit for the *Transition-Extension* Period for Study SB2-G31-RA; Available Data Only Analysis (Ex-FAS)[a]

ACR Response	Time Point	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)
ACR-N[a]	Week 54	201/201	(40.5)	94/94	(42.9%)	101/101	(39.9)
	Week 62	193/201	(39.6)	94/94	(42.8%)	101/101	(40.9)
	Week 70	180/201	(41.7)	88/94	(40.3%)	98/101	(42.9)
	Week 78	180/201	(41.7)	85/94	(39.1%)	93/101	(44.2)

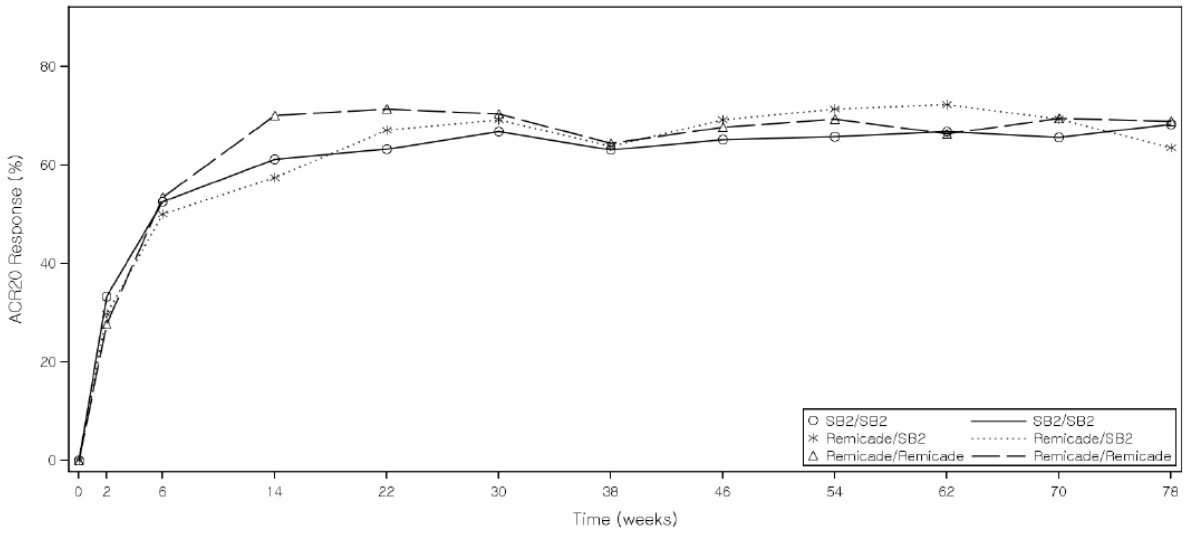
n' = number of subjects with an available assessment; n = number of responders

[a] Except for ACR-N where the Extended Full Analysis Set data is presented; number in bracket represents the percentage of improvement from baseline that a patient has experienced in analogy to ACR20, ACR50, and ACR70 responses

Source: 78-week CSR SB2-G31-RA, Tables 11-14 and 14.2-1.7

Post-hoc analysis of the response pattern of ACR20 for the Ex-FAS tracking back to Week 0 is shown in Figure 2. Overall, the ACR20 response rate of the SB2/SB2 group appeared stable over time, whereas the response rates for the Remicade/SB2 and Remicade/Remicade groups showed minor fluctuations. This was likely due to the smaller sample size in these latter groups. The overall ACR20 response pattern over time between the transition treatment groups (Remicade/SB2 and Remicade/Remicade) as well as the SB2/SB2 treatment group were considered to be relatively similar.

Figure 2: ACR20 Response Pattern of the Three Treatment Groups from the Ex-FAS, Retrospectively Tracking Back to Week 0



ACR20 response was calculated from the data as observed.

ACR20 response between weeks 0-54 in the Ex-FAS was tracked-back in the Remicade/SB2 group.

Source: 78-week CSR SB2-G31-RA

In a sub-group analysis in the *transition-extension* period, the ACR20, ACR50 and ACR70 response rates for the Ex-FAS at Week 78 by ADA status (78-week CSR SB2-G31-RA, Tables 14.2-1.4 [ACR20] and 14.2-1.5 [ACR50 and 70]) were generally similar between across the three groups among subjects who had an overall post-dose negative ADA result and those with overall post-dose positive ADA results. Minor variation was seen, particularly for the ACR50 response rate in the post-dose positive ADA group (SB2/SB2: 38.5% [45/117]; Remicade/SB2: 31.5% [17/54]; Remicade/Remicade: 49.1% [26/53]) but again this is likely the result of low number of subjects in the latter two groups. This is supported by DAS28 results below (based on ESR) where similar efficacy response was seen between groups. Overall, any clinical meaningful difference on efficacy potentially impacted by ADAs was not found based on the long-term data.

AUC of ACR-N

The mean AUC of ACR-N up to Week 30 for the FAS was similar in the two treatment groups: 6071.96 in the SB2 group and 6209.99 in the Remicade group. The treatment difference in the LS Means estimated by ANCOVA and its 95% CI in AUC of ACR-N up to Week 30 was −105.7 (−862.4, 651.0).

Major Clinical Response

The major clinical response rate (maintenance of an ACR70 response over a 6-consecutive month period) at Week 54 for the FAS was 7.9% (23/290) in the SB2 group and 6.5% (19/293) in the Remicade group. These results demonstrated that the proportion of patients achieving major clinical response at Week 54 was similar between the two treatment groups.

DAS28

Similar to ACR responses, the DAS28 (FAS) results were also similar between the SB2 and the Remicade groups in the *randomized, double-blind* period (Table 12). The 95% CI of treatment difference in the LS Means at both Weeks 30 and 54 were contained within the equivalence margin of ±0.6. Therefore, DAS28 results further supported the therapeutic similarity between SB2 and Remicade.

Table 12: Mean and ANCOVA for Change in DAS28 Scores from Baseline in the *Randomized, Double-blind* Period for Study SB2-G31-RA (FAS)

Time Point	Treatments	n'	Mean Change	LS Means difference	95% CI
Week 30	SB2 (N=290)	253	2.3275	0.044	−0.186, 0.274
	Remicade (N=293)	265	2.3309		
Week 54	SB2 (N=290)	227	2.4219	-0.004	−0.246, 0.239
	Remicade (N=293)	222	2.4735		

CI = confidence interval; LS Mean = Least-Squares Mean; N = number of subjects in the full analysis set;

n' = number of subjects with an assessment

Source: 78-week CSR SB2-G31-RA, Table 11-15

In the *transition-extension* period of the study, the mean changes in DAS28 from baseline to Week were similar between the 3 groups. However, a very minor difference was observed between Week 54 and Week 78 (Table 13). Overall, in a similar context with the ACR response, the change of DAS28 scores between the transition treatment groups (Remicade/SB2 and Remicade/Remicade) as well as the SB2/SB2 treatment group were considered to be similar.

Table 13: Mean and ANCOVA for Change in DAS28 Scores in the *Transition-Extension* Period in Study SB2-G31-RA (Ex-FAS)

Time Point	Treatment	n'	Mean Change
Week 0-78	SB2/SB2 (N=201)	180	2.6189
	Remicade/SB2 (N=94)	85	2.5228
	Remicade/Remicade (N=101)	91	2.5844
Week 54-78	SB2/SB2 (N=201)	180	0.1262
	Remicade/SB2 (N=94)	85	−0.1226
	Remicade/Remicade (N=101)	91	0.1238

CI = confidence interval; LS Mean = Least-Squares Mean; N = number of subjects in the full analysis set;

n' = number of subjects with an assessment

Source: 78-week CSR SB2-G31-RA, Table 14.2-1.8

AUC of the Change in DAS28 from Baseline up to Week 30

The mean AUC of the change in DAS28 score from Baseline up to Week 30 was 387.89 (± 207.87) in the SB2 treatment group and 401.34 (± 223.26) in the Remicade treatment group in the FAS. The adjusted treatment difference in LS Means and its 95% CI were −6.3 (−41.0, 28.4) which showed that the AUC of DAS28 up to Week 30 was similar between the SB2 and Remicade treatment groups.

EULAR Response at Week 30 and Week 54

In the *randomized, double-blind* period, the proportion of subjects who had good, moderate and no response was generally similar between the SB2 and Remicade treatment groups at Week 30 and Week 54 (Table 14). EULAR responses at other time points are detailed in the 54-week CSR SB2-G31-RA, Table 14.2-5.5.

Table 14: EULAR Response Rate in the *Randomized, Double-blind* Period of Study SB2-G31-RA (FAS)

Time Point	Treatment	Response [% (n/n')]		
		Good	Moderate	No
Week 30	SB2 (N=290)	25.7% (65/253)	58.1% (147/253)	16.2% (41/253)
	Remicade (N=293)	25.7% (68/265)	54.7% (145/265)	19.6% (52/265)
Week 54	SB2 (N=290)	31.7% (72/227)	48.5% (110/227)	19.8% (45/227)
	Remicade (N=293)	27.9% (62/222)	55.4% (123/222)	16.7% (37/222)

N: number of patients in the FAS; n': number of subjects with available assessment results at each time point; n: number of responders

Source: 54-week CSR SB2-G31-RA, Table 14.2-5.5.

In the *Transition-Extension* period, up to Week 78, the distribution of the EULAR response was similar between the transition treatment groups (Remicade/SB2 and Remicade/Remicade) as well as the SB2/SB2 treatment group (Table 15).

Table 15: EULAR Response Rate in the *Transition-Extension* Period of Study SB2-G31-RA (Ex-FAS)

Time Point	Treatment	Response [% (n/n')]		
		Good	Moderate	No
Week 54	SB2/SB2 (N=201)	33.8% (68/201)	46.8% (94/201)	19.4% (39/201)
	Remicade/SB2 (N=94)	29.8% (28/94)	57.4% (54/ 94)	12.8% (12/94)
	Remicade/Remicade (N=101)	29.3% (29/99)	53.5% (53/99)	17.2% (17/99)
Week 62	SB2/SB2 (N=201)	30.7% (59/192)	55.2% (106/192)	14.1% (27/192)
	Remicade/SB2 (N=94)	35.1% (33/94)	48.9% (46/94)	16.0% (15/94)
	Remicade/Remicade (N=101)	38.6% (39/101)	44.6% (45/101)	16.8% (17/101)
Week 70	SB2/SB2 (N=201)	37.2% (67/180)	46.1% (83/180)	16.7% (30/180)
	Remicade/SB2 (N=94)	31.8% (28/88)	56.8% (50/88)	11.4% (10/88)
	Remicade/Remicade (N=101)	34.7% (34/98)	52.0% (51/98)	13.3% (13/98)
Week 78	SB2/SB2 (N=201)	35.6% (64/180)	51.7% (93/180)	12.8% (23/180)
	Remicade/SB2 (N=94)	32.9% (28/85)	51.8% (44/85)	15.3% (13/85)
	Remicade/Remicade (N=101)	34.4% (32/93)	50.5% (47/93)	15.1% (14/93)

N: number of patients in the FAS; **n'**: number of subjects with available assessment results at each timepoint; **n**: number of responders

Source: 78-week CSR SB2-G31-RA, Table 14.2-1.9

HAQ-DI

Results for the physical function test as assessed by HAQ-DI in the *randomized, double-blind* period are provided in Table 16. Overall, results showed similar degree of physical function between treatment groups at different assessment time points.

Table 16: Summary of Physical Function Test Results at Baseline, Weeks 30 and 54 in the *Randomized, Double-blind* Period of Study SB2-G31-RA (FAS)

HAQ-DI (0-3)		SB2 (N=290)	Remicade (N=293)
Baseline	n	290	293
	Mean (SD)	1.4720 (0.61994)	1.5444 (0.58103)
	Min, Max	0.000, 3.000	0.000, 2.875
Week 30	n	253	265
	Mean (SD)	0.9990 (0.64068)	1.0028 (0.66438)
	Min, Max	0.000, 2.625	0.000, 2.500
Week 54	n	228	225
	Mean (SD)	0.9890 (0.65318)	0.9867 (0.63964)
	Min, Max	0.000, 2.750	0.000, 2.500

HAQ-DI: Health Assessment Questionnaire-Disability Index; SD: standard deviation; Min: minimum; Max: maximum

Source: SB2 Product Monograph, Table 22

Joint Damage

The change from baseline in mean modified total Sharp score (mTSS) in the *randomized, double-blind* period was similar between SB2 and Remicade treatment groups (0.38 and 0.37, respectively) (Table 17). In the ANCOVA analysis, the difference between SB2 and Remicade in the mean change from Baseline in mean mTSS at Week 54 and the 95% CI was 0.01 and (–0.53, 0.56), demonstrating similar prevention of radiographic progression between treatment groups.

Table 17: Summary of Structural Joint Damage at Week 54 in the *Randomized, Double-blind* Period of Study SB2-G31-RA (FAS)

		SB2 (N=290)		EU-Remicade (N=293)	
Modified total sharp score, mean (SD)					
	n	213		209	
	Week 0	37.06	(57.527)	38.92	(56.272)
	Week 54	37.44	(57.784)	39.29	(56.360)
	Change	0.38	(2.154)	0.37	(3.391)
Joint erosion score, mean (SD)					
	n	213		209	
	Week 0	19.24	(31.689)	20.54	(31.116)
	Week 54	19.38	(31.754)	20.50	(30.994)
	Change	0.14	(1.157)	−0.03	(1.245)
Joint space narrowing score, mean (SD)					
	n	213		209	
	Week 0	17.83	(27.672)	18.38	(26.779)
	Week 54	18.07	(27.829)	18.78	(27.010)
	Change	0.24	(1.392)	0.40	(2.562)

n: number of completers with available radiographic assessment results at Week 0 and Week 54

Source: CTD 2.7.3, Table 2.7.3.2-15

Since subjects had the opportunity to receive doses higher than 3 mg/kg, the dosing pattern and the associated clinical effect was examined. The increment pattern in dosing in the SB2 and the Remicade treatment groups was generally similar at all time points with the minor exceptions; however, no specific trend or pattern was observed, and additional analysis demonstrated that ADA incidences in higher dose patients in both treatment groups were also similar (CTD 2.7.3, sections 2.7.3.4 & 2.7.3.5, Table of Clarifax). Overall, the efficacy of SB2 (ACR20; FAS) was maintained as far as the dosing schedule was adhered and was also consistently similar to EU-Remicade during the study period.

In sum, long-term (78 weeks) efficacy data in RA subjects supported the conclusion that SB2 is therapeutically similar to Remicade, and that subjects who are switched to SB2 after treatment with Remicade can expect to achieve similar efficacy profile.

Safety Results

Adverse Events

In the *randomized, double-blind* period, 1177 TEAEs were reported by total of 370 (63.5%) patients any time after the first dose of the study drugs (Table 18). The number (%) of patients with TEAEs and number of TEAEs that occurred in ≥ 2% of patients are in Table 44 in Appendix 1. Commonly occurring TEAEs included latent TB (SB2: 19 events in 19 [6.6%] subjects; Remicade: 21 events in 21 [7.2%] subjects), nasopharyngitis (SB2: 23 events in 18 [6.2%] subjects; Remicade: 27 events in 20 [6.8%] subjects), and alanine aminotransferase increased (SB2: 27 events in 23 [7.9%] subjects; Remicade: 10 events in 9 [3.1%] subjects). Overall, the proportion of subjects that experienced drug-related TEAEs were similar between the SB2 and the Remicade groups. The majority of TEAEs were considered to be unrelated to the study drugs.

In both treatment groups, similar number of subjects experienced SAEs and those SAEs were generally considered unrelated to the study drugs. Of 68 SAEs reported, 2 SAEs, 1 in each treatment group, were noted not to have resolved (SB2: prostate cancer – subject withdrew; Remicade: subject developed pneumonia and died due to congestive heart failure; both were unrelated to study drug). One SAE in the SB2 treatment group was of unknown outcome (non-malignant brain neoplasm related to study drug; subject withdrew consent).

Overall, the incidence of TEAEs leading to study drug discontinuation was similar between the treatment groups. A total of 62 TEAEs that led to discontinuations were reported in 54 (9.3%) subjects (SB2: 30 [10.3%] subjects; Remicade: 24 [8.2%] subjects). Among these, those considered to be related to study drugs were reported in 21 (7.2%) subjects in the SB2 treatment group and 17 (5.8%) subjects in the Remicade treatment group. TEAEs leading to IP discontinuation reported in more than 3 subjects in any treatment were latent TB (SB2: 2 events in 2 [0.7%] subjects; Remicade: 4 events in 4 [1.4%] subjects), RA (SB2: 4 events in 4 [1.4%] subjects), pneumonia (SB2: 3 events in 3 [1.0%] subjects; Remicade: 1 event in 1 [0.3%] subject), and hypersensitivity (SB2: 3 events in 3 [1.0%] subjects). Overall, the incidence of TEAEs leading to IP discontinuation was similar between treatment groups (see CTD 2.7.4, Table 2.7.4.2-13 for details).

One death was reported in the Remicade treatment group due to severe worsening of the left ventricular failure (congestive heart failure). The event was not considered related to the treatment by the Investigator.

Table 18: Summary of TEAEs in the *Randomized, Double-blind* Period in Study SB2-G31-RA (SAF)

	SB2 (N=290)	EU-Remicade (N=293)	Total (N=583)
Total number of TEAEs	565	612	1177
Related	*121*	*129*	*250*
Unrelated	*442*	*483*	*925*
Unknown	*2*	*0*	*2*
Number (%) of patients with at least 1 TEAE	179 (61.7%)	191 (65.2%)	370 (63.5%)
Related	*70 (24.1%)*	*69 (23.5%)*	*139 (23.8%)*
Unrelated	*109 (37.6%)*	*122 (41.6%)*	*231 (39.6%)*
Unknown	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*
Total number of SAEs	33	35	68
Related	*10*	*8*	*18*
Unrelated	*23*	*27*	*50*
Number (%) of patients with at least 1 SAE	29 (10.0%)	31 (10.6%)	60 (10.3%)
Related	*10 (3.4%)*	*7 (2.4%)*	*17 (2.9%)*
Unrelated	*19 (6.6%)*	*24 (8.2%)*	*43 (7.4%)*
Total number of AEs leading to permanent IP discontinuation	36	26	62
Number (%) of patients with at least 1 AE leading to permanent IP discontinuation	30 (10.3%)	24 (8.2%)	54 (9.3%)
Deaths	0 (0.0%)	1 (0.3%)	1 (0.2%)

IP: investigational product; SAE: serious adverse events; TEAE: treatment-emergent adverse event

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

If a subject had multiple events of the same severity or causality, then the subject was counted only once in that severity or causality. If a subject had multiple events with different severity or causality, then the subject was counted only once for more severe adverse event or related adverse event.

Source: CTD 2.7.4, Tables 2.7.4.2-3

Although not presented here, the subgroup analysis of TEAEs by ADA status up to Week 54 (positive vs. negative), age (<65 and ≥65 years old), and gender revealed that the subgroups within these factors did not impact safety profile between treatments.

In the *transition-extension* period, 285 TEAEs were reported by total of 151 (38.1%) patients (Table 19). The number (%) of patients with TEAEs and number of TEAEs that occurred in ≥ 2% of patients are in Table 45 in Appendix 1. Commonly occurring TEAEs in the SB2/SB2, Remicade/SB2, Remicade/Remicade treatment groups, respectively, included latent TB (14 events in 11 [5.5%], 9 events in 7 [7.4%] and 4 events in 4 [4.0%] subjects), nasopharyngitis (11 event in 11 [5.5%], 2 events in 2 [2.1%] and 5 events in 4 [4.0%] subjects, respectively), and RA (8 events in 7 [3.5%], 2 events in 2 [2.1%] and 5 events in 4 [4.0%] subjects, respectively). Overall, the proportion of subjects that experienced drug-related TEAEs were similar across the 3 groups. The majority of TEAEs were considered to be unrelated to the study drugs.

Across the treatment groups, very few subjects experienced SAEs and half of the SAEs were considered unrelated to the study drugs. All SAEs in the *transition-extension* period were resolved.

The incidence of TEAEs leading to study drug discontinuation in the *transition-extension* period was similar across the 3 groups, with 11 TEAEs leading to discontinuations in 9

(2.3%) subjects (4 events in 3 [1.5%] subjects, 3 events in 3 [3.2%] subjects, and 4 events in 3 [3.0%] subjects, in the SB2/SB2, Remicade/SB2, and Remicade/Remicade, groups, respectively).

There were no deaths in the *transition-extension* period.

Table 19: Summary of TEAEs in the *Transition-Extension* Period in Study SB2-G31-RA (Ex-SAF)

	SB2	Remicade			Total
		Overall	SB2	Remicade	
	N=201	N=195	N=94	N=101	N=396
Total number of TEAEs[a]	147	138	65	73	285
Related	*37*	*48*	*21*	*27*	*85*
Unrelated	*110*	*90*	*44*	*46*	*200*
Number (%) of patients with at least 1 TEAE	81 (40.3%)	70 (35.9%)	34 (36.2%)	36 (35.6%)	151 (38.1%)
Related	*28 (13.9%)*	*26 (13.3%)*	*13 (13.8%)*	*13 (12.9%)*	*54 (13.6%)*
Unrelated	*53 (26.4%)*	*44 (22.6%)*	*21 (22.3%)*	*23 (22.8%)*	*97 (24.5%)*
Total number of SAEs	8	10	7	3	18
Related	*2*	*7*	*5*	*2*	*9*
Unrelated	*6*	*3*	*2*	*1*	*9*
Number (%) of patients with at least 1 SAE	7 (3.5%)	9 (4.6%)	6 (6.4%)	3 (3.0%)	16 (4.0%)
Related	*2 (1.0%)*	*6 (3.1%)*	*4 (4.3%)*	*2 (2.0%)*	*8 (2.0%)*
Unrelated	*5 (2.5%)*	*3 (1.5%)*	*2 (2.1%)*	*1 (1.0%)*	*8 (2.0%)*
Total number of AEs leading to permanent IP discontinuation	4	7	3	4	11
Number (%) of patients with at least 1 AE leading to permanent IP discontinuation	3 (1.5%)	6 (3.1%)	3 (3.2%)	3 (3.0%)	9 (2.3%)
Deaths	0	0	0	0	0

IP: investigational product; TEAE: treatment-emergent adverse event

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

[a] All TEAEs associated with infusion-related reaction presented in this table were causally related.

If a subject had multiple events of the same severity or causality, then the subject was counted only once in that severity or causality. If a subject had multiple events with different severity or causality, then the subject was counted only once for more severe adverse event or related adverse event.

If a subject had at least one attributable event, then the subject was counted once in attributable category, otherwise, if a subject only had indeterminate events, then the subject was counted once in indeterminate category.

Source: 78-week CSR SB2-G31-RA, Table 12-5

Although not presented here, similar to the *randomized, double-blind* period, the subgroup analysis of TEAEs by ADA status (positive vs. negative), age (<65 and ≥65 years old), and gender revealed that the subgroups within these factors generally did not impact safety profile between treatments.

TEAEs by Severity

The summary of TEAEs and Serious TEAEs (SAEs) by severity in the *randomized, double-blind* period is presented in Table 20. Majority of the TEAEs experienced in both groups were considered to be mild or moderate in nature. In addition, similar proportion of subjects experienced mild and moderate TEAEs across both SB2 and Remicade treatment groups. In terms of SAEs, similar proportion of subjects and numbers of events occurred between SB2 and Remicade treatment groups; most of the SAEs were considered moderate in nature.

Table 20: Summary of TEAEs and Serious TEAEs (SAEs) by Severity in the *Randomized, Double-blind* Period in Study SB2-G31-RA (Safety Set)

	SB2 (N=290)			EU-Remicade (N=293)		
	n	(%)	E	n	(%)	E
Any TEAE	179	(61.7)	565	191	(65.2)	612
Mild	*76*	*(26.2)*	*376*	*92*	*(31.4)*	*394*
Moderate	*78*	*(26.9)*	*153*	*79*	*(27.0)*	*189*
Severe	*25*	*(8.6)*	*36*	*20*	*(6.8)*	*29*
Serious TEAE	29	(10.0)	33	31	(10.6)	35
Mild	*1*	*(0.3)*	*3*	*3*	*(1.0)*	*4*
Moderate	*14*	*(4.8)*	*16*	*18*	*(6.1)*	*20*
Severe	*14*	*(4.8)*	*14*	*10*	*(3.4)*	*11*

E: frequency of adverse events; TEAE: treatment-emergent adverse event.

Percentages were based on the number of patients in the safety set.

If a subject had multiple events of the same severity or causality, then the subject was counted only once in that severity or causality. If a subject had multiple events with different severity or causality, then the subject was counted only once for more severe adverse event or related adverse event.

Source: CTD 2.7.4, Table 2.7.4.2-3

In the *transition-extension* period, the majority of the TEAEs experienced across the 3 groups were mild or moderate in nature. In addition, similar proportion of subjects experienced mild and moderate TEAEs across the 3 groups. Very few subjects experienced SAEs across the 3 groups and overall, most were moderate in severity (Table 21). All SAEs had been resolved.

Table 21: Summary of TEAEs and Serious TEAEs (SAEs) by Severity in the *Transition-Extension* Period in Study SB2-G31-RA (Safety Set)

	SB2			Remicade									Total		
				Overall			SB2			Remicade					
	N=201			N=195			N=94			N=101			N=396		
	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Any TEAE	81	(40.3)	147	70	(35.9)	138	34	(36.2)	65	36	(35.6)	73	151	(38.1)	285
Mild	44	(21.9)	95	38	(19.5)	75	18	(19.1)	35	20	(19.8)	40	82	(20.7)	170
Moderate	33	(16.4)	48	25	(12.8)	54	12	(12.8)	25	13	(12.9)	29	58	(14.6)	102
Severe	4	(2.0)	4	7	(3.6)	9	4	(4.3)	5	3	(3.0)	4	11	(2.8)	13
Serious TEAE	7	(3.5)	8	9	(4.6)	10	6	(6.4)	7	3	(3.0)	3	16	(4.0)	18
Mild	1	(0.5)	1	2	(1.0)	2	1	(1.1)	1	1	(1.0)	1	3	(0.8)	3
Moderate	4	(2.0)	5	3	(1.5)	3	2	(2.1)	2	1	(1.0)	1	7	(1.8)	8
Severe	2	(1.0)	2	4	(2.1)	5	3	(3.2)	4	1	(1.0)	1	6	(1.5)	7

E = frequency of treatment-emergent adverse events; TEAE = treatment-emergent adverse event

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

If a subject had multiple events of the same severity or causality, then the subject was counted only once in that severity or causality. If a subject had multiple events with different severity or causality, then the subject was counted only once for more severe adverse event or related adverse event.

If a subject had at least one attributable event, then the subject was counted once in attributable category, otherwise, if a subject only had indeterminate events, then the subject was counted once in indeterminate category.

Source: 78-week CSR, Table 12-5

Infusion-Related Reactions (IRRs)

In the randomized, double-blind period, there were 37 TEAEs associated with IRRs in 32 (5.5%) patients (SB2: 19 events in 17 [5.9%] patients; Remicade: 18 events in 15 [5.1%] patients). Of these, 5 reactions were considered as SAEs (SB2: 2 events of hypersensitivity and 1 event of anaphylactic reaction in 3 [1.0%]; Remicade: 1 event of urticaria and 1 event of anaphylactic shock each in 2 [0.7%] subjects).

The incidence of IRRs was higher in ADA-positive subjects (SB2: 15 [5.2%] subjects; Remicade: 11 [3.8%] subjects) than in ADA-negative subjects (SB2: 2 [0.7%] subjects; Remicade: 4 [1.4%] subjects) (up to Week 54). However, the incidence was similar between the two treatment groups within each ADA subgroup. There were no reported cases of serum sickness or delayed hypersensitivity.

In the transition-extension period, 22 TEAEs were associated with IRRs in 12 (3.0%) subjects (9 events in 7 [3.5%] subjects, 4 events in 3 [3.2%] subjects, and 9 events in 2 [2.0%] subjects, in the SB2/SB2, Remicade/SB2, and Remicade/Remicade, groups, respectively; 78-week CSR, Table 14.3.1-2.9).

Safety of Special Interest – Serious Infections or Tuberculosis

During the randomized, double-blind period of the study, there were 16 TEAEs of special interest in 16 (2.7%) subjects (SB2: 9 events in 9 [3.1%] subjects; Remicade: 7 events in 7 [2.4%] subjects). The most common TEAE of special interest was pneumonia, which was reported by similar number of subjects between groups (SB2: 3 events in 3 [1.0%] subjects; Remicade: 2 events in 2 [0.7%] subjects).

The incidence of active (or clinically overt) TB was similar with 1 (0.3%) subject in each of the treatment groups reported the AE (SB2: tuberculosis pleurisy; Remicade: pulmonary tuberculosis). None of these subjects had a positive QuantiFERON® Gold test or were reported to have latent TB at Screening. All other TEAEs of special interests occurred once in 1 subject in either the SB2 or Remicade group (see CTD 2.7.4, Table 2.7.4.2-17 for details).

In the transition-extension period of the study, there were 4 TEAEs of special interest (1 event in 1 [0.5%] subjects, 2 events in 2 [2.1%] subjects, and 1 event in 1 [1.0%] subject, in the SB2/SB2, Remicade/SB2, and Remicade/Remicade, groups, respectively). Serious infections occurred in 1 (0.5%) subject in the SB2/SB2 treatment group, 2 (2.1%) subjects in the Remicade/SB2 treatment group and 1 (1.0%) subject in the Remicade/Remicade treatment group. There were no cases of pneumonia or active TB reported in any of the treatment groups in this period (78-week CSR, Table 14.3.1-2.6).

Malignancies

In the randomized, double-blind period, malignancies were reported for 2 subjects in the SB2 group (breast cancer [unrelated to study drug] and prostate cancer [unrelated to study drug]; each reported for 1 subject). No malignancies were reported in the Remicade group. An AE (related to SB2 treatment) of brain neoplasm (verbatim term: suspicion of neoplasm – pathological changes in the right hemisphere) was a suspected diagnosis as a result of brain computer tomography/magnetic resonance imaging that was initially reported as epilepsy; there was no pathological confirmation and it was not considered to be a malignancy.

In the transition-extension period, there were 2 subjects with malignancies in the Remicade/SB2 treatment group (lip and/or oral cavity cancer, and basal cell carcinoma in subject each) and 1 subject with malignancy (papillary thyroid cancer; initially diagnosed with benign neoplasm of the thyroid gland) in the Remicade/Remicade group.

Laboratory Parameters

Hematology

In the randomized, double-blind period, the mean and median values of hematology parameters did not show any notable differences between the SB2 and Remicade treatment groups. The number of patients reported with at least one post-dose significant abnormality in any hematology parameters up to Week 54 was similar between SB2 and Remicade (summarized in Table 46 in Appendix 1). The most commonly reported significant abnormality in haematology was high neutrophil count (SB2: 8 [2.8%] patients; Remicade: 4 [1.4%] patients) and low lymphocyte (SB2: 6 [2.1%] patients; Remicade: 3 [1.0%] patients). Notable shifts from baseline to Week 54 in the parameters of neutrophil and lymphocytes were observed. However; most of the shifts associated with neutrophils were from high levels at Baseline to normal levels at Week 54, and shifts associated with lymphocytes were from low levels at Baseline to normal levels at Week 54. The proportions of subjects in each SB2 and Remicade groups showing shifts for each parameter were similar (CTD 2.7.4, section 2.7.4.3.2.1).

In the transition-extension period, the mean and median values of hematology parameters did not show any notable differences across the 3 groups. The number of patients reported with at least one post-dose significant abnormality in any hematology parameters up to Week 78 was similar between SB2 and Remicade (summarized in Table 47 in Appendix 1). Minor proportion of subjects experienced shifts in the neutrophils parameter but most of which were from high (at extended baseline) to normal level at Week 78 (78-week CSR SB2-G31-RA, sections 12.4.2.1, 12.4.2.2, 12.4.2.3).

Biochemistry

In the randomized, double-blind period, the mean and median values of biochemistry parameters did not show any notable differences between the SB2 and Remicade treatment groups over time. The number of subjects with at least 1 post-dose significant abnormality in biochemistry parameters was generally similar between the SB2 and Remicade treatment groups (summarized in Table 48 in Appendix 1). The most commonly reported significant abnormalities in biochemistry were increased alanine aminotransferase (ALT) (SB2: 15 [5.2%] patients; Remicade: 7 [2.4%] patients), high glucose levels (SB2: 8 [2.8%] patients; Remicade: 4 [1.4%] patients), and high gamma-glutamyl transferase (γGT) (5 [1.7%] patients in each SB2 and Remicade groups). Notable shifts from baseline to Week 54 in aspartate aminotransferase (AST), ALT, and creatinine were observed. Briefly, majority of shifts in AST and ALT were from normal levels at Baseline to high levels at Week 54. For creatinine levels, similar proportion of shifts from normal to high and high to normal was observed (CTD 2.7.4, section 2.7.4.3.2.2).

In the transition-extension period, the mean and median values of biochemistry parameters did not show any notable differences. The number of subjects with at least 1 post-dose significant abnormality in biochemistry parameters was generally similar between the SB2 and Remicade treatment groups (summarized in Table 49 in Appendix 1). Minor proportion of subjects experienced shifts in the AST and ALT parameters but most of which were

generally from high (at extended baseline) to normal levels at Week 78 (78-week CSR SB2-G31-RA, sections 12.4.2.1, 12.4.2.2, 12.4.2.3).

Drug-induced Liver Injury according to Hy's Law cases

Possible Hy's law cases were not reported during the study in either the randomized, double-blind period or the transition-extension period.

Auto-Antibodies

In the randomized, double-blind period, the majority of subjects in the SB2 and Remicade treatment groups had negative anti-nuclear antibodies (ANAs) up to Week 54 (158 [72.1%] versus 160 [73.4%] subjects). In the SB2 treatment group, 3 (1.4%) subjects had a shift from positive ANAs at baseline to negative and 40 (18.3%) subjects had a shift from negative ANAs at baseline to positive at Week 54. In the Remicade treatment group, 2 (0.9%) subjects had a shift from positive ANAs at baseline to negative and 36 (16.5%) subjects had a shift from negative ANAs at baseline to positive at Week 54. No autoimmune AEs (i.e, drug-induced lupus or demyelinating disorders) were reported in the study.

A total of 18 (30.5%) subjects from the SB2 treatment group tested positive for anti-dsDNA antibodies up to Week 54. In the EU-Remicade treatment group, 26 (46.4%) subjects tested positive for anti-dsDNA antibodies up to Week 54.

In the transition-extension period, at Extended Baseline (Week 54), the majority of subjects across the 3 groups had negative ANA: 293 (75.3%). At Week 78, 272 (73.9%) subjects were negative for ANA. Shifts in ANA status, AE reporting for ADA status, and anti-dsDNA antibody status are shown in Table 22. There was 1 case of lupus-like syndrome reported in the SB2/SB2 treatment group.

Within this context, the incidence of positive ANA among the transition treatment groups as well as the SB2/SB2 treatment group seem to be similar.

Table 22: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[a] [redacted]

[b] [redacted]

Source: [redacted]

Urinalysis

In the *randomized, double-blind* period in both treatment groups, there were no notable changes over time in urinalysis parameters. Appearance, colour, leukocytes esterase, nitrite, pH, specific gravity, bilirubin, blood, glucose, ketones, protein and urobilinogen were normal in the majority of subjects throughout the study.

In the *transition-extension* period, there were no notable changes over time in urinary parameters for the 3 groups. Urinalysis parameters were normal in the majority of subjects throughout the study in all 3 treatment groups.

Vitals, Physicals, and ECGs

In the *randomized, double-blind* period, up to Week 54, the incidence of clinically significant abnormalities reported for systolic and diastolic blood pressure, heart rate, and temperature were low and similar between the two treatment groups (reported by no more than 2 subjects in each group for each parameter/criteria [H/L] at each time point). There were minimal changes in vitals from Baseline to Week 54 with no marked differences observed between the 2 treatment groups.

Similar observation was also seen across the 3 groups in the *transition-extension* period. Minimal changes in mean systolic and diastolic blood pressure, heart rate and body temperature were observed with no marked differences across the 3 treatment groups. No more than 1 subject in each of the 3 groups had clinical significant abnormalities for each parameter/criteria [H/L] at each time point.

In the *randomized, double-blind* period, clinically significant abnormal physical examination findings, not present at Baseline, were reported in the respiratory, general appearance, lymph nodes and abdomen categories. The most frequently reported significant abnormal physical examination parameter was general appearance (SB2: 10/284 [3.5%]; Remicade: 12/290 [4.1%]) and respiratory (SB2: 5/284 [1.8%]; EU-Remicade: 6/290 [2.1%]). The incidence of abnormal findings was similar between the two treatment groups.

In the *transition-extension* period, the most frequently reported significant abnormal physical examination parameter not present at Week 0 was general appearance (8 [4.1 %] subjects in the SB2/SB2 treatment group, 5 [5.3%] subjects in the Remicade/SB2 treatment group and 6 [5.9%] subjects in the Remicade/Remicade treatment group). The incidence of abnormal findings was similar across the 3 groups.

In the *randomized, double-blind* period, a total of 74 subjects in the SB2 treatment group and 66 subjects in the Remicade treatment group were reported with abnormalities in 12-lead ECG at Screening, however, only 1 subject from the SB2 treatment group was considered as clinically significant.

In sum, long-term (78 weeks) safety data in RA subjects supported the conclusion that SB2 is therapeutically similar to Remicade, and that subjects who are switched to SB2 after treatment with Remicade can expect to achieve similar safety profile.

SB2-G11-NHV

Study Characteristics

Brief description of the study

Study SB2-G11-NHV is a single-blind, parallel group, single-dose study with three treatment groups designed to compare the PK, safety / tolerability, and immunogenicity of three formulations of infliximab (SB2, EU-Remicade, US-Remicade), in healthy male subjects. The primary endpoints (PK) were AUC_{inf}, AUC_{last}, and C_{max}, through which pharmacokinetic similarity was conclude between SB2 and Remicade if the 90% CI of the ratios of the geometric means were entirely contained within the equivalence margin of 80-125%. Additional safety, PK, and immunogenicity outcomes were also assessed.

Characteristics		Details for SB2-G11-NHV
Study Design	**Objective**	Pivotal pharmacokinetic, safety, and immunogenicity study
	Blinding	Single-blind (subject)
	Study period	2013-07 to 2013-10
	Study centers	1
	Design	Equivalence (pharmacokinetic)
Study Population	**Randomized (N)**	159
	Inclusion criteria	• Healthy female subjects of non-childbearing potential and healthy male subjects • 18–55 years • Have a bodyweight between 60.0 and 94.9 kg and body mass index (BMI) was between 20.0 and 29.9 kg/m^2 • In good health without any infectious disease including active or latent tuberculosis
	Exclusion criteria	• Had a history and/or current presence of clinically significant atopic allergy (e.g., asthma, urticaria, angio-oedema, eczematous dermatitis), hypersensitivity or allergic reactions (either spontaneous or following drug administration), also including known or suspected clinically relevant drug hypersensitivity to any components of the test and reference IP formulation or similar drugs. • Had either active or latent tuberculosis (TB; as indicated by a positive test result for Mycobacterium tuberculosis) or who had a history of TB. • Had a history of invasive systemic fungal infections (e.g., histoplasmosis) or other opportunistic infections judged relevant by the Investigator, including local fungal infections or a history of herpes zoster. • Had any systemic or local infection, a known risk for developing sepsis and/or known active inflammatory process within 6 months prior to the administration of IP. Subjects with C-reactive protein > 1.5 times the upper limit of normal (ULN) at Screening or Baseline were not enrolled in order to exclude those subjects with chronic inflammatory processes. • Had a serious infection (associated with hospitalisation and/or which required intravenous antibiotics) within 6 months prior to the administration of IP. • Had previously been treated with infliximab or received infliximab for investigational purpose. • Had a history of and/or current cardiac disease • Had a history of and/or current gastrointestinal, renal, hepatic, cardiovascular, haematological (including pancytopenia, aplastic anaemia or blood dycrasia), metabolic (including known diabetes mellitus) or pulmonary disease classed as significant by the Investigator. • Had a history of cancer including lymphoma, leukaemia and skin cancer. • Had a history of immunodeficiency including those subjects with a positive test for human immunodeficiency virus. • Received live vaccine(s) within 30 days prior to Screening or who were to require live vaccine(s) between Screening and the final study visit. • Took medication with a half-life of > 24 hours within 1 month or 10 half-lives of the medication prior to the administration of IP. • Pregnant or nursing (lactating) women.

Characteristics		Details for SB2-G11-NHV
Drugs	**Intervention**	SB2 (infliximab biosimilar), 5 mg/kg, administered by IV infusion for 120 min
	Comparator(s)	• EU-sourced Remicade, 5 mg/kg, administered by IV infusion for 120 min • US-sourced Remicade, 5 mg/kg, administered by IV infusion for 120 min
Duration	**Run-in**	Not applicable
	Treatment	Treatment was given on first day of study and then were followed for 10 weeks
	Follow-up	Not applicable
Outcomes	**Primary End Point(s)**	• AUC from time zero to infinity (AUC_{inf}) • AUC from time zero to the last quantifiable concentration (AUC_{last}) • Maximum concentration (C_{max})
	Other End Points	• Time to C_{max} (T_{max}) • Terminal rate constant (k_{el}) • Volume of distribution during the terminal phase (V_z) • Terminal half-life ($t_{½}$) • Total body clearance (CL) • AUC extrapolated from last time having a measurable concentration to infinity as a percentage of total AUC ($\%AUC_{extrap}$) • Safety • Immunogenicity
Notes	**Publications**	• Shin D, Kim Y, Kim YS, Kornicke T, Fuhr R. A Randomized, Phase I Pharmacokinetic Study Comparing SB2 and Infliximab Reference Product (Remicade) in Healthy Subjects. BioDrugs. 2015;29(6):381-8 (42) • SB2, An Infliximab Biosimilar, And Infliximab Reference Product (Remicade) in Healthy Subjects. Ann Rheum Dis. 2015;74(Suppl 2):703. (43) • Shin D, Kang JW, Park S, Lee Y, Lee S. Evaluation of Pharmacokinetic Profiles of SB2 as a Biosimilar of Reference Infliximab. Gastroenterology. 2017;152(5):S589. (44) • Shin D, Kang JW, Park S, Lee Y, Lee S. P393 Evaluation of pharmacokinetic profiles of SB2 as a biosimilar of reference infliximab. J Crohns Colitis. 2017;11(suppl_1):S277-S8. (45) NCT01922336 EudraCT 2012-005306-22

Intervention and Comparators

Interventions Employed (e.g., dose, route and frequency of administration, duration, etc.)

- Single dose SB2, 5 mg/kg, infused intravenously over 120 min
- Single dose EU-Remicade, 5 mg/kg, infused intravenously over 120 min
- Single dose US-Remicade, 5 mg/kg, infused intravenously over 120 min

After drug administration on the first day of study and then were followed for 10 weeks during which the PK, safety and immunogenicity measurements were made.

Reference Products Used

- All batches of the reference product, Remicade, used in the trial, were sourced from the EU and the US.

Placebos and Controls (if applicable)

- Active comparators were used in this trial; therefore no placebo was used.

Concomitant Medications

- Subjects were permitted to take paracetamol (acetaminophen) at single doses up to 1 g and at maximum daily doses of up to 4 g. Except in emergency situations, approval had

to be obtained from the Investigator and/or Sponsor prior to the subject taking any other concomitant medication.

Outcomes (Key Efficacy and Safety)

Efficacy: This study was conducted in healthy volunteers and therefore no efficacy outcomes were evaluated. Please refer to section *4.3 Pharmacokinetics* of this report for PK (primary) outcomes.

Safety: AEs recorded during the course of the study were categorized by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Safety was assessed by vital signs, clinical laboratory tests, 12-lead ECG, and physical examinations.

Immunogenicity: Blood samples for immunogenicity were collected to detect ADAs and neutralizing antibodies (NAbs) to infliximab at pre-dose, 29 and 71 days after dosing (Weeks 4 and 10).

Statistical Analyses

Statistics Protocol for PK Equivalence

Please note that while the term bioequivalence is used below, in this context it is used to refer to specific procedure (e.g. bioequivalence testing).

The analysis of the PK data was based on the PK population. The primary endpoints (AUC_{inf}, AUC_{last}, C_{max}) were analyzed by an ANOVA using the log_e-transformed values of each PK parameters as dependent variables. The difference in least-squares means (LS Means) between treatments (SB2 and EU-Remicade, SB2 and US-Remicade, and EU-Remicade and US-Remicade) and the associated 90% CIs were estimated. Back transformation provided the ratio of geometric LS Means and the related 90% CIs for the original parameters. Equivalence of the primary endpoint was determined if 90% CI for the ratio of geometric LS Mean of the test to the reference products was within the acceptance interval of 0.8 to 1.25.

Rationale for the PK Equivalence Margins Used

The rationale for the bioequivalence testing procedures and equivalence margins used for the primary (i.e., AUC_{inf}, AUC_{last}, and C_{max}) followed the usual standards (Guideline on the Investigation of Bioequivalence, CHMP/EWP/QWP 1401/98 Rev. 1/Corr **; Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, EMA/CHMP/BMWP/403543/2010) (15, 46) as well as per FDA recommendation (PIND 113461).

Analysis Sets (e.g., intention to treat or per-protocol)

Safety Set (SAF) - The SAF consisted of all subjects who received at least 1 dose of IP. Analyses of safety, demographics and other baseline characteristics were performed on the SAF.

Pharmacokinetic population (PK population) - The PK population included all subjects who were randomised and had received 1 IP, with evaluable primary PK parameters and without any major protocol deviation judged to interfere with the absorption, distribution, metabolism and excretion of the compounds to be measured. All PK analysis was performed with the PK population.

Reference Locations (e.g., sections of the Common Technical Document and/or Clinical Study Report)

- For the description of the statistics protocol for pharmacokinetic equivalence testing, please refer to CTD Module 2.7.2, section 2.7.2.2.1.2 and CSR SB2-G11-HHV, section 9.7.1.8.3.
- For the description of the rationale for the pharmacokinetic equivalence margins used, please refer to CTD Module 2.7.2, section 2.7.2.2.1.2.
- For description of the analysis set, please refer to CSR SB2-G11-NHV, section 9.7.1.1.

Results

Baseline Characteristics

Table 23: Major Demographic and Baseline Characteristics for Study SB2-G11-NHV

Characteristics Mean (SD), unless specified	SB2 (N=53)	EU-Remicade (N=53)	US-Remicade (N=53)
Age, years	40.7 (9.7)	40.3 (9.7)	39.4 (9.9)
Gender, male (%)	49 (92.5)	51 (96.2)	50 (94.3)
Race, n (%)			
White	51 (96.2)	52 (98.1)	52 (98.1)
Asian	1 (1.9)	0 (0.0)	1 (1.9)
Black or Africa American	1 (1.9)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (1.9)	0 (0.0)
Ethnicity, no (%)			
Not Hispanic or Latino	53 (100.0)	52 (98.1)	53 (100.0)
Hispanic or Latino	0 (0.0)	1 (1.9)	0 (0.0)
Height, cm	178.5 (7.7)	178.1 (6.0)	178.6 (7.2)
Body Weight, kg	78.4 (8.7)	80.5 (7.5)	79.1 (8.3)
BMI, kg/m^2	24.6 (2.1)	25.4 (2.1)	24.8 (2.1)

BMI: Body Mass Index

Source: CSR SB2-G11-NHV, Table 11-2

Similarity/Differences

The average age, height, weight and BMI were generally similar between the sequences. Majority of subjects were males and white.

Concomitant Conditions/Medications

All volunteers in this study were healthy individuals. As such, only a minor number of subjects had concomitant conditions (CSR SB2-G11-NHV, Table 16.2.4.3). A similar proportion of subjects received concomitant medications (SB2: 8 [15.1%]; EU-Remicade: 6 [11.3%]; US-Remicade: 6 [11.3%]) with the most common being anlilides (SB2: 4 [7.5%]; EU-Remicade: 2 [3.8%]; US-Remicade: 4 [7.5%]) (CSR SB2-G11-NHV, Table 14.3.6.3.1).

Patient Disposition

A total of 319 subjects were screened, of which 159 subjects were randomized. No subjects discontinued from the study. Two subjects in the SB2 treatment group had major protocol deviations reported (i.e., they received PK influencing concomitant medication for treatment of AEs) and were therefore not included in the PK population.

Table 24: Summary of Patient Disposition for Study SB2-G11-NHV

Disposition	SB2-G11-NHV		
	SB2	EU-Remicade	US-Remicade
Screened, N	319		
Randomized, N	53	53	53
Discontinued, N (%)	0 (0%)	0 (0%)	0 (0%)
***WDAEs,* N (%)**	0 (0%)	0 (0%)	0 (0%)
***Withdrawal due to SAEs,* N (%)**	0 (0%)	0 (0%)	0 (0%)
***Lost to follow-up,* N (%)**	0 (0%)	0 (0%)	0 (0%)
Pharmacokinetic Set, N	51[a]	53	53
Safety, N	53	53	53

SAE = serious adverse event; WDAE = withdrawal due to adverse event

[a] 2 subjects had major protocol deviations and were therefore not included in the PK population

Source: CSR SB2-G11-NHV, Tables 10-1, 11-1

Efficacy Results

This bioequivalence study was conducted in healthy volunteers (see Acceptability of Healthy Volunteers as a Sensitive PK Population, under section 4.2.1 Introduction)

Safety Results

Adverse Events

A total of 124 TEAEs was reported in 71 (44.7%) subjects (SB2: 50 events in 27 [50.9%] subjects; EU-Remicade: 36 events in 21 [39.6%] subjects; US-Remicade: 38 events in 23 [43.4%] of subjects) (Table 25). The TEAEs most frequently reported for volunteers across the three groups were nasopharyngitis and headache (Table 50, Appendix 1).

The proportions of subjects who experienced TEAEs considered related to the IPs were 47.2% (SB2), 26.4% (EU-Remicade), and 26.4% (US-Remicade) (Table 26) The most frequently reported TEAEs suspected to be related to the study drugs were nasopharyngitis (11.3%, 7.5% and 5.7% of subjects) and headache (9.4%, 11.3% and 13.2% of subjects) in the SB2, EU-Remicade and US-Remicade treatment groups, respectively.

The observed difference in the proportion of subjects with treatment-related TEAEs appears to be a chance finding considering the limited sample size and the characteristics of a single-dose PK study in healthy volunteer. This notion was further supported by the results from the clinical Phase III pivotal Study SB2-G31-RA demonstrating the similar safety profiles between SB2 and Remicade in a larger patient population (Table 27).

The majority of reported TEAEs were mild (103 events) with few moderate (21 events) (Table 26) Three SAEs were reported by two subjects receiving SB2: *Borrelia* infection [related to SB2] in one subject and concussion as well as ruptured renal cyst due to car accident [unrelated to SB2] in another subject. No malignancies or TB infections were reported. There were no discontinuations due to AEs or deaths in this study. No subjects reported infusion related reactions.

Table 25: Summary of TEAEs in Study SB2-G11-NHV (SAF)

	SB2 N=53	EU-Remicade N=53	US-Remicade N=53
Total number of TEAEs	50	36	38
Unrelated	*13*	*19*	*18*
Related	*37*	*17*	*20*
Number (%) of patients with at least 1 TEAE	27 (50.9)	21 (39.6)	23 (43.4)
Unrelated	*9 (17.0)*	*14 (26.4)*	*13 (24.5)*
Related	*25 (47.2)*	*14 (26.4)*	*14 (26.4)*
Total number of SAEs	3	0	0
Related	*1*	*0*	*0*
Unrelated	*2*	*0*	*0*
Number (%) of patients with at least 1 SAE	2 (3.8)	0 (0)	0 (0)
Related	*1 (1.9)*	*0 (0)*	*0 (0)*
Unrelated	*1 (1.9)*	*0 (0)*	*0 (0)*
Total number of TEAEs leading to permanent study discontinuation	0	0	0
Number (%) of patients with at least 1 AE leading to permanent study discontinuation	0 (0)	0 (0)	0 (0)
Deaths	0	0	0

Source: CTD 2.7.4, Table 2.7.4.2-1, section 2.7.4.2.1.3.1

Table 26: Summary of TEAEs by severity in study SB2-G11-NHV (SAF)

	SB2 (N=53)			EU-2urcd Remicade (N=53)			US-Remicade (N=53)		
	n	(%)	E	n	(%)	E	n	(%)	E
Any TEAE	27	(50.9)	50	21	(39.6)	36	23	(43.3)	38
Mild	*26*	*(49.1)*	*41*	*19*	*(38.5)*	*29*	*18*	*(34.0)*	*33*
Moderate	*7*	*(13.2)*	*9*	*5*	*(9.4)*	*7*	*5*	*(9.4)*	*5*

Source: CTD 2.7.4, Table 2.7.4.2-1

Infusion-Related Reactions (IRRs)

No subjects experienced IRRs in this study.

Safety of Special Interest – Serious Infections or Tuberculosis

No subjects experienced serious infections or TB in this study.

Malignancies

No subjects developed malignancies in this study.

Laboratory Parameters

Across the three treatments, the mean and median values of hematology, blood chemistry, and urinalysis parameters did not show any changes over time. Minor alterations were similar to those usually seen in a healthy population. There were no clinically meaningful post-dose changes in any parameters from baseline after SB2, EU-Remicade or US-Remicade administrations.

The majority of the subjects showed single minor changes in any of the parameters. For none of the parameters, any of the subjects showed changes over time. There were no out-of-range values identified by the Investigator as being clinically significant.

Vitals, Physicals, and ECGs

Mean and median values of all parameter of vital signs did not show any changes over time. A few subjects showed minor changes over time, but none of them reached clinical relevance and none constituted an AE. There were no significant changes from baseline in the vital sign parameters in each treatment group. The results of the vital signs measurements were similar between treatment groups.

Mean and median values of all parameters of ECG did not show any relevant changes over time. Minor alterations are those usually observed in healthy subjects. There was 1 subject (Subject 1235) with a QTcF (QT Interval Corrected According to Fridericia's Formula) interval > 450 msec (but ≤ 480 msec) on Day 8 (EU-Remicade treatment group). At the follow-up visit on Day 71, the QTcF interval for this subject was ≤ 450 msec. A change of QTcF > 30 msec was observed in 5 subjects at 6 hours post-dose on Day 1, in 1 subject on Day 4, in 5 subjects on Day 8, and in 2 subjects on Day 71. These subjects were generally distributed across the treatment groups. Interpretation of ECG recordings showed some abnormalities, but none of them were considered to be clinically relevant by the Investigator. There was no difference across the 3 treatment groups with regard to the ECG findings and evaluation.

There were no abnormal physical examination results considered to be clinically relevant by the Investigator (see CTD 2.7.4, section 2.7.4.4.1 for details).

In sum, safety data in a sensitive population supported the conclusion that SB2 is therapeutically similar to Remicade.

Summary of Safety

SB2 has been developed by Samsung Bioepis as a similar biological medicinal product to Remicade. Remicade was first approved by the US FDA in 1998. Remicade, infliximab, has been widely used in clinical practice for almost 20 years with a well-established and characterized pharmacological, efficacy, and safety profile (Remicade SmPC and Remicade Product Monograph).

The clinical safety of SB2 has been assessed in two clinical studies, a clinical Phase I PK study in healthy subjects and a clinical Phase III safety and efficacy study in subjects with RA. Safety of the studies was assessed by monitoring AEs and SAEs as well as vital signs, laboratory panels and immunogenicity which are important safety aspect of protein products.

Safety Evaluation Plan

The Phase I study SB2-G11-NHV evaluated healthy subjects after a single dose of 5 mg/kg SB2, EU-Remicade or US-Remicade and followed for 10 weeks. Post randomization, a total of 159 subjects (53 subjects per arm) received a single administration of IP and were included in the safety set.

The *randomized, double-blind* period (Weeks 0 – 54) of the Phase III study SB2-G31-RA included 584 randomized RA subjects. Of these, 583 were included in the SAF. One subject (in the SB2 group) was excluded from the randomized set because that subject was

withdrawn prior to administration of the first dose due to not meeting inclusion/exclusion criteria.

The safety results for the above two populations were included in the CTD 2.7.4.

The *transition-extension* period of study SB2-G31-RA ran from Week 54 to 78. Of the 227 (SB2) and 225 (Remicade) subjects that completed the *randomized, double-blind* period, 201 (SB2) and 195 (Remicade) subjects consented and entered into *transition-extension* period. The 195 subjects from the Remicade group were re-randomized and 94 subjects received SB2 and 101 subjects received Remicade. All 396 subjects were included in the Ex-SAF.

For the **Overview of Safety** section below, summary safety data from the *overall study* period (Week 0 to 78) are presented. Specifically, the SB2 treatment group and Remicade (including subjects treated with SB2 in the *transition-extension* period) treatment group from Week 0 to Week 78 were compared. In the *overall study* period, 290 SB2 and 293 Remicade subjects were assessed. Because the *overall study* period analysis included the Remicade/SB2 subjects (Weeks 54 to 78) as the Remicade (Weeks 0-78) group, the results shown below was only used to identify long-term patterns and should be interpreted with caution.

Safety Populations Evaluated

Summarize the largest controlled safety population that is addressed in the Summary of Clinical Safety module of the Common Technical Document. Please keep this description to a maximum of a half page.

Overview of Safety

In the *overall study* period analysis, the same proportion of SB2 and Remicade subjects experienced TEAE between SB2 and Remicade (Table 27).

Commonly occurring TEAEs included nasopharyngitis (26 [9.0%] and 25 [8.5%] subjects in the SB2 and Remicade treatment groups, respectively), latent TB (24 [8.3%] and 27 [9.2%] subjects, respectively), and ALT increased (27 [9.3%] and 14 [4.8%] subjects, respectively) (78-week CSR SB2-G31-RA, Table 12-9).

The numbers of TEAEs were similar between groups and most were mild and moderate in nature. Majority of the TEAEs were unrelated to study treatment. The relatedness and severity of SAEs were also similar between the 2 groups. The incidence of TEAEs of special interests and TEAEs leading to IP discontinuation were similar between groups (Table 27).

Table 27: Summary of TEAEs in the *Overall Study* Period (Weeks 0 to 78) in Study SB2-G31-RA (SAF)

Treatment	SB2			EU-Remicade			Total		
	N=290			N=293			N=583		
Number of subject experiencing	**n**	**(%)**	**E**	**n**	**(%)**	**E**	**n**	**(%)**	**E**
TEAEs	201	(69.3)	710	203	(69.3)	754	404	(69.3)	1464
TEAE severity									
Mild	84	(29.0)	469	90	(30.7)	472	174	(29.8)	941
Moderate	89	(30.7)	202	87	(29.7)	244	176	(30.2)	446

Treatment	SB2			EU-Remicade			Total		
	N=290			N=293			N=583		
Number of subject experiencing	**n**	**(%)**	**E**	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Severe	28	(9.7)	39	26	(8.9)	38	54	(9.3)	77
TEAE causality									
Related	88	(30.3)	158	85	(29.0)	176	173	(29.7)	334
Not related	113	(39.0)	550	118	(40.3)	578	231	(39.6)	1128
Unknown	0	(0.0)	2	0	(0.0)	0	0	(0.0)	2
TEAEs of special interest (AESIs)	10	(3.4)	10	10	(3.4)	10	20	(3.4)	20
TEAEs leading to IP discontinuation	33	(11.4)	40	30	(10.2)	33	63	(10.8)	73
Serious TEAEs	36	(12.4)	41	38	(13.0)	45	74	(12.7)	86
Severity									
Mild	2	(0.7)	4	5	(1.7)	6	7	(1.2)	10
Moderate	18	(6.2)	21	19	(6.5)	23	37	(6.3)	44
Severe	16	(5.5)	16	14	(4.8)	16	30	(5.1)	32
Causality									
Related	12	(4.1)	12	13	(4.4)	15	25	(4.3)	27
Not related	24	(8.3)	29	25	(8.5)	30	49	(8.4)	59

AESI: adverse event of special interest; E: frequency of treatment-emergent adverse events; IP: investigational product; TEAE: treatment-emergent adverse event

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

a All TEAEs associated with infusion-related reaction presented in this table were causally related.

If a subject had multiple events of the same severity or causality, then the subject was counted only once in that severity or causality. If a subject had multiple events with different severity or causality, then the subject was counted only once for more severe adverse event or related adverse event.

Remicade group includes subjects who were treated with SB2 in the transition-extension period.

Source**:** 78-week CSR SB2-G31-RA, Table 12-6

Subgroup Analysis

The proportion of subjects who experienced TEAEs associated with an IRR for the overall study period up to 78 weeks with an overall post-dose positive ADA result up to Week 78 was 21 (11.1%) subjects in the SB2 treatment group and 16 (8.8%) subjects in the Remicade treatment group, and with an overall post-dose negative ADA result up to Week 78 was 2 (2.1%) subjects in the SB2 treatment group and 4 (3.6%) subjects in the Remicade treatment group. The incidence of IRRs was higher in ADA-positive subjects than in ADA-negative subjects, however the incidence was similar between the 2 treatment groups within each ADA subgroup, up to Week 78 (78-week CSR SB2-G31-RA, section 12.2.5.1).

In terms of age, the proportion of subjects who experienced any TEAEs was generally similar between the SB2 and Remicade treatment groups in subjects < 65 years (69.7% and 71.4%, respectively) and in subjects ≥ 65 years (66.7% and 57.8%, respectively).

In terms of gender, the proportion of subjects who experienced any TEAEs was similar between the SB2 and Remicade treatment groups in male subjects (69.5% and 70.2%, respectively) and in female subjects (69.3% and 69.1% of subjects, respectively).

Overall, the incidences of TEAEs and SAEs were similar between the SB2 and Remicade treatment groups in the *randomized, double-blind* period, the *overall study* period, and

between the Remicade/SB2 and Remicade/Remicade treatment groups as well as the SB2/SB2 treatment group in the *transition-extension* period. The incidence of TEAEs leading to IP discontinuation was similar between these treatment groups in each of these 3 periods.

Pharmacokinetics

PK similarity between SB2 and Remicade was evaluated in both healthy volunteers (SB2-G11-NHV) and RA patients (SB2-G31-RA). The primary objective of study SB2-G11-NHV was to demonstrate PK similarity between SB2 and EU-Remicade, between SB2 and US-Remicade, and between EU- and US-Remicade. **For the primary PK endpoints of AUC_{inf}, AUC_{last}, and C_{max}, the 90% CI of the ratios of the geometric means all lie within the acceptance equivalence range of 80-125%** for the comparisons between SB2 and EU- or US-Remicade (Table 28; see Table 51 in Appendix 1 for EU- vs. US-Remicade results). Other PK variables (T_{max}, $T_{1/2}$) were also similar between SB2 and EU- and US-Remicade (Table 28, Table 52 [Appendix 1]). The comparative serum concentration-time profiles are located in Appendix 1 (Figure 3, Figure 4, Figure 5). No differences in these parameters were also seen by ADA status (Table 29).

Table 28: Serum PK Parameters and ANOVA Results for Study SB2-G11-NHV (PK Population)

	n	SB2 5 mg/kg (N=51)	n	Remicade 5 mg/kg (N=53)[a]	Ratios of Geometric Means; 90% CI
AUC_{inf} (µg·h/mL), Mean ± SD	51[b]	38,703 ± 11,114	53[c]	39,360 ± 12,332	0.986 (0.897–1.083)
			53[d]	39,270 ± 10,064	0.979 (0.894–1.072)
AUC_{last} (µg·h/mL), Mean ± SD	51[b]	36,862 ± 9133	53[c]	37,022 ± 9398	0.994 (0.915–1.079)
			53[d]	37,368 ± 8332	0.981 (0.904–1.064)
C_{max} (µg/mL), Mean ± SD	51[b]	127.0 ± 16.9	53[c]	126.2 ± 17.9	1.007 (0.964–1.052)
			53[d]	129.2 ± 18.8	0.985 (0.942–1.030)
T_{max} (h), Median (range)	51[b]	3.0 (2.0 – 6.0)	53[c]	2.1 (2.0–6.1)	Not applicable
			53[d]	3.0 (2.0–6.1)	
$T_{1/2}$ (h), Mean ± SD	51[b]	324.1 ± 148.7	53[c]	339.5 ± 155.4	
			53[d]	339.7 ± 135.6	

AUC_{inf}: area under the curve to infinity; CI: confidence interval; C_{max}: maximum concentration; SD: standard deviation

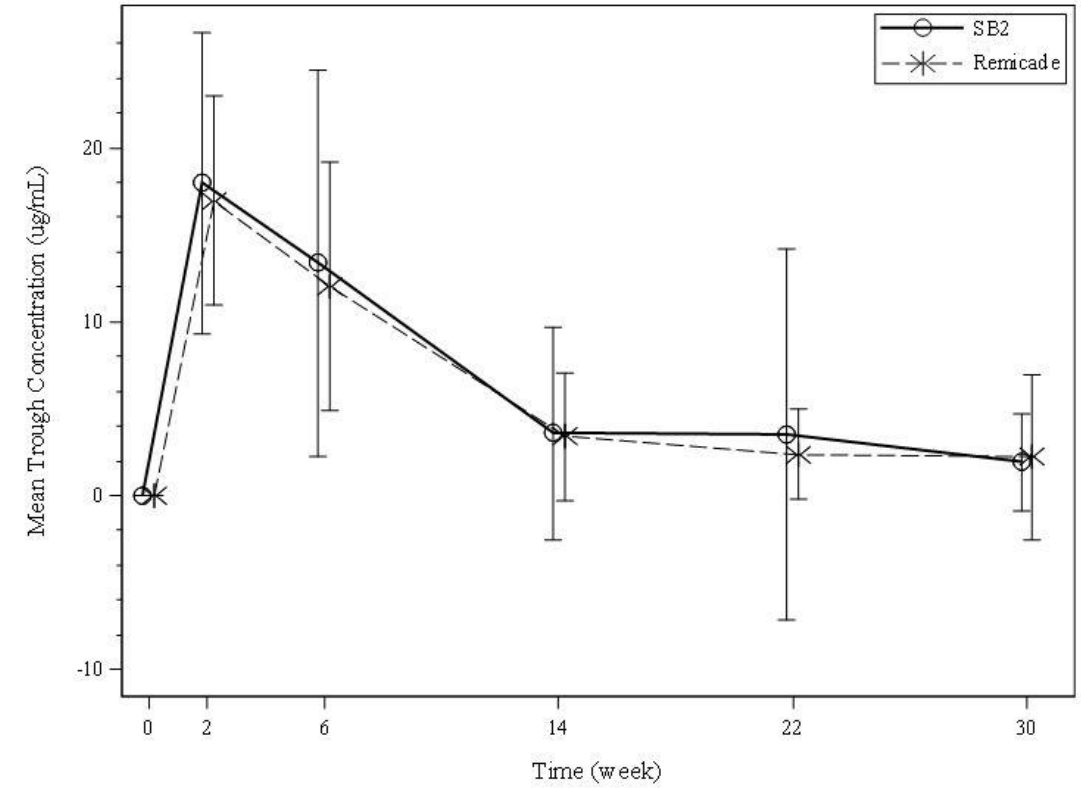
[a] For each of the EU- and US-Remicade group; [b] Two subjects were excluded due to protocol deviation; [c] EU-Remicade; [d] US-Remicade. Source: CTD 2.7.2, Tables 2.7.2.2-3, 2.7.2.2-4, 2.7.2.2-5; CSR SB2-G11-NHV, Table 11-3

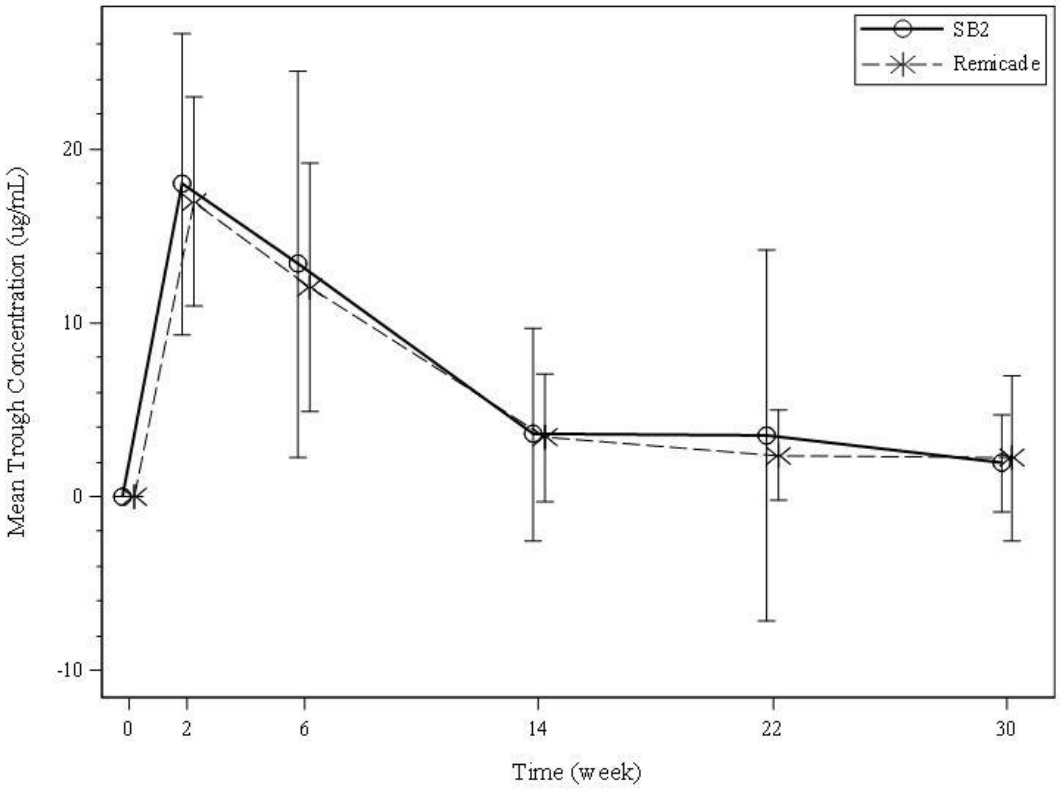
Table 29: ANOVA Results for PK Parameters by ADA Status for Study SB2-G11-NHV (PK Population)

ADA Status	Parameter	vs. Remicade	n/N	LS Mean Ratio	90% CI of Ratio
ADA-negative	AUC_{inf} (µg·h/mL)	EU	33/53	1.013	0.911 - 1.127
		US	33/53	1.019	0.927 - 1.120
	AUC_{last} (µg·h/mL)	EU	33/53	1.022	0.936 - 1.117
		US	33/53	1.016	0.936 - 1.103
	C_{max} (µg/mL)	EU	33/53	1.019	0.957 - 1.086
		US	33/53	1.000	0.938 - 1.066
ADA-positive	AUC_{inf} (µg·h/mL)	EU	20/53	1.009	0.902 - 1.128
		US	20/53	0.980	0.867 - 1.107
	AUC_{last} (µg·h/mL)	EU	20/53	1.006	0.902 - 1.122
		US	20/53	0.982	0.873 - 1.104
	C_{max} (µg/mL)	EU	20/53	0.994	0.938 - 1.054
		US	20/53	0.969	0.910 - 1.032

N: number of subjects in the PK population; n: number of subjects with ADA results at Day 71 included in the analysis. n/N for SB2 in ADA negative = 28/51 and ADA positive = 23/51. Source: CTD 2.7.2, Table 2.7.2.4-3

In study SB2-G31-RA, mean trough serum concentration (Ctrough) prior to each dosing up to Week 30 were measured in 325 subjects (the first 50% of the enrolled subject) to provide supportive evidence of PK equivalence of SB2 and EU Remicade. The trough levels were similar at each time point between treatments (Table 53, Appendix 1). Overall steady state concentrations for SB2 and Remicade appeared to be achieved by approximately 14 to 22 weeks (Appendix 1). **Overall, all PK endpoints in both healthy volunteers and RA patients demonstrated that SB2 is similar to Remicade.**


SB2
Remicade
Mean Trough Concentration (ug/mL)
20
10
0
-10
0
2
6
14
22
30
Time (week)


SB2
Remicade
Mean Trough Concentration (ug/mL)
20
10
0
-10
0
2
6
14
22
30
Time (week)

Immunogenicity

Overall immunogenicity results are presented for baseline, Weeks 30 and 54 overall of the *randomized, double-blind* period of study SB2-G31-RA (Table 30). Results for other time points are in Appendix 1 (Table 54). Numerically more subjects in the SB2 group developed ADAs compared to EU-Remicade at the Weak 54 overall period. **However, there was no statistical difference and no meaningful effect on any efficacy or safety parameters analysed, even after stratification by ADA status between groups.**

Table 30: Incidence of ADAs and NAbs to in Infliximab in RA Patients in the *Randomized, Double-blind* Study SB2-G31-RA (SAF)

Timepoint	Parameter	SB2 (N=290)			EU-Remicade (N=293)			Total (N=583)		
		n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 0	ADA	290	5	(1.7)	293	7	(2.4)	583	12	(2.1)
	NAb	5	0	(0.0)	7	0	(0.0)	12	0	(0.0)
Week 30 overall	ADA	287	158	(55.1)	292	145	(49.7)	579	303	(52.3)
	NAb	158	146	(92.4)	145	130	(89.7)	303	276	(91.1)
Week 54 overall	ADA	287	179	(62.4)	292	168	(57.5)	579	347	(59.9)
	NAb	179	166	(92.7)	168	147	(87.5)	347	313	(90.2)

ADA: anti-drug antibody; Nab: neutralizing antibody; n': number of subjects with available ADA/NAb results against SB2 at each timepoint. ADA was determined as positive if at least 1 ADA positive result was obtained up to the timepoint regardless of the ADA result at Week 0. Percentages were based on n'. Source: CTD 2.7.2, Table 2.7.2.4-4

The incidence of ADA and NAb in the Ex-SAF is presented in Table 31 (full results in Table 55 in Appendix 1). For overall ADA that developed from Week 0 up to 78, there was no statistically significant difference between treatment groups in the proportion of subjects with ADA positive results against SB2. Similar proportion of subjects across the 3 groups developed NAbs from Week 0 to Week 78. Additional details are provided in the 78-week CSR SB2-G31-RA, section 12.6.2.

Table 31: Incidence of ADAs and NAbs to in Infliximab in RA Patients in the *Transition-Extension* Period in Study SB2-G31-RA (Ex-SAF)

Timepoint	Parameter	SB2			Remicade									Total		
					Overall			SB2			Remicade					
		N=201			N=195			N=94			N=101			N=396		
		n'	n	(%)	n'	n	(%)	n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 0 (St-BL)	ADA	201	4	(2.0)	195	3	(1.5)	94	3	(3.2)	101	0	(0.0)	396	7	(1.8)
	NAb	4	0	(0.0)	3	0	(0.0)	3	0	(0.0)	0	0	(0.0)	7	0	(0.0)
Week 54 (Ex-BL)	ADA	198	101	(51.0)	193	75	(38.9)	92	31	(33.7)	101	44	(43.6)	391	176	(45.0)
	NAb	101	82	(81.2)	75	66	(88.0)	31	28	(90.3)	44	38	(86.4)	176	148	(84.1)
Week 78 overall*	ADA	201	133	(66.2)	195	120	(61.5)	94	59	(62.8)	101	61	(60.4)	396	253	(63.9)
	NAb	133	126	(94.7)	120	104	(86.7)	59	49	(83.1)	61	55	(90.2)	253	230	(90.9)
Week 78 overall**	ADA	194	104	(53.6)	195	94	(48.2)	94	43	(45.7)	101	51	(50.5)	389	198	(50.9)
	NAb	104	95	(91.3)	94	83	(88.3)	43	38	(88.4)	51	45	(88.2)	198	178	(89.9)

ADA: anti-drug antibody; Ex-BL: Extended Baseline; Nab: neutralizing antibody; n': number of subjects with available ADA/NAb results against SB2 at each timepoint; St-BL: Study Baseline. Percentages were based on n'. *Overall ADA (or NAb) results were defined as "Positive" for subjects with ≥1 ADA (or NAb) positive up to Week 78 after Week 0, otherwise results were determined as "Negative". **Overall ADA (or NAb) results were defined as "Positive" for subjects with ≥1 ADA (or NAb) positive up to Week 78 after Week 54, otherwise results were determined as "Negative". **Source:** 78-week CSR SB2-G31-RA, Table 12-21

Similar to RA patients, SB2 is equally well-tolerated in healthy volunteers in study SB2-G11-NHV (See Table 56 in Appendix 1). No statistically significant difference was observed in post-dose (Day 71) ADA or Nab incidence between groups. More ADA positive patients treated with EU-Remicade developed NAbs compared to SB2, but the absolute difference was small and these differences did not have a marked impact on the PK similarity between treatment groups (see Table 29 above).

From these findings, it is concluded that immunogenicity profiles of SB2 and Remicade were similar. Furthermore, following the long-term treatment of either SB2 or Remicade, the impact of immunogenicity on clinical outcomes were similar among the SB2/SB2, Remicade/Remicade and Remicade/SB2 treatment groups, which adds to the totality of the evidence to support a demonstration of no clinically meaningful differences between SB2 and Remicade.

Critical Appraisal of Clinical Studies

Internal Validity

The manufacturer submitted two studies to support the use of infliximab biosimilar SB2 for RA, AS, CD (adult and pediatric), fistulizing CD, UC (adult and pediatric), PsA, and PsO: (1) Study SB2-G11-NHV was conducted in healthy adult volunteers; and (2) Study SB2-G31-RA was conducted in adult patients with moderate to severe RA.

Study SB2-G11-NHV

In this phase I, randomized, three-arm, single-blind study, SB2 was compared with EU-Remicade and US-Remicade reference products for PK, safety, and immunogenicity outcomes among 159 healthy patients from a single centre in Germany. A single dose of 5 mg/kg SB2 (N = 53), EU-Remicade (N = 53), or US-Remicade (N = 53) was infused intravenously over 120 minutes and patients were followed for 10 weeks. The primary outcomes were AUC_{inf}, AUC_{last}, and C_{max}; if the 90% CI of the GM was within the equivalence margin of 80% to 125%, then SB2 was deemed pharmacokinetically equivalent to the reference products. Secondary outcomes were other PK parameters (e.g., T_{max}, terminal rate constant [k_{el}] V_z), safety (i.e., AEs, vital signs, lab tests, ECG, and physical examination], and immunogenicity (i.e., ADA and NAb). Subjects were assessed post-dose on days 6, 8, 15, 22, 29, 43, 57, and 71. Blood samples for testing ADA and NAbs were collected before infusion on day 29 and day 71. Prior to infusion, all patients received IV hydrocortisone (100 mg), oral acetaminophen (1,000 mg), and oral loratadine (10 mg). Concomitant use of acetaminophen (maximum 4,000 mg/d) was also permitted.

The groups were well balanced with respect to age, gender (majority males), race (majority white), height, weight, and BMI. Two patients from the SB2 group were eliminated from PK analyses because they received concomitant medications that affected PK parameters; these two patients were included in the safety and immunogenicity analyses. There were no other withdrawals, losses to follow-up, or deaths during the 10-week period. A sample size of 50 was needed in each group to achieve 90% power to reject the null hypothesis that the ratio of PK GM was less than 0.80 or greater than 1.25. Therefore, the study was adequately powered to test for PK equivalence even with the omission of the two patients from the SB2 group. The procedures to randomize and blind patients have not been provided; therefore, they cannot be evaluated. Given the IV route of treatment, single dose of administration, and objective assessment of PK and immunogenicity outcomes, compromises in blinding are of less concern.

The PKs of SB2 were equivalent to EU-Remicade and US-Remicade, as all parameters were within the pre-specified equivalence margin of 80% to 125%. When the PK analyses were stratified based on ADA-positive and -negative status, the results remained within the equivalence margin. No IRRs, serious infections, TB, or malignancies were observed in any group. There were some differences between groups in the occurrence of TEAEs. Among the SB2 group, the percentage of patients experiencing at least one TEAE was 50.9% (mostly mild) in SB2, compared with 39.6% in EU-Remicade and 43.4% in US-Remicade (Table 25). Similarly, TEAEs related to treatment were experienced by 47.2% in SB2, compared with 26.4% in EU-Remicade and 26.4% in US-Remicade (Table 25). There was one SAE (Borrelia infection) related to SB2; there were no SAEs with the reference products (Table 25). The incidence of ADA formation was also higher in the SB2 group: 3.8% versus 0% and 1.9% in EU-Remicade and US-Remicade respectively on day 29, and 47.2% in SB2 versus 37.7% in EU- and US-Remicade on day 71 (Table 56). The P values were 0.432 for both SB2 versus EU-Remicade and SB2 versus US-Remicade (Clinical Study Report SB2-G11-NHV, p. 84). The incidence of NAb was 56% in SB2 group compared with 70% in EU-Remicade and 35% in US-Remicade on day 71 (Table 53). The manufacturer states that, "**There was no statistical difference between any pair of treatment groups for ADA incidence and NAb incidence. Therefore, SB2 was similar to Remicade with respect to incidence of ADAs and/or Nabs**" (CTD Section 2.5, p.30). However, it should be noted that the study was not designed to demonstrate equivalence in immunogenicity.

Study SB2-G31-RA

A phase III randomized, double-blind, multinational (11 countries in Europe and Asia) trial was conducted to evaluate the efficacy, safety, immunogenicity, and PKs of SB2 compared with EU-Remicade in patients with moderate to severe RA despite MTX therapy. Patients were administered SB2 or EU-Remicade at doses of 3 mg/kg IV at weeks 0, 2, and 6, then every eight weeks thereafter, and received MTX (10 mg/week to 25 mg/week) and folic acid (5 mg/week to 10 mg/week). Patients may also have received pre-medications to prevent IRRs, and were permitted to take NSAIDs (nonsteroidal anti-inflammatory drugs) and corticosteroids if a stable dose was maintained for four weeks prior to randomization. Dose increases of SB2 or Remicade were permitted by 1.5 mg/kg up to a maximum of 7.5 mg/kg from week 30 onwards. The initial study lasted for 54 weeks, and was followed by a 24-week double-blind transition study in which patients from the EU-Remicade group were again randomized to either switch to SB2 or remain on Remicade (patients receiving SB2 during the 54-week study continued SB2 during the transition phase).[3] A separate bridging study demonstrated comparability between EU-Remicade and US-Remicade to justify the use of EU-Remicade as the comparator. The primary end point was the ACR 20 at week 30; equivalence was based on the 95% CI of the treatment difference lying within a margin of ± 15%. Secondary outcomes included ACR 50, ACR 70, DAS28, the EULAR response, incidence of AEs and SAEs, clinical lab tests, vital signs, immunogenicity, and PKs.

A total of 584 patients were randomized in the initial study, 291 to SB2 and 293 to EU-Remicade. The primary analysis set for efficacy consisted of the PP set, which included patients who completed week 30, adhered to infliximab and MTX therapy, and did not have major protocol deviations (N = 231 SB2, 79%; and N = 247 EU-Remicade, 84%). The FAS was based on intention-to-treat analysis and included all randomized patients who received at least one dose of treatment (N = 290 SB2, 99.7%; and N = 293 EU-Remicade, 100%). Withdrawal due to AEs was higher in the SB2 group compared with EU-Remicade (7.2% versus 3.4% before week 30 and 9.3% versus 7.2% before week 54). Given the large number of withdrawals in the PP analysis, greater weight was placed on the efficacy results of the FAS. Missing was not at random because more patients from the SB2 group withdrew before week 30 due to AEs. Missing data points for patients who discontinued before week 30 were imputed as nonresponders for the FAS, which provided conservative estimates. The SAF included all patients who received at least one dose of treatment and were analyzed according to the treatment received. The PK results were based on the first 50% enrolled and included the mean C_{trough} prior to each dose up to week 30.

Randomization and treatment allocation were carried out with an interactive Web response system. The groups were balanced in age, gender, race, disease duration and severity, baseline dose of MTX, CRP, ESR, and rheumatoid factor. Cumulative doses of MTX were similar for SB2 and EU-Remicade at week 30 (mean: 422.9 mg and 428.6 mg respectively) and at week 54 (mean: 704.1 mg and 716.6 mg respectively) (54-week Clinical Study Report SB2-G31-RA, Table 14.3-1.2). Blinding of patients and investigators was maintained through identical appearance, packaging, and labelling of drug vials. A comprehensive set of efficacy outcomes (all appropriate for RA) and safety end points were considered.[4] The equivalence margin of ± 15% on the ACR 20 was based on previous studies of infliximab (Table 3) and FDA/EMA regulatory guidelines.[5,6] The study required 292 patients in each group to evaluate equivalence with appropriate power. The transition study was added to the protocol after the initiation of the study and included 396 (67.8%) patients: 201 from the SB2 group (SB2/SB2) and 195 from the EU-Remicade group, 94 of whom were randomized to switch to SB2 (Remicade/SB2) and 101 to remain on Remicade (Remicade/Remicade). During the transition study, cumulative MTX doses were also similar (mean: 328.3 mg SB2/SB2; 322.0 mg Remicade/SB2; and 350.9 mg Remicade/Remicade) (78-week CSR SB2-G31-RA, Table 14.3-1.2) There was no washout period before patients were switched from Remicade to SB2.

SB2 was equivalent to EU-Remicade with respect to ACR 20 at week 30. The treatments were also similar on secondary efficacy outcomes, such as ACR 20 at week 54, ACR 50 at weeks 30 and 54, and ACR 70 at weeks 30 and 54. Although primary and secondary outcomes were similar after the transition phase (*P* values not provided), in a post hoc analysis that examined ACR 20 over the entire 78-week period, response patterns showed greater fluctuation for Remicade/SB2 and Remicade/Remicade than for SB2/SB2 (Figure 2), which the manufacturer attributed to smaller sample sizes of the former two groups.

At the end of 54-week treatment, no statistically significant difference was observed in immunogenicity between SB2 and Remicade. The proportion of overall ADA-positive patients up to week 54 was 62.4% for SB2 and 57.5% for Remicade (*P* = 0.270) (Table 54 and manufacturer feedback).7 Among those with positive ADA, the percentage with NAb was higher in the SB2 group at earlier time points (e.g., at week 2, 40% versus 28.6%; and at week 6, 52.4% versus 43.8%) (Table 54). [redacted]. Anti-ds DNA antibodies are associated with increased risk of drug-induced lupus; [redacted]. Other differences include: a higher percentage of patients receiving SB2 with an increase of ALT (7.9% SB2 versus 3.1% EU-Remicade) and in the extended transition phase (2.5% SB2/SB2, 4.3% Remicade/SB2, 1.0% Remicade/Remicade); a higher percentage with latent TB in the switch group (5.5% SB2/SB2, 7.4% Remicade/SB2, and 4.0% Remicade/Remicade); and a higher percentage with abnormal neutrophils in the SB2 group (2.8% SB2 versus 1.4% EU-Remicade). Mean C_{trough} levels were similar between SB2 and EU-Remicade; however, the variability (i.e., the SD) of concentrations was much greater among the SB2 group.

External Validity

Study SB2-G11-NHV

This study was conducted in healthy adults, which is a homogenous population for evaluating PKs and recommended by Health Canada for biosimilar biologic drugs.[8] Among the 159 healthy patients in the study, the majority were male (only nine of the 159 patients were female) and white (96.2% in SB2 and 98.1% in reference products); the average age was 39.4 to 40.7 years. The follow-up time of 10 weeks was adequate for assessing PK parameters. As this was a phase I PK study, the results are not generalizable to patients with RA, AS, CD, UC, PsA, or PsO who will present with additional complexities, including comorbidities and the use of medications — such as MTX or other immunosuppressives — that may alter the PKs and immunogenicity of infliximab.[9,10]

Study SB2-G31-RA

The study population consisted of patients experiencing moderate to severe RA (average disease duration: 6.4 years) despite taking MTX for at least six months, and was applicable to patients with RA. Many patients had other medical conditions, such as vascular disorders and musculoskeletal and connective tissue disorders. Most patients were also taking other medications, such as glucocorticoids, which would be commonly encountered in practice. The interventions were administered at clinically appropriate doses and intervals, and outcomes were clinically relevant. The follow-up of 54 weeks provided evidence of long-term equivalence in the efficacy of SB2 versus EU-Remicade; the extended transition phase provided some data on switching from Remicade to SB2. The average age of patients was 52 years. The majority were female (80.1% in the main study and 79.3% in the extended transition phase) and white (86.6% and 90.4%, respectively). No North American sites were included in the study. The applicability of the results to males, children, and patients of other ethnicities is unclear.

Extrapolation of Indications

Manufacturer's Rationale for Extrapolation

During the clinical development of SB2, similarity with respect to efficacy of SB2 and Remicade was evaluated in RA patients (SB2-G31-RA), whereas similarity for PK, safety and immunogenicity was evaluated in healthy subjects and RA patients (SB2-G11-NHV and SB2-G31-RA, respectively).

Since similarity was demonstrated from the extensive quality, non-clinical and clinical similarity exercises between SB2 and Remicade, extrapolation of indications is claimed to all other indications such as AS, PsA, plaque psoriasis in adults, CD in adults, pediatric CD, fistulising CD in adults, UC in adults and pediatric UC in accordance with the Health Canada guidance "Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics" and EMA guidelines (EMA/CHMP/BMWP/403543/2010) (15).

The possibility to extrapolate indications has also been endorsed by the EMA during SA (EMA/CHMP/SAWP/70331/2012), by the FDA during a pre-IND meeting on Feb 14, 2012 (PIND 113461) and by the Health Canada during the pre-NDS meeting on Jul 07, 2015 (CTD 2.5, p. 16). Detailed discussion of the extrapolation of indication is presented below.

In accordance with the EMA guideline (EMA/CHMP/BMWP/403543/2010) (15) and Health Canada guidance "Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics" (16, 17), the 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.

As a proposed biosimilar to Remicade, SB2 should demonstrate biosimilarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability (similarity) exercise as stated in the guidelines "Guideline on similar biological medicinal products" (CHMP/437/04 Rev 1) (47) and "EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications" (EMA/940451/2011) (48).

During the development of SB2, a comprehensive similarity exercise of SB2 has been conducted. The exercise aimed at demonstrating the similarity between SB2 and the reference product (EU-Remicade; linkage of EU-Remicade to Canadian Remicade is considered established, see section 1.2 above) was carried out in a step-wise approach using the SB2 DS or SB2 DP batches from different development stages in order to ensure biosimilarity throughout the development.

Extensive characterization studies were conducted between SB2 and the reference product in terms of structural characteristics (primary, high order and carbohydrate), physiochemical properties, and Fab- and Fc-related biological activities associated with infliximab mechanism of action (MoA). Summary of results from selected characterization studies are provided in this submission; detail results are presented in CTD 3.2.R, section 3.2.R.5 Biosimilarity (available at request). Overall, characterization study results showed that SB2 is considered to be similar to the reference product in terms of structural, physicochemical and biological attributes.

Based on the demonstration of similarity in terms of quality, the non-clinical programme for SB2 was conducted according to the “Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues” (EMA/CHMP/BMWP/403543/2010) (15). The programme comprised a series of in vitro studies including TNF-α binding, Fc receptor binding and cell-based assays in order to demonstrate similarity between SB2 and the reference product. In addition, an in vivo efficacy study in the Tg197 transgenic mouse model of arthritis, in vivo PK studies in both Sprague Dawley rats and Tg197 mice, and an immunogenicity assessment in vivo as part of the repeated dose PK study in Tg197 mice were conducted to support the similarity of SB2 with the reference product (refer to 2.4 Non-clinical Overview). As agreed with the EMA, no toxicity study was conducted since there is no relevant model for toxicity assessment available. Also in accordance with the current EMA guideline (EMA/CHMP/BMWP/403543/2010) (15), further studies regarding safety pharmacology, genotoxicity, reproduction toxicology and carcinogenicity have not been performed. Overall, the non-clinical study results showed that SB2 is considered to be similar to the reference product in terms of in vitro characteristics, animal pharmacokinetic characteristics and animal pharmacodynamic characteristics, thus these findings supported continued clinical development of the product.

Based on the supportive quality similarity results and the in vitro and in vivo non-clinical study results, two pivotal clinical studies – a Phase I and a Phase III study – were conducted. From the results, the PK bioequivalence (see Justification of Extrapolation – Pharmacokinetic below) for and the clinical equivalence with respect to efficacy were demonstrated in the Phase I study and the Phase III study, respectively (for the CSRs, refer to Sections 5.3.3.1 and Section 5.3.5.1, respectively). Since the Phase III study has demonstrated clinical similarity with Remicade in RA patients, SB2 is expected to act in a same manner with the reference product Remicade in RA patients.

For the other indications, extrapolation of efficacy and safety data to other indications of the reference mAb should be based on overall evidence of similarity provided from the similarity exercise and with adequate justification (EMA/CHMP/BMWP/403543/2010 (15), FDA Center for Drug Evaluation and Research (CDER)).

The mechanism of action of infliximab involves binding with high affinity to both soluble and transmembrane TNF-α (sTNF-α and tmTNF-α, respectively) (49). The elevated concentrations of TNF-α have been found in affected tissues and fluids of patients with rheumatoid arthritis (RA), Crohn’s disease (CD), ankylosing spondylitis (AS), psoriatic arthritis (PsA), ulcerative colitis (UC) and psoriasis (50).

Furthermore, from the Scientific Advice (EMA/CHMP/SAWP/70331/2012), it was noted that the extrapolation to indications where pathogenesis appears to be dominated by soluble TNF- α (i.e. ankylosing spondylitis, psoriatic arthritis and plaque psoriasis) is considered acceptable. For the indications where membrane bound TNF-α may play an important role (i.e. paediatric and adult Crohn’s disease and ulcerative colitis), the CHMP stated that the extrapolation is acceptable, depending on the strength of the totality of evidence, especially for binding and effector functions in the setting of membrane bound TNF-α. This suggestion was also shared by a group of regulators from the EMA (51), who also indicated that the main mode of action in all therapeutic indications was binding to soluble and/or membrane bound TNF-α. With respect to soluble TNF-α, SB2 showed similar activities to the reference product Remicade in binding assays and a cell-based assay (neutralization assay) (Table 32). Thus, the extrapolation to the indications where pathogenesis appears to be dominated

by soluble TNF-α is considered acceptable: ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.

With respect to the membrane bound TNF-α, it was reported that at least four distinct mechanisms were involved in the inhibition of TNF-α-bearing cells by anti-TNF agents: (i) inhibition of tmTNF-α-mediated effector functions, (ii) destruction of TNF-α-bearing cells by CDC, (iii) destruction of TNF-α-bearing cells by ADCC and (iv) destruction of TNF-α-bearing cells by outside-to-inside signal (reverse signalling) (52). Therefore, not only tmTNF-α binding assays, but also Fc receptor binding assays, CDC assays (in several conditions), ADCC assays (in several conditions) and apoptosis assays (in several conditions including IBD models) were performed to show the similarity between SB2 and the reference product Remicade with respect to tmTNF-α related activities (Table 32). Overall, the results showed that SB2 is considered to be similar to the reference product in terms of tmTNF-α related activities (for details, refer to CTD 3.2.R, section 3.2.R.5; available at request).

In addition, the induction of regulatory macrophage function and the inhibition of cytokine release were evaluated between SB2 and Remicade since these were also known to be associated with IBD indications (51). The results showed that SB2 is considered to be similar to the reference product in terms of the regulatory macrophage function and the cytokine release inhibition (Table 32).

Table 32: Biological Assays Related with the Mechanism of Action of Infliximab

Category of MOA	Biological Assay Test
Acting on Soluble TNF-α	TNF-α binding assay
	TNF-α neutralization assay by NF-κB reporter gene
Acting via Transmembrane TNF-α	Transmembrane TNF-α binding assay
	Apoptosis assay
	Inhibitory activity of apoptosis in an *in vitro* IBD model
	FcγRIa binding assay
	FcγRIIa binding assay
	FcγRIIIa binding assay (V/V type)
	FcγRIIIa binding assay (F/F type)
	FcγRIIIa binding assay using NK cell from PBMCs
	FcγRIIb binding assay
	FcγRIIIb binding assay
	FcγRIIIb binding assay using neutrophils
	ADCC assay using NK92-CD16 cells
	ADCC assay using healthy donor PBMC
	C1q binding assay
	CDC assay
	FcRn binding assay
Others	Evaluation of regulatory macrophage function
	Cytokine release activity in an *in vitro* IBD model

NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells

Although the extrapolation of efficacy is generally granted based on the data focusing on the MoA, the basis to extrapolate immunogenicity to other indications could be of question. According to studies with Remicade, the incidence of immunogenicity has been reported to be variable across the disease, and immunomodulating drugs have been suggested as one of the major factors for lowering the incidence of immunogenicity (53). However, recent

infliximab biosimilar studies have shown a different pattern of immunogenicity. Higher ADA incidence was observed in RA patients (with the concomitant use of MTX) than in AS patients (without the concomitant use of immunomodulators), in both infliximab biosimilar and Remicade (54, 55). In addition, poor correlation between ADA incidence and immunomodulating drug use such as MTX or corticosteroid use was observed in the infliximab biosimilar study (56). In such findings, the prediction of ADA incidence across the diseases might not be predictable (57). Overall, there is no scientific evidence that suggests that immunogenicity data cannot be extrapolated across indications. Based on reported incidences for the reference product and other biosimilars, the RA-population is a sufficiently sensitive model to establish similarity in terms of immunogenicity between SB2 and Remicade. Most importantly; extensive physicochemical characterization demonstrated a high degree of similarity between SB2 and Remicade and no new epitopes were identified in SB2 using a sensitive antibody-array (see Table of Clarifax). Therefore, the similar immunogenicity in RA between SB2 and Remicade could be applicable to other approved indications.

In summary, the development programme of SB2 including extensive characterisation, *in vitro* and *in vivo* non-clinical studies and clinical studies demonstrated that there are no significant differences that would suggest that SB2 would behave differently or has a different potency that might affect efficacy or safety in human subjects compared with the reference product, across all indications. Therefore, with the totality of evidence, it is considered justifiable to extrapolate the equivalent clinical efficacy and the similar safety profile from the SB2 study in RA patients to all of the indications where Remicade has been approved. Therefore, all approved indications for Remicade are claimed for SB2 in this application. Full details can be found at in CTD 2.5, sections 2.5.1.2 & 2.5.4.3).

Justification of Extrapolation – Pharmacokinetic (see CTD 2.5, section 2.5.3.1.3)

In accordance with EMA guideline (EMEA/CHMP/BMWP/42832/2005 Rev. 1) (14) and the given Scientific Advice (EMA/CHMP/SAWP/70331/2012), a single PK study in healthy subjects and the supportive PK assessments in RA patients are considered sufficient for the similarity exercise of a biosimilar. However, the relevance of the PK results observed from the non-clinical (not discussed here) and clinical studies to all approved indications is briefly elaborated below.

In the clinical Phase I study in healthy subjects, PK equivalence with respect to C_{max}, AUC_{inf} and AUC_{last} was demonstrated between SB2, EU-Remicade and US-Remicade. Also, time-concentration profiles were similar between products. Similarly, in the clinical Phase III study in RA patients, C_{trough} was similar up to Week 30 between SB2 and EU Remicade.

Healthy subjects represent a sensitive model for PK analysis as they do not require concomitant medication or have underlying disease that can increase target-mediated clearance. RA patients also reflect the extensively studied patient pool for PK. The comparison of PK profiles demonstrated there were no significant differences between SB2 and the reference product (see [CTD 2.5] section 2.5.3.1 Pharmacokinetics). Therefore, the PK profile of SB2 and the reference product was similar. In addition, the relevance of these PK results to all approved indications of Remicade is considered appropriate with the following perspectives:

- Infliximab gives a dose-dependent linear increase in C_{max} and AUC after a single *i.v.* infusion of 1, 3, 5, 10 and 20 mg/kg and does not accumulate after multiple administrations given according to the frequency indicated in the SmPC (58-60) (EMA/CHMP/SAWP/70331/2012).

- Different doses are required for different indications, but the frequency of administrations is the same. Furthermore, the overall range of therapeutic doses between indications is the same if dose increases are allowed for non-responders (53, 61).
- During the clinical development, two dose levels were used, 3 mg/kg and 5 mg/kg, which represent the most common therapeutic doses (it should be noted that from Week 30, dose level could be increased step-wise by 1.5 mg/kg to a maximum of 7.5 mg/kg i.v. every 8 weeks if the subject's RA symptoms were not controlled by the existing dose).
- Following single and multiple administration of infliximab, no relevant differences in median concentration-time profiles have been observed between patients with CD, RA or with psoriasis (58, 59, 61). This opinion that there is no difference in PK between indications was supported in Scientific Advice procedures (EMA/CHMP/SAWP/70331/2012).
- In terms of paediatric indications for CD and UC, no significant differences between the PK profiles have been reported in patients with RA, AS, psoriasis and adult and paediatric CD (58, 59, 61). Studies suggest that infliximab serum levels in paediatric CD and UC patients were similar to those in adult patients (62, 63) (additional details below).

Justification of Extrapolation – Pediatric Crohn's Diseaese and Pediatric Ulcerative Colitis

A summary of detailed rationale that scientifically justifies for the claim on the IBD (pediatric CD and pediatric UC) indication is provided below (details can be found in Response to Clarifax)

1. **MoA of Infliximab in IBD:** The similarity assessment of SB2 and Remicade was demonstrated in terms of biological properties associated with the MoA of infliximab via various cell-based assays and binding assays. Overall, the MoA of infliximab in pediatric IBD is considered similar to adult counterpart, although the pathophysiology of pediatric IBD might be different from that of adult IBD (64). Based on the expected similar mechanisms of infliximab in pediatric IBD and observed similarity between SB2 and Remicade in biological functions relevant to both pediatric and adult IBD, the extrapolation of pediatric IBD is warranted.
2. **Immunogenicity:** Literatures references suggest that, in general, ADA incidences in pediatric indications were similar to those of adult indications (1, 65, 66). This would indicate that there are no differential factors for the immunogenicity of infliximab in the pediatric population than adult population.
3. **PK of Infliximab for Pediatric UC and CD:** Recent study suggested similarity of PK characteristics of infliximab among pediatric UC, adult UC and pediatric CD patients (66, 67). Based on PK linearity of infliximab and similar PK characteristics between SB2 and Remicade in adult population (as well as in the sensitive population of healthy volunteers in Study SB2-G11-NHV), similar PK profile of SB2 is expected in pediatric patients of UC and CD compared to Remicade; therefore, can be applied to other indications.
4. **Dosing and duration treatment:** Remicade has been approved for pediatric CD and UC as same body weight based dosing as adult counterparts in Canada. Since PK of infliximab in pediatric IBD patient is similar as that in adults IBD patients as mentioned above, it is believed that SB2 can be administered to pediatric CD and pediatric UC as the approved posology of Remicade when PK bioequivalence between SB2 and Remicade is demonstrated.

Although the pathophysiology of pediatric IBD might be somewhat different from that of adult IBD, the Applicant did not find any scientific knowledges indicating that MOA of infliximab

acts differently on pediatric IBD. Various biological assays performed showed similarity between SB2 and Remicade in biological functions which was considered to be pertinent to MOA of infliximab in both pediatric and adult IBD. Furthermore, ADA incidences in patients with pediatric CD and UC were similar to those of adult indications and PK profiles were similar across the indication including pediatric IBD. Therefore, based on the HC guidance "*Information and Submission Requirements for Biosimilar Drugs*" and the provided scientific rationales, the Applicant believes that the benefit/risk profile observed in RA patients can be extrapolated to all authorized indications of infliximab including pediatric IBD.

Finally, there is also some evidence to suggest that another infliximab biosimilar, CT-P13, may have similar clinical profile as with Remicade in pediatric IBD patients (68-70). Therefore, considering SB2 is also a proposed infliximab biosimilar, the data supports the extrapolation of indication of SB2 infliximab to the pediatric IBD indications.

Therefore, considering all of the information, PK results from the clinical Phase I and Phase III studies can be considered relevant to all the approved indications.

Health Canada's Conclusion on Extrapolation

As this is a pre-NOC submission, SB2 is currently under regulatory review by Health Canada. It is expected that the NOC for all requested indications will be granted.

International Regulatory Conclusions on Extrapolation

SB2 (under the tradename of Flixabi™ in Europe), has received a positive opinion from the EMA's Committee for Medicinal Products for Human Use on April 1, 2016 (71). Subsequently, the European Commission granted marketing authorization of Flixabi in EU on May 30, 2016. As per CHMP's Flixabi Assessment Report (p.81-82) (3):

> "*For indications for which pathogenesis appears to be dominated by soluble TNF-α (ankylosing spondylitis, psoriatic arthritis and plaque psoriasis) extrapolation is supported by the TNF-α binding assay and the cell-based assay (TNF-α neutralisation assay by NF-κB reporter gene).*
>
> *With respect to the membrane bound TNF-α, it has been reported that at least four distinct mechanisms are involved in the inhibition of TNF-α-bearing cells by anti-TNF agents: (i) inhibition of tmTNF-α-mediated effector functions, (ii) destruction of TNF-α-bearing cells by CDC, (iii) destruction of TNF-α-bearing cells by ADCC and (iv) destruction of TNF-α-bearing cells by outside-to-inside signal (reverse signalling). Transmembrane-TNF-α binding assays, but also Fc receptor binding assays, CDC, ADCC and apoptosis assays were performed. Overall, these results showed that Flixabi is similar to the reference product in terms of tmTNF-α related activities.*
>
> *It has been described that the rate of ADA positivity is amongst other factors dependent on the population, dose, dose interruptions and co-medication. However, there is no reason to believe that the ADA formation would be affected differentially by these factors for molecules that are considered highly similar such as Flixabi and Remicade. Although, it may be argued that methotrexate used in the clinical trial may have reduced the immune response, it should be noted that anti-drug antibody development is nevertheless reportedly highest in patients with rheumatoid arthritis compared to other licensed indications of Remicade.*

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

SB2 (under the tradename of Renflexis™ in the US) has also received licensing approval by the FDA in 2017 (4, 72):

> *"Therefore, SB2 meets both parts of the statutory definition to demonstrate biosimilarity to the reference product in that SB2 is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between SB2 and the US-licensed Remicade in terms of safety, purity and potency. The applicant has also provided adequate scientific justification to allow for extrapolation of data to support biosimilarity in all indications that US-licensed Remicade is licensed for, and Samsung is seeking licensure of SB2, namely, Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Psoriasis (PsO), adult and pediatric Crohn's Disease (CD), and adult and pediatric Ulcerative Colitis (UC)[1].*
>
> [1] We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018."

In Australia, the Australian Therapeutic Goods Administration has also approved Renflexis for all of Remicade's approved indications (5). The Australian Public Assessment Report (AusPAR) is currently not available to detail the conclusions of extrapolation of indications.

In summary, following the demonstration of overall biosimilarity between SB2 and Remicade in the form of physicochemical and functional characterizations as well as PK, safety, efficacy, and immunogenic evaluation in the clinical development program, this submission provided sufficient evidence to support the recommendation of SB2 for all the requested indications, under the same labeling as Remicade.

CDR Comments on Extrapolation

Health Canada considers several factors when deciding on the appropriateness of extrapolating from one indication to another. These factors include:[11]

- Similarity between products (minor, seemingly unimportant differences may have clinical impact)
- Similar MoA for each condition
- Mechanisms of the diseases to be treated
- Similarities in clinical experience
- Type and design of the clinical trials, populations, and end points measured
- Route of administration, dosage, and regimen

Health Canada reviews quality information about the biosimilar compared with the reference product, assesses whether the most sensitive populations and best end points were included in clinical trials, and evaluates whether the biosimilar and reference product have similar safety and immunogenicity (> 100 patients and sufficiently long duration).[11] Specific factors that are considered in the evaluation of similarity are physiochemical properties, biological activity, immunochemical properties, presence of impurities, specifications, stability, and manufacturing processes.8 The weight of the evidence is provided by structural and functional studies, which determine the scope and breadth of non-clinical (in vivo) and clinical data.8 On December 1, 2017 Health Canada approved Renflexis for RA, AS, CD (adult and pediatric patients > 9 years of age), fistulizing CD, UC (adult and pediatric patients > 6 years of age), PsA, and PsO.[12]

The manufacturer has justified extrapolation to the indications of AS, CD (adult and pediatric), fistulizing CD, UC (adult and pediatric), PsA, and PsO based on similarities in structural characteristics, physiochemical properties, Fab- and Fc- biological properties, non-clinical evidence in animal models, and clinical evidence of similar efficacy in patients with RA (Study SB2-G31-RA) and similar PKs, safety, and immunogenicity in healthy patients (Study SB2-G11-NHV) and in patients with RA (Study SB2-G31-RA). Although minor differences were observed in glycosylation patterns, these differences did not affect biological activities. In AS, PsA, and PsO, the MoA is dominated by soluble TNF alpha, whereas in CD and UC, tmTNF alpha plays a greater role. Similarities in both soluble and tm TNF alpha biological test assays were demonstrated. The manufacturer has justified extrapolation to pediatric CD and UC based on similarities among the pediatric and adult populations in the MoA of infliximab, immunogenicity, PKs, and body weight dosing.

The FDA approved SB2 for AS, PsA, PsO, adult and pediatric CD, and adult UC (pediatric UC is protected by orphan drug exclusivity that expires September 23, 2018). The weight of evidence is placed on analytical data that demonstrate similarities in structural and functional properties; data from clinical studies provide additional supporting evidence.[13] The FDA evaluation of SB2 indicated that, although small numerical differences were observed in ADA formation between SB2, EU-Remicade, and US-Remicade, the observed differences were not clinically meaningful based on the totality of the evidence on immunogenicity.[13]

The EMA also approved SB2 for AS, PsA, PsO, adult and pediatric CD, and adult and pediatric UC (under trade name Flixabi). The higher incidence of ADA among the SB2 group was deemed clinically non-relevant, which was supported by the observation that a similar percentage of patients in both groups required dose increases irrespective of ADA status. In addition, adverse reactions associated with ADA (i.e., hypersensitivity and IRRs) were not higher with SB2 compared with Remicade.[14] The risk management plan for SB2 included ongoing monitoring of immunogenicity with a prospective two-year observational study in patients with AS and CD.[14]

Given the role of TNF alpha across all proposed indications and evidence of similar infliximab PKs in patients with CD, RA, and psoriasis,[10] as well as in pediatric and adult patients with CD,[10] extrapolation from RA to the other requested indications may be reasonable. One difference among the indications is in the use of concomitant immunosuppressant therapy, which may affect the development of ADA and interact with infliximab. Methotrexate, for example, is used more commonly in RA than in AS, and has been shown to interact with infliximab by slowing the decline in median serum concentration, possibly by inhibiting ADA formation.[10] The clinical implications of such interactions with SB2 are currently unclear, although there is no evidence to suggest that concomitant immunosuppressant therapy would affect SB2 and Remicade differently. Another difference among the indications is infliximab dose, with higher doses up to 10 mg/kg used for the indications of CD and UC. The two clinical studies examined doses of 5 mg/kg in healthy patients and 3 mg/kg in patients with RA, with increases up to 7.5 mg/kg permitted in the latter. In other clinical trials of patients with CD, infliximab PKs were shown to be linear (i.e., serum concentrations and AUC increased in proportion to dose, and clearance was independent of dose), without any accumulation, at maintenance doses of 5 mg/kg or 10 mg/kg every eight weeks.[10]

Cost Comparison

The SB2 100 mg /vial drug product will carry a ~47% lower price ($525.0000) relative to the publicly available Ontario Formulary price of Remicade 100 mg /vial, which is at $987.5600. Consequently, the ~47% cost differential equates to $462.5600 savings per 100 mg vial. SB2 has the same price as Inflectra, the first infliximab biosimilar approved by Health Canada ($525.0000 per 100 mg vial)

Even if dose escalation is possible with infliximab, it would affect SB2, Remicade and Inflectra equally and it would not impact their relative cost difference. Similarly, should patients discontinue infliximab therapy in any of the subsequent years beyond the first year, the relative cost difference between the infliximab products would not be different. Therefore, the cost comparison analysis for the 1st year of treatment is considered to be sufficient (i.e., assuming treatment is effective and no discontinuation). The presentation of the treatment costs for the 1st year across the indications is consistent with those provided by the reviewers in the CDR SUBSEQUENT ENTRY BIOLOGIC REVIEW REPORT FOR INFLECTRA for the indications of RA, AS, PsO, and PsA (Appendix 4 for the Report).

For the pediatric Crohn Disease and Ulcerative Colitis indications, the only comparator is Remicade, since Inflectra is not approved for these indications.

Table 33: Cost Comparison of SB2, Remicade, and Inflectra for Rheumatoid Arthritis (Adult)

Drug/ Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost/Yr[c] ($)[d]
SB2	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	3 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$12,600
Remicade	100 mg/vial	Lyophilized powder for reconstitution	$987.5600	3 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$23,701
Inflectra	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	3 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$12,600

[a] Quintiles IMS Delta PA, Ontario Formulary price (August 2017) or price submitted by manufacturer (SB2 only).

[b] SB2, Remicade, and Inflectra product monographs.

[c] For year 1. Based on 8 doses in the first year.

[d] For a patient weight of 70 kg. Includes wastage of unused product.

Table 34: Cost Comparison of SB2, Remicade, and Inflectra for Ankylosing Spondylitis

Drug/ Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost/Yr[c] ($)[d]
SB2	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$16,800
Remicade	100 mg/vial	Lyophilized powder for reconstitution	$987.5600	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$31,602
Inflectra	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$16,800

[a] Quintiles IMS Delta PA, Ontario Formulary price (August 2017) or price submitted by manufacturer (SB2 only).

[b] SB2, Remicade, and Inflectra product monographs.

[c] For year 1. Based on 8 doses in the first year.

[d] For a patient weight of 70 kg. Includes wastage of unused product.

Table 35: Cost Comparison of SB2, Remicade, and Inflectra for Psoriatic Arthritis

Drug/ Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost/Yr[c] ($)[d]
SB2	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$16,800
Remicade	100 mg/vial	Lyophilized powder for reconstitution	$987.5600	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$31,602
Inflectra	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$16,800

[a] Quintiles IMS Delta PA, Ontario Formulary price (August 2017) or price submitted by manufacturer (SB2 only).

[b] SB2, Remicade, and Inflectra product monographs.

[c] For year 1. Based on 8 doses in the first year.

[d] For a patient weight of 70 kg. Includes wastage of unused product.

Table 36: Cost Comparison of SB2, Remicade, and Inflectra for Plaque Psoriasis (Adult)

Drug/ Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost/Yr[c] ($)[d]
SB2	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$16,800
Remicade	100 mg/vial	Lyophilized powder for reconstitution	$987.5600	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$31,602
Inflectra	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$16,800

[a] Quintiles IMS Delta PA, Ontario Formulary price (August 2017) or price submitted by manufacturer (SB2 only).

[b] SB2, Remicade, and Inflectra product monographs.

[c] For year 1. Based on 8 doses in the first year.

[d] For a patient weight of 70 kg. Includes wastage of unused product.

Table 37: Cost Comparison of SB2, Remicade, and Inflectra for Crohn's Disease (Adult and Fistulizing) and Ulcerative Colitis (Adult)

Drug/ Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost/Yr[c] ($)[d]
SB2	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$16,800
Remicade	100 mg/vial	Lyophilized powder for reconstitution	$987.5600	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$31,602
Inflectra	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$16,800

[a] Quintiles IMS Delta PA, Ontario Formulary price (August 2017) or price submitted by manufacturer (SB2 only).

[b] SB2, Remicade, and Inflectra product monographs.

[c] For year 1. Based on 8 doses in the first year.

[d] For a patient weight of 70 kg. Includes wastage of unused product.

Table 38: Cost Comparison of SB2 and Remicade for Pediatric Crohn's Disease and Pediatric Ulcerative Colitis

Drug / Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost/Yr[c] ($)[d]
SB2	100 mg/vial	Lyophilized powder for reconstitution	$525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$8,400
Remicade	100 mg/vial	Lyophilized powder for reconstitution	$987.5600	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	$15,801

[a] Quintiles IMS Delta PA, Ontario Formulary price (August 2017) or price submitted by manufacturer (SB2 only).

[b] SB2, Remicade, and Inflectra product monographs.

[c] For year 1. Based on 8 doses in the first year.

[d] For a patient weight of 40 kg. Includes wastage of unused product.

CDR Reviewers' Comments Regarding Cost Information

Summary of the Manufacturer's Analysis

The infliximab biosimilar, SB2, is available as a 100 mg/vial lyophilized powder at a manufacturer-submitted price of $525.0000 per vial, the same price as Inflectra, the first infliximab biosimilar approved in Canada. The manufacturer submitted cost comparisons for nine indications: (1) RA, (2) AS, (3) adult CD, (4) pediatric CD, (5) fistulizing CD, (6) adult UC, (7) pediatric UC, (8) PsA, and (9) PsO. Most comparisons involved SB2, Inflectra, and reference infliximab (Remicade), except for pediatric UC and pediatric CD indications, where the manufacturer reported that Inflectra was not approved for these two indications and excluded it from the comparison. The manufacturer assumed equivalent weight-based doses (i.e., 3 mg/kg for RA, 5 mg/kg for other indications) based on similar treatment effects and patterns across the three versions of infliximab, and accounted for wastage of partially used vials. The manufacturer deemed the relative cost differences between the interventions to remain the same beyond the first year of treatment and did not report cost comparisons for the subsequent years of treatment. The cost savings of SB2 compared with Remicade were reported to be 47%, which was the same compared with Inflectra.

CADTH Common Drug Review Assessment of the Manufacturer's Cost Comparison

- The comparison of the Ontario Drug Benefit price of Inflectra[15] and Ontario Exceptional Access Program (EAP) price of Remicade[16] confirms that the first-year cost of SB2 is 47% lower than for Remicade and the same as Inflectra for Ontario (refer to Table 39). As Inflectra is also listed for pediatric CD and pediatric UC in at least one CDR-participating drug plan (e.g., BC[17]), CDR also included Inflectra as a comparator for these indications.

Table 39: First-Year Cost Comparison for Pediatric CD and Pediatric UC Including Inflectra

Treatment	Price Per 100 mg Vial($)[a]	Recommended Dose[b]	Number of Treatments Per Year[b]	First Year Cost($)[c]
SB2	525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	8	8,400
Remicade	987.5600	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	8	15,801
Inflectra	525.0000	5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	8	8,400

[a] Manufacturer-submitted price for SB2; Ontario Drug Benefit price for Inflectra15 and Ontario EAP price for Remicade.[16]
[b] Inflectra and Remicade product monographs.[18,19]
[c] Assumes patient weight is 40 kg.

- The dose and dosing schedules vary between indications; however, the same doses and dosing regimens are recommended for SB2, Inflectra, and Remicade.[18-20] The annual acquisition cost differs based on indication, which influences the absolute difference in drug acquisition cost between treatments; however, as the relative differences in annual drug acquisition costs are driven by the proportional differences in list prices, the proportional difference remains the same across the recommended doses (Table 40). Therefore, for Ontario, the annual drug acquisition cost of SB2 remains 47% lower than for Remicade and equals that of Inflectra across indications, recommended dose ranges, and years of treatment. The relative and absolute differences in the annual drug acquisition costs of SB2, Inflectra, and Remicade in other plans may differ and reflect each plan's relative differences between SB2, Inflectra, and Remicade list prices.

Table 40: Upper-Bound and Lower-Bound Cost Comparison for Ankylosing Spondylitis

Treatment	Price Per 100 mg Vial($)[b]	Recommended Dose[a]	Number of Treatments Per Year[a]	First Year Cost($)[c]	Relative Cost Reduction From Equal Remicade Doses (%)
Remicade	987.5600	5 mg/kg week 0, 2, and 6, then every 6 weeks thereafter	10 (upper bound)	39,502	N/A
		5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	8 (lower bound)	31,602	N/A
SB2	525.0000	5 mg/kg week 0, 2, and 6, then every 6 weeks thereafter	10 (upper bound)	21,000	47%
		5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	8 (lower bound)	16,800	47%
Inflectra	525.0000	5 mg/kg week 0, 2, and 6, then every 6 weeks thereafter	10 (upper bound)	21,000	47%
		5 mg/kg week 0, 2, and 6, then every 8 weeks thereafter	8 (lower bound)	16,800	47%

[a] Inflectra and Remicade product monographs.
[b] Manufacturer-submitted price for SB2; Ontario Drug Benefit price for Inflectra15 and Ontario EAP price for Remicade.[16]
[c] Assumes patient weight is 70 kg.

Issues for Consideration

- Inflectra (subsequent entry biosimilar infliximab) was previously reviewed by CDR for the same indications requested by SB2. CDEC recommended that Inflectra be listed in accordance with the Health Canada indication and in a similar manner to Remicade.[21,22]
- The dosage of SB2 is based on patient weight, assumed to be 70 kg for adult indications and 40 kg for pediatric indications. Considering that SB2, Inflectra, and Remicade are expected to require the same dose due to similar PKs, pharmacodynamics, clinical efficacy, and safety profiles, the relative cost differences between the drugs would be consistently maintained across patient characteristics and required administration dose.
- It is known that the manufacturers of Remicade and Inflectra sponsor infusion centres for the administration of Remicade and Inflectra, respectively, and may also cover patient follow-up and monitoring costs. The manufacturer of SB2 claimed that a competitive manufacturer-funded patient support program is planned for the product launch and will be a modification of an existing program for Brenzys, an etanercept biosmilar.[20] This program will include nationwide infusion clinics and associated nursing support, patient reimbursement navigation, and patient financial assistance services.[20]The comparability between these patient support programs and the ease of implementing the full scope of the SB2 patient support program are unknown at this time.
- List prices for Remicade and Inflectra vary across CDR-participating plans (refer to Table 41; e.g., Inflectra's price is 33% lower than Remicade's in Saskatchewan[23,24]). At the submitted price, SB2 might be less costly than Inflectra in some jurisdictions.

Table 41: Remicade and Inflectra Price Variation Across CDR-Participating Drug Plans

Remicade Prices in CDR-Participating Drug Plans ($)						
BC	**AB**	**SK**	**MB**	**ON**	**NB**	**NS**
1,036.9380	962.6800	977.0000	987.5600[a]	987.5600	987.5600	987.5600
PE	**NL**	**YK**	**NT**	**NIHB**	**DND**	**VAC**
987.5600[a]	1,071.5026	987.5600	987.5600[a]	RES	RES	EX
Inflectra Prices in CDR-Participating Drug Plans ($)						
BC	**AB**	**SK**	**MB**	**ON**	**NB**	**NS**
551.2500	525.0000	650.0000	525.0000[a]	525.0000	525.0000	525.0000
PE	**NL**	**YK**	**NT**	**NIHB**	**DND**	**VAC**
525.0000[a]	569.6250	525.0000	525.0000[a]	RES	RES	N/A

AB = Alberta; BC = British Columbia; DND = Department of National Defence; EX = Case-by-case coverage for some indications; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; N/A = Coverage unavailable; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; RES = Restricted use, price unavailable; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.
Note: Prices sourced from formulary plans where possible. [15,17,23,25-34]
[a] Wholesale acquisition price from Quintiles IMS Delta PA.[27] Actual price paid by the plan may vary.

- The listing criteria for Remicade and Inflectra differ across publicly funded drug plans in Canada (Appendix 2). While both medications are available as a restricted benefit, Remicade is unavailable for new patients across most plans. Additionally, a clinical expert noted that physicians and patients may be reluctant to switch from existing infliximab products to SB2 when a patient is already adequately managed. The literature also describes potential discontinuations associated with a "nocebo," or negative placebo,[35] effect for patients who switch to an infliximab biosimilar.[36-38] As a result, SB2 may be more likely to be used in infliximab-naive patients rather than in those switching from Remicade or Inflectra. Remicade was estimated to capture over 96% of the infliximab market during the second quarter of 2017.[39]

Conclusion

At the submitted price, the annual drug acquisition cost of SB2 is 47% less than for Remicade and equivalent to Inflectra across all indications when considering Ontario list prices.

Whether the manufacturer sponsors the cost of administering (and monitoring) SB2, price variation for Inflectra and Remicade across CDR-participating drug plans, demand and feasibility of biosimilar switching, and treatment market share will affect the actual cost or savings to participating drug plans.

Discussion

Patients with inflammatory arthritis, psoriasis, or IBDs may experience many distressing symptoms that significantly impair their daily functioning and reduce their quality of life (Appendix 3). The biologics are an important class of medication for these conditions and offer patients and clinicians additional treatment options, along with other immunosuppressant or disease-modifying antirheumatic drug (DMARD) therapies. Innovator infliximab (Remicade) has been used in clinical practice for several years. CT-P13 was the first biosimilar of infliximab to come to market in Canada; it received a NOC from Health Canada and was reviewed by CDR for the treatment of adult RA, AS, PsA, PsO, CD, fistulizing CD, and UC.[21,22] SB2 is now the second proposed biosimilar to Remicade being reviewed by CDR.

The clinical evidence for SB2 comes from two randomized trials, one in healthy patients and one in patients with moderate to severe RA. The phase I trial in healthy patients demonstrated similar PK profiles between SB2, EU-Remicade, and US-Remicade over 10 weeks based on a single 5 mg/kg dose. Although there are limitations with generalizing the results of this study to the conditions of interest, the homogenous study sample was appropriate for the examination of PK outcomes, as recommended by Health Canada. The phase III trial in patients with RA included the administration of SB2 or EU-Remicade at doses of 3 mg/kg (up to 7.5 mg/kg), along with MTX and folic acid. After the initial 54-week study, a 24-week extended transition period was also incorporated post hoc, during which patients on Remicade were re-randomized to either remain on Remicade or switch to SB2. The trial was well conducted and demonstrated equivalent ACR 20 responses based on a justified equivalence margin of ±15% between SB2 and EU-Remicade at weeks 30 and 54. The study population was relevant to patients with RA, although the majority were Caucasian females and no North American study sites were included.

In both the phase I and phase III trials, numerical differences in some safety end points were observed (i.e., phase I study: higher percentage of TEAEs in the SB2 group; phase III study: higher percentage with ALT increase in the SB2 group and higher percentage with latent TB in the switch group), although the small sample size and/or small number of events render these results inconclusive. There were also some numerical differences in ADA formation in the phase I and III trials. These differences in ADA were recognized by the FDA and EMA; however, both organizations deemed them not clinically relevant based on the totality of evidence.[13,14] Further evaluation of SB2 immunogenicity compared with Remicade will occur in a planned two-year prospective, observational cohort study in patients with AS and CD (part of the Risk Management Plan of the Committee for Medicinal Products for Human Use).[14]

Extrapolation from RA to AS, PsO, PsA, CD, and UC may be reasonable given the role of TNF alpha in all indications and demonstrated similarities between SB2 and Remicade in structural characteristics, physiochemical properties, Fab- and Fc-biological properties, non-clinical evidence in animal models, and clinical evidence in healthy patients and patients with RA. The pattern of use of immunosuppressant therapies and dosing requirements do differ among the indications. The FDA approved SB2 for AS, PsA, PsO, adult and pediatric CD, and adult UC (pediatric UC is protected by orphan drug exclusivity that expires September 23, 2018).[13] The EMA also approved SB2 for AS, PsA, PsO, adult and pediatric CD, and adult and pediatric UC (under trade name Flixabi).14 Most recently, in December 2017, Health Canada granted a NOC to Renflexis for RA, AS, CD (adult and pediatric patients > 9 years of age), fistulizing CD, UC (adult and pediatric patients > 6 years of age), PsA, and PsO.[12]

[redacted]. It is important to emphasize that regulatory approval of a biosimilar does not mean that it is interchangeable, and it cannot be automatically substituted for the reference product. Input from patient groups has indicated that switching from one biologic to another, including a biosimilar, must be considered carefully as it may have taken time and trials of different medication regimens to achieve disease stability (Appendix 3). The clinical expert for this review indicated that, in practice, patients would rarely be switched to a biosimilar once stabilized on a particular product. In addition, the

"nocebo" effect of switching to a biosimilar has been described in the literature.[36-38] This effect is the opposite of the placebo effect and occurs when a patient's negative expectations cause a larger negative effect than ascribed to the treatment itself.[35] Among patients with inflammatory arthritis who were switched from Remicade to biosimilar infliximab, one study observed that 15% of discontinuations were due to subjective reasons, with no objective deterioration of disease;[36] another study found that 23% of discontinuations were due to subjective perceptions of decreases in efficacy.[38] The nobeco effect has not been observed in all studies. Buer et al., for example, found that among patients with IBD who switched to an infliximab biosimilar, AEs were few and treatment retention was high up to six months.[40] The nocebo effect may also be attenuated by providing proper patient education and monitoring, as was demonstrated in a switching program at a UK teaching hospital.[41]

Potential Place in Therapy

The infliximab reference product has been widely used for all proposed indications for more than 10 years. For rheumatologic diseases specifically, anti-TNF drugs have been the first biologic of choice after DMARDs for RA and PsA, and after NSAIDs (nonsteroidal anti-inflammatory drugs) for AS, most often in conjunction with MTX or another DMARD if MTX is contraindicated. In rheumatology, the subcutaneous biologic drugs (and recently the Janus kinase inhibitors) are a more frequent choice than the IV medications. This is not the case in some of the other proposed indications, such as the more frequent use of infliximab for IBDs.

Adult and pediatric patients with IBD currently have a number of unmet medical needs. While anti-TNF drugs are excellent in inducing clinical remission in adult and pediatric patients with CD and active inflammation, these patients often still go on to develop fibrostenotic disease.[1] There are no medications available to treat CD strictures, and these patients require surgery or endoscopic dilation. Patients with UC do not all respond to existing therapies and many go on to require colectomy. According to a clinical expert consulted by CDR for this review, anti-TNF therapies, vedolizumab, and ustekinumab are delivered by IV or injection, making them uncomfortable, especially for younger patients. All have worrisome side effects, including the risk of significant infection. These three classes of therapy are also extremely expensive, making them inaccessible for some patients, and causing a significant financial burden for others. SB2 does not offer a novel MoA; it may address the financial concern simply by introducing more competition into the market. However, SB2 will not fulfill any other currently unmet needs of IBD patients.

SB2 might be appropriate for anti–TNF-naive adult IBD patients who have failed traditional therapy or who have features at presentation predictive of a severe course. SB2 is also likely to be appropriate for anti-TNF-naive pediatric IBD patients in the same situations, although pediatric data on biosimilars are lacking. IBD patients who have antibody-mediated secondary loss of response to another anti-TNF drug (not Remicade) may also benefit from SB2. However, switching a patient with adult or pediatric IBD to SB2 who is well on Remicade is not currently supported by high-quality data specific to the IBD population.[2] According to a clinical expert consulted by CDR for this review, switching could have risks to the patient, including AEs, such as infusion reactions, possibly related to anti-infliximab antibody development. Switching back to Remicade in the future may be impossible because of the subsequent anti-Remicade antibody development. Similarly, for rheumatology, SB2 would be an appropriate medical choice for any biologic-naive or biologic-experienced patient who would receive the reference product. Although there is evolving clinical evidence that might in the future support switching the patient from the reference product, non-medical switching has not been commonly observed with the first biosimilar of infliximab (Inflectra). The uncertainty of response and safety, the availability of a location to administer this IV drug, as well as the lack of acknowledgement of interchangeability by the heath authorities would suggest that switching from originator infliximab to a biosimilar should be undertaken only after extensive discussion between the patient and their medical team.

Conclusion

SB2 is the second proposed biosimilar of Remicade that has received market authorization in Canada. The clinical data for SB2 consist of two studies: a phase I PK study in healthy patients and a phase III efficacy and safety trial in patients with RA. The PK profile of SB2 was shown to be equivalent to its reference products, and equivalence in efficacy up to 54 weeks was demonstrated in patients with RA based on an equivalence margin of ± 15%. In both the phase I and phase III trials, numerical differences in some safety end points and immunogenicity were observed; however, the clinical interpretation of these results is uncertain given the small sample size and small number of events. There is evidence from a 24-week, double-blind, transition-extension study that suggests efficacy outcomes remain similar after switching from Remicade to SB2. The use of efficacy and safety data from the phase III trial in patients with RA to support market authorization for all other indications may be reasonable given: (a) the role of TNF alpha in all indications, and (b) demonstrated similarities between SB2 and Remicade in structural characteristics, physiochemical properties, Fab- and Fc- biological properties, non-clinical evidence in animal models, and clinical evidence in healthy patients and patients with RA.

Appendix 1: Additional Data

Table 42: Detailed summary of physicochemical test methods and results for the similarity of SB2 and Remicade (IFN)

Test Method(s)	Summary of Results	Reference(s)
Structural Characterization and Confirmation: Primary Structure		CTD 2.3.R, section 2.3.R.5.3.1 CTD 2.3.S, section 2.3.S.3.1.1
• Molecular weight (MW)	• The MWs of intact and deglycosylated SB2 under non-reducing or reducing conditions were determined by using ultra performance liquid chromatography (UPLC) coupled to high-definition mass spectrometry (HDMS). • **The measured major protein mass was 148517±2 Da, which was essentially identical to the theoretical mass of intact SB2 (148514 Da).** • The MW of all other forms of SB2 (light chain, heavy chain, deglycosylated) were as expected.	
• Amino acid (full) sequencing	• Digested peptides were analysed using liquid chromatography-electrospray ionisation coupled to tandem mass spectrometry (LC-ESI-MS/MS) after digestion with three different proteases. • The full amino acid sequence of SB2 DP was compared to the amino acid sequence encoded by the proposed DNA sequence. • **The amino acid sequence of SB2 was identical to that of EU-Remicade.**	

• N-terminal sequence analysis	• N-terminal sequencing was performed by LC-ESI-MS/MS.
	• For heavy chain, two forms of N-terminal peptide were found for SB2 and EU-Remicade:
	  ○ Intact: 1-EVKLEESGGGLVQPGGSMK-19
	  ○ Pyroglutamate: 1-$_{pyro}$EVKLEESGGGLVQPGGSMK-19
	• For light chain, one form of N-terminal peptide was found for SB2 and EU-Remicade:
	  ○ Intact form: 1-DILLTQSPAILSVSPGER-18
	• The relative levels of each form (intact and pyroglutamate) of the heavy chain N-terminal peptides as well as the intact form of the light chain N-terminal peptide were similar between SB2 and EU-Remicade.
	• The heavy and light chain N-terminal sequences of SB2 were similar to those of EU-Remicade.	

• C-terminal sequence analysis	• The C-terminal sequence of SB2 and Remicade was analyzed by using LC-ESI-MS/MS after digestion with Lys-C. One form of C-terminus in the light chain; three different forms of the C-terminus in the heavy chain were identified in both SB2 and EU-Remicade:
	  ○ Intact (Lys undeleted) form: 443-SLSLSPGK-450
	  ○ Lys deleted: 443-SLSLSPG-449
	  ○ α-amidated Pro: 443-SLSLSP$_{amidated}$-448
	• For the heavy chain, the C-terminal sequence of intact form and Lys deleted form were identical between SB2 and EU-Remicade.
	• The α-amidated Pro form was detected only in SB2.
	  ○ It is a well-known and widely occurring modification in Chinese hamster ovary (CHO) cells, resulting from chemical and enzymatic reactions (73, 74).
	• For the light chain, the C-terminal sequence was identical between SB2 and EU-Remicade with no detectable modification.
	• Overall, the C-terminal sequence of SB2 and EU-Remicade was identical to the expected sequence.
	• In addition, since the difference in α-amidation at the C-terminus was considered to be insignificant, SB2 was considered similar to EU-Remicade in terms of C-terminal sequence.	

• Peptide mapping	• Peptide mapping was performed using LC-ESI-MS/MS after subsequent digestion with different proteases (trypsin, Lys-C and Asp-N). The resulting peptides were analysed with respect to their post-translational modifications (PTMs), sequence variants, and whole sequence. • The digests were separated and more than 15 major peaks in a chromatogram. • The chromatograms showed identical patterns between SB2 and EU-Remicade, irrespective of the protease used. • **Therefore, the peptide map for SB2 was considered similar to the peptide map for EU-Remicade.**	
• Disulphide bond	• The disulphide linkage pattern of the protein was assessed by LC-ESI-MS/MS to determine its higher-order structure.	

Test Method(s)	Summary of Results	Reference(s)
Structural Characterization and Confirmation: Primary Structure		CTD 2.3.R, section 2.3.R.5.3.1 CTD 2.3.S, section 2.3.S.3.1.1
	• Infliximab contains 16 disulphide bonds formed by 32 cysteine (Cys) residues located in the heavy and light chains and there was theoretically no free sulfhydryl group from free cysteine residues. ○ Of these, Cys223 at the HC and Cys214 at the LC were linked by inter-chain disulphide bonds and each Cys229 and Cys232 at the two HC were linked by inter-chain disulphide bonds to compose the homodimer. The rest of the Cys residues were linked by intra-chain disulphide bonds. • **Results showed that the disulphide linkage patterns are similar between SB2 and EU-Remicade**	
• Free sulfhydryl group quantification	• The free sulfhydryl groups in SB2 and EU-Remicade were quantified using a fluorescence (FLR) assay kit. • Minor differences were observed in the molar concentration of free sulfhydryl content between SB2 and EU-Remicade. • However, as the relative content of free sulfhydryl group was less than 1.5% in both SB2 and EU-Remicade, the result suggests that essentially all 32 Cysteine (Cys) residues were linked by disulphide bonds and there was practically no free Cys residue. • **Therefore, the minor difference in free sulfhydryl group content is not considered significant.**	
• Methionine (Met) oxidation	• The oxidation level of all Met residues was quantified using UPLC-ESI-MS/MS after digestion with trypsin • Some SB2 results were outside the range of those of EU-Remicade ○ The relative content of the oxidized form of Met residues was slightly higher in SB2 ○ However, biological assays showed that the **FcRn binding affinity, which is associated with protein binding activity, was similar for SB2 and EU-Remicade** ○ **In addition, the TNF-α binding activity was similar for SB2 and EU-Remicade** • **Therefore, the slight differences observed were not considered to have an impact on the biological activity**	
• Deamdiation	• The deamidation level of Asn residues was quantified using UPLC-ESI-MS/MS after digestion with trypsin. • The relative deamidation levels of 10 Asparagine (Asn) residues (Asn57, Asn162, Asn204, Asn206, Asn211, Asn279, Asn289, and Asn318 in the HC, and Asn137 and Asn138 in the LC) both SB2 and EU-Remicade were less than 5%. • The maximum difference between SB2 and EU-Remicade was no more than 1.1% in three of the Asn residues. • Of note, Asn57 is known to be a site of complementarity determining region of infliximab, and may influence antigen binding activity. **However, structure-activity relationship study showed that deamidation of up to 20% at this position did not impact TNF-α and FcγRIIIa binding.** • **Overall, the relative deamidation levels on Asn residues of SB2 were similar to those of EU-Remicade.**	
• C-terminal Lys variant analysis	• The relative level of the Lys variants at the C-terminus of the heavy chain was determined from the peptide mapping results. • The level of α-amidated and intact forms of SB2 DS and DP was 1.2-1.4% and 1.5-2.0%, respectively. • The relative level of the Lys variant in SB2 was lower than that in EU-Remicade, indicating that most of the Lys residues on the C-terminus of SB2 were found cleaved. • The difference in relative contents of C-terminal Lys of the heavy chain was caused mainly by the use of Chinese hamster ovary (CHO) cells as host cells instead of SP2/0 cells, which are used by the originator. • The heterogeneity of C-terminal residues is a characteristic of therapeutic mAb and C-terminal Lys variation is known not to impact PK profiles (75). • It has been suggested that there is no relationship between the presence of C-terminal Lys and the biological activity of the Fc fusion protein, and that the C-terminus is oriented away from the Fc receptor epitope (76). • In addition, the C-terminal Lys does not possess any physiological effect as it is cleaved by the carboxypeptidase enzyme as it enters the blood (77). • **Results from a structure-activity relationship (SAR) study showed that C-terminal Lys of the heavy chain content did not impact TNF-α binding activity, which is directly related to the mechanism of action of infliximab. Therefore, the difference in C-terminal Lys content was not considered significant.**	
Structural Characterization and Confirmation: Carbohydrate Structure/Glycan Profile (Physicochemical)		CTD 2.3.R, section 2.3.R.5.3.2 CTD 2.3.S, section 2.3.S.3.1.2
• N-linked	• The N-linked glycosylation site of SB2 was determined using LC-ESI-MS/MS.	

Test Method(s)	Summary of Results	Reference(s)
Structural Characterization and Confirmation: Primary Structure		CTD 2.3.R, section 2.3.R.5.3.1 CTD 2.3.S, section 2.3.S.3.1.1
Glycosylation Site	• Treatment with peptide-N-glycosidase F (PNGase F) resulted in the conversion of the glycan-linked Asn to aspartic acid (Asp), which was the target site of Asp-N endopeptidase. • The fragment ion spectra of SB2 for major N-glycopeptide were identical to those of EU-Remicade and were identical with the expected masses. • **From these results, the single N-linked glycosylation site of SB2 and EU-Remicade was identified as Asn300.**	
• N-glycan Identification	• The N-glycan structures of SB2 and EU-Remicade were identified using LC-ESI-MS/MS by procainamide labeling. • Majority of the identified glycan peaks was identical between SB2 and EU-Remicade. • Minor differences in the N-glycan species between products were observed: ○ N-acetylneuraminic acid (NANA) forms were observed as charged glycosylated forms in SB2 ○ N-glycolylneuraminic acid (NGNA) forms were observed in EU-Remicade only • These differences were caused by the different cell line used in the manufacturing • **As this is well known not to affect the biological activity of mAbs in the literature (78), it was considered that the differences were non-significant, and thus that the N-glycan profile of SB2 could be considered similar to that of EU-Remicade.**	
• N-glycan Profile by 2-amino-benzamide (2-AB) by HILIC-UPLC	• Hydrophilic interaction ultra-performance liquid chromatography (HILIC-UPLC) by labelling with 2-AB was used to determine the relative content of N-glycan species in SB2 and EU-Remicade. • N-glycan profiles were categorized into four different groups according to structural compositions: ○ afucosylated glycans (%Afucose) ○ neutral galactosylated glycans (%Gal) ○ mannosyl-chitobiose core without L-fucose (%High Mannose (%HM)) ○ charged glycans (%Charged) • The %Afucose level of SB2 was slightly higher than that of the upper limit of the similarity range, however: ○ The %HM and %Afucosylated glycan (%afucose + %HM) level of SB2 was within the similarity range ○ **The FcγRIIIa binding and ADCC activities (associated with afucosylated glycans), were similar between SB2 and Remicade** ○ In the subsequent assessment via Min/Max approach, the results for %Afucose glycans were found between the Min/Max of EU-Remicade. ○ Therefore, the difference in %Afucose level between SB2 and EU-Remicade is not considered to be significant. • %Charged glycan level of SB2 was lower than that of EU-Remicade but was within the similarity range. • %Gal level of SB2 was within the similarity range. • **Overall, although there were minor differences in level of some N-glycan species between SB2 and EU-Remicade, these differences were not considered significant. Therefore, SB2 and EU-Remicade were considered to be similar.**	
Physicochemical Properties: Liquid Chromatographic Patterns		CTD 2.3.R, section 2.3.R.5.3.3 CTD 2.3.S, section 2.3.S.3.1.3
• Size Exclusion Chromatography (SEC)	• SEC under native conditions was used to determine the percent aggregate and percent main peak in SB2. • High molecular weight (%HMW) level of SB2 was slightly higher than that of EU-Remicade and was also slightly above the similarity range (set to ≤ 0.4% of %HMW). • Though the %HMW level of SB2 was out of the similarity range, the relative percentage of HMW was very low (< 1.0%) in both SB2 and EU-Remicade. • **Additional analysis with sedimentation velocity-analytical ultracentrifugation (SV-AUC) showed that % total aggregates were similar between SB2 and EU-Remicade.** • **Therefore, SB2 was considered similar to EU-Remicade in terms of purity.**	
• Cation-exchange chromatography (CEX)	• CEX was used to evaluate the charge heterogeneity of SB2 and EU-Remicade. • The relative contents of both acidic and basic variants in SB2 were slightly higher than those of EU-Remicade (in Carboxypeptidase-B-treated samples). • The difference in charge variant content was characterized through a SAR study including imaged capillary isoelectric focusing (icIEF) analysis, peptide mapping and intact mass analysis LC-ESI-MS, and biological assays (TNF-α and FcγRIIIa binding activities). • **Results demonstrated that there were slight differences in post-translational modifications of SB2**	

Test Method(s)	Summary of Results	Reference(s)
Structural Characterization and Confirmation: Primary Structure		CTD 2.3.R, section 2.3.R.5.3.1 CTD 2.3.S, section 2.3.S.3.1.1
	and Remicade, which influenced their respective charge heterogeneity. However, these differences had no effects on biological activities in terms of TNF-α binding and FcγRIIIa binding activities, which are directly related to the MoA of infliximab.	
Physicochemical Properties: Electrophoretic Patterns		CTD 2.3.R, section 2.3.R.5.3.4 CTD 2.3.S, section 2.3.S.3.1.4
• Capillary Electrophoresis-Sodium Dodecyl Sulfate (CE-SDS): Reducing	• CE-SDS (reducing) was performed to determine the main peak content. Reducing CE-SDS was performed using the reducing agent, 2-mercaptoethanol. • The %purity of SB2 was slightly lower than that of EU-Remicade, which was attributed to the higher % non-glycosylated heavy chain (NGHC) level of SB2 than that of EU-Remicade. • The N-glycosylation at Fc region of antibodies is known to be associated with Fc- related functional activities. • **However, the gap of %NGHC level corresponding to the less than 0.7% difference was too low to estimate the effect of potency.** • **Therefore, %purity of SB2 was considered to be similar to EU-Remicade.**	
• CE-SDS: Non-Reducing	• Non-reducing CE-SDS was performed using a similar procedure as that of CE-SDS under reducing conditions, but without the use of 2-mercaptoethanol. • The purity of SB2 was shown to be similar to that of EU-Remicade, and was within the similarity range (≥ 94.1 %). • **Therefore, SB2 was considered similar to EU-Remicade in terms of purity.**	
• Charge Heterogeneities by Imaged Capillary Isoelectric Focusing (icIEF)	• icIEF was used to determine the relative contents of charge variants in SB2 and EU-Remicade. • The similarity range for the charge variants established was 22.8-37.2% for acidic variants, 60.2-74.9% for main portion, and 0.6-4.2% for basic variants. • SB2 possessed a lower content of main peak and a higher content of basic variants compared to those of EU-Remicade, whereas the content of acidic variants was similar for SB2 and EU-Remicade, within the similarity range. • **Despite these differences, SAR studies performed using CEX-fractionated peaks showed that the charge variant content did not affect TNF-α and FcγRIIIa binding activities.** • These results therefore indicate that the difference in charge variants does not translate into differences in the biological activity of SB2. • **Therefore, the differences in charge variants were not considered significant.**	
Physicochemical Properties: Biophysical		CTD 2.3.R, section 2.3.R.5.3.5 CTD 2.3.S, section 2.3.S.3.1.5
• Far-UV CD Spectroscopy	• Far-UV analysis (190-250 nm) is a rapid analysis method for assessing secondary structure and folding, and also protein interactions. Mutations that may affect protein conformation or stability can also be detected. Analysis was performed after dialysis of the samples in PBS (arginine and sucrose free buffer). • Results showed good overlap in the far-UV plots between SB2 and EU-Remicade. • There was some variability observed at the low wavelength region about 200-205 nm, which would be resulted from the interference of sucrose in the SB2 DP formulation buffer, rather than the different structure. • **Therefore, SB2 and EU-Remicade were considered similar in terms of far-UV CD spectroscopic profiles.**	
• Near UV CD Spectroscopy	• Near-UV analysis (250-350 nm) measures the tertiary structure of proteins • Results showed similar spectra overlap between SB2 and EU-Remicade (maximum wavelength between 294-295 nm). • **Therefore, SB2 and EU-Remicade were considered similar in terms of near-UV CD spectroscopic profiles.**	
• Fluorescence Spectroscopy: Intrinsic Fluorescence	• Intrinsic fluorescence spectroscopy was used to analyze the three-dimensional structure of proteins. • Fluorescence measurements were performed at the excitation wavelength of λ = 280 nm and in the emission range of λ = 310-480 nm. • Intrinsic fluorescence spectra of all samples featured similar maxima fluorescence intensity profiles between SB2 and EU-Remicade. • The spectra acquired under both native and denaturing conditions overlapped and emission maxima were similar between SB2 and EU-Remicade.	

Test Method(s)	Summary of Results	Reference(s)
Structural Characterization and Confirmation: Primary Structure		CTD 2.3.R, section 2.3.R.5.3.1 CTD 2.3.S, section 2.3.S.3.1.1
	• **Overall, the intrinsic fluorescence spectrum of SB2 was considered to be similar to that of EU-Remicade, as the spectra for SB2 were within the range of the spectra for EU-Remicade.**	
• Fluorescence Spectroscopy: Extrinsic Fluorescence	• Extrinsic fluorescence spectroscopy used Bis-ANS, a fluorescent dye, to characterize folding intermediates, measures surface hydrophobicity, and detect aggregation or fibrillation of SB2 and EU-Remicade. • Extrinsic fluorescence spectra for SB2 and EU-Remicade exhibited similar broad emission peaks. • SB2 and EU-Remicade had fluorescence maxima (λ_{max}) between 513-518 nm and the intensities at the peak were between 3700-4200 cps • Minor differences were at the margin of the assay variability and therefore were not considered significant. • **Overall, the extrinsic fluorescence spectrum of SB2 was considered to be similar to that of EU-Remicade.**	
• Fourier Transform Infrared Spectroscopy (FTIR)	• FTIR was used to analyze the secondary structure of SB2 and EU-Remicade • The spectra observed for SB2 and EU-Remicade were similar • Overall, there were no differences in the spectral region of the major peak. ○ The FTIR spectrum of SB2 is a normalized profile of the amide I (1600-1700 cm-1) region, where elements of beta-sheet and beta-turn are strong contributors. • **Therefore, the FTIR spectra of SB2 were considered to be similar to those of EU-Remicade**	
• Hydrogen / Deuterium Exchange (H/DX)	• H/DX analysis provides information about the solvent accessibility of various parts of the molecule (by the exchange of covalently bonded hydrogen atom with a deuterium atom, or vice versa), and thus the tertiary structure of the protein. • The peptides detected in this assay covered 90.9% (147 peptides) of the infliximab heavy chain sequence and 98.6% (69 peptides) of the light chain sequence. • **The deuterium uptake profile indicated that the higher-order structure of SB2 was similar to EU-Remicade.**	
• Differential Scanning Calorimeter (DSC)	• DSC was used to determine the heat-induced protein denaturation pattern of SB2 and EU-Remicade. • The two main thermal transitions (T_m) were observed. • The shapes of the thermal scans for SB2 and EU-Remicade were similar. • Results also indicated that all T_m values were similar within 2 SD of the mean. • **Therefore, SB2 was considered similar to EU-Remicade in terms of thermal stability profiles.**	
• Size-exclusion Chromatography (SEC) with multiangle laser light scattering (MALLS) Detection	• SEC with MALLS detection was used to characterize the molecular weight for HMW, monomer, and LMW species in SB2 and EU-Remicade. • Average levels of Monomer and Dimer peak % (and molecular mass) were all similar between SB2 and EU-Remicade (Monomer peak all >99% and Dimer [HMW] peak all <1%) • Putative LMW SB2 was detected, but the level (≤0.05%) was negligible. • **SB2 was similar to EU-Remicade in terms of scattering profiles, the calculated mass of the monomer and dimer, and peak percentage from UV detection.**	
• Sedimentation Velocity-Analytical Ultra-centrifugation (SV-AUC)	• SV-AUC provides information on the size and shape of macromolecules in solution with very few restrictions on the sample or the nature of the solvent. • SV-AUC was used as an orthogonal method to SEC/MALLS to investigate the monomer content, the presence of aggregates and fragments, as well as the MW of the main molecular species in a protein solution in SB2 and EU-Remicade. • The %total aggregates ranged between 56-61% for SB2 and EU-Remicade • The %HMW by SEC was <1% for SB2 and EU-Remicade. • %HMW from SEC analysis includes only irreversible aggregates and dimers, while that from SV-AUC includes reversible and non-reversible aggregates. • These findings showed that over a half protein in SB2 and EU-Remicade existed as reversible dimer and the irreversible aggregates existed in a very low level (< 1.0%) in both SB2 and EU-Remicade. • **SB2 was considered similar to EU-Remicade in terms of SV-AUC profile.**	
• Dynamic Light Scattering (DLS)	• DLS was used to analyze subvisible aggregates in the nm-size range. • The hydrodynamic diameter of SB2 was smaller than that of EU-Remicade on average • However, it was not considered significant based on the results from SEC/MALLS. • **Therefore, SB2 was similar to EU-Remicade in terms of the hydrodynamic diameter and polydispersity.**	

Test Method(s)	Summary of Results	Reference(s)
Structural Characterization and Confirmation: Primary Structure		CTD 2.3.R, section 2.3.R.5.3.1 CTD 2.3.S, section 2.3.S.3.1.1
• Extinction Coefficient	• Extinction coefficient was determined by amino acid analysis using Pico Tag® method. • The average extinction coefficient value for SB2 and EU-Remicade were 1.57 $(mg/mL)^{-1}$ cm^{-1} and 1.60 $(mg/mL)^{-1}$ cm^{-1}, respectively. • **Therefore, the extinction coefficient value of SB2 was similar to that of EU-Remicade.**	
• Micro-Flow Imaging (MFI)	• MFI was used for the quantification and visualization of subvisible particles in the µm-size range. • MFI results showed that both SB2 and EU-Remicade contained particles in the range of ≥ 1 µm to ≥ 25 µm. • Particle concentrations for particles in all size ranges were lower in SB2 when compared to EU-Remicade. • However, the particle concentrations were generally low and no obvious trends were observed among all samples. • **Therefore, SB2 was similar to EU-Remicade in terms of subvisible particles.**	
Quantity		CTD 2.3.R, section 2.3.R.5.3.6
• Ultraviolet/visible (UV/VIS) spectroscopy	• The protein contents of SB2 and Remicade were determined by ultraviolet/visible (UV/VIS) spectroscopy at 280 nm. • Protein contents of SB2 DP and EU-Remicade were 98.4-103.8 mg/vial and 95.9-96.9 mg/vial, respectively. • **Therefore, SB2 was considered to be similar with EU-Remicade in terms of the protein content.**	

Table 43: Detailed summary of *in vitro* functional test methods and results for the similarity of SB2 and Remicade (IFN)

Test Method(s)	Summary of Results	Reference(s)
Biological Characterization: Fab-Related Binding Assays		CTD 2.3.R, section 2.3.R.5.3.7 CTD 2.3.S, section 2.3.S.3.1.6
• TNF-α Binding Assay	• The relative binding activity of SB2 and EU-Remicade to TNF-α was determined by fluorescence resonance energy transfer-based competitive binding assay (fluorescence resonance energy transfer [FRET assay]). • TNF-α binding activity of SB2 was within the similarity range (85-111%). • **Therefore, the TNF-α binding activity between SB2 and EU-Remicade was considered to be similar.**	
• TNF-α Neutralization Assay by NF-κB Reporter Gene	• The inhibitory effect of SB2 and EU-Remicade on the TNF-α signaling pathway was measured through the TNF-α neutralization assay using a 293-NF-κB-Luc cell line with luciferase activity. • The relative potency of SB2 was within the similarity range (84-116%). • **Therefore, the relative potency between SB2 and EU-Remicade was considered similar.**	
• Apotosis	• The apoptosis activity of SB2 and EU-Remicade was determined in Jurkat cells expressing membrane TNF-α by measurement of caspase activity using a Caspase-Glo® 3/7 kit. • The apoptosis activity of SB2 was within the similarity range (81-119%). • **Therefore, the apoptosis activity between SB2 and Remicade was considered to be similar.**	
Fc-Related Biological Activities		CTD 2.3.R, section 2.3.R.5.3.8 CTD 2.3.S, section 2.3.S.3.1.7
• FcγRIa Binding Assay	• The relative binding activity of SB2 and EU-Remicade to FcγRIa was determined by the FRET assay. • FcγRIa binding activity of SB2 was within the similarity range (82- 118%). • **Therefore, FcγRIa binding activity between SB2 and EU-Remicade was considered to be similar.**	
• FcγRIIa Binding Assay	• The relative binding activity of SB2 and EU-Remicade to FcγRIIa was determined by an amplified luminescence proximity homogeneous, competitive binding assay (AlphaScreen®). • FcγRIIa binding activity of SB2 was within the similarity range (75-127%). • **Therefore, FcγRIIa binding affinity between SB2 and EU-Remicade was considered to be similar.**	
• FcγRIIb Binding Assay	• The relative binding activity of SB2 and EU-Remicade to FcγRIIb was determined by the same method as the FcγRIIa binding assay. • FcγRIIb binding activity of SB2 was within the similarity range (78-116%) except five SB2 batches. • However, no significant difference was observed in orthogonal method (binding affinity measurement by SPR) and the binding activity of SB2 was within the similarity range of the US-IFN. • **Also, as results from the ADCC assay were within the similarity range, it was considered that the FcγRIIb binding activity between SB2 and EU-Remicade was similar.**	

Test Method(s)	Summary of Results	Reference(s)
Biological Characterization: Fab-Related Binding Assays		CTD 2.3.R, section 2.3.R.5.3.7 CTD 2.3.S, section 2.3.S.3.1.6
• FcγRIIIa Binding Assay (158 V/V Form)	• The relative binding activity of SB2 and EU-Remicade to FcγRIIIa was determined by the same method as the FcγRIIa binding assay. • FcγRIIIa binding activity of SB2 was within the similarity range (69-127%) except five SB2 batches. • Despite this difference, the deviation was as minimal as 4-15%, the slight difference in FcγRIIIa binding activity was not considered to be significant. • Specifically, results of ADCC, which is closely related to FcγRIIIa, was within similarity range. • There was also no significant difference observed in orthogonal method (binding affinity measurement by SPR). • Finally, there was no signification difference in physiologically more relevant assay condition (NK cell binding assay). • **Therefore, the FcγRIIIa binding activity between SB2 and EU-Remicade was considered to be similar.**	
• FcγRIIIb Binding Assay	• The binding affinity of SB2 and EU-Remicade to FcγRIIIb was determined by surface plasmon resonance (SPR). • The *p*-value of the *t*-test analysis on the affinity between SB2 DP and EU-Remicade was 0.834, which shows that there is no statistical difference in the FcγRIIIb binding activity of SB2 and EU-Remicade. • **Therefore, the FcγRIIIb binding affinity between SB2 and EU-Remicade was considered similar.**	
• FcRn Binding Assay	• The relative binding activity of SB2 and EU-Remicade to FcRn was determined by the same method as the FcγRIIa binding assay. • Results showed that the FcRn binding activity of SB2 except one batch was within the similarity range (83-117%). • **As this observed difference was within assay variability, it was not considered significant.** • **Therefore FcRn binding activity between SB2 and EU-Remicade was considered to be similar.**	
• C1q Binding Assay	• The binding activity of SB2 and EU-Remicade to the complement component C1q was assessed by a sandwich enzyme-linked immunosorbent assay (ELISA). • Results showed that the C1q binding activity of SB2 was within the similarity range (75- 115%). • **Therefore, C1q binding activity between SB2 and EU-Remicade was considered similar.**	
• Antibody-dependent Cell-mediated Cytotoxicity (ADCC) Assay	• ADCC activity in SB2 and EU-Remicade was analyzed by a cell based assay using a stable mouse cell line that overexpress human membrane TNF-α on the cell surface (3T3mTNFα cells) as target cells, and a human natural killer (NK) cell line expressing CD16 (FcγRIII) (FNK92-CD16 cells presenting V/V forms) as effector cells. • Results showed that the ADCC activity of SB2 was within the similarity range (51-150%). Therefore, ADCC activity between SB2 and EU-Remicade was considered similar.	
• Complement-dependent Cytotoxicity (CDC) Assay	• The CDC activity of SB2 and EU-Remicade was analyzed by an enzyme reaction-based CDC assay, using a cell line over-expressing human membrane TNF-α on the cell surface (Jurkat-mTNF-α cell). Human serum was used as a complement source. • **The CDC activity of SB2 was within the similarity range (79-120%). Therefore, CDC activity between SB2 and EU-Remicade was considered similar.**	
Additional Biological Assays		CTD 2.3.R, section 2.3.R.5.3.9 CTD 2.3.S, section 2.3.S.3.1.8
• TNF-β (LTα3) Binding Assay	• TNF-β (lymphotoxin alpha-3; LTα3) binding to SB2 and EU-Remicade was determined by a FRET assay. • Since infliximab is known to bind to both soluble and membrane TNF-α, but not to TNF-β, (lack of) TNF-β binding activity was assessed for further confirmation of SB2 characteristics and similarity to EU-Remicade. • Compared to the positive control (infliximab), SB2 and EU-Remicade showed no signal, which demonstrated a significant lack of TNF-β binding activity.	
• Transmembrane (tm) TNF-α Binding Assay	• The tmTNF-α binding activity of SB2 and EU-Remicade was determined by TNF-α overexpressing Jurkat cells and measuring the relative binding activity of SB2/EU-Remicade to CD20 surface antigen a flow cytometry-based method fluorescence-activated cell sorting (FACS) • tmTNF-α binding activity of SB2 was slightly different to the range observed for EU-Remicade. • **However, the *p*-value of the *t*-test analysis was 0.971, which demonstrated that there was no difference between the tmTNF-α binding activity of SB2 compared to EU-Remicade.** • **Therefore, the tmTNF-α binding activity of SB2 was considered to be similar to that of EU-Remicade.**	

Test Method(s)	Summary of Results	Reference(s)
Biological Characterization: Fab-Related Binding Assays		CTD 2.3.R, section 2.3.R.5.3.7 CTD 2.3.S, section 2.3.S.3.1.6
• ADCC Using Healthy Donor PBMC	• ADCC activity of SB2 and EU-Remicade was determined by using health donor peripheral blood mononuclear cells (PBMC) as effector cells instead of NK92-CD16 cells. • **The *p*-value of the *t*-test analysis was 0.390, which demonstrates that there was no statistical difference between the ADCC activity of SB2 compared to EU-Remicade.** • **These results were found consistent with those found with the ADCC assay using NK92-CD16 cells, so that SB2 was considered to be similar to that of EU-Remicade.**	
• FcγRIIIa Binding Assay (F158 F/F Type)	• The binding affinity of SB2 and EU-Remicade to FcγRIIIa (F158 F/F Type) was determined by SPR. • Similar binding affinity of SB2 and EU-Remicade to FcγRIIIa (F158 allotype) was seen. • **The minor observed differences were considered not statistically significant (*t*- test: *p*-value = 0.527).** • **Therefore SB2 and EU-Remicade were similar with respect to the FcγRIIIa binding (F/F type).**	
• FcγRIIIa Binding Assay Using NK Cells from PBMC	• The FcγRIIIa binding activity of SB2 and EU-Remicade was determined with NK cells from peripheral blood mononuclear cell (PBMC), and the relative binding activity was detected using FACS. • **FcγRIIIa binding activity between SB2 and EU-Remicade had no statistical significant difference (*t*-test: *p*-value = 0.153).** • **These results showed that FcγRIIIa binding activity was similar between SB2 and EU-Remicade, and that the differences to FcγRIIIa binding observed using NK92-CD16 cells would not imply any biological impact in the clinical setting.**	
• FcγRIIIb Binding Assay Using Neutrophils	• The binding affinity of SB2 and EU-Remicade to FcγRIIIb receptors was determined by a cell-based assay using neutrophils. • **FcγRIIIb binding activity between SB2 and EU-Remicade had no statistical significant difference (*t*-test: *p*-value=0.250).** • This study results were consistent with the results of FcγRIIIb binding activity using the SPR method. • **Therefore, the binding affinity of SB2 was considered similar to that of EU-Remicade.**	
• Evaluation of Regulatory Macrophage Function	• Two sets of experiments were performed to assess regulatory macrophage function associated with inflammatory bowel disease (IBD). • First, the function of regulatory macrophages was confirmed by a specific marker (anti-human CD206) whereby the amount of induced regulatory macrophage function was determined by flow cytometry. • Second, the capability of induced regulatory macrophage function was confirmed by measuring the T-cell anti-proliferation activity of SB2 in a two-way mixed lymphocyte reaction (MLR). • **The regulatory macrophages induction and T-cell anti-proliferation activity of SB2 was similar to that of EU-Remicade.**	
• Cytokine Release Activity in *In Vitro* IBD Model	• The suppression of IL-8 release by SB2 and EU-Remicade was assessed by ELISA. • **There were no statistically significant difference (*t*-test: *p*-value = 0.509) in the IL-8 release activity of SB2 DP and EU-Remicade relative to the bioassay standard.** • **Therefore, suppression of IL-8 release by SB2 and EU-Remicade was considered to be similar.**	
• Inhibitory Activity of Apoptosis in *In Vitro* IBD Model	• In addition to apoptosis assay in Jurkat cells, the inhibitory activity of apoptosis in an *in vitro* IBD model was assessed between SB2 and EU-Remicade. • **The inhibitory activity of apoptosis between SB2 and EU-Remicade had no statistical significant difference (*t*-test: *p*-value = 0.377).** • **Therefore, inhibitory activity of apoptosis was considered to be similar between SB2 and EU-Remicade.**	

Table 44: Number (%) of patients with TEAEs and number of events by preferred term that occurred in ≥ 2% of patients in any treatment group in the *randomized, double-blind* study SB2-GB31-RA (SAF)

Treatment	SB2			Reimcade®			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

Adverse events were coded by system organ class and preferred term using the MedDRA Version 16.0 coding dictionary. E: Frequency of treatment-emergent adverse events

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

Source: CTD 2.7.4, Table 2.7.4.2-4

Table 45: Number (%) of subjects with TEAEs and number of events by preferred term that occurred during the *transition-extension* period in ≥ 2% of subjects in any treatment group in study SB2-GB31-RA (Ex-SAF)

Treatment	SB2			Remicade									Total		
				Overall			SB2			Remicade					
	N=201			N=195			N=94			N=101			N=396		
Preferred term	**n**	**(%)**	**E**	**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.

Source: 78-week CSR SB2-G31-RA, Table 12-8

Table 46: Number (%) of subjects with at least 1 post-dose significant abnormality in haematology parameters in the randomized, double-blind period (up to Week 54) in study SB2-GB31-RA (SAF)

Parameter	Criteria	SB2	Remicade	Total
		N= 290 n/n' (%)	N= 293 n/n' (%)	N=583 n/n' (%)
Haematocrit (V/V)	L2	0/287 (0.0)	1/291 (0.3)	1/578 (0.2)
	H2	0/287 (0.0)	0/291 (0.0)	0/578 (0.0)
Haemoglobin (g/L)	L2	0/287 (0.0)	1/292 (0.3)	1/579 (0.2)
	H2	0/287 (0.0)	0/292 (0.0)	0/579 (0.0)
Leukocytes (10^9/L)	L2	2/287 (0.7)	0/292 (0.0)	2/579 (0.3)
	H2	3/287 (1.0)	2/292 (0.7)	5/579 (0.9)
Lymphocytes (10^9/L)	L2	6/287 (2.1)	3/292 (1.0)	9/579 (1.6)
	H2	0/287 (0.0)	0/292 (0.0)	0/579 (0.0)
Neutrophils (10^9/L)	L2	3/287 (1.0)	1/292 (0.3)	4/579 (0.7)
	H2	8/287 (2.8)	4/292 (1.4)	12/579 (2.1)
Platelet (10^9/L)	L2	0/287 (0.0)	1/292 (0.3)	1/579 (0.2)
	H2	3/287 (1.0)	4/292 (1.4)	7/579 (1.2)

n': number of subjects with available assessment results at each time point

Percentages were based on the number of subjects with available assessment results in each treatment group.

Significant abnormalities were defined with L2/H2 (significant abnormal laboratory range).

Source: CTD 2.7.4, Table 2.7.4.3-1

Table 47: Number (%) of subjects with at least 1 post-dose significant abnormality in haematology parameters in the transition-extension period (up to Week 78) in study SB2-G31-RA (Ex-SAF)

Parameter	Criteria	SB2		Remicade						Total	
				Overall		SB2		Remicade			
		N=201		N=195		N=94		N=101		N=396	
		n/n'	(%)	n/n'	(%)	n/n'	(%)	n/n'	(%)	n/n'	(%)
Platelet (10^9/L)	L2	0/194	(0.0)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	0/389	(0.0)
	H2	1/194	(0.5)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	1/389	(0.3)
Neutrophils (10^9/L)	L2	1/194	(0.5)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	1/389	(0.3)
	H2	1/194	(0.5)	1/195	(0.5)	0/94	(0.0)	1/101	(1.0)	2/389	(0.5)
Lymphocytes (10^9/L)	L2	1/194	(0.5)	2/195	(1.0)	1/94	(1.1)	1/101	(1.0)	3/389	(0.8)
	H2	0/194	(0.0)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	0/389	(0.0)

n' = number of subjects with available assessment results at each timepoint

Overall incidence of significant abnormalities at Week 78 were determined if there was at least one significant abnormality from after Week 54 up to Week 78 regardless of the result at Week 54.

Percentages were based on the number of subjects with available assessment results in each treatment group.

Significant abnormalities were defined with L2/H2 (significant abnormal laboratory range).

Source: 78-week CSR SB2-G31-RA, Table 12-16

Table 48: Number (%) of subjects with at least 1 post-dose significant abnormality in biochemistry parameters in the randomized, double-blind period (up to Week 54) in study SB2-GB31-RA (SAF)

Parameter	Criteria	SB2	Remicade	Total
		N= 290 n/n' (%)	N= 293 n/n' (%)	N= 583 n/n' (%)
ALP (IU/L)	L2	0/287 (0.0)	0/292 (0.0)	0/579 (0.0)
	H2	0/287 (0.0)	1/292 (0.3)	1/579 (0.2)
ALT (IU/L)	L2	0/287 (0.0)	0/292 (0.0)	0/579 (0.0)
	H2	15/287 (5.2)	7/292 (2.4)	22/579 (3.8)
AST (U/L)	L2	0/287 (0.0)	0/292 (0.0)	0/579 (0.0)
	H2	5/287 (1.7)	2/292 (0.7)	7/579 (1.2)
γGT (U/L)	L2	0/287 (0.0)	0/292 (0.0)	0/579 (0.0)
	H2	5/287 (1.7)	5/292 (1.7)	10/579 (1.7)
Glucose (mmol/L)	L2	0/287 (0.0)	0/292 (0.0)	0/579 (0.0)
	H2	8/287 (2.8)	4/292 (1.4)	12/579 (2.1)
Lactate dehydrogenase (U/L)	L2	0/287 (0.0)	0/291 (0.0)	0/578 (0.0)
	H2	0/287 (0.0)	1/291 (0.3)	1/578 (0.2)
Sodium (mmol/L)	L2	1/287 (0.3)	0/292 (0.0)	1/579 (0.2)
	H2	0/287 (0.0)	0/292 (0.0)	0/579 (0.0)
Total bilirubin (µmol/L)	L2	0/287 (0.0)	0/292 (0.0)	0/579 (0.0)
	H2	2/287 (0.7)	2/292 (0.7)	4/579 (0.7)

AST: aspartate aminotransferase; ALP: alkaline phosphatase; ALT: alanine *aminotransferase*; γGT: gamma-glutamyl transferase; n' = number of subjects with available assessment results at each time point

Percentages were based on the number of subjects with available assessment results in each treatment group.

Significant abnormalities were defined with L2/H2 (significant abnormal laboratory range).

Source: CTD 2.7.4, Table 2.7.4.3-3

Table 49: Number (%) of subjects with at least 1 post-dose significant abnormality in biochemistry parameters in the transition-extension period (up to Week 78) in study SB2-G31-RA (Ex-SAF)

Parameter	Criteria	SB2		Remicade						Total	
				Overall		SB2		Remicade			
		N=201		N=195		N=94		N=101		N=396	
		n/n'	(%)	n/n'	(%)	n/n'	(%)	n/n'	(%)	n/n'	(%)
ALP (IU/L)	L2	0/194	(0.0)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	0/389	(0.0)
	H2	1/194	(0.5)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	1/389	(0.3)
AST (U/L)	L2	0/194	(0.0)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	0/389	(0.0)
	H2	1/194	(0.5)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	1/389	(0.3)
ALT (IU/L)	L2	0/194	(0.0)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	0/389	(0.0)
	H2	2/194	(1.0)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	2/389	(0.5)
Total bilirubin (µmol/L)	L2	0/194	(0.0)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	0/389	(0.0)
	H2	0/194	(0.0)	1/195	(0.5)	0/94	(0.0)	1/101	(1.0)	1/389	(0.3)
γGT (U/L)	L2	0/194	(0.0)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	0/389	(0.0)
	H2	0/194	(0.0)	1/195	(0.5)	0/94	(0.0)	1/101	(1.0)	1/389	(0.3)
Potassium (mmol/L)	L2	0/194	(0.0)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	0/389	(0.0)
	H2	0/194	(0.0)	2/195	(1.0)	1/94	(1.1)	1/101	(1.0)	2/389	(0.5)
Glucose	L2	0/194	(0.0)	0/195	(0.0)	0/94	(0.0)	0/101	(0.0)	0/389	(0.0)
	H2	4/194	(2.1)	3/195	(1.5)	1/94	(1.1)	2/101	(2.0)	7/389	(1.8)

ALP = Alkaline phosphatase; ALT = alanine *aminotransferase*; AST = aspartate aminotransferase; γGT = gamma-glutamyl transferase; n' = number of subjects with available assessment results at each timepoint

Overall incidence of significant abnormalities at Week 78 were determined if there was at least one significant abnormality from after Week 54 up to Week 78 regardless of the result at Week 54.

Percentages were based on the number of subjects with available assessment results in each treatment group.

Significant abnormalities were defined with L2/H2 (significant abnormal laboratory range).

Source: 78-week CSR SB2-G31-RA, Table 12-17

Table 50: Number (%) of subjects with treatment-emergent adverse events and number of events by preferred term that occurred in ≥ 5% of subjects in study SB2-G11-NHV (SAF)

Treatment	SB2		EU-Remicade		US-Remicade		Total	
	N=53		N=53		N=53		N=159	
Preferred term	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**
Any TEAEs	27 (50.9)	50	21 (39.6)	36	23 (43.4)	38	71 (44.7)	124
Nasopharyngitis	6 (11.3)	6	4 (7.5)	4	3 (5.7)	3	13 (8.2)	13
Headache	5 (9.4)	9	6 (11.3)	8	7 (13.2)	7	18 (11.3)	24
Diarrhoea	3 (5.7)	3	2 (3.8)	2	1 (1.9)	1	6 (3.8)	6
Rhinitis	3 (5.7)	3	2 (3.8)	2	1 (1.9)	1	6 (3.8)	6
Dry skin	3 (5.7)	3	0 (0.0)	0	1 (1.9)	1	4 (2.5)	4

N = number of subjects in the safety set; Subjects n = number of subjects who experienced each event; Events n = number of events experienced.

Percentages were Subjects n divided by N.

Source: Table 2.7.4.2-1

Table 51: Serum PK parameters for EU- vs. US-Remicade in study SB2-G11-NHV (PK Population)

	n	EU-Remicade 5 mg/kg (N=53)	n	US-Remicade 5 mg/kg (N=53)	Ratios of Geometric Means; 90% CI
AUC_{inf} (µg·h/mL), Mean ± SD	53	39,360 ± 12,332	53	39,270 ± 10,064	0.993 (0.908–1.086)
AUC_{last} (µg·h/mL), Mean ± (SD)	53	37,022 ± 9398	53	37,368 ± 8332	0.987 (0.913–1.067)
C_{max} (µg/mL), Mean ± SD	53	126.2 ± 17.9	53	129.2 ± 18.8	0.978 (0.935–1.024)
T_{max} (h), Median (range)	53	2.1 (2.0–6.1)	53	3.0 (2.0–6.1)	Not applicable
$T_{1/2}$ (h), Mean ± SD	53	339.5 ± 155.4	53	339.7 ± 135.6	Not applicable

AUC_{inf} = area under the curve to infinity; AUC_{last}: area under the concentration-time curve from time zero to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum concentration; SD = standard deviation.

Source: CTD 2.7.2, Tables 2.7.2.2-3 and 2.7.2.2-6; CSR SB2-G11-NHV, Table 11-3

Table 52: Summary of select PK parameters in study SB2-G11-NHV (PK population)

	n	SB2 (N=53)	n	EU-Remicade (N=53)	n	US-Remicade (N=53)
Vz (mL), Mean ± SD	51[a]	4,587 ± 1,583	53	4,846 ± 1,287	53	4,806 ± 1216
k_{el} (1/h), Mean ± SD	51[a]	0.0031 ± 0.0028	53	0.0026 ± 0.0014	53	0.0025 ± 0.0014
CL (mL/h), Mean ± SD	51[a]	10.90 ± 3.17	53	11.06 ± 3.04	53	10.70 ± 2.86
$\%AUC_{extrap}$ (%), Mean (SD)	51[a]	3.85 ± 3.94	53	4.57 ± 5.01	53	4.08 ±3.85

k_{el} = terminal rate constant; N = number of subjects in the PK population; n = number of subjects who contributed to summary statistics.

[a] 2 subjects were excluded from the PK population due to major protocol deviations.

Source: CSR SB2-G11-NHV

Figure 3: Mean serum concentrations vs. nominal times on linear (top) and semi-logarithmic (bottom) scale of SB2 vs. EU-Remicade in study SB2-G11-NHV (PK Population).

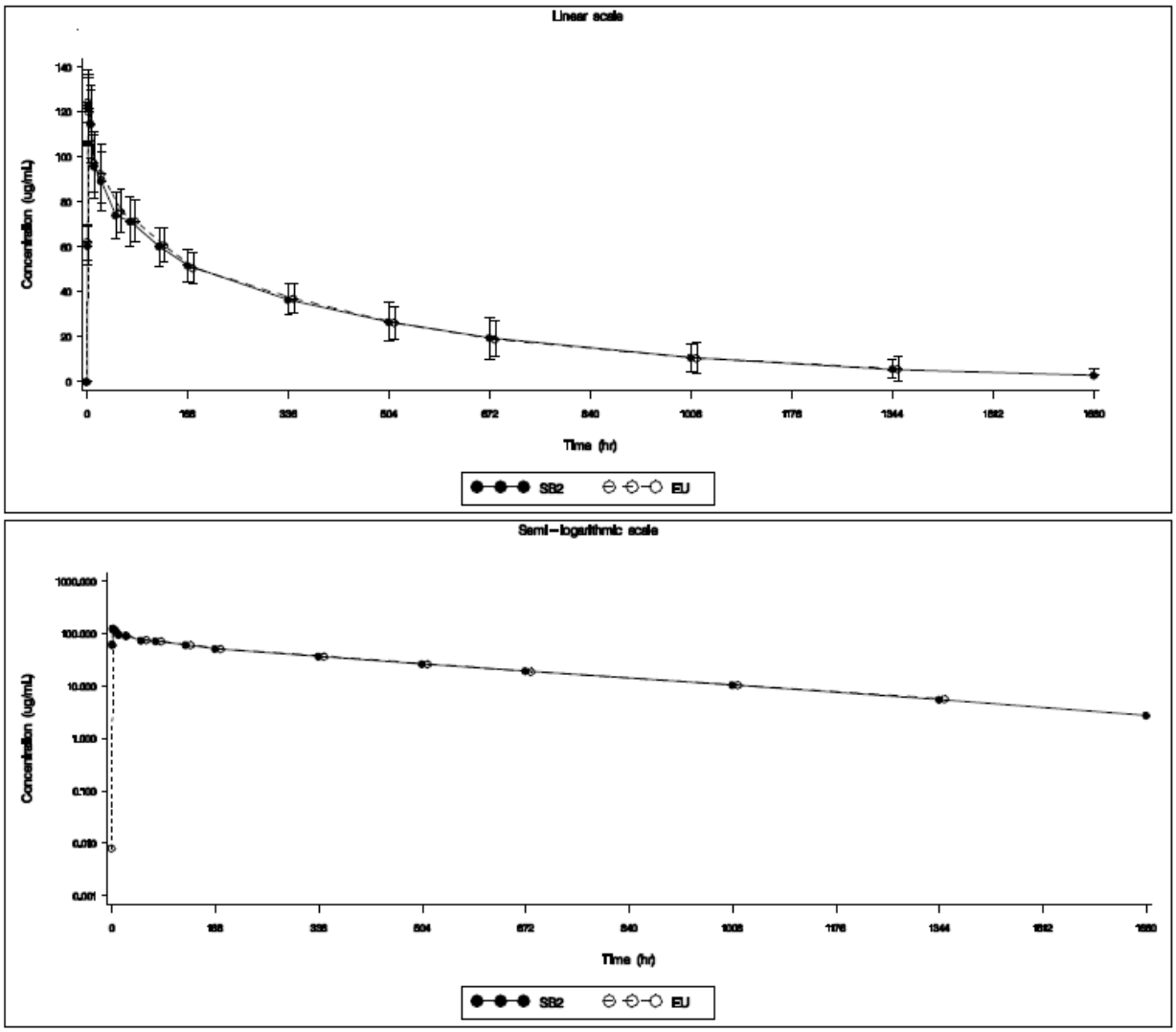


Figure 4: Mean serum concentrations vs. nominal times on linear (top) and semi-logarithmic (bottom) scale of SB2 vs. US-Remicade ® in study SB2-G11- NHV (PK Population).

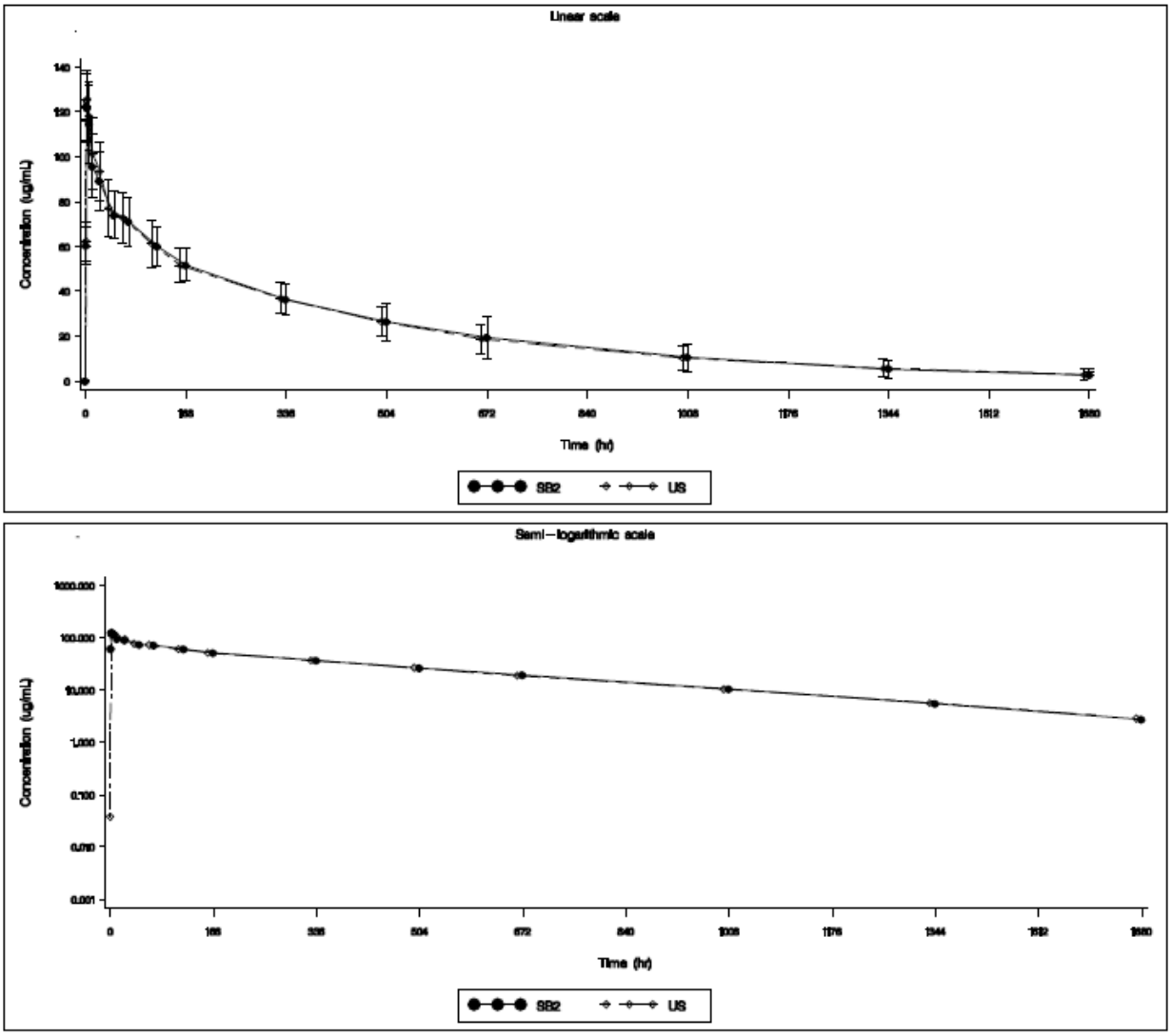


Figure 5: Mean serum concentrations vs. nominal times on linear (top) and semi-logarithmic (bottom) scale of EU-Remicade vs. US-Remicade ®) in study SB2-G11-NHV (PK Population)

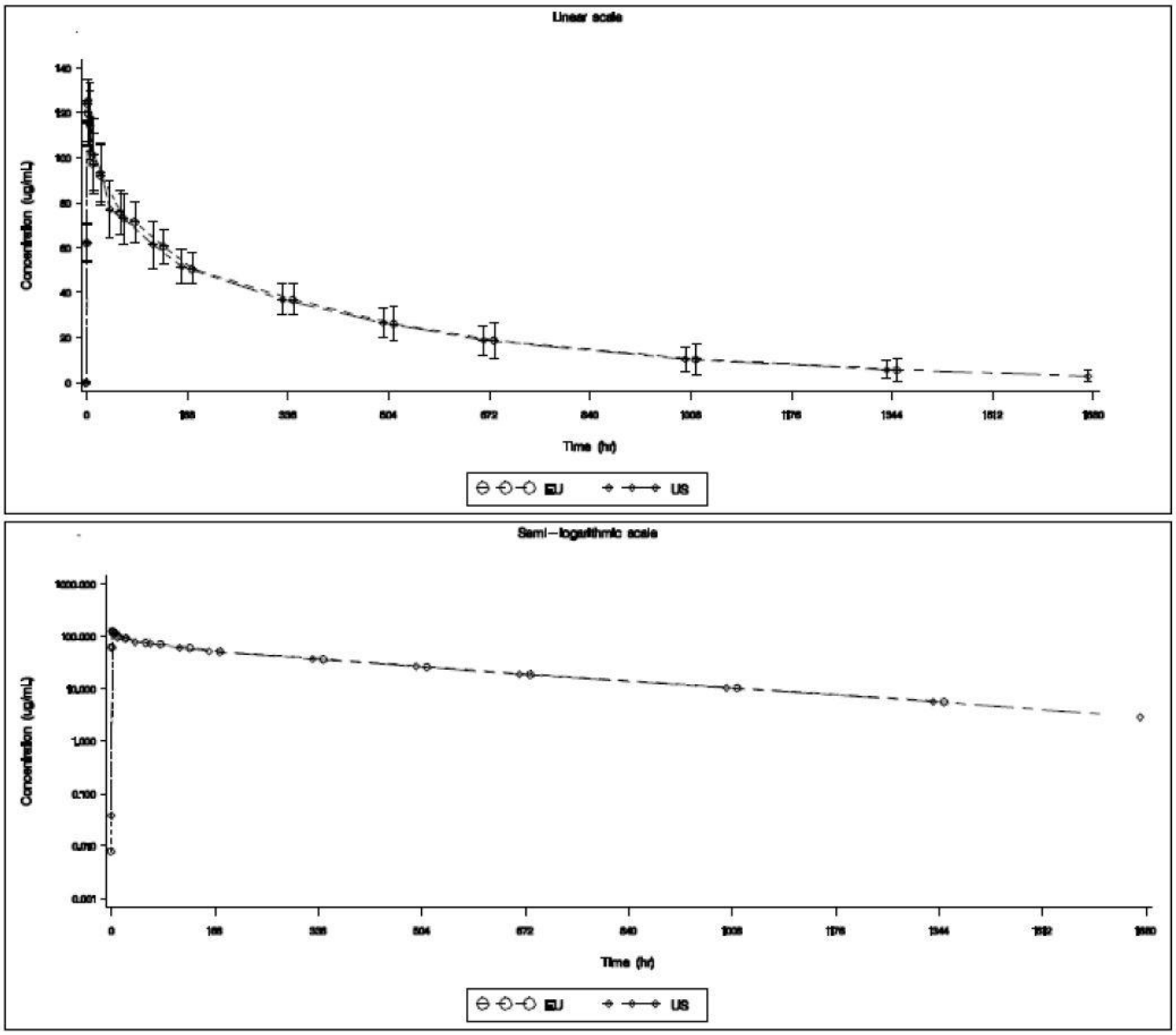


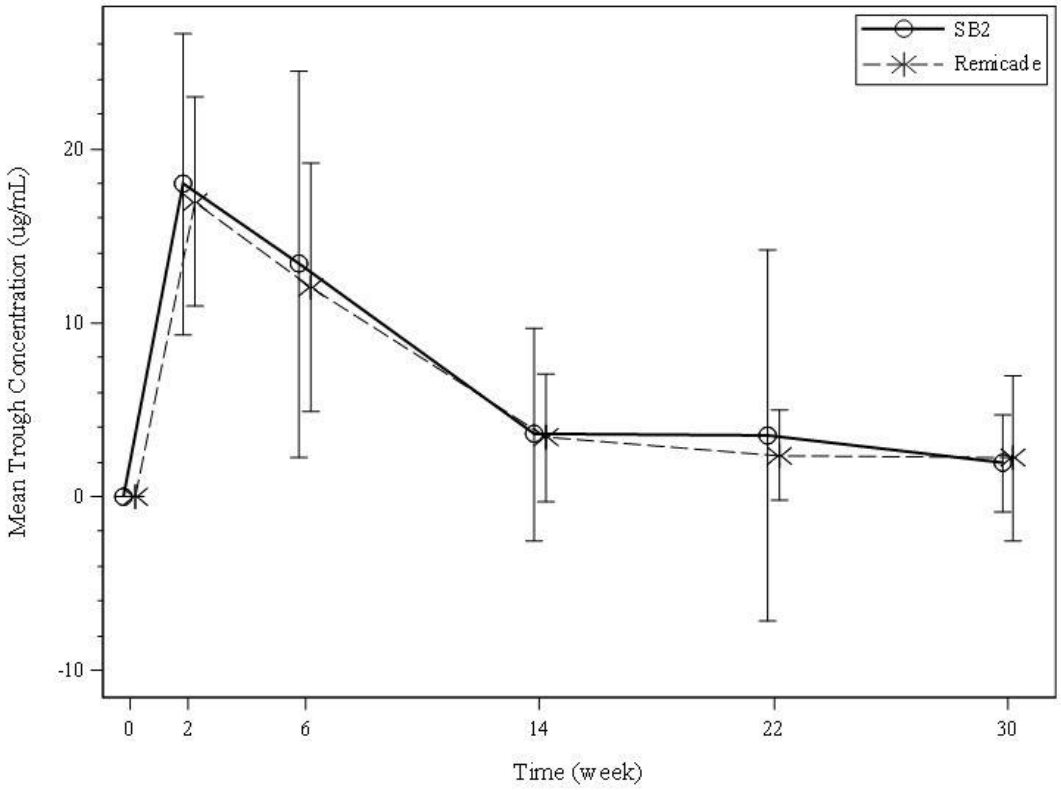
Table 53: Summary of infliximab serum trough (pre-dose) concentrations for SB2 and Remicade in in randomized, double-blind period of study SB2-G31-RA (PK Population)

		n	SB2 N=165	n	EU-Remicade N=160
Week 0	Mean (SD) CV% Min, Max	160	0.0 (0.0000) NC 0.00, 0.00	149	0.0 (0.0000) NC 0.00, 0.00
Week 2	Mean (SD) CV% Min, Max	161	17.965 (8.6612) 48.2125 0.00, 90.08	156	16.954 (6.0218) 35.5191 0.00, 34.79
Week 6	Mean (SD) CV% Min, Max	155	13.374 (11.1216) 83.1586 0.00, 73.32	153	12.039 (7.1710) 59.5654 0.00, 35.87
Week 14	Mean (SD) CV% Min, Max	153	3.593 (6.0938) 169.6090 0.00, 54.66	143	3.380 (3.6535) 108.0864 0.00, 23.24
Week 22	Mean (SD) CV% Min, Max	146	3.538 (10.6475) 300.9453 0.00, 110.54	147	2.390 (2.6090) 109.1630 0.00, 12.90
Week 30	Mean (SD) CV% Min, Max	139	1.915 (2.8055) 146.5085 0.00, 19.33	143	2.224 (4.7326) 212.7572 0.00, 50.71

CV%: coefficient of variation; Max: maximum; Min: minimum; SD: standard deviation

Source: CTD 2.7.2, Table 2.7.2.2-8

Figure 6: Mean Serum Trough (Pre-dose) Concentration-time Profiles from Week 0 to Week 30 in Study SB2-G31-RA



Source: CTD 2.7.2, Figure 2.7.2.2-5

Table 54: Incidence of ADAs and NAbs to in Infliximab in RA patients in the randomized, double-blind study SB2-G31-RA (SAF)

Timepoint		SB2 3 mg/kg (N=290)			Remicade 3 mg/kg (N=293)			Total (N=583)		
	Parameter	n'	n	(%)	n'	n	(%)	n'	n	(%)
W0	ADA-Pos	290	5	(1.7)	293	7	(2.4)	583	12	(2.1)
	NAb-Pos	5	0	(0.0)	7	0	(0.0)	12	0	(0.0)
W2	ADA-Pos	286	10	(3.5)	291	14	(4.8)	577	24	(4.2)
	NAb-Pos	10	4	(40.0)	14	4	(28.6)	24	8	(33.3)
W6	ADA-Pos	282	21	(7.4)	286	16	(5.6)	568	37	(6.5)
	NAb-Pos	21	11	(52.4)	16	7	(43.8)	37	18	(48.6)
W14	ADA-Pos	274	73	(26.6)	280	63	(22.5)	554	136	(24.5)
	NAb-Pos	73	70	(95.9)	63	60	(95.2)	136	130	(95.6)
W22	ADA-Pos	268	121	(45.1)	273	108	(39.6)	541	229	(42.3)
	NAb-Pos	121	113	(93.4)	108	96	(88.9)	229	209	(91.3)
W30	ADA-Pos	251	133	(53.0)	264	116	(43.9)	515	249	(48.3)
	NAb-Pos	133	129	(97.0)	116	109	(94.0)	249	238	(95.6)
W30 overall*	ADA-Pos	287	158	(55.1)	292	145	(49.7)	579	303	(52.3)
	NAb-Pos	158	146	(92.4)	145	130	(89.7)	303	276	(91.1)
W38	ADA-Pos	243	123	(50.6)	255	115	(45.1)	498	238	(47.8)
	NAb-Pos	123	114	(92.7)	115	103	(89.6)	238	217	(91.2)
W46	ADA-Pos	237	121	(51.1)	231	99	(42.9)	468	220	(47.0)
	NAb-Pos	121	113	(93.4)	99	87	(87.9)	220	200	(90.9)
W54	ADA-Pos	223	118	(52.9)	222	89	(40.1)	445	207	(46.5)
	NAb-Pos	118	99	(83.9)	89	78	(87.6)	207	177	(85.5)
W54 overall*	ADA-Pos	287	179	(62.4)	292	168	(57.5)	579	347	(59.9)
	NAb-Pos	179	166	(92.7)	168	147	(87.5)	347	313	(90.2)

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

Source: CTD 2.7.2, Table 2.7.2.4-4

Table 55: Incidence of ADAs and NAbs to in infliximab in RA patients in the transition-extension period in study SB2-G31-RA (Ex-SAF)

Timepoint	Parameter	SB2			Remicade									Total		
					Overall			SB2			Remicade					
		N=201			N=195			N=94			N=101			N=396		
		n'	n	(%)	n'	n	(%)	n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 0 (St-BL)	ADA	201	4	(2.0)	195	3	(1.5)	94	3	(3.2)	101	0	(0.0)	396	7	(1.8)
	Nab	4	0	(0.0)	3	0	(0.0)	3	0	(0.0)	0	0	(0.0)	7	0	(0.0)
Week 54 (Ex-BL)	ADA	198	101	(51.0)	193	75	(38.9)	92	31	(33.7)	101	44	(43.6)	391	176	(45.0)
	NAb	101	82	(81.2)	75	66	(88.0)	31	28	(90.3)	44	38	(86.4)	176	148	(84.1)
Week 62	ADA	193	92	(47.7)	195	79	(40.5)	94	35	(37.2)	101	44	(43.6)	388	171	(44.1)
	NAb	92	82	(89.1)	79	69	(87.3)	35	33	(94.3)	44	36	(81.8)	171	151	(88.3)
Week 70	ADA	188	89	(47.3)	191	76	(39.8)	91	34	(37.4)	100	42	(42.0)	379	165	(43.5)
	NAb	89	80	(89.9)	76	71	(93.4)	34	32	(94.1)	42	39	(92.9)	165	151	(91.5)
Week 78	ADA	187	88	(47.1)	182	70	(38.5)	88	32	(36.4)	94	38	(40.4)	369	158	(42.8)
	NAb	88	84	(95.5)	70	63	(90.0)	32	28	(87.5)	38	35	(92.1)	158	147	(93.0)
Week 78 overall*	ADA	201	133	(66.2)	195	120	(61.5)	94	59	(62.8)	101	61	(60.4)	396	253	(63.9)
	NAb	133	126	(94.7)	120	104	(86.7)	59	49	(83.1)	61	55	(90.2)	253	230	(90.9)
Week 78 overall**	ADA	194	104	(53.6)	195	94	(48.2)	94	43	(45.7)	101	51	(50.5)	389	198	(50.9)
	NAb	104	95	(91.3)	94	83	(88.3)	43	38	(88.4)	51	45	(88.2)	198	178	(89.9)

ADA: anti-drug antibody; Ex-BL: Extended Baseline; Nab: neutralising antibody; n': number of subjects with available ADA/NAb results against SB2 at each timepoint; St-BL: Study Baseline.

Percentages were based on n'.

*Overall ADA (or NAb) results were defined as "Positive" for subjects with ≥1 ADA (or NAb) positive up to Week 78 after Week 0, otherwise results were determined as "Negative".

**Overall ADA (or NAb) results were defined as "Positive" for subjects with ≥1 ADA (or NAb) positive up to Week 78 after Week 54, otherwise results were determined as "Negative".

Source: 78-week CSR SB2-G31-RA, Table 12-21

Table 56: Incidence of ADAs and NAbs to infliximab in study SB2-G11-NHV in Healthy Subjects (Safety Population)

Parameter	Time point	Result	SB2 *n/n'* (%)	EU-Remicade *n/n'* (%)	US-Remicade *n/n'* (%)
ADA	Day 1 Pre-dose	Positive	0/53 (0.0)	0/53 (0.0)	0/53 (0.0)
		Negative	53/53 (100.0)	53/53 (100.0)	53/53 (100.0)
	Day 29	Positive	2/53 (3.8)	0/53 (0.0)	1/53 (1.9)
		Negative	51/53 (96.2)	53/53 (100.0)	52/53 (98.1)
	Day 71	Positive	25/53 (47.2)	20/53 (37.7)	20/53 (37.7)
		Negative	28/53 (52.8)	33/53 (62.3)	33/53 (62.3)
	Post-dose	Positive	25/53 (47.2)	20/53 (37.7)	20/53 (37.7)
NAb	Day 1 Pre-dose	Positive	0/0	0/0	0/0
		Negative	0/0	0/0	0/0
	Day 29	Positive	1/2 (50.0)	0/0	0/1 (0.0)
		Negative	1/2 (50.0)	0/0	1/1 (100.0)
	Day 71	Positive	14/25 (56.0)	14/20 (70.0)	7/20 (35.0)
		Negative	11/25 (44.0)	6/20 (30.0)	13/20 (65.0)

ADA anti-drug antibody, n number of subjects with each assessment result at each time point, n' number of subjects with available assessment results at each time point, NAb neutralizing antibody

Percentages for ADA result were based on the number of subjects with available ADA results at each time point (except post-dose).

ADA result at post-dose was for the subjects with a positive result at either Day 29 or Day 71 follow-up.

Percentages for ADA results at post-dose were based on the number of subjects in the safety set.

Percentages for NAb results were based on the number of subjects with positive ADA at each time point.

Source: CSR SB2-G11-NHV, Table 12-2

Appendix 2: Listing Status for Reference Product and Other Biosimilars

For each indication that is approved by Health Canada for the biosimilar (or likely to be approved, in the case of a submission filed on a pre-NOC basis), please provide the publicly available listing status and criteria for the reference product and other biosimilars, if applicable. CADTH may update the information provided by the manufacturer with new information provided by the CDR-participating drug plans, as required.

Step 1: Use the following abbreviations to complete the table. Use a separate row for each indication and add more rows if necessary.

Abbreviation	Description
EX	Exception item for which coverage is determined on a case-by-case basis
FB	Full benefit
NB	Not a benefit
RES	Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit)
UR	Under review
–	Information not available

Listing Status for Remicade

Indication(s)	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON[c,d]	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Rheumatoid arthritis	RES[a]	RES[a]	RES	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	EX
Ankylosing spondylitis	RES[a]	RES[a]	RES	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	NB	NB	RES[a]	EX
Crohn's disease (adult)	RES[a,b]	RES[a]	RES[b]	RES[a,b]	RES[a,b]	RES[a,b]	RES[a,b]	RES[a,b]	RES[a,b]	RES[a,b]	RES[a,b]	RES[a.b]	RES	EX
Crohn's disease (pediatric)	RES[a,b]	-	RES[b]	-	RES	-	-	-	-	-	-	-	NB	NB
Fistulising Crohn's disease	RES[a]	RES[a]	RES	RES[a]	RES[a]	NB	RES[a]	RES[a]	-	RES[a]	RES[a]	RES[a]	RES	EX
Ulcerative colitis (adult)	NB	RES[a]	RES[b]	RES[a,b]	RES[a,b]	NB	RES[a,b]	NB	NB	RES[a,b]	NB	NB	NB	EX
Ulcerative colitis (pediatric)	NB	-	RES[b]	-	RES	NB	-	NB	NB	-	-	-	NB	NB
Psoriatic arthritis	RES[a]	RES[a]	RES	RES[a]	RES[a]	NB	RES[a]	NB	NB	RES[a]	NB	NB	NB	EX
Plaque psoriasis	RES[a]	RES[a]	RES	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	NB	NB	RES[a]	EX

AB = Alberta, BC = British Columbia, DND = Department of National Defence; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC =Veterans Affairs Canada; YK = Yukon.

[a] New patients not eligible for Remicade.

[b] No age restriction specified in criteria

[c] EAP renewals are accepted for existing patients on Remicade while new patients are eligible to receive Inflectra (LU benefit with code)

[d] Remicade is also reimbursed for the treatment of severe non-infectious ocular inflammatory disease (OID), polyarticular-course juvenile idiopathic arthritis, juvenile spondyloarthritis (JSpA) or enthesitis-related arthritis (ERA) under the ODB EAP.

Listing Status for Inflectra

Indication(s)	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Rheumatoid arthritis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	NB
Ankylosing spondylitis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	NB
Crohn's disease (adult)	RES[a]	RES	RES[a]	RES[a]	RES	RES[a]	RES	RES[a]	RES[a]	RES[a]	RES[a]	RES[a]	NB	NB
Crohn's disease (pediatric)	RES	NB	NB	-	NB	-	-	-	-	-	-	-	NB	NB
Fistulising Crohn's disease	RES	RES	RES	RES	RES	NB	RES	RES	-	RES	RES	RES	NB	NB
Ulcerative colitis (adult)	RES	RES	RES[a]	RES[a]	RES	RES[a]	RES	NB	RES[a]	RES[a]	RES[a]	RES[a]	NB	NB
Ulcerative colitis (pediatric)	RES	NB	NB	-	NB	-	-	NB	-	-	-	-	NB	NB
Psoriatic arthritis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	NB	NB
Plaque psoriasis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	NB

AB = Alberta, BC = British Columbia, DND = Department of National Defence; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC =Veterans Affairs Canada; YK = Yukon.

[a] No age restriction specified in criteria

Step 2: For all restricted benefit entries (RES), please state the criteria used by each drug plan. Use a separate table for each indication and add or delete rows as necessary.

Restricted Benefit Criteria for Remicade for the treatment of Rheumatoid Arthritis

Drug Plan	Criteria for Restricted Benefit
BC	Patients granted Special Authority prior to Feb. 19, 2016 Treatment of Rheumatoid Arthritis according to established criteria* when prescribed by a rheumatologist. *Initial / Switch:* • Not eligible *Renewal:* • Indefinite coverage, 3 mg/kg every 8 weeks, OR • Renewal of one year
AB	Not eligible for new patients starting April 1, 2016. *Renewal:* For continued coverage beyond three doses, the patient must meet the following criteria: 1) The patient must be assessed by an RA Specialist after the initial three doses to determine response. 2) The RA Specialist must confirm in writing that the patient is a 'responder' that meets the following criteria: • ACR20 OR an improvement of 1.2 units in the DAS28 score [reported to one (1) decimal place]; AND • An improvement of 0.22 in HAQ score [reported to two (2) decimal places]. It should be noted that the initial score for the DAS28 or HAQ score on record will be rounded to the correct number of decimal places as indicated above. Following this assessment, continued coverage may be approved for one 3 mg/kg dose every 8 weeks for a period of 12 months [Note: For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg and/or treating as often as every 4 weeks]. Ongoing coverage may be considered only if the following criteria are met at the end of each 12-month period: 1) The patient has been assessed by an RA Specialist to determine response; 2) The RA Specialist must confirm in writing that the patient has maintained a response to therapy as indicated by: • confirmation of maintenance of ACR20, OR • maintenance of a minimum improvement of 1.2 units in DAS28 score [reported to one (1) decimal place] from baseline. 3) A current HAQ score [reported to two (2) decimal places] must be included with all renewal requests. It should be noted that the initial score for the DAS28 or HAQ score on record will be rounded to the correct number of decimal places as indicated above.
SK	• Active rheumatoid arthritis in patients who have failed treatment with methotrexate and leflunomide; OR • Active rheumatoid arthritis in patients intolerant to methotrexate and leflunomide. Treatment should be combined with an immunosuppressant. Exceptions can be considered in cases where methotrexate or leflunomide are contraindicated. This product should be used in consultation with a specialist in this area.
MB	For the treatment of patients over 18 years of age who have moderate to severe active rheumatoid arthritis who have failed treatment with at least 3 DMARD therapies, one of which is methotrexate and/or leflunomide unless intolerance or contraindications to these agents is documented. One combination therapy of

Drug Plan	Criteria for Restricted Benefit
	DMARDs must also be tried. Initial application information should include information on disease activity such as the number of tender joins, swollen joints, erythrocyte sedimentation rate and C-reactive protein value. Request for coverage must be made by a specialist in rheumatology. Inflectra will be the preferred infliximab option for all infliximab-naive patients prescribed an infliximab product for Rheumatoid Arthritis. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naive patients. Patients will not be permitted to switch from Remicade to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy.
ON	For the treatment of rheumatoid arthritis in patients who have: • Severe active disease (≥ 5 swollen joints and rheumatoid factor positive and/or, anti-CCP positive, and/or radiographic evidence of rheumatoid arthritis) despite the optimal use of various formulary disease-modifying anti-rheumatic drugs (DMARDs)*. *Optimal use of DMARDs include: • Methotrexate (20 mg/week) for at least 3 months and leflunomide (20 mg/day) for at least 3 months in addition to an adequate trial (3 months) of at least one combination of DMARDs; or • Methotrexate (20 mg/week) for at least 3 months and leflunomide in combination with methotrexate for at least 3 months. • If the patient could not receive adequate trial(s) of methotrexate and/or leflunomide due to contraindication(s) or intolerance(s), the nature of contraindication(s) or intolerance(s) must be provided along with details of trials of other DMARDs or clear rationale why other DMARDs cannot be considered. OR • Methotrexate (20mg/week), sulfasalazine (2 GM/day) and hydroxychloroquine (400mg/day)* for at least 3 months. If the patient could not receive an adequate trial of methotrexate, sulfasalazine and hydroxychloroquine due to intolerance, then the above DMARD trial criteria must be met. Hydroxychloroquine is based by weight up to 400 mg per day Renewal will be considered for patients with objective evidence of at least a 20% reduction in swollen joint count and a minimum of improvement in 2 swollen joints over the previous year. For renewals beyond the second year, objective evidence of preservation of treatment effect must be provided. The planned dosing regimen for the requested biologic should be provided. The recommended doses for the treatment of rheumatoid arthritis are as follows: • Adalimumab 40mg every two weeks • Anakinra 100mg per day • Certolizumab pegol 400mg at 0, 2 and 4 weeks followed by maintenance therapy of 200 mg every 2 weeks. For maintenance dosing, 400mg every 4 weeks may be considered • Etanercept 25mg twice weekly or 50mg once weekly

Drug Plan	Criteria for Restricted Benefit
	• Golimumab 50mg once a month • Infliximab 3mg/kg/dose at 0, 2 and 6 weeks followed by maintenance therapy of 3mg/kg/dose every 8 weeks up to a maximum of six maintenance doses per year (Note that effective December 22, 2016, Tofacitinib (Xeljanz) 5 mg is available on the ODB Formulary in patients meeting the Limited Use criteria)
NB	• For the treatment of severely active rheumatoid arthritis, in combination with methotrexate or other diseasemodifying antirheumatic drugs (DMARDs), in adult patients who are refractory or intolerant to: o Methotrexate (oral or parenteral), alone or in combination with another DMARD, at a dose of ≥ 20 mg weekly (≥15mg if patient is ≥65 years of age) for a minimum of 12 weeks; and o Methotrexate in combination with at least two other DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 12 weeks. Clinical Notes: 1. For patients who do not demonstrate a clinical response to oral methotrexate, or who experience gastrointestinal intolerance, a trial of parenteral methotrexate must be considered. 2. Optimal treatment response to DMARDs may take up to 24 weeks, however coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. 3. For patients who have intolerances preventing the use of triple DMARD therapy, these must be described and dual therapy with DMARDs must be tried. 4. Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above. 5. Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented. Claim Notes: • Must be prescribed by a rheumatologist. • Combined use of more than one biologic DMARD will not be reimbursed. • All requests for coverage of infliximab for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra brand only. • Approvals will be for a maximum of 3mg/kg/dose at 0, 2 and 6 weeks, then every 8 weeks thereafter. • Initial Approval: 6 months. • Renewal Approval: 1 year. Confirmation of continued response is required. • Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions as outlined here.
NS	• For the treatment of severely active rheumatoid arthritis, in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDs), in adult patients who are refractory or intolerant to: o methotrexate (oral or parenteral) at a dose of ≥ 20 mg weekly (≥15mg if patient is ≥65 years of age), or use in combination with another DMARD, for a minimum of 12 weeks AND o methotrexate in combination with at least two other DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 12 weeks Clinical Notes: • For patients who do not demonstrate a clinical response to oral methotrexate, or who experience gastrointestinal intolerance, a trial of parenteral methotrexate must be considered.

Drug Plan	Criteria for Restricted Benefit
	• Optimal treatment response to DMARDs may take up to 24 weeks, however coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. • If patient factors (e.g. intolerance) prevent the use of triple DMARD therapy, these must be described and dual therapy with DMARDs must be tried. • Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above. • Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented. Claim Notes: • Must be prescribed by a rheumatologist. • Combined use of more than one biologic DMARD will not be reimbursed. • Initial Approval: 6 months • Renewal Approval: 1 year. Confirmation of continued response is required. Maximum dosage approved: Infliximab (Remicade): 3mg/kg/dose at 0, 2 and 6 weeks, then every 8 weeks thereafter For infliximab-naïve patients whose infliximab therapy is initiated after June 1, 2016, Inflectra will be the product approved.
PE	Initial approval for adults is for Infliximab is for 3mg/kg/dose given at 0, 2, and 6 weeks. For the treatment of Rheumatoid Arthritis in patients who: i) Have not responded to a trial of at least 3 months of Leflunomide, AND ii) Have not responded to or have had intolerable toxicity to an adequate trial of Methotrexate and at least one of the following DMARDs (disease modifying antirheumatic drugs): IM Gold, Sulfasalazine, Hydroxychloroquine, Azathioprine, Chloroquine, or Penicillamine, OR iii) Are intolerant to or have a contraindication to Methotrexate and are refractory to at least two of the following DMARDs (disease modifying antirheumatic drugs): IM Gold, Sulfasalazine, Hydroxychloroquine, Azathioprine, Chloroquine, or Penicillamine, OR iv) Are not a candidate for combination DMARD therapy but have had an adequate trial of Methotrexate and at least two of the following DMARDs in sequence: IM Gold, Sulfasalazine, Hydroxychloroquine, Azathioprine, Chloroquine, or Penicillamine. An adequate trial is considered to be 5 months for IM Gold, 6 months for Penicillamine, 4 months for Hydroxychloroquine, and 3 months for all other traditional DMARDs. Unless limited by toxicity, the Methotrexate dosage should be increased up to 25mg/week unless a response is achieved at a lower dose. Renewal of coverage will require reassessment of the patient and submission of a new Special Authorization form. Initial approval* will be for a 6 month period. Coverage will NOT be considered for use in combination with other biologic agents.

Drug Plan	Criteria for Restricted Benefit
NL	For the treatment of severely active rheumatoid arthritis, in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDs), in adult patients who are refractory or intolerant to: • Methotrexate (oral or parenteral) at a dose of ≥ 20 mg weekly (≥15mg if patient is ≥65 years of age) for a minimum of 12 weeks, followed by methotrexate in combination with at least two other DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 12 weeks; OR • Initial use of triple DMARD therapy with methotrexate in combination with at least twoother DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 24 weeks. Clinical Notes: • For patients who do not demonstrate a clinical response to oral methotrexate, or who experience gastrointestinal intolerance, a trial of parenteral methotrexate must be considered. • Optimal treatment response may take up to 24 weeks, however if no improvement is seen after 12 weeks of triple DMARD use, therapy should be changed. • If the patient is intolerant to triple DMARD therapy, then dual therapy with DMARDs (methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) must be considered. • Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above. • Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented. Claim Notes: • Must be prescribed by a rheumatologist. • Combined use of more than one biologic DMARD will not be reimbursed. • Patients will not be permitted to switch from Inflectra™ to another infliximab product or vice versa, if previously trialed and deemed unresponsive to therapy. • Initial Approval: 6 months • Renewal Approval: 1 year. Confirmation of continued response is required. • Maximum Dosage Approved: ○ Infliximab (Remicade): 3mg/kg/dose at 0, 2 and 6 weeks followed by maintenance therapy of 3mg/kg/dose every 8 weeks. Please note: Inflectra is the preferred infliximab therapy for treatment naïve patients (coverage will only be considered for Remicade in patients stabilized prior to June 1, 2016) To facilitate this process specific RA Medications Special Authorization Forms have been developed and can be found at: http://www.health.gov.nl.ca/health/prescription/ra_meds_initiation.pdf http://www.health.gov.nl.ca/health/prescription/ra_meds_continuation_request.pdf
YK	For severely active Rheumatoid Arthritis on recommendation of specialist. Specialist's consult to be provided. For patients refractory or intolerant to parenteral methotrexate after at least a 12 week trial AND A 3 month trial of at least 2 of the following; leflunomide, sulfasalazine, azathioprine AND A 3 month trial of at least one DMARD combination such as a)methotrexate & cyclosporine b) methotrexate with hydroxychloroquine and sulfasalazine c) methotrexate with leflunomide.

Drug Plan	Criteria for Restricted Benefit
	NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Coverage is provided for an initial three doses of 3 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a rheumatologist Coverage is provided, in combination with methotrexate (MTX) or other disease modifying anti-rheumatic drugs (DMARDs), for the reduction in signs and symptoms of severely active RA in adult patients ≥ 18 years who have failed: • MTX (oral or parenteral) at a dose ≥ 20 mg weekly (≥ 15 mg weekly if patient is ≥ 65 years) for a minimum of 12 weeks of continuous treatment. Note: Patients who do not exhibit a clinical response to oral MTX or who experience gastrointestinal intolerance may consider a trial of parenteral MTX; AND • MTX in combination with at least two other DMARDS, such as sulfasalazine and hydroxychloroquine, for a minimum of 12 weeks of continuous treatment; OR, if the patient has a contraindication, failure, or intolerance to MTX: • A combination of at least two DMARDS, such as sulfasalazine, hydroxychloroquine, azathioprine, leflunomide, cyclosporine or gold, for a minimum of 12 weeks of continuous treatment. Coverage beyond the initial three doses will be based on a 20% improvement in 3 of 5 baseline clinical parameters. • >20% reduction in number of tender and swollen joints; PLUS • >20% improvement in Physician Global Assessment scale; PLUS either • >20% improvement in Patient Global Assessment scale; OR • >20% reduction in the acute phase as measured by ESR or CRP.
NIHB	Coverage is provided for an initial three doses of 3 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a rheumatologist Coverage is provided, in combination with methotrexate (MTX) or other disease modifying anti-rheumatic drugs (DMARDs), for the reduction in signs and symptoms of severely active RA in adult patients ≥ 18 years who have failed: • MTX (oral or parenteral) at a dose ≥ 20 mg weekly (≥ 15 mg weekly if patient is ≥ 65 years) for a minimum of 12 weeks of continuous treatment. Note: Patients who do not exhibit a clinical response to oral MTX or who experience gastrointestinal intolerance may consider a trial of parenteral MTX; AND • MTX in combination with at least two other DMARDS, such as sulfasalazine and hydroxychloroquine, for a minimum of 12 weeks of continuous treatment; OR, if the patient has a contraindication, failure, or intolerance to MTX: • A combination of at least two DMARDS, such as sulfasalazine, hydroxychloroquine, azathioprine, leflunomide, cyclosporine or gold, for a minimum of 12 weeks of continuous treatment. Coverage beyond the initial three doses will be based on a 20% improvement in 3 of 5 baseline clinical parameters. • >20% reduction in number of tender and swollen joints; PLUS • >20% improvement in Physician Global Assessment scale; PLUS either • >20% improvement in Patient Global Assessment scale; OR • >20% reduction in the acute phase as measured by ESR or CRP.
DND	• As of September 1st 2016, all new patients using infliximab for rheumatoid arthritis, ankylosing spondylitis and plaque psoriasis will be covered for Inflectra

Drug Plan	Criteria for Restricted Benefit
	brand only • Patients that have previously received Special Authorization coverage for Remicade for rheumatoid arthritis, ankylosing spondylitis and plaque psoriasis will continue to receive coverage for this drug. When prescribed by a rheumatologist or a prescriber with a specialty in rheumatology for patients with moderate to severe active rheumatoid arthritis despite treatment with at least 2 DMARDs [including methotrexate unless contraindicated] in mono or combination therapy after 3 months at target dose. Note: Methotrexate at 20mg (PO, SC, IM) or greater total weekly dosage for more than 12 weeks. Patients who do not exhibit a clinical response to PO methotrexate or experience gastrointestinal intolerance to PO methotrexate must have a trial of parenteral methotrexate before being accepted as refractory AND One or more of the following: • Leflunomide 20mg daily for 10 weeks • Gold weekly injections for 20 weeks • Sulfasalazine ≥ 2gm daily for 3 months • Azathioprine 2-3mg/kg/day for 3 months
VAC	Case-by-case

Restricted Benefit Criteria for Inflectra for the treatment of Rheumatoid Arthritis

Drug Plan	Criteria for Restricted Benefit
BC	New Patients Treatment of Rheumatoid Arthritis according to established criteria* when prescribed by a rheumatologist. *Initial / Switch:* • 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks for 1 year *Switch:* • Never achieving a 20% improvement • At least 20% improvement in first 12 weeks of a TNF inhibitor (24 weeks for abatacept and rituximab) but loss of benefit *Renewal:* • Indefinite coverage, 3 mg/kg every 8 weeks, OR • Renewal of one year
AB	*Initial:* Special authorization coverage may be provided for use in combination with methotrexate for the reduction in signs and symptoms of severely active Rheumatoid Arthritis (RA) in adult patients (18 years of age or older) who are refractory or intolerant to: • Methotrexate at 20 mg (PO, SC or IM) or greater total weekly dosage (15 mg or greater if patient is 65 years of age or older) for more than 12 weeks. Patients who do not exhibit a clinical response to PO methotrexate or experience gastrointestinal intolerance to PO methotrexate must have a trial of parenteral methotrexate before being accepted as refractory; AND • Methotrexate with other disease modifying anti-rheumatic agent(s) (minimum 4 month trial) [e.g., methotrexate with hydroxychloroquine or methotrexate with sulfasalazine]; AND • Leflunomide (minimum 10 week trial at 20 mg daily) 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. For coverage, this drug must be initiated by a Specialist in Rheumatology ("RA Specialist"). *Renewal:* For continued coverage beyond three doses, the patient must meet the following criteria: 1) The patient must be assessed by an RA Specialist after the initial three doses to determine response. 2) The RA Specialist must confirm in writing that the patient is a 'responder' that meets the following criteria:

Drug Plan	Criteria for Restricted Benefit
	• ACR20 OR an improvement of 1.2 units in the DAS28 score [reported to one (1) decimal place]; AND • An improvement of 0.22 in HAQ score [reported to two (2) decimal places]. It should be noted that the initial score for the DAS28 or HAQ score on record will be rounded to the correct number of decimal places as indicated above. Following this assessment, continued coverage may be approved for one 3 mg/kg dose every 8 weeks for a period of 12 months [Note: For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg and/or treating as often as every 4 weeks]. Ongoing coverage may be considered only if the following criteria are met at the end of each 12-month period: 1) The patient has been assessed by an RA Specialist to determine response; 2) The RA Specialist must confirm in writing that the patient has maintained a response to therapy as indicated by: • confirmation of maintenance of ACR20, OR • maintenance of a minimum improvement of 1.2 units in DAS28 score [reported to one (1) decimal place] from baseline. 3) A current HAQ score [reported to two (2) decimal places] must be included with all renewal requests. It should be noted that the initial score for the DAS28 or HAQ score on record will be rounded to the correct number of decimal places as indicated above.
SK	• For treatment of active rheumatoid arthritis in patients who have failed treatment with methotrexate and leflunomide; OR • For treatment of active rheumatoid arthritis in patients intolerant to methotrexate and leflunomide. Treatment should be combined with an immunosuppressant. Exceptions can be considered in cases where methotrexate or leflunomide are contraindicated. This product should be used in consultation with a specialist in this area.
MB	For the treatment of patients over 18 years of age who have moderate to severe active rheumatoid arthritis who have failed treatment with at least 3 DMARD therapies, one of which is methotrexate and/or leflunomide unless intolerance or contraindications to these agents is documented. One combination therapy of DMARDs must also be tried. Initial application information should include information on disease activity such as the number of tender joints, swollen joints, erythrocyte sedimentation rate and C-reactive protein value. Request for coverage must be made by a specialist in rheumatology. Inflectra will be the preferred infliximab option for all infliximab-naive patients prescribed an infliximab product for Rheumatoid Arthritis. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naive patients. Patients will not be permitted to switch from Inflectra to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy
ON	Limited Use Notes: For the treatment of rheumatoid arthritis (RA) in patients who have severe active disease (greater than or equal to 5 swollen joints and rheumatoid factor positive and/or, anti-CCP positive, and/or radiographic evidence of rheumatoid arthritis) and have experienced failure, intolerance, or have a contraindication to adequate trials of disease-modifying anti-rheumatic drugs (DMARDs) treatment regimens, such as one of the following combinations of treatments: A. i) Methotrexate (20mg/week) for at least 3 months, AND ii) leflunomide (20mg/day) for at least 3 months, in addition to

Drug Plan	Criteria for Restricted Benefit
	iii) an adequate trial of at least one combination of DMARDs for 3 months; OR B. i) Methotrexate (20mg/week) for at least 3 months, AND ii) leflunomide in combination with methotrexate for at least 3 months; OR C. i) Methotrexate (20mg/week), sulfasalazine (2g/day) and hydroxychloroquine (400mg/day) for at least 3 months. (Hydroxychloroquine is based by weight up to 400mg per day.) Maintenance/Renewal: After 12 months of treatment, maintenance therapy is funded for patients with objective evidence of at least a 20 percent reduction in swollen joint count and a minimum of improvement in 2 swollen joints over the previous year. For renewals beyond the second year, the patient must demonstrate objective evidence of preservation of treatment effect. Therapy must be prescribed by a rheumatologist or a physician with expertise in rheumatology. The recommended dosing regimen is 3mg/kg/dose at 0, 2 and 6 weeks followed by maintenance therapy of 3mg/kg/dose every 8 weeks up to a maximum of six maintenance doses per year.
NB	• For the treatment of severely active rheumatoid arthritis, in combination with methotrexate or other disease modifying antirheumatic drugs (DMARDs), in adult patients who are refractory or intolerant to: ○ Methotrexate (oral or parenteral), alone or in combination with another DMARD, at a dose of ≥ 20 mg weekly (≥15mg if patient is ≥65 years of age) for a minimum of 12 weeks; and ○ Methotrexate in combination with at least two other DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 12 weeks. Clinical Notes: 1. For patients who do not demonstrate a clinical response to oral methotrexate, or who experience gastrointestinal intolerance, a trial of parenteral methotrexate must be considered. 2. Optimal treatment response to DMARDs may take up to 24 weeks, however coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. 3. For patients who have intolerances preventing the use of triple DMARD therapy, these must be described and dual therapy with DMARDs must be tried. 4. Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above. 5. Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented. Claim Notes: • Must be prescribed by a rheumatologist. • Combined use of more than one biologic DMARD will not be reimbursed. • All requests for coverage of infliximab for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra brand only. • Initial Approval: 6 months.

Drug Plan	Criteria for Restricted Benefit
	• Renewal Approval: 1 year. Confirmation of continued response is required. • Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions as outlined here.
NS	For infliximab-naïve patients whose infliximab therapy is initiated after June 1, 2016, Infectra will be the product approved for the following indications. • For the treatment of severely active rheumatoid arthritis, in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDs), in adult patients who are refractory or intolerant to: o methotrexate (oral or parenteral) at a dose of ≥ 20 mg weekly (≥15mg if patient is ≥65 years of age), or use in combination with another DMARD, for a minimum of 12 weeks AND o methotrexate in combination with at least two other DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 12 weeks Clinical Notes: • For patients who do not demonstrate a clinical response to oral methotrexate, or who experience gastrointestinal intolerance, a trial of parenteral methotrexate must be considered. • Optimal treatment response to DMARDs may take up to 24 weeks, however coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. • If patient factors (e.g. intolerance) prevent the use of triple DMARD therapy, these must be described and dual therapy with DMARDs must be tried. • Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above. • Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented. Claim Notes: • Must be prescribed by a rheumatologist. • Combined use of more than one biologic DMARD will not be reimbursed. • Initial Approval: 6 months • Renewal Approval: 1 year. Confirmation of continued response is required. • Maxium Dosage Approved: o Infliximab (Inflectra): 3mg/kg/dose at 0, 2 and 6 weeks, then every 8 weeks thereafter For infliximab-naïve patients whose infliximab therapy is initiated after December 1, 2016, Infectra will be the product approved for the following indications.
PE	Infliximab, injection powder, 100mg/vial (Inflectra-HOS) Initial approval for adults is 3mg/kg/dose given at 0, 2, and 6 weeks, and then every 8 weeks thereafter. For the treatment of severely active rheumatoid arthritis, in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDs), in adult patients who are refractory or intolerant to: Methotrexate (oral or parenteral) at a dose of ≥ 20 mg weekly (≥15mg if patient is ≥65 years of age), (or use in combination with another DMARD) for a minimum of 12 weeks

Drug Plan	Criteria for Restricted Benefit
	AND Methotrexate in combination with at least two other DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 12 weeks; Clinical Notes: • For patients who do not demonstrate a clinical response to oral methotrexate, or who experience gastrointestinal intolerance, a trial of parenteral methotrexate must be considered. • Optimal treatment response to DMARDs may take up to 24 weeks, however coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. • If patient factors (e.g. intolerance) prevent the use of triple DMARD therapy, these must be described and dual therapy with DMARDs must be tried. • Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above. • Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented. Claim Notes: • Must be prescribed by a rheumatologist. • Combined use of more than one biologic DMARD will not be reimbursed. • Initial Approval: 6 months • Renewal Approval: 1 year. Confirmation of continued response is required. The request for coverage must be made by a rheumatologist or prescriber with a specialty in rheumatology, using the Rheumatoid Arthritis Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms Patients must also apply for coverage through the High-Cost Drug Program. The patient application is available from the Drug Programs Office or online at http://healthpei.ca/pharmacareforms
NL	For the treatment of severely active rheumatoid arthritis, in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDs), in adult patients who are refractory or intolerant to: • Methotrexate (oral or parenteral) at a dose of ≥ 20 mg weekly (≥15mg if patient is ≥65 years of age) for a minimum of 12 weeks, followed by methotrexate in combination with at least two other DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 12 weeks; OR • Initial use of triple DMARD therapy with methotrexate in combination with at least twoother DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 24 weeks. Clinical Notes: • For patients who do not demonstrate a clinical response to oral methotrexate, or who experience gastrointestinal intolerance, a trial of parenteral methotrexate must be considered. • Optimal treatment response may take up to 24 weeks, however if no improvement is seen after 12 weeks of triple DMARD use, therapy should be changed. • If the patient is intolerant to triple DMARD therapy, then dual therapy with DMARDs (methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) must be

Drug Plan	Criteria for Restricted Benefit
	considered. • Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above. • Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented. Claim Notes: • Must be prescribed by a rheumatologist. • Combined use of more than one biologic DMARD will not be reimbursed. • Patients will not be permitted to switch from Inflectra™ to another infliximab product or vice versa, if previously trialed and deemed unresponsive to therapy. • Initial Approval: 6 months • Renewal Approval: 1 year. Confirmation of continued response is required. • Maximum Dosage Approved: o Infliximab (Remicade): 3mg/kg/dose at 0, 2 and 6 weeks followed by maintenance therapy of 3mg/kg/dose every 8 weeks. Please note: Inflectra is the preferred infliximab therapy for treatment naïve patients (coverage will only be considered for Remicade in patients stabilized prior to June 1, 2016) To facilitate this process specific RA Medications Special Authorization Forms have been developed and can be found at: http://www.health.gov.nl.ca/health/prescription/ra_meds_initiation.pdf http://www.health.gov.nl.ca/health/prescription/ra_meds_continuation_request.pdf
YK	For severely active Rheumatoid Arthritis on recommendation of specialist. Specialist's consult to be provided. For patients refractory or intolerant to parenteral methotrexate after at least a 12 week trial AND A 3 month trial of at least 2 of the following; leflunomide, sulfasalazine, azathioprine AND A 3 month trial of at least one DMARD combination such as a)methotrexate & cyclosporine b) methotrexate with hydroxychloroquine and sulfasalazine c) methotrexate with leflunomide. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Coverage is provided for an initial three doses of 3 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a rheumatologist Coverage is provided, in combination with methotrexate (MTX) or other disease modifying anti-rheumatic drugs (DMARDs), for the reduction in signs and symptoms of severely active RA in adult patients ≥ 18 years who have failed: • MTX (oral or parenteral) at a dose ≥ 20 mg weekly (≥ 15 mg weekly if patient is ≥ 65 years) for a minimum of 12 weeks of continuous treatment. Note: Patients who do not exhibit a clinical response to oral MTX or who experience gastrointestinal intolerance may consider a trial of parenteral MTX; AND • MTX in combination with at least two other DMARDS, such as sulfasalazine and hydroxychloroquine, for a minimum of 12 weeks of continuous treatment; OR, if the patient has a contraindication, failure, or intolerance to MTX:

Drug Plan	Criteria for Restricted Benefit
	• A combination of at least two DMARDS, such as sulfasalazine, hydroxychloroquine, azathioprine, leflunomide, cyclosporine or gold, for a minimum of 12 weeks of continuous treatment. Coverage beyond the initial three doses will be based on a 20% improvement in 3 of 5 baseline clinical parameters. • >20% reduction in number of tender and swollen joints; PLUS • >20% improvement in Physician Global Assessment scale; PLUS either • >20% improvement in Patient Global Assessment scale; OR • >20% reduction in the acute phase as measured by ESR or CRP.
NIHB	Coverage is provided for an initial three doses of 3 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a rheumatologist Coverage is provided, in combination with methotrexate (MTX) or other disease modifying anti-rheumatic drugs (DMARDs), for the reduction in signs and symptoms of severely active RA in adult patients ≥ 18 years who have failed: • MTX (oral or parenteral) at a dose ≥ 20 mg weekly (≥ 15 mg weekly if patient is ≥ 65 years) for a minimum of 12 weeks of continuous treatment. Note: Patients who do not exhibit a clinical response to oral MTX or who experience gastrointestinal intolerance may consider a trial of parenteral MTX; AND • MTX in combination with at least two other DMARDS, such as sulfasalazine and hydroxychloroquine, for a minimum of 12 weeks of continuous treatment; OR, if the patient has a contraindication, failure, or intolerance to MTX: • A combination of at least two DMARDS, such as sulfasalazine, hydroxychloroquine, azathioprine, leflunomide, cyclosporine or gold, for a minimum of 12 weeks of continuous treatment. Coverage beyond the initial three doses will be based on a 20% improvement in 3 of 5 baseline clinical parameters. • >20% reduction in number of tender and swollen joints; PLUS • >20% improvement in Physician Global Assessment scale; PLUS either • >20% improvement in Patient Global Assessment scale; OR • >20% reduction in the acute phase as measured by ESR or CRP.
DND	• As of September 1st 2016, all new patients using infliximab for rheumatoid arthritis, ankylosing spondylitis and plaque psoriasis will be covered for Inflectra brand only • Patients that have previously received Special Authorization coverage for Remicade for rheumatoid arthritis, ankylosing spondylitis and plaque psoriasis will continue to receive coverage for this drug. Inflectra: Requests for special authorization are considered for members starting on infliximab for the FIRST TIME (infliximab naïve with one of the following Health Canada approved indication for use: Rheumatoid Arthritis: when prescribed by a rheumatologist or a prescriber with a specialty in rheumatology for patients with moderate to severe active rheumatoid arthritis despite treatment with at least 2 DMARDs [including methotrexate unless contraindicated] in mono or combination therapy after 3 months at target dose.

Drug Plan	Criteria for Restricted Benefit
	Note: • Methotrexate at 20mg (PO, SC, IM) or greater total weekly dosage for more than 12 weeks. Patients who do not exhibit a clinical response to PO methotrexate or experience gastrointestinal intolerance to PO methotrexate must have a trial of parenteral methotrexate before being accepted as refractory AND One or more of the following: Leflunomide 20mg daily for 10 weeks Gold weekly injections for 20 weeks Sulfasalazine ≥ 2gm daily for 3 months Azathioprine 2-3mg/kg/day for 3 months
VAC	Not a benefit

Restricted Benefit Criteria for Remicade for the treatment of Ankylosing Spondylitis

Drug Plan	Criteria for Restricted Benefit

BC	Patients granted Special Authority prior to Feb. 19, 2016
	
	Treatment of Ankylosing Spondylitis according to established criteria* when prescribed by a rheumatologist.
	
	Initial / Switch:
	• Not eligible
	
	Renewal:
	• Indefinite coverage, 3 mg/kg every 8 weeks, OR
	• Renewal of one year
	
	• Medication is being prescribed by a rheumatologist or medical specialist in rheumatology
	• Extra-articular manifestations (Worsened to Resolved compared to baseline)
	• Axial disease
	  ○ Spinal pain (Worsened to Resolved compared to baseline)
	• Peripheral disease
	  ○ Active joints (Worsened to Resolved compared to baseline)
	  ○ Active tenosynovitis and/or enthesitis (Worsened to Resolved compared to baseline)

AB	Not eligible for new patients starting April 1, 2016. Special authorization coverage may be provided for the reduction in the signs and symptoms and improvement in physical function of severely active Ankylosing Spondylitis, as defined by the Modified New York criteria for Ankylosing Spondylitis, in adult patients (18 years of age or older) who have active disease as

Drug Plan	Criteria for Restricted Benefit
	demonstrated by: • a BASDAI greater than or equal to 4 units, demonstrated on 2 occasions at least 8 weeks apart AND • a Spinal Pain VAS of greater than or equal to 4 cm (on a 0-10 cm scale), demonstrated on 2 occasions at least 8 weeks apart AND • who are refractory or intolerant to treatment with 2 or more NSAIDS each taken for a minimum of 4 weeks at maximum tolerated or recommended doses. 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. For coverage, this drug must be initiated by a Specialist in Rheumatology ("RA Specialist"). For continued coverage beyond three doses, the patient must meet the following criteria: 1) The patient must be assessed by an RA Specialist after the initial three doses to determine response. 2) The RA Specialist must confirm, in writing, that the patient is a 'responder' that meets the following criteria: • Reduction of the BASDAI score by at least 50% of the pre-treatment value or by 2 or more units, AND • Reduction of the Spinal Pain VAS by 2 cm or more. Following this assessment, continued coverage may be approved for one 5 mg/kg dose of infliximab every 6 to 8 weeks for a period of 12 months. Ongoing coverage may be considered if the patient is re-assessed by an RA Specialist every 12 months and is confirmed to be continuing to respond to therapy by meeting criteria as outlined in (2) above.
SK	For treatment of ankylosing spondylitis (AS) according to the following criteria: **Initial Application (for a 12-week medication trial):** • For patients who have already been treated conventionally with two or more non-steroidal anti-inflammatory drugs (NSAIDs) taken sequentially at maximum tolerated or recommended doses for four weeks without symptom control; AND • Satisfy New York diagnostic criteria: a score ≥ 4 on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) AND a score of ≥ 4 cm on the 0-10cm spinal pain visual analogue scale (VAS) on two occasions at least 12 weeks apart without any change of treatment. **Second Application (following the initial 12-week approval, requests will be considered for a one-year approval timeframe):** • Adequate response to treatment assessed at 12 weeks defined as at least 50% reduction in pre-treatment baseline BASDAI score by ≥ 2 units AND a reduction of ≥ 2cm in the spinal pain VAS. **Subsequent Annual Renewal Applications (beyond the first 15 months, requests are to be submitted annually for consideration of ongoing approval on a yearly basis):** • The BASDAI score does not worsen (i.e. remains within two units of the second assessment) AND remains at least two units less than the initial application's BASDAI score.

Drug Plan	Criteria for Restricted Benefit
	Notes: • Requests for coverage for this indication must be made by a rheumatologist. • Applications for this indication must be submitted on the designated EDS Application – Ankylosing Spondylitis Drugs form found on the Formulary website. • Coverage may be provided for one switch for patients transitioning to another anti-TNF biologic agent following an adequate trial of the first agent if the patient fails to respond, if there is a loss of response, or is intolerant, to the first agent. Approval will be subject to the published Exception Drug Status criteria for the requested biologic agent. • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. • Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed.
MB	For the treatment of patients with active ankylosing spondylitis who have failed to respond to an adequate trial of at least three different non-steroidal anti-inflammatory drugs (NSAIDs) and, in patients with peripheral joint involvement, have failed to respond to methotrexate or sulfasalazine. Request for coverage must be made by a specialist in rheumatology. Inflectra will be the preferred infliximab option for all infliximab-naive patients prescribed an infliximab product for Ankylosing Spondylitis. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naive patients. Patients will not be permitted to switch from Remicade to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy.
ON	(Note that effective February 25, 2016, Infliximab as Remicade for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis will only be considered for funding for existing EAP renewals. Infliximab as Inflectra can be considered through Limited Use criteria on the Ontario Drug Benefit Formulary. For the treatment of ankylosing spondylitis (AS) OR psoriatic spondylitis (PS) in patients who have severe active disease with: • Age of disease onset ≤ 50; AND • Low back pain and stiffness for > 3 months that improves with exercise and not relieved by rest; AND • Failure to respond to or documented intolerance to adequate trials of 2 non-steroidal anti-inflammatory drugs (NSAIDs) for at least 4 weeks each; AND • BASDAI score of ≥ 4 for at least 4 weeks while on standard therapy; AND The information submitted with the request must include the following: • A list of current concomitant medications related to the AS/PS, including pain medications (if relevant). Please include dosing regimens. • Details of review of radiographic reports for severe active disease. o X-ray or CT scan report stating the presence of “SI joint fusion” or “SI joint erosion” OR o MRI report stating the presence of “inflammation” or “edema” of the SI joint o Actual radiographic reports must be submitted with the request. If the radiographic reports do not specify the above, the request will be reviewed by external medical experts. Additional information that should be provided if applicable: • Schober measurement and chest expansion measurement • Evidence of restricted spinal mobility • If the patient has AS/PS with predominantly peripheral joint involvement, additional information pertaining to trials of DMARDs must be provided, and these requests will be reviewed by external medical experts.

Drug Plan	Criteria for Restricted Benefit
	Renewal will be considered for patients with objective evidence of at least a 50% reduction in BASDAI score or ≥ 2 absolute point reduction in BASDAI score. Please provide an update on concomitant medications for AS/PS and whether there has been a reduction in pain medication for AS/PS since initiating the biologic (if applicable). For renewals beyond the second year, objective evidence of preservation of treatment effect must be provided. The planned dosing regimen for the requested biologic should be provided. The recommended doses for the treatment of AS/PS are as follows: 1. Adalimumab 40mg every other week. 2. Certolizumab 400 mg at week 0, 2, 4 then maintenance doses of 200 mg every 2 weeks or 400 mg every 4 weeks 3. Etanercept 25mg twice weekly or 50mg once weekly 4. Golimumab 50 mg once a month 5. Infliximab 3-5mg/kg/dose at 0, 2 and 6 weeks followed by maintenance therapy of up to 5mg/kg/dose every 6 to 8 weeks.
NB	• For the treatment of patients with moderate to severe ankylosing spondylitis (e.g. Bath AS Disease Activity Index (BASDAI) score ≥ 4 on 10 point scale) who: o Have axial symptoms and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months or in whom NSAIDs are contraindicated, or o Have peripheral symptoms and who have failed to respond, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD. o Requests for renewal must include information demonstrating the beneficial effects of the treatment, specifically: o A decrease of at least 2 points on the BASDAI scale, compared with the pre-treatment score, or o Patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as HAQ or "ability to return to work"). Clinical Note: • Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication to axial disease do not require a trial of NSAIDs alone. Claim Notes: • Must be prescribed by a rheumatologist or internist. • Combined use of more than one biologic DMARD will not be reimbursed. • All requests for coverage of infliximab for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra brand only. • Approvals will be for a maximum of 5mg/kg at weeks 0, 2 and 6, then every 6-8 weeks thereafter. • Initial Approval: 6 months • Renewal Approval: 1 year. • Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions as outlined here.
NS	• for the treatment of patients with moderate to severe ankylosing spondylitis (e.g., Bath AS Disease Activity Index (BASDAI) score ≥4 on 10 point scale) who: o have axial symptoms1 and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation, or in whom NSAIDs are contraindicated OR o have peripheral symptoms and who have failed to respond to, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD • must be prescribed by a rheumatologist or prescriber with a specialty in rheumatology • requests for renewal must include information showing the beneficial effects of the treatment, specifically:

Drug Plan	Criteria for Restricted Benefit
	○ a decrease of at least 2 points on the BASDAI scale, compared with the pre-treatment score; OR ○ patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as HAQ or "ability to return to work") 1. Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication of axial disease, do not require a trial of 2 NSAIDs. Initial coverage duration and maximum dosage approved: Infliximab: initial coverage period 6 months, maximum dose 5mg/kg at 0, 2, and 6 weeks then every 6-8 weeks thereafter and not in combination with other anti-TNF agents For infliximab-naïve patients whose infliximab therapy is initiated after June 1, 2016, Inflectra will be the product approved.
PE	Approvals will be for a maximum adult dose of 5mg/kg at 0, 2, and 6 weeks then every 6 to 8 weeks. For the treatment of patients with moderate to severe ankylosing spondylitis (Bath AS Disease Activity Index (BASDAI) score ≥4 on 10 point scale who: a) have axial symptoms* and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation or in whom NSAIDs are contraindicated OR b) have peripheral symptoms and who have failed to respond to, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD. *Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication to axial disease, do not require a trial of NSAIDs alone. Approvals for Ankylosing Spondylitis anti-TNF agents will be for a maximum of six months, and will NOT be considered in combination with other biologic agents. Requests for renewal must include information showing the beneficial effects of the treatment, specifically: a) a decrease of at least two points on the BASDAI scale, compared with pre-treatment score OR b) patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as Health Assessment Questionnaire (HAQ) or ability to return to work). The request for coverage must be made by a rheumatologist or prescriber with a specialty in rheumatology, using the Ankylosing Spondylitis Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms. Patients must also apply for coverage through the High-Cost Drug Program. The patient application is available from the Drug Programs Office or online at http://healthpei.ca/pharmacareforms
NL	For the treatment of patients with moderate to severe ankylosing spondylitis (e.g. Bath AS Disease Activity Index (BASDAI) score ≥ 4 on 10 point scale) who: • have axial symptoms* and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months

Drug Plan	Criteria for Restricted Benefit
	observation or in whom NSAIDs are contraindicated OR • have peripheral symptoms and who have failed to respond to, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD. Renewal Requests: • Requests for renewal must include information showing the beneficial effects of the treatment, specifically: ○ a decrease of at least 2 points on the BASDAI scale, compared with the pretreatment score; OR ○ patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as HAQ or "ability to return to work"). Clinical Notes: 1. Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication to axial disease, do not require a trial of NSAIDs alone 2. Combined use of more than one biologic DMARD will not be reimbursed. 3. Patients will not be permitted to switch from Inflectra™ to another infliximab product or vice versa, if previously trialed and deemed unresponsive to therapy. Claim Notes: • Must be prescribed by a rheumatologist or internist • Approval will be for a maximum of 6 months • Approvals will be for a maximum of 5mg/kg at weeks 0, 2 and 6, then every 6 to 8 weeks thereafter. Please note: Inflectra is the preferred infliximab therapy for treatment naïve patients (coverage will only be considered for Remicade in patients stabilized prior to June 1, 2016) To facilitate this process specific RA Medications Special Authorization Forms have been developed and can be found at: http://www.health.gov.nl.ca/health/prescription/ra_meds_initiation.pdf http://www.health.gov.nl.ca/health/prescription/ra_meds_continuation_request.pdf
YK	For Ankylosing Spondylitis patients with a BASDAI score ≥ 4. For patients with predominantly axial disease who are refractory or intolerant to a minimum 4 week trial of 2 NSAIDs at maximal dosage. OR for predominantly peripheral disease, patients refractory to a 3 month trial of parenteral methotrexate and a 3 month trial of sulfasalazine. Specialist's consult to be provided. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Not a benefit
NIHB	Not a benefit

Drug Plan	Criteria for Restricted Benefit
DND	• As of September 1st 2016, all new patients using infliximab for rheumatoid arthritis, ankylosing spondylitis and plaque psoriasis will be covered for Inflectra brand only • Patients that have previously received Special Authorization coverage for Remicade for rheumatoid arthritis, ankylosing spondylitis and plaque psoriasis will continue to receive coverage for this drug. • when prescribed by a rheumatologist or a prescriber with a specialty in rheumatology and meets the following criteria: • A diagnosis of moderate to severe Ankylosing Spondylitis as demonstrated by a BASDAI greater than or equal to 4 units. • Treatment failure or intolerance to three NSAIDs each taken for a minimum of 4 weeks sequentially and at maximum tolerated or recommended dosage AND If peripheral involvement, patient is refractory to a minimum 3 month trial of an optimal dose or maximum tolerated dose of methotrexate or sulfasalazine.
VAC	Case-by-case

Restricted Benefit Criteria for Inflectra for the treatment of Ankylosing Spondylitis

Drug Plan	Criteria for Restricted Benefit

BC	New Patients
	
	Treatment of Ankylosing Spondylitis according to established criteria* when prescribed by a rheumatologist.
	
	Initial / Switch:
	• 3-5 mg/kg at 0, 2, and 6 weeks then every 8 weeks thereafter for 1 year
	
	Switch:
	• Never achieving a 20% improvement
	• At least 20% improvement in first 12 weeks of a TNF inhibitor but then loss of benefit
	
	Renewal:
	• Indefinite coverage, 3 mg/kg every 8 weeks, OR
	• Renewal of one year
	• Medication is being prescribed by a rheumatologist or medical specialist in rheumatology
	• Extra-articular manifestations (Worsened to Resolved compared to baseline)
	• Axial disease
	  ○ Spinal pain (Worsened to Resolved compared to baseline)
	• Peripheral disease
	  ○ Active joints (Worsened to Resolved compared to baseline)

Drug Plan	Criteria for Restricted Benefit
	○ Active tenosynovitis and/or enthesitis (Worsened to Resolved compared to baseline)
AB	Special authorization coverage may be provided for the reduction in the signs and symptoms and improvement in physical function of severely active Ankylosing Spondylitis, as defined by the Modified New York criteria for Ankylosing Spondylitis, in adult patients (18 years of age or older) who have active disease as demonstrated by: • a BASDAI greater than or equal to 4 units, demonstrated on 2 occasions at least 8 weeks apart AND • a Spinal Pain VAS of greater than or equal to 4 cm (on a 0-10 cm scale), demonstrated on 2 occasions at least 8 weeks apart AND • who are refractory or intolerant to treatment with 2 or more NSAIDS each taken for a minimum of 4 weeks at maximum tolerated or recommended doses. 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. For coverage, this drug must be initiated by a Specialist in Rheumatology ("RA Specialist"). • Initial coverage may be approved for three doses as follows: An initial dose of 5 mg/kg, followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion. • Patients will be limited to receiving one dose of infliximab per prescription at their pharmacy. • Patients will be permitted to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy, or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period). • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. • Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. For continued coverage beyond three doses, the patient must meet the following criteria: 1) The patient must be assessed by an RA Specialist after the initial three doses to determine response. 2) The RA Specialist must confirm, in writing, that the patient is a 'responder' that meets the following criteria: • Reduction of the BASDAI score by at least 50% of the pre-treatment value or by 2 or more units, AND • Reduction of the Spinal Pain VAS by 2 cm or more. Following this assessment, continued coverage may be approved for one 5 mg/kg dose of infliximab every 6 to 8 weeks for a period of 12 months. Ongoing coverage may be considered if the patient is re-assessed by an RA Specialist every 12 months and is confirmed to be continuing to respond to therapy by meeting criteria as outlined in (2) above.
SK	**Initial Application (for a 12-week medication trial):** • For patients who have already been treated conventionally with two or more non-steroidal anti-inflammatory drugs (NSAIDs) taken sequentially at maximum tolerated or recommended doses for four weeks without symptom control; AND • Satisfy New York diagnostic criteria: a score ≥ 4 on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) AND a score of ≥ 4 cm on the 0-10cm spinal pain visual analogue scale (VAS) on two occasions at least 12 weeks apart without any change of treatment. **Second Application (following the initial 12-week approval, requests will be considered for a one-year approval timeframe):**

Drug Plan	Criteria for Restricted Benefit
	• Adequate response to treatment assessed at 12 weeks defined as at least 50% reduction in pre-treatment baseline BASDAI score by ≥ 2 units AND a reduction of ≥ 2cm in the spinal pain VAS. **Subsequent Annual Renewal Applications (beyond the first 15 months, requests are to be submitted annually for consideration of ongoing approval on a yearly basis):** • The BASDAI score does not worsen (i.e. remains within two units of the second assessment) AND remains at least two units less than the initial application's BASDAI score. **Notes:** • Requests for coverage for this indication must be made by a rheumatologist. • Applications for this indication must be submitted on the designated EDS Application – Ankylosing Spondylitis Drugs form found on the Formulary website. • Coverage may be provided for one switch for patients transitioning to another anti-TNF biologic agent following an adequate trial of the first agent if the patient fails to respond, if there is a loss of response, or is intolerant, to the first agent. Approval will be subject to the published Exception Drug Status criteria for the requested biologic agent. • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed.
MB	For the treatment of patients with active ankylosing spondylitis who have failed to respond to an adequate trial of at least three different non-steroidal anti-inflammatory drugs (NSAIDs) and, in patients with peripheral joint involvement, have failed to respond to methotrexate or sulfazalazine. Request for coverage must be made by a specialist in rheumatology. Inflectra will be the preferred infliximab option for all infliximab-naive patients prescribed an infliximab product for Ankylosing Spondylitis. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naive patients. Patients will not be permitted to switch from Inflectra to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy.
ON	Limited Use Notes: For the treatment of ankylosing spondylitis (AS) in patients who have severe active disease (confirmed by radiographic evidence (see notes below) with: • Age of disease onset less than or equal to 50; AND • Low back pain and stiffness for greater than 3 months that improves with exercise and not relieved by rest; AND • Failure to respond to or documented intolerance to adequate trials of 2 non-steroidal anti-inflammatory drugs (NSAIDs) for at least 4 weeks each; AND • Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of greater than or equal to 4 for at least 4 weeks while on standard therapy. Note: Radiographic evidence demonstrating the presence of "SI joint fusion" or "SI joint erosion" on x-ray or CT scan, or MRI demonstrating the presence of "inflammation" or "edema" of the SI joint. Maintenance/Renewal: After 12 months of treatment, maintenance therapy is funded for patients with objective evidence of at least a 50 percent reduction in BASDAI score or greater than or equal to 2 absolute point reduction in BASDAI score. For funding beyond the second year, the patient must demonstrate objective evidence of preservation of treatment effect.

Drug Plan	Criteria for Restricted Benefit
	Therapy must be prescribed by a rheumatologist or a physician with expertise in rheumatology. The recommended dosing regimen is 3 to 5mg/kg/dose at 0, 2 and 6 weeks followed by maintenance therapy of up to 5mg/kg/dose every 6 to 8 weeks.

NB	• For the treatment of patients with moderate to severe ankylosing spondylitis (e.g. Bath AS Disease Activity Index (BASDAI) score ≥ 4 on 10 point scale) who:
	  ○ Have axial symptoms and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months or in whom NSAIDs are contraindicated, or
	  ○ Have peripheral symptoms and who have failed to respond, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD.
	• Requests for renewal must include information demonstrating the beneficial effects of the treatment, specifically:
	  ○ A decrease of at least 2 points on the BASDAI scale, compared with the pre-treatment score, or
	  ○ Patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as HAQ or "ability to return to work").
	
	Clinical Note:
	• Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication to axial disease do not require a trial of NSAIDs alone.
	
	Claim Notes:
	• Must be prescribed by a rheumatologist or internist.
	• Combined use of more than one biologic DMARD will not be reimbursed.
	• All requests for coverage of infliximab for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra brand only.
	• Initial Approval: 6 months.
	• Renewal Approval: 1 year.
	• Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions as outlined here.

NS	For infliximab-naïve patients whose infliximab therapy is initiated after June 1, 2016, Infectra will be the product approved for the following indications.
	• for the treatment of patients with moderate to severe ankylosing spondylitis (e.g., Bath AS Disease Activity Index (BASDAI) score ≥4 on 10 point scale) who:
	  ○ have axial symptoms1 and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation, or in whom NSAIDs are contraindicated OR
	  ○ have peripheral symptoms and who have failed to respond to, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD
	
	Notes:
	• must be prescribed by a rheumatologist or prescriber with a specialty in rheumatology
	• requests for renewal must include information showing the beneficial effects of the treatment, specifically:
	  ○ a decrease of at least 2 points on the BASDAI scale, compared with the pre-treatment score; OR
	  ○ patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as HAQ or "ability to return to work")
	• Initial coverage period 6 months, maximum dose 5mg/kg at 0, 2, and 6 weeks then every 6-8 weeks thereafter and not in combination with other anti-TNF agents.

Drug Plan	Criteria for Restricted Benefit
	1. Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication of axial disease, do not require a trial of 2 NSAIDs.
PE	For the treatment of patients with moderate to severe ankylosing spondylitis (Bath AS Disease Activity Index (BASDAI) score 4 on 10 point scale who: a) have axial symptoms* and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation or in whom NSAIDs are contraindicated OR b) have peripheral symptoms and who have failed to respond to, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD. *Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication to axial disease, do not require a trial of NSAIDs alone. Approvals for Ankylosing Spondylitis anti-TNF agents will be for a maximum of six months, and will NOT be considered in combination with other biologic agents. Requests for renewal must include information showing the beneficial effects of the treatment, specifically: a) a decrease of at least two points on the BASDAI scale, compared with pre-treatment score OR b) patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as Health Assessment Questionnaire (HAQ) or ability to return to work). The request for coverage must be made by a rheumatologist or prescriber with a specialty in rheumatology, using the Ankylosing Spondylitis Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms . Patients must also apply for coverage through the High-Cost Drug Program. The patient application is available from the Drug Programs Office or online at http://healthpei.ca/pharmacareforms
NL	For the treatment of patients with moderate to severe ankylosing spondylitis (e.g. Bath AS Disease Activity Index (BASDAI) score ≥ 4 on 10 point scale) who: • have axial symptoms* and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation or in whom NSAIDs are contraindicated OR • have peripheral symptoms and who have failed to respond to, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD. Renewal Requests: • Requests for renewal must include information showing the beneficial effects of the treatment, specifically: ○ a decrease of at least 2 points on the BASDAI scale, compared with the pretreatment score; OR ○ patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as HAQ or “ability to return to work”).

Drug Plan	Criteria for Restricted Benefit
	Clinical Notes: 1. Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication to axial disease, do not require a trial of NSAIDs alone 2. Combined use of more than one biologic DMARD will not be reimbursed. 3. Patients will not be permitted to switch from Inflectra™ to another infliximab product or vice versa, if previously trialed and deemed unresponsive to therapy. Claim Notes: • Must be prescribed by a rheumatologist or internist • Approval will be for a maximum of 6 months • Approvals will be for a maximum of 5mg/kg at weeks 0, 2 and 6, then every 6 to 8 weeks thereafter. Please note: Inflectra is the preferred infliximab therapy for treatment naïve patients (coverage will only be considered for Remicade in patients stabilized prior to June 1, 2016) To facilitate this process specific RA Medications Special Authorization Forms have been developed and can be found at: http://www.health.gov.nl.ca/health/prescription/ra_meds_initiation.pdf http://www.health.gov.nl.ca/health/prescription/ra_meds_continuation_request.pdf
YK	For Ankylosing Spondylitis patients with a BASDAI score ≥ 4. For patients with predominantly axial disease who are refractory or intolerant to a minimum 4 week trial of 2 NSAIDs at maximal dosage. OR for predominantly peripheral disease, patients refractory to a 3 month trial of parenteral methotrexate and a 3 month trial of sulfasalazine. Specialist's consult to be provided. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a rheumatologist • BASDAI > 4; AND • Patient is refractory to a trial of two different NSAIDs at maximum tolerated doses for a combined total duration of at least 4 weeks; AND for peripheral joint involvement, patient is refractory: • Methotrexate (MTX) weekly at 20 mg or greater (15 mg or greater if patient is >65 years of age) for more than 8 weeks; AND • Sulfasalazine 2 g/day for at least 3 months. NOTE: For axial involvement, patient does not need to be tried on methotrexate or sulfasalazine. Coverage beyond the initial three doses will be based on improvement in the BASDAI score. • Improvement of at least 50% or 2 units in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score.
NIHB	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a rheumatologist

Drug Plan	Criteria for Restricted Benefit
	• BASDAI > 4; AND • Patient is refractory to a trial of two different NSAIDs at maximum tolerated doses for a combined total duration of at least 4 weeks; AND for peripheral joint involvement, patient is refractory: • Methotrexate (MTX) weekly at 20 mg or greater (15 mg or greater if patient is >65 years of age) for more than 8 weeks; AND • Sulfasalazine 2 g/day for at least 3 months. NOTE: For axial involvement, patient does not need to be tried on methotrexate or sulfasalazine. Coverage beyond the initial three doses will be based on improvement in the BASDAI score. • Improvement of at least 50% or 2 units in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score.
DND	• As of September 1st 2016, all new patients using infliximab for rheumatoid arthritis, ankylosing spondylitis and plaque psoriasis will be covered for Inflectra brand only • Patients that have previously received Special Authorization coverage for Remicade for rheumatoid arthritis, ankylosing spondylitis and plaque psoriasis will continue to receive coverage for this drug. When prescribed by a rheumatologist or a prescriber with a specialty in rheumatology and meets the following criteria: • A diagnosis of moderate to severe Ankylosing Spondylitis as demonstrated by a BASDAI greater than or equal to 4 units. • Treatment failure or intolerance to three NSAIDs each taken for a minimum of 4 weeks sequentially and at maximum tolerated or recommended dosage. AND • If peripheral involvement, patient is refractory to a minimum 3 month trial of an optimal dose or maximum tolerated dose of methotrexate or sulfasalazine
VAC	Not a benefit

Restricted Benefit Criteria for Remicade for the treatment of Crohn's Disease (Adult)

Drug Plan	Criteria for Restricted Benefit
BC	Patients granted Special Authority prior to Nov. 1, 2016 Treatment of moderate to severe active Crohn's disease according to established criteria* when prescribed by a gastroenterologist. First approval (induction period): Not eligible Prior Medication Therapy (Initial Coverage) Details of glucocorticoid trial • Corticosteroid resistant: lack of a symptomatic response despite a course of oral prednisone 40-60mg/day (or equivalent) for a minimum of 14 days. • Corticosteroid dependent: unable to withdraw oral corticosteroid within 3 months of initiation without a recurrence of symptoms; a symptomatic relapse within 3 months of stopping; or the need for two or more courses of corticosteroids within one year.

Drug Plan	Criteria for Restricted Benefit
	• Corticosteroid use is contraindicated (specify): • intolerant/side effect(s) (specify): Details of other medication trial(s) *Renewal:* 1 year; 5MG/KG EVERY 8 WEEKS CURRENT HARVEY BRADSHAW INDEX SCORE WHILE ON TREATMENT (REQUIRES HBI SCORE <5 OR A DECREASE IN SCORE >4)
AB	Not eligible for new patients starting December 1, 2016. Special authorization coverage may be approved for coverage of infliximab for the reduction in signs and symptoms and induction and maintenance of clinical remission of Moderately to Severely Active Crohn's Disease in patients who meet the following criteria: • Infliximab must be prescribed by a Specialist in Gastroenterology or a physician appropriately trained by the University of Alberta or the University of Calgary and recognized as a prescriber by Alberta Blue Cross for infliximab for coverage for the treatment of Moderately to Severely Active Crohn's Disease patients ('Specialist'). • Patients must be 18 years of age or older to be considered for coverage of infliximab. • Patients will be limited to receiving one dose of infliximab per prescription at their pharmacy. • Patients may be allowed to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy (both primary loss of response and secondary loss of response) or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period). • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. • Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. [Existing Remicade patients] Maintenance Dosing: 'Maintenance Dosing' means one 5 mg/kg dose of infliximab per patient provided no more often than every 8 weeks for a period of 12 months to: • Existing Patients, who are patients that are being treated, or have previously been treated, with infliximab. Maintenance Dosing for Existing Patients: • The patient must be assessed by a Specialist at least 4 to 8 weeks after the day the last dose of infliximab was administered to the patient and prior to administration of the next dose to obtain a Modified Harvey Bradshaw Index Score (Existing Patient's Baseline Score); AND • these measures must be provided to Alberta Blue Cross for assessment for continued coverage for maintenance dosing. (For existing patients with Moderately to Severely Active Crohn's Disease with an incomplete response, the dose may be adjusted to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.) Continued Coverage for Maintenance Dosing: Continued coverage may be considered for one 5 mg/kg dose of infliximab per patient provided no more often than every 8 weeks for a period of 12 months, if the following criteria are met at the end of each 12 month period: • For Existing Patients: The Specialist must confirm that the patient has maintained the Existing Patient's Baseline Score.

Drug Plan	Criteria for Restricted Benefit
	(For existing patients with an incomplete response, the maintenance dose may be adjusted to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.)
SK	• For treatment of patients who demonstrate continuing symptoms despite the use of optimal conventional therapies, such as glucocorticoids and immunosuppressive therapy. • For treatment of patients who are intolerant to conventional therapy, including glucocorticoids and immunosuppressive therapy. Clinical response should be assessed after the induction dose. Ongoing coverage will only be provided for those who respond to treatment. Patients undergoing this treatment should be reviewed every six months by a specialist in this area.
MB	For the treatment of moderate to severly active Crohn's Disease in patients refractory or with contraindications to an adequate course of 5-aminosalicyclic acid and corticosteroids and/or other immunosuppressive therapy. Request for coverage must be made by a physician who is a specialist in gastroenterology.
ON	Note that effective November 30, 2016, Infliximab as Remicade for Moderate to Severe Crohn's Disase will only be considered for funding for existing EAP renewals. Infliximab as Inflectra can be considered through Limited Use criteria on the Ontario Drug Benefit Formulary. **Renewal** will be considered for patients with 50% reduction in HBI from pre-treatment as well as improvement of symptoms (e.g., absence of bloody diarrhea and weight stabilization or increase) and no longer using steroids. Biochemical improvements may also be required. The planned dosing regimen for the requested biologic should be provided. The recommended dose for the treatment of Crohn's Disease is 5mg/kg/dose at 0, 2 and 6 weeks followed by 5mg/kg/dose every 8 weeks.
NB	• For the treatment of adult patients with moderately to severely active Crohn's disease who have contraindications, or are refractory, to therapy with corticosteroids and other immunosuppressants. Claim Notes: • Must be prescribed by a gastroenterologist or physician with a specialty in gastroenterology. • Combined use of more than one biologic DMARD will not be reimbursed. • All requests for coverage of infliximab for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra brand only. • Approvals will be for a maximum of 5mg/kg at weeks 0, 2 and 6, then every 8 weeks thereafter. • Initial Approval: 12 weeks. • Renewal Approval: 1 year. Confirmation of continued response is required. • Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions as outlined here.
NS	• For treatment of Crohn's disease in adults, in patients with moderate to severe active disease refractory to 5-ASA products AND glucocorticoids (e.g.,prednisone) AND immunosuppressive therapy (azathioprine or 6-mercaptopurine or methotrexate)1. • Initial approval of infliximab will be for a single infusion of 5mg/kg/dose. A second infusion may be warranted in patients not responding to the first infusion or in patients responding initially but then worsening before maintenance therapy is effective. Request for approval beyond induction therapy will be considered on a case by case basis. • Initial approval is for three infusions of infliximab of 5mg/kg/dose at 0, 2 and 6 week intervals.

Drug Plan	Criteria for Restricted Benefit
	1. Patients who are very ill and not candidates for surgery may qualify for infliximab therapy without a trial of AZA, 6-MP or MTX, as they may require a more rapid onset of response. Notes: • Requires a written request by a gastroenterologist or physician with a specialty in gastroenterology. For infliximab-naïve patients whose infliximab therapy is initiated after December 1, 2016, Inflectra will be the product approved.
PE	For the treatment of moderate to severe Crohn's Disease in patients who: 1. Have a Harvey Bradshaw Index score of 7 or more, AND 2. Have not responded to 5-ASA products (minimum trial of 3 grams per day for 6 weeks), AND 3. Have not responded to or are intolerant to glucocorticosteroid therapy (e.g. Prednisone) or where such therapy is contraindicated, AND 4. Have not responded to or are intolerant to immunosupressive therapy (Azathioprine, Mercaptopurine or Methotrexate) or where such therapy is contraindicated. Initial approval for Infliximab will allow for 3 doses of 5mg/kg/dose administered at 0, 2, and 6 weeks. Renewal of coverage will require reassessment of the patient and submission of a new Crohn's Disease Special Authorization form. Continued coverage will be approved at a dose not exceeding 5mg/kg every 8 weeks. The request for coverage must be made by a gastroenterologist using the Crohn's Disease Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms Patients must also apply for coverage to the High-Cost Drug Program. The patient application is available from the Drug Program Office or online at http://healthpei.ca/pharmacareforms
NL	For the treatment of patients with moderate or severe active disease* with contraindications to or not achieving remission with glucocorticosteroids AND immunosuppressive therapy. • Initial request must include current Crohn's Disease Activity Index (CDAI) or the Harvey Bradshaw Index Assessment (HBI) score. Claim Notes: • Must be prescribed by a gastroenterologist or physician with a specialty in gastroenterology. • Concurrent use of other biologic DMARDS not approved. • All requests for coverage for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra only. • Initial Approval: 3 infusions of infliximab 5mg/kg at week 0, 2 & 6. • Renewal Approval: Continued coverage dependent on evidence of response using criteria such the 100 point reduction in Crohn's Disease Activity Index (CDAI) or the Harvey-Bradshaw Index Assessment (HBI) with a score of 5 or less or a decrease in score of 4 or more. The maximum approved dose is 5mg/kg every 8 weeks. To facilitate this process, a specific Anti-TNF agents for Crohn's disease Special Authorization Form has been developed and can be found at: http://www.health.gov.nl.ca/health/prescription/crohns_meds.pdf

Drug Plan	Criteria for Restricted Benefit
YK	For moderate to severely active Crohn's Disease on recommendation of a specialist. Consult to be provided. For patients with a current Harvey Bradshaw Index (HBI) >7, who are intolerant or refractroy to 5-ASA (3 g daily for at least 6 weeks) AND are refractory, intolerant or dependant on glucocorticoids, AND who are refractory or intolerant to at least one of azathioprine, 6-mercaptopurine or methotrexate after a 3 month trial. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a gastroenterology specialist Patient meets the following criteria: • Therapy with 5-ASA products (at least 3g/day for a minimum of 6 weeks); PLUS • Glucocorticoids equivalent to prednisone 40 mg/day for a minimum of 2 weeks OR treatment discontinued due to serious adverse reactions OR contraindication to glucocorticoid therapy; PLUS • Azathioprine 2 to 2.5 mg/kg/day for a minimum of 3 months; OR • 6-mercaptopurine 50 to 70 mg/day for a minimum of 3 months; OR • MTX (oral or parenteral) 15 to 25 mg per week for a minimum of 3 months. Coverage beyond the initial three doses will be based on improvement in the CDAI or HBI scores. • At least a 100-point reduction in the Crohn's Disease Activity Index (CDAI) OR at least a 4-point reduction in the Harvey Bradshaw Index (HBI).
NIHB	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a gastroenterology specialist Patient meets the following criteria: • Therapy with 5-ASA products (at least 3g/day for a minimum of 6 weeks); PLUS • Glucocorticoids equivalent to prednisone 40 mg/day for a minimum of 2 weeks OR treatment discontinued due to serious adverse reactions OR contraindication to glucocorticoid therapy; PLUS • Azathioprine 2 to 2.5 mg/kg/day for a minimum of 3 months; OR • 6-mercaptopurine 50 to 70 mg/day for a minimum of 3 months; OR • MTX (oral or parenteral) 15 to 25 mg per week for a minimum of 3 months. Coverage beyond the initial three doses will be based on improvement in the CDAI or HBI scores. • At least a 100-point reduction in the Crohn's Disease Activity Index (CDAI) OR at least a 4-point reduction in the Harvey Bradshaw Index (HBI).
DND	• When prescribed by a gastroenterologist for patients with moderate to severe Crohn's Disease who are refractory or intolerant to: • 5-ASA products at 3g/day for 6 weeks AND

Drug Plan	Criteria for Restricted Benefit
	prednisone 40mg/day for 2 weeks AND Immunosuppressive therapy as follows: • azathioprine 2-2.5mg/kg/day for 3 months OR • mercaptopurine 50-75mg/day for 3 months OR • methotrexate 15-25mg/week for 3 months OR • Immunosuppressive therapy discontinued at less than 3 months due to serious adverse effects or reactions.
VAC	Case-by-case

Restricted Benefit Criteria for Inflectra for the treatment of Crohn's Disease (Adult)

Drug Plan	Criteria for Restricted Benefit
BC	New Patients Treatment of moderate to severe active Crohn's disease according to established criteria* when prescribed by a gastroenterologist. First approval (induction period): 3 doses (5 MG/KG AT 0, 2, AND 6 WEEKS) Prior Medication Therapy (Initial Coverage) Details of glucocorticoid trial • Corticosteroid resistant: lack of a symptomatic response despite a course of oral prednisone 40-60mg/day (or equivalent) for a minimum of 14 days. • Corticosteroid dependent: unable to withdraw oral corticosteroid within 3 months of initiation without a recurrence of symptoms; a symptomatic relapse within 3 months of stopping; or the need for two or more courses of corticosteroids within one year. • Corticosteroid use is contraindicated (specify): • intolerant/side effect(s) (specify): Details of other medication trial(s) *Renewal:* 1 year; 5MG/KG EVERY 8 WEEKS CURRENT HARVEY BRADSHAW INDEX SCORE WHILE ON TREATMENT (REQUIRES HBI SCORE <5 OR A DECREASE IN SCORE >4)
AB	*Initial:* Special authorization coverage may be approved for coverage of infliximab for the reduction in signs and symptoms and induction and maintenance of clinical remission of Moderately to Severely Active Crohn's Disease in patients who meet the following criteria: • Infliximab must be prescribed by a Specialist in Gastroenterology or a physician appropriately trained by the University of Alberta or the University of Calgary and recognized as a prescriber by Alberta Blue Cross for infliximab for coverage for the treatment of Moderately to Severely Active Crohn's Disease patients

Drug Plan	Criteria for Restricted Benefit
	('Specialist'). • Patients must be 18 years of age or older to be considered for coverage of infliximab. • Patients will be limited to receiving one dose of infliximab per prescription at their pharmacy. • Patients may be allowed to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy (both primary loss of response and secondary loss of response) or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period). • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. • Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. Prior to initiation of infliximab therapy for New Patients: 'New Patients' are patients who have never been treated with infliximab by any health care provider. New Patients must have a current Modified (without the physical exam) Harvey Bradshaw Index score of greater than or equal to 7 (New Patient's Baseline Score), AND be Refractory. Refractory is defined as one or more of the following: 1) Serious adverse effects or reactions to the treatments specified below; OR 2) Contraindications (as defined in product monographs) to the treatments specified below; OR 3) Previous documented lack of effect at doses and for duration of all treatments specified below: a) mesalamine: minimum of 3 grams/day for a minimum of 6 weeks; AND refractory to, or dependent on, glucocorticoids: following at least one tapering dosing schedule of 40 mg/day, tapering by 5 mg each week to 20 mg, then tapering by 2.5 mg each week to zero, or similar; [Note: Patients who have used the above treatments in combination will not be required to be challenged with individual treatments as monotherapy] AND b) Immunosuppressive therapy as follows: • Azathioprine: minimum of 2 mg/kg/day for a minimum of 3 months; OR • 6-mercaptopurine: minimum of 1 mg/kg/day for a minimum of 3 months; OR • Methotrexate: minimum or 15 mg/week for a minimum of 3 months. OR • Immunosuppressive therapy discontinued at less than 3 months due to serious adverse effects or reactions. Applications for coverage must include information regarding the dosages and duration of trial of each treatment the patient received, a description of any adverse effects, reactions, contraindications and/or lack of effect, as well as any other information requested by Alberta Blue Cross. • New Patients must meet the criteria above prior to being considered for approval. • All approvals are also subject to the following applicable criteria.

Drug Plan	Criteria for Restricted Benefit
	Induction Dosing for New Patients: • Coverage for Induction Dosing may only be approved for New Patients (those who have never been treated with infliximab by any health care provider). • 'Induction Dosing' means a maximum of one 5 mg/kg dose of infliximab per New Patient at each 0, 2 and 6 weeks (for a maximum total of three doses). • New Patients are eligible to receive Induction Dosing only once, after which time the Maintenance Dosing for New Patients and Continued Coverage for Maintenance Dosing criteria will apply. Maintenance Dosing: 'Maintenance Dosing' means one 5 mg/kg dose of infliximab per patient provided no more often than every 8 weeks for a period of 12 months to: • New Patients following the completion of Induction Dosing; OR • Existing Patients, who are patients that are being treated, or have previously been treated, with infliximab. Maintenance Dosing for New Patients after Completion of Induction Dosing: • The New Patient must be assessed by a Specialist between weeks 10 and 14 after the initiation of Induction Dosing to determine response by obtaining a Modified Harvey Bradshaw Index score; AND • The Specialist must confirm the Modified Harvey Bradshaw Index score shows a decrease from the New Patient's Baseline Score of greater than or equal to 3 points. Maintenance Dosing for Existing Patients: • The patient must be assessed by a Specialist at least 4 to 8 weeks after the day the last dose of infliximab was administered to the patient and prior to administration of the next dose to obtain a Modified Harvey Bradshaw Index Score (Existing Patient's • Baseline Score); AND • these measures must be provided to Alberta Blue Cross for assessment for continued coverage for maintenance dosing. (For existing patients with Moderately to Severely Active Crohn's Disease with an incomplete response, the dose may be adjusted to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.) Continued Coverage for Maintenance Dosing: Continued coverage may be considered for one 5 mg/kg dose of infliximab per patient provided no more often than every 8 weeks for a period of 12 months, if the following criteria are met at the end of each 12 month period: • The New Patient or the Existing Patient must be assessed by a Specialist at least 4 to 6 weeks after the day the last dose of infliximab was administered to the patient and prior to the administration of the next dose to obtain a Modified Harvey Bradshaw Index Score; AND • For New Patients: The Specialist must confirm that the patient has maintained a greater than or equal to 3 point decrease from the New Patient's Baseline Score; OR • For Existing Patients: The Specialist must confirm that the patient has maintained the Existing Patient's Baseline Score. (For new and existing patients with an incomplete response, the maintenance dose may be adjusted to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.)
SK	• For treatment of patients who demonstrate continuing symptoms despite the use of optimal conventional therapies, such as glucocorticoids and immunosuppressive therapy.

Drug Plan	Criteria for Restricted Benefit
	• For treatment of patients who are intolerant to conventional therapy, including glucocorticoids and immunosuppressive therapy. Clinical response should be assessed after the induction dose. Ongoing coverage will only be provided for those who respond to treatment. Patients undergoing this treatment should be reviewed every six months by a specialist in this area.
MB	For the treatment of patients over 18 years of age with moderate to severely active Crohn's Disease in patients refractory or with contraindications to an adequate course of 5-aminosalicyclic acid and corticosteroids and/or other immunosuppressive therapy. Request for coverage must be made by a physician who is a specialist in gastroenterology. Inflectra will be the preferred infliximab option for all infliximab-naïve patients prescribed an infliximab product for Crohn's Disease. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naïve patients. Patients will not be permitted to switch from Inflectra to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy.
ON	Limited Use Notes: For the treatment of moderate to severe (luminal) Crohn's Disease in patients who meet the following criteria: • HBI (Harvey Bradshaw Index) score greater than or equal to 7; and • Failed to respond to conventional treatment with a corticosteroid equivalent to a daily dose of prednisone 40mg daily for at least 2 weeks OR the patient is stabilized on corticosteroid but cannot be tapered to a corticosteroid dose below prednisone 20mg daily or equivalent; and • Failed to respond to an immunosuppressive agent (azathioprine, 6-mercaptopurine, methotrexate, or cyclosporine) tried for at least 3 months (or where the use of immunosuppressants is contraindicated). The recommended dosing regimen is 5mg/kg/dose at 0, 2 and 6 weeks followed by 5mg/kg/dose every 8 weeks. (Note: Higher doses up to 10mg/kg/dose may be considered in patients who have failed to respond to lower doses) Maintenance/Renewal: Maintenance therapy is funded for patients who meet the Ministry initiation criteria and whose disease is maintained with a 50% reduction in the Harvey Bradshaw Index (HBI) from pre-treatment measurement, AND improvement of symptoms (For example: absence of bloody diarrhea, weight is stable or increased), AND the use of corticosteroids and/or other immunosuppressive therapy is reduced, being tapered, or discontinued. For funding beyond the second year, the patient must continue to demonstrate benefit and if unable to be discontinued on corticosteroids, the physician may wish to consider other funded alternatives. The recommended dosing regimen is 5mg/kg/dose every 8 weeks.
NB	• For the treatment of adult patients with moderately to severely active Crohn's disease who have contraindications, or are refractory, to therapy with corticosteroids and other immunosuppressants.

Drug Plan	Criteria for Restricted Benefit
	Claim Notes: • Must be prescribed by a gastroenterologist or physician with a specialty in gastroenterology. • Combined use of more than one biologic DMARD will not be reimbursed. • All requests for coverage for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra only. • Initial Approval: 12 weeks. • Renewal Approval: 1 year. Confirmation of continued response is required. • Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions as outlined here.
NS	For infliximab-naïve patients whose infliximab therapy is initiated after December 1, 2016, Infectra will be the product approved for the following indications. • For treatment of Crohn's disease in adults, in patients with moderate to severe active disease refractory to 5-ASA products AND glucocorticoids (e.g.,prednisone) AND immunosuppressive therapy (azathioprine or 6-mercaptopurine or methotrexate)1. o Initial approval of infliximab will be for a single infusion of 5mg/kg/dose. A second infusion may be warranted in patients not responding to the first infusion or in patients responding initially but then worsening before maintenance therapy is effective. Request for approval beyond induction therapy will be considered on a case by case basis. o Initial approval is for three infusions of infliximab of 5mg/kg/dose at 0, 2 and 6 week intervals. 1. Patients who are very ill and not candidates for surgery may qualify for infliximab therapy without a trial of AZA, 6-MP or MTX, as they may require a more rapid onset of response. Notes: • Requires a written request by a gastroenterologist or physician with a specialty in gastroenterology.
PE	For the treatment of moderate to severe Crohn's Disease in patients who: 1. Have a Harvey Bradshaw Index score of 7 or more, AND 2. Have not responded to 5-ASA products (minimum trial of 3 grams per day for 6 weeks), AND 3. Have not responded to or are intolerant to glucocorticosteroid therapy (e.g. Prednisone) or where such therapy is contraindicated, AND 4. Have not responded to or are intolerant to immunosupressive therapy (Azathioprine, Mercaptopurine or Methotrexate) or where such therapy is contraindicated. Infliximab, injection powder, 100mg/vial (Inflectra-HOS) Initial approval for Infliximab will allow for 3 doses of 5mg/kg/dose administered at 0, 2, and 6 weeks. Renewal of coverage will require reassessment of the patient and submission of a new Crohn's Disease Special Authorization form. Continue coverage will be approved at a dose not exceeding 5mg/kg every 8 weeks. The request for coverage must be made by a gastroenterologist using the Crohn's Disease Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms Patients must also apply for coverage to the High-Cost Drug Program. The patient application is available from the Drug Program Office or online at http://healthpei.ca/pharmacareforms
NL	For the treatment of patients with moderate or severe active disease* with contraindications to or not achieving remission with glucocorticosteroids AND immunosuppressive therapy.

Drug Plan	Criteria for Restricted Benefit
	• Initial request must include current Crohn's Disease Activity Index (CDAI) or the Harvey Bradshaw Index Assessment (HBI) score. Claim Notes: • Must be prescribed by a gastroenterologist or physician with a specialty in gastroenterology. • Concurrent use of other biologic DMARDS not approved. • All requests for coverage for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra only. • Initial Approval: 3 infusions of infliximab 5mg/kg at week 0, 2 & 6. • Renewal Approval: Continued coverage dependent on evidence of response using criteria such the 100 point reduction in Crohn's Disease Activity Index (CDAI) or the Harvey-Bradshaw Index Assessment (HBI) with a score of 5 or less or a decrease in score of 4 or more. The maximum approved dose is 5mg/kg every 8 weeks. To facilitate this process, a specific Anti-TNF agents for Crohn's disease Special Authorization Form has been developed and can be found at: http://www.health.gov.nl.ca/health/prescription/crohns_meds.pdf
YK	For moderate to severely active Crohn's Disease on recommendation of a specialist. Consult to be provided. For patients with a current Harvey Bradshaw Index (HBI) >7, who are intolerant or refractroy to 5-ASA (3 g daily for at least 6 weeks) AND are refractory, intolerant or dependant on glucocorticoids, AND who are refractory or intolerant to at least one of azathioprine, 6-mercaptopurine or methotrexate after a 3 month trial. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a gastroenterology specialist Patient meets the following criteria: • Therapy with 5-ASA products (at least 3g/day for a minimum of 6 weeks); PLUS • Glucocorticoids equivalent to prednisone 40 mg/day for a minimum of 2 weeks OR treatment discontinued due to serious adverse reactions OR contraindication to glucocorticoid therapy; PLUS • Azathioprine 2 to 2.5 mg/kg/day for a minimum of 3 months; OR • 6-mercaptopurine 50 to 70 mg/day for a minimum of 3 months; OR • MTX (oral or parenteral) 15 to 25 mg per week for a minimum of 3 months. Coverage beyond the initial three doses will be based on improvement in the CDAI or HBI scores. • At least a 100-point reduction in the Crohn's Disease Activity Index (CDAI) OR at least a 4-point reduction in the Harvey Bradshaw Index (HBI).
NIHB	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a gastroenterology specialist Patient meets the following criteria: • Therapy with 5-ASA products (at least 3g/day for a minimum of 6 weeks);

Drug Plan	Criteria for Restricted Benefit
	PLUS • Glucocorticoids equivalent to prednisone 40 mg/day for a minimum of 2 weeks OR treatment discontinued due to serious adverse reactions OR contraindication to glucocorticoid therapy; PLUS • Azathioprine 2 to 2.5 mg/kg/day for a minimum of 3 months; OR • 6-mercaptopurine 50 to 70 mg/day for a minimum of 3 months; OR • MTX (oral or parenteral) 15 to 25 mg per week for a minimum of 3 months. Coverage beyond the initial three doses will be based on improvement in the CDAI or HBI scores. • At least a 100-point reduction in the Crohn's Disease Activity Index (CDAI) OR at least a 4-point reduction in the Harvey Bradshaw Index (HBI).
DND	Not a benefit
VAC	Not a benefit

Restricted Benefit Criteria for Remicade for the treatment of Crohn's Disease (Pediatric)

Drug Plan	Criteria for Restricted Benefit
BC	Patients granted Special Authority prior to Nov. 1, 2016 Treatment of moderate to severe active Crohn's disease according to established criteria* when prescribed by a gastroenterologist. First approval (induction period): Not eligible Prior Medication Therapy (Initial Coverage) Details of glucocorticoid trial • Corticosteroid resistant: lack of a symptomatic response despite a course of oral prednisone 40-60mg/day (or equivalent) for a minimum of 14 days. • Corticosteroid dependent: unable to withdraw oral corticosteroid within 3 months of initiation without a recurrence of symptoms; a symptomatic relapse within 3 months of stopping; or the need for two or more courses of corticosteroids within one year. • Corticosteroid use is contraindicated (specify): • intolerant/side effect(s) (specify): Details of other medication trial(s) *Renewal:* 1 year; 5MG/KG EVERY 8 WEEKS CURRENT HARVEY BRADSHAW INDEX SCORE WHILE ON TREATMENT (REQUIRES HBI SCORE <5 OR A DECREASE IN SCORE >4)
AB	Information not available
SK	• For treatment of patients who demonstrate continuing symptoms despite the use of optimal conventional therapies, such as glucocorticoids and immunosuppressive therapy.

Drug Plan	Criteria for Restricted Benefit
	• For treatment of patients who are intolerant to conventional therapy, including glucocorticoids and immunosuppressive therapy. Clinical response should be assessed after the induction dose. Ongoing coverage will only be provided for those who respond to treatment. Patients undergoing this treatment should be reviewed every six months by a specialist in this area.
MB	Information not available
ON	Note that effective November 30, 2016, Infliximab as Remicade for Moderate to Severe Crohn's Disase will only be considered for funding for existing EAP renewals. Infliximab as Inflectra can be considered through Limited Use criteria on the Ontario Drug Benefit Formulary. **Renewal** will be considered for patients with 50% reduction in HBI from pre-treatment as well as improvement of symptoms (e.g., absence of bloody diarrhea and weight stabilization or increase) and no longer using steroids. Biochemical improvements may also be required. The planned dosing regimen for the requested biologic should be provided. The recommended dose for the treatment of Crohn's Disease is 5mg/kg/dose at 0, 2 and 6 weeks followed by 5mg/kg/dose every 8 weeks.
NB	Information not available
NS	Information not available
PE	Information not available
NL	Information not available
YK	Information not available
NT	Information not available
NIHB	Information not available
DND	Not a benefit
VAC	Not a benefit

Restricted Benefit Criteria for Inflectra for the treatment of Crohn's Disease (Pediatric)

Drug Plan	Criteria for Restricted Benefit
BC	New Patients Treatment of moderate to severe active Crohn's disease according to established criteria* when prescribed by a gastroenterologist. First approval (induction period): 3 doses (5 MG/KG AT 0, 2, AND 6 WEEKS) Prior Medication Therapy (Initial Coverage) Details of glucocorticoid trial Corticosteroid resistant: lack of a symptomatic response despite a course of oral prednisone 40-60mg/day (or equivalent) for a minimum of 14 days. Corticosteroid dependent: unable to withdraw oral corticosteroid within 3 months of initiation without a recurrence of symptoms; a symptomatic relapse within 3 months of stopping; or the need for two or more courses of corticosteroids within one year. Corticosteroid use is contraindicated (specify): intolerant/side effect(s) (specify): Details of other medication trial(s) *Renewal:* 1 year; 5MG/KG EVERY 8 WEEKS CURRENT HARVEY BRADSHAW INDEX SCORE WHILE ON TREATMENT (REQUIRES HBI SCORE <5 OR A DECREASE IN SCORE >4)
AB	Not a benefit
SK	Not a benefit
MB	Information not available
ON	Not a benefit
NB	Information not available
NS	Information not available
PE	Information not available
NL	Information not available
YK	Information not available
NT	Information not available
NIHB	Information not available
DND	Not a benefit

Drug Plan	Criteria for Restricted Benefit
VAC	Not a benefit

Restricted Benefit Criteria for Remicade for the treatment of Fistulising Crohn's Disease

Drug Plan	Criteria for Restricted Benefit
BC	Patients granted Special Authority prior to Nov. 1, 2016 Treatment of fistulising Crohn's disease according to established criteria* when prescribed by a gastroenterologist. First approval (induction period): Not eligible Renewal: 1 year; 5MG/KG EVERY 8 WEEKS Prior Medication Therapy (Initial Coverage) Details of glucocorticoid trial • Corticosteroid resistant: lack of a symptomatic response despite a course of oral prednisone 40-60mg/day (or equivalent) for a minimum of 14 days. • Corticosteroid dependent: unable to withdraw oral corticosteroid within 3 months of initiation without a recurrence of symptoms; a symptomatic relapse within 3 months of stopping; or the need for two or more courses of corticosteroids within one year. • Corticosteroid use is contraindicated (specify): • intolerant/side effect(s) (specify): Details of other medication trial(s)
AB	Not eligible for new patients starting December 1, 2016. Special authorization coverage may be approved for coverage of infliximab for the treatment of Fistulizing Crohn's Disease in patients who meet the following criteria: • Infliximab must be prescribed by a Specialist in Gastroenterology or a physician appropriately trained by the University of Alberta or the University of Calgary and recognized as a prescriber by Alberta Blue Cross for infliximab for coverage for the treatment of Fistulizing Crohn's Disease patients (`Specialist'). • Patients must be 18 years of age or older to be considered for coverage of infliximab. • Patients will be limited to receiving one dose of infliximab per prescription at their pharmacy. • Patients may be allowed to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy (both primary loss of response and secondary loss of response) or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period). • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. • Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. [Existing Remicade patients]

Drug Plan	Criteria for Restricted Benefit
	Maintenance Dosing: 'Maintenance Dosing' means one 5 mg/kg dose of infliximab per patient provided no more often than every 8 weeks for a period of 12 months to: • Existing Patients, who are patients that are being treated, or have previously been treated, with infliximab. Maintenance Dosing for Existing Patients: • The patient must be assessed by a Specialist at least 4 to 8 weeks after the day the last dose of infliximab was administered to the patient and prior to administration of the next dose to obtain closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline; AND • these measures must be provided to Alberta Blue Cross for assessment for continued coverage for maintenance dosing. (For existing patients with Fistulizing Crohn's who respond then lose their response, the dose may be adjusted to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.) Continued Coverage for Maintenance Dosing: Continued coverage may be considered for one 5 mg/kg dose of infliximab per patient provided no more often than every 8 weeks for a period of 12 months, if the following criteria are met at the end of each 12 month period: • For Existing Patients: The Specialist must confirm that the patient has maintained closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline. (For new and existing patients who respond then lose their response, the maintenance dose may be adjusted to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.)
SK	• For treatment of patients with symptomatic enterocutaneous or perineal fistulae, enterovaginal fistulae or enterovesical fistulae (i.e. any type of fistulizing Crohn's Disease). Clinical response should be assessed after the induction dose. Ongoing coverage will only be provided for those who respond to treatment. Patients undergoing this treatment should be reviewed every six months by a specialist in this area.
MB	For the treatment of Fistulating Crohn's Disease in patients refractory or with contraindications to an adequate course of 5-aminosalicyclic acid and corticosteroids and/or other immunosuppressive therapy. Request for coverage must be made by a physician who is a specialist in gastroenterology.
ON	Note that effective November 30, 2016, Infliximab as Remicade for fistulizing Crohn's Disease will only be considered for funding for existing EAP renewals. Infliximab as Inflectra can be considered through Limited Use criteria on the Ontario Drug Benefit Formulary. **Renewal** of funding of patients using Remicade for the treatment of fistulizing Crohn's Disease will be considered for patients with resolution of fistulae. The planned dosing regimen for the requested biologic should be provided. The recommended dose for the treatment of Crohn's Disease is 5mg/kg/dose at 0, 2

Drug Plan	Criteria for Restricted Benefit
	and 6 weeks followed by 5mg/kg/dose every 8 weeks.
NB	Not a benefit
NS	• In patients with fistulizing disease who have actively draining perianal or enterocutaneous fistula(e) that have recurred or persisted despite a course of appropriate antibiotic therapy (e.g., metronidazole +/-ciprofloxacin for a minimum of 3 weeks) AND immunosuppressive therapy (azathioprine or 6-mercaptopurine or methotrexate)**. • Initial approval is for three infusions of infliximab of 5mg/kg/dose at 0, 2 and 6 week intervals. 1. Patients who are very ill and not candidates for surgery may qualify for infliximab therapy without a trial of AZA, 6-MP or MTX, as they may require a more rapid onset of response. Notes: • Requires a written request by a gastroenterologist or physician with a specialty in gastroenterology. For infliximab-naïve patients whose infliximab therapy is initiated after December 1, 2016, Inflectra will be the product approved.
PE	For the treatment of fistulizing Crohn's Disease in patients who: 1. Have a Harvey Bradshaw Index score of 7 or more, AND 2. Have an actively draining perianal or enercutaneious fistula(e) that have recurred or persisted despite a course of appropriate antibiotic therapy (e.g. Ciprofloxacin with or without Metronidazole for a minimum of 3 weeks), AND 3. Have not responded to or are intolerant to immunosupressive therapy (Azathioprine, Mercaptopurine or Methotrexate) or where such therapy is contraindicated. Initial approval for Infliximab will allow for 3 doses of 5mg/kg/dose administered at 0, 2, and 6 weeks. Renewal of coverage will require reassessment of the patient and submission of a new Crohn's Disease Special Authorization form. Continued coverage will be approved at a dose not exceeding 5mg/kg every 8 weeks. The request for coverage must be made by a gastroenterologist using the Crohn's Disease Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms Patients must also apply for coverage to the High-Cost Drug Program. The patient application is available from the Drug Program Office or online at http://healthpei.ca/pharmacareforms
NL	Information not available
YK	For fistulizing Crohn's Disease on recommendation of a specialist. Consult to be provided. For patients with actively draining fistula(s) despite a 3 week trial of ciprofloxacin or metronidazole, AND at least a 6 week trial of azathioprine or 6-mercaptopurine. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a gastroenterology specialist

Drug Plan	Criteria for Restricted Benefit
	Patient meets all the following criteria: • Patients with actively draining perianal or enterocutaneous fistulae that are refractory to a course of appropriate antibiotic therapy (e.g. ciprofloxacin with or without metronidazole for a minimum of 3 weeks); PLUS Patient has failed a trial of one (1) immunosuppressive agent: • Azathioprine 2 to 2.5 mg/kg/day for a minimum of 3 months or treatment discontinued at < 3 months due to severe adverse: reactions. OR • 6-mercaptopurine 50-70 mg/day for a minimum of 3 months or treatment discontinued at <3 months due to severe adverse reactions. Coverage beyond the initial three doses will be based on improvement or closure of actively draining fistulae • Closure of individual fistulae as evidenced by no, or minimal, fistulae drainage and bleeding
NIHB	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a gastroenterology specialist Patient meets all the following criteria: • Patients with actively draining perianal or enterocutaneous fistulae that are refractory to a course of appropriate antibiotic therapy (e.g. ciprofloxacin with or without metronidazole for a minimum of 3 weeks); PLUS Patient has failed a trial of one (1) immunosuppressive agent: • Azathioprine 2 to 2.5 mg/kg/day for a minimum of 3 months or treatment discontinued at < 3 months due to severe adverse: reactions. OR • 6-mercaptopurine 50-70 mg/day for a minimum of 3 months or treatment discontinued at <3 months due to severe adverse reactions. Coverage beyond the initial three doses will be based on improvement or closure of actively draining fistulae • Closure of individual fistulae as evidenced by no, or minimal, fistulae drainage and bleeding
DND	• when prescribed by a gastroenterologist for patients with active draining fistulas despite: • ciprofloxacin + metronidazole for 3 weeks AND • azathioprine for a minimum of 6 weeks OR • 6-mercaptopurine for 6 weeks.
VAC	Case-by-case

Restricted Benefit Criteria for Inflectra for the treatment of Fistulising Crohn's Disease

Drug Plan	Criteria for Restricted Benefit
BC	New Patients Treatment of fistulising Crohn's disease according to established criteria* when prescribed by a gastroenterologist. First approval (induction period): 3 doses (5 MG/KG AT 0, 2, AND 6 WEEKS) Renewal: 1 year; 5MG/KG EVERY 8 WEEKS Prior Medication Therapy (Initial Coverage) Details of glucocorticoid trial • Corticosteroid resistant: lack of a symptomatic response despite a course of oral prednisone 40-60mg/day (or equivalent) for a minimum of 14 days. • Corticosteroid dependent: unable to withdraw oral corticosteroid within 3 months of initiation without a recurrence of symptoms; a symptomatic relapse within 3 months of stopping; or the need for two or more courses of corticosteroids within one year. • Corticosteroid use is contraindicated (specify): • intolerant/side effect(s) (specify): Details of other medication trial(s)
AB	*Initial:* Special authorization coverage may be approved for coverage of infliximab for the treatment of Fistulizing Crohn's Disease in patients who meet the following criteria: • Infliximab must be prescribed by a Specialist in Gastroenterology or a physician appropriately trained by the University of Alberta or the University of Calgary and recognized as a prescriber by Alberta Blue Cross for infliximab for coverage for the treatment of Fistulizing Crohn's Disease patients (`Specialist'). • Patients must be 18 years of age or older to be considered for coverage of infliximab. • Patients will be limited to receiving one dose of infliximab per prescription at their pharmacy. • Patients may be allowed to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy (both primary loss of response and secondary loss of response) or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period). • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. • Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. • Patients must be 18 years of age or older to be considered for coverage of infliximab. Prior to initiation of infliximab therapy for New Patients: 'New Patients' are patients who have never been treated with infliximab by any health care provider. New Patients must have actively draining perianal or enterocutaneous fistula(s) that have recurred or persisted despite: a) A course of an appropriate dose of antibiotic therapy (e.g. ciprofloxacin or metronidazole) for a minimum of 3 weeks; AND b) Immunosuppressive therapy:

Drug Plan	Criteria for Restricted Benefit
	• Azathioprine: minimum of 2 mg/kg/day for a minimum of 6 weeks; OR • 6-mercaptopurine: minimum of 1 mg/kg/day for a minimum of 6 weeks; OR • Immunosuppressive therapy discontinued at less than 6 weeks due to serious adverse effects or reactions. [Note: Patients who have used the above treatments in combination for the treatment of Fistulizing Crohn's will not be required to be challenged with individual treatments as monotherapy] Applications for coverage must include information regarding the dosages and duration of trial of each treatment the patient received, a description of any adverse effects, reactions, contraindications and/or lack of effect, as well as any other information requested by Alberta Blue Cross. • New Patients must meet the criteria above prior to being considered for approval. • All approvals are also subject to the following applicable criteria. Induction Dosing for New Patients: • Coverage for Induction Dosing may only be approved for New Patients (those who have never been treated with infliximab by any health care provider). • 'Induction Dosing' means a maximum of one 5 mg/kg dose of infliximab per New Patient at each 0, 2 and 6 weeks (for a maximum total of three doses). • New Patients are eligible to receive Induction Dosing only once, after which time the Maintenance Dosing for New Patients and Continued Coverage for Maintenance Dosing criteria will apply. Maintenance Dosing: 'Maintenance Dosing' means one 5 mg/kg dose of infliximab per patient provided no more often than every 8 weeks for a period of 12 months to: • New Patients following the completion of Induction Dosing; OR • Existing Patients, who are patients that are being treated, or have previously been treated, with infliximab. Maintenance Dosing for New Patients after Completion of Induction Dosing: • The New Patient must be assessed by a Specialist between weeks 10 and 14 after the initiation of Induction Dosing to determine response by obtaining closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline; AND • The Specialist must confirm closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline. Maintenance Dosing for Existing Patients: • The patient must be assessed by a Specialist at least 4 to 8 weeks after the day the last dose of infliximab was administered to the patient and prior to administration of the next dose to obtain closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline; AND • these measures must be provided to Alberta Blue Cross for assessment for continued coverage for maintenance dosing. (For existing patients with Fistulizing Crohn's who respond then lose their response, the dose may be adjusted to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.)

Drug Plan	Criteria for Restricted Benefit
	Continued Coverage for Maintenance Dosing: Continued coverage may be considered for one 5 mg/kg dose of infliximab per patient provided no more often than every 8 weeks for a period of 12 months, if the following criteria are met at the end of each 12 month period: • The New Patient or the Existing Patient must be assessed by a Specialist at least 4 to 6 weeks after the day the last dose of infliximab was administered to the patient and prior to the administration of the next dose to obtain closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline; AND • For New Patients: The Specialist must confirm that the patient has maintained closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline; OR • For Existing Patients: The Specialist must confirm that the patient has maintained closure of individual fistulas as evidenced by no or minimal fistula drainage despite gentle finger compression of fistulas that were draining at baseline. (For new and existing patients who respond then lose their response, the maintenance dose may be adjusted to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.)
SK	• For treatment of patients with symptomatic enterocutaneous or perineal fistulae, enterovaginal fistulae or enterovesical fistulae (i.e. any type of fistulizing Crohn's Disease). Clinical response should be assessed after the induction dose. Ongoing coverage will only be provided for those who respond to treatment. Patients undergoing this treatment should be reviewed every six months by a specialist in this area.
MB	For the treatment of patients over 18 years of age with Fistulating Crohn's Disease in patients refractory or with contraindications to an adequate course of 5-aminosalicyclic acid and corticosteroids and/or other immunosuppressive therapy. Request for coverage must be made by a physician who is a specialist in gastroenterology. Inflectra will be the preferred infliximab option for all infliximab-naïve patients prescribed an infliximab product for Crohn's Disease. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naïve patients. Patients will not be permitted to switch from Inflectra to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy.
ON	Limited Use Notes: For the treatment of fistulizing Crohn's Disease in patients with actively draining perianal or enterocutaneous fistula(e) who meet the following criteria; Fistula has persisted despite a course of antibiotic therapy (ciprofloxacin and/or metronidazole) and immunosuppressive therapy (azathioprine or 6-mercaptopurine). The recommended dosing regimen is 5mg/kg/dose at 0, 2 and 6 weeks followed by 5mg/kg/dose every 8 weeks. Maintenance/Renewal: Maintenance therapy is funded for patients who meet the Ministry initiation criteria for fistulizing Crohn's disease and who have demonstrated benefit from treatment (e.g. partial resolution of fistulae and symptom improvement.). The recommended dosing regimen is 5mg/kg/dose every 8 weeks.

Drug Plan	Criteria for Restricted Benefit
NB	Not a benefit
NS	For infliximab-naïve patients whose infliximab therapy is initiated after December 1, 2016, Infectra will be the product approved for the following indications. • In patients with fistulizing disease who have actively draining perianal or enterocutaneous fistula(e) that have recurred or persisted despite a course of appropriate antibiotic therapy (e.g., metronidazole +/- ciprofloxacin for a minimum of 3 weeks) AND immunosuppressive therapy (azathioprine or 6-mercaptopurine or methotrexate)1. • Initial approval is for three infusions of infliximab of 5mg/kg/dose at 0, 2 and 6 week intervals. 1. Patients who are very ill and not candidates for surgery may qualify for infliximab therapy without a trial of AZA, 6-MP or MTX, as they may require a more rapid onset of response. Notes: • Requires a written request by a gastroenterologist or physician with a specialty in gastroenterology.
PE	For the treatment of fistulizing Crohn=s Disease in patients who: 1. Have a Harvey Bradshaw Index score of 7 or more, AND 2. Have an actively draining perianal or enercutaneious fistula(e) that have recurred or persisted despite a course of appropriate antibiotic therapy (e.g. Ciprofloxacin with or without Metronidazole for a minimum of 3 weeks), AND 3. Have not responded to or are intolerant to immunosupressive therapy (Azathioprine, Mercaptopurine or Methotrexate) or where such therapy is contraindicated. Infliximab, injection powder, 100mg/vial (Inflectra-HOS) Initial approval for Infliximab will allow for 3 doses of 5mg/kg/dose administered at 0, 2, and 6 weeks. Renewal of coverage will require reassessment of the patient and submission of a new Crohn's Disease Special Authorization form. Continue coverage will be approved at a dose not exceeding 5mg/kg every 8 weeks. The request for coverage must be made by a gastroenterologist using the Crohn's Disease Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms . Patients must also apply for coverage to the High-Cost Drug Program. The patient application is available from the Drug Program Office or online at http://healthpei.ca/pharmacareforms
NL	Information not available
YK	For fistulizing Crohn's Disease on recommendation of a specialist. Consult to be provided. For patients with actively draining fistula(s) despite a 3 week trial of ciprofloxacin or metronidazole, AND at least a 6 week trial of azathioprine or 6-mercaptopurine. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a gastroenterology specialist

Drug Plan	Criteria for Restricted Benefit
	Patient meets all the following criteria: • Patients with actively draining perianal or enterocutaneous fistulae that are refractory to a course of appropriate antibiotic therapy (e.g. ciprofloxacin with or without metronidazole for a minimum of 3 weeks); PLUS Patient has failed a trial of one (1) immunosuppressive agent: • Azathioprine 2 to 2.5 mg/kg/day for a minimum of 3 months or treatment discontinued at < 3 months due to severe adverse: reactions. OR • 6-mercaptopurine 50-70 mg/day for a minimum of 3 months or treatment discontinued at <3 months due to severe adverse reactions. Coverage beyond the initial three doses will be based on improvement or closure of actively draining fistulae • Closure of individual fistulae as evidenced by no, or minimal, fistulae drainage and bleeding.
NIHB	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a gastroenterology specialist Patient meets all the following criteria: • Patients with actively draining perianal or enterocutaneous fistulae that are refractory to a course of appropriate antibiotic therapy (e.g. ciprofloxacin with or without metronidazole for a minimum of 3 weeks); PLUS Patient has failed a trial of one (1) immunosuppressive agent: • Azathioprine 2 to 2.5 mg/kg/day for a minimum of 3 months or treatment discontinued at < 3 months due to severe adverse: reactions. OR • 6-mercaptopurine 50-70 mg/day for a minimum of 3 months or treatment discontinued at <3 months due to severe adverse reactions. Coverage beyond the initial three doses will be based on improvement or closure of actively draining fistulae • Closure of individual fistulae as evidenced by no, or minimal, fistulae drainage and bleeding.
DND	Not a benefit
VAC	Not a benefit

Restricted Benefit Criteria for Remicade for the treatment of Ulcerative Colitis (Adult)

Drug Plan	Criteria for Restricted Benefit
BC	Not a benefit
AB	Not eligible for new patients starting December 1, 2016. Special authorization coverage may be provided for the reduction in signs and symptoms and induction and maintenance of clinical remission of Ulcerative Colitis in adult patients (18 years of age or older) with active disease (characterized by a partial Mayo score >4 prior to initiation of biologic therapy) and who are refractory or intolerant to: • mesalamine: minimum of 4 grams/day for a minimum of 4 weeks AND • corticosteroids (failure to respond to prednisone 40 mg daily for 2 weeks, or; steroid dependent i.e. failure to taper off steroids without recurrence of disease or disease requiring a second dose of steroids within 12 months of previous dose). 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. Immunosuppressive therapy as follows may also be initiated if in the clinician's judgment a trial is warranted: i) Azathioprine: minimum of 2 mg/kg/day for a minimum of 2 months; OR ii) 6-mercaptopurine: minimum of 1 mg/kg/day for a minimum of 2 months For continued coverage beyond three doses, the patient must meet the following criteria: 1) The patient must be assessed by a Specialist between weeks 10 and 14 after the initiation of therapy to determine response. 2) The Specialist must confirm in writing that the patient is a 'responder' that meets the following criteria: • a decrease in the partial Mayo score of greater than or equal to 2 points Following this assessment, continued coverage may be approved for dose of 5 mg/kg every 8 weeks for a period of 12 months. Ongoing coverage may be considered only if the following criteria are met at the end of each 12-month period: 1) The patient has been assessed by a Specialist in Gastroenterology to determine response; 2) The Specialist must confirm in writing that the patient has maintained a response to therapy as indicated by: • a decrease in the partial Mayo score of greater than or equal to 2 points from the score prior to initiation of infliximab therapy Note: For patients who showed a response to induction therapy then experienced secondary loss of response while on maintenance dosing with 5 mg/kg, the maintenance dose may be adjusted from 5 mg/kg to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.
SK	• For treatment of ulcerative colitis in patients unresponsive to high dose intravenous steroids. Clinical response should be assessed after the three-dose induction phase before proceeding to maintenance therapy. Ongoing coverage will only be provided for those who respond to therapy.

Drug Plan	Criteria for Restricted Benefit
	Patients undergoing this treatment should be reviewed every six months by a specialist in this area.
MB	For the treatment of patients with moderately to severly active ulcerative colitis who have had an inadequate response to conventional therapy including 5-aminosalicylate compounds, corticosteroids and immunomodulators. Request for coverage must be made by a specialist in gastroenterology.
ON	Note that effective November 30, 2016, Infliximab as Remicade for Ulcerative Colitis will only be considered for funding for existing EAP renewals. Infliximab as Inflectra can be considered through Limited Use criteria on the Ontario Drug Benefit Formulary. Initial induction requests for infliximab for patients with mild Ulcerative Colitis (Mayo score < 6) may be considered for Infliximab as Inflectra on a case-by-case basis through EAP but the submission must include the rationale for coverage. Renewal requests for Maintenance therapy of Ulcerative Colitis will be considered for Remicade in patients meeting the following criteria: **Maintenance Criteria:** 1. After 3 loading doses of Remicade: a. Mayo score[1] < 6 AND b. 50% reduction in prednisone from the starting dose Approval: 3 months at 5 mg/kg/dose every 8 weeks If patient is completely off steroids. Approval: 12 months at 5 mg/kg/dose every 8 weeks 2. Subsequent renewals: a. Mayo[1] score < 6; AND b. Must be off steroids (Patients who remain on steroids will be considered on a case-by-case basis) Approval: 12 months at 5 mg/kg/dose every 8 weeks [1]Note that the endoscopy procedure must be done within the last year but does not have to be full endoscopy.
NB	Not a benefit
NS	• For the treatment of adult patients with moderately to severely active ulcerative colitis who have a partial Mayo score > 4, and a rectal bleeding subscore ≥ 2 and are: ○ refractory or intolerant to conventional therapy (i.e. 5-ASA for a minimum of 4 weeks, and prednisone ≥40mg daily for two weeks or IV equivalent for one week); or ○ corticosteroid dependent (i.e. cannot be tapered from corticosteroids without disease recurrence; or have relapsed within three months of stopping

Drug Plan	Criteria for Restricted Benefit
	corticosteroids; or require two or more courses of corticosteroids within one year.) • Renewal requests must include information demonstrating the beneficial effects of the treatment, specifically: ○ a decrease in the partial Mayo score ≥ 2 from baseline, and ○ a decrease in the rectal bleeding subscore ≥1. Clinical Notes: • Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above. • Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented. • Patients with severe disease do not require a trial of 5-ASA Claim Notes: • Must be prescribed by a gastroenterologist or physician with a specialty in gastroenterology. • Combined use of more than one biologic DMARD will not be reimbursed. • Initial Approval: 16 weeks. • Renewal Approval: 1 year. For infliximab-naïve patients whose infliximab therapy is initiated after December 1, 2016, Inflectra will be the product approved.
PE	Not a benefit
NL	Not a benefit
YK	For Ulcerative Colitis on recommendation of a specialist.Consult to be provided. For patients with a Mayo score >6 AND an endoscopic subscore ≥ 2 (within last 12 months) AND failed 2 weeks of oral prednisone ≥ 40mg (or 1 week IV equivalent) AND 3 months of azathioprine or 6-mercaptopurine OR stablizied on prednisone as above but the prednisone dose cannot be tapered despite 3 months of DMARDS. Only one month's dose to be dispensed at a time. Approval for 12 month period. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Not a benefit
NIHB	Not a benefit
DND	Not a benefit
VAC	Case-by-case

Restricted Benefit Criteria for Inflectra for the treatment of Ulcerative Colitis (Adult)

Drug Plan	Criteria for Restricted Benefit
BC	Treatment of moderate to severe Ulcerative Colitis according to established criteria* when prescribed by a gastroenterologist. First approval (induction period): 3 doses (5 MG/KG AT 0, 2, AND 6 WEEKS) Prior Medication Therapy (Initial Coverage) Details of glucocorticoid trial • Corticosteroid resistant: lack of a symptomatic response despite a course of oral prednisone 40-60mg/day (or equivalent) for a minimum of 14 days. • Corticosteroid dependent: unable to withdraw oral corticosteroid within 3 months of initiation without a recurrence of symptoms; a symptomatic relapse within 3 months of stopping; or the need for two or more courses of corticosteroids within one year. • Corticosteroid use is contraindicated (specify): • intolerant/side effect(s) (specify): Details of other medication trial(s) *Renewal:* 1 year (5MG/KG EVERY 8 WEEKS) • Requires a score reduction from baseline >=2 with a decrease in baseline from rectal bleeding subscore of >=1, or a bleeding subscore of 0 or 1
AB	Special authorization coverage may be provided for the reduction in signs and symptoms and induction and maintenance of clinical remission of Ulcerative Colitis in adult patients (18 years of age or older) with active disease (characterized by a partial Mayo score >4 prior to initiation of biologic therapy) and who are refractory or intolerant to: • mesalamine: minimum of 4 grams/day for a minimum of 4 weeks AND • corticosteroids (failure to respond to prednisone 40 mg daily for 2 weeks, or; steroid dependent i.e. failure to taper off steroids without recurrence of disease or disease requiring a second dose of steroids within 12 months of previous dose). 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. Immunosuppressive therapy as follows may also be initiated if in the clinician's judgment a trial is warranted: i) Azathioprine: minimum of 2 mg/kg/day for a minimum of 2 months; OR ii) 6-mercaptopurine: minimum of 1 mg/kg/day for a minimum of 2 months For coverage, this drug must be prescribed by a Specialist in Gastroenterology or a physician appropriately trained by the University of Alberta or the University of Calgary and recognized as a prescriber by Alberta Blue Cross ('Specialist'). Initial coverage may be approved for three doses of 5 mg/kg of infliximab at 0, 2 and 6 weeks. • Patients will be limited to receiving a one dose of infliximab per prescription at their pharmacy.

Drug Plan	Criteria for Restricted Benefit
	• Patients will be permitted to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy, or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period). • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. • Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. For continued coverage beyond three doses, the patient must meet the following criteria: 1) The patient must be assessed by a Specialist between weeks 10 and 14 after the initiation of therapy to determine response. 2) The Specialist must confirm in writing that the patient is a 'responder' that meets the following criteria: • a decrease in the partial Mayo score of greater than or equal to 2 points Following this assessment, continued coverage may be approved for dose of 5 mg/kg every 8 weeks for a period of 12 months. Ongoing coverage may be considered only if the following criteria are met at the end of each 12-month period: 1) The patient has been assessed by a Specialist in Gastroenterology to determine response; 2) The Specialist must confirm in writing that the patient has maintained a response to therapy as indicated by: • a decrease in the partial Mayo score of greater than or equal to 2 points from the score prior to initiation of infliximab therapy Note: For patients who showed a response to induction therapy then experienced secondary loss of response while on maintenance dosing with 5 mg/kg, the maintenance dose may be adjusted from 5 mg/kg to 10 mg/kg by making an additional special authorization request to Alberta Blue Cross for the increased dose.
SK	• For treatment of ulcerative colitis in patients unresponsive to high dose intravenous steroids. Clinical response should be assessed after the three-dose induction phase before proceeding to maintenance therapy. Ongoing coverage will only be provided for those who respond to therapy. Patients undergoing this treatment should be reviewed every six months by a specialist in this area.
MB	For the treatment of patients over 18 years of age with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy including 5-aminosalicylate compounds, corticosteroids and immunomodulators. Request for coverage must be made by a specialist in gastroenterology. Inflectra will be the preferred infliximab option for all infliximab-naïve patients prescribed an infliximab product for Ulcerative Coliits. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naïve patients. Patients will not be permitted to switch from Inflectra to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy.
ON	Limited Use Notes: For the treatment of ulcerative colitis disease in patients who meet the following criteria: 1. Moderate disease a. Mayo score between 6 and 10 (inclusive) AND b. Endoscopic* subscore of 2 AND c. Failed 2 weeks of oral prednisone at daily doses greater than or equal to 40mg (or a 1 week course of IV equivalent)

Drug Plan	Criteria for Restricted Benefit
	OR d. Stabilized with 2 weeks oral prednisone at daily doses greater than or equal to 40mg (or 1 week of IV equivalent) but demonstrated that the corticosteroid dose cannot be tapered despite 3 months of AZA/6MP (or where the use of immunosuppressants is contraindicated) 2. Severe disease a. Mayo score greater than 10 AND b. Endoscopy* subscore of greater than or equal to 2 AND c. Failed 2 weeks of oral prednisone at daily doses greater than or equal to 40mg (or 1 week IV equivalent) OR d. Stabilized with 2 weeks oral prednisone at daily doses greater than or equal to 40mg (or 1 week of IV equivalent) but the demonstrated that the corticosteroid dose cannot be tapered despite 3 months of AZA/6MP (or where the use of immunosuppressants is contraindicated) *The endoscopy procedure must be done within the 12 months prior to initiation of treatment. The recommended dosing regimen for induction is 5mg/kg/dose at 0, 2 and 6 weeks followed by 5mg/kg/dose every 8 weeks. Maintenance/Renewal: Maintenance therapy is funded for patients who meet the Ministry initiation criteria and whose disease is maintained at Mayo score less than 6 AND who demonstrate at least 50% reduction in the dose of prednisone compared with the starting dose following the first 6 months of treatment with Inflectra or be off corticosteroids after the first year of treatment. The recommended dosing regimen is 5mg/kg/dose every 8 weeks.
NB	• For the treatment of adult patients with moderately to severely active ulcerative colitis who have a partial Mayo score > 4, and a rectal bleeding subscore ≥ 2 and are: • refractory or intolerant to conventional therapy (i.e. aminosalicylates for a minimum of four weeks, and prednisone ≥ 40mg daily for two weeks or IV equivalent for one week); or • corticosteroid dependent (i.e. cannot be tapered from corticosteroids without disease recurrence; or have relapsed within three months of stopping corticosteroids; or require two or more courses of corticosteroids within one year). • Renewal requests must include information demonstrating the beneficial effects of the treatment, specifically: • a decrease in the partial Mayo score ≥ 2 from baseline, and • a decrease in the rectal bleeding subscore ≥1. Clinical Notes: 1. Consideration will be given for patients who have not received a four week trial of aminosalicylates if disease is severe (partial Mayo score > 6). 2. Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above. 3. Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented.

Drug Plan	Criteria for Restricted Benefit
	Claim Notes: • Must be prescribed by a gastroenterologist or physician with a specialty in gastroenterology. • Combined use of more than one biologic DMARD will not be reimbursed. • All requests will be approved for Inflectra only; requests for coverage of Remicade will not be considered. • Initial Approval: 12 weeks. • Renewal Approval: 1 year. • Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions as outlined here.

NS	For infliximab-naïve patients whose infliximab therapy is initiated after December 1, 2016, Infectra will be the product approved for the following indications.
	• For the treatment of adult patients with moderately to severely active ulcerative colitis who have a partial Mayo score > 4, and a rectal bleeding subscore ≥ 2 and are:
	  ○ refractory or intolerant to conventional therapy (i.e. 5-ASA for a minimum of 4 weeks, and prednisone ≥40mg daily for two weeks or IV equivalent for one week); or
	  ○ corticosteroid dependent (i.e. cannot be tapered from corticosteroids without disease recurrence; or have relapsed within three months of stopping corticosteroids; or require two or more courses of corticosteroids within one year.)
	• Renewal requests must include information demonstrating the beneficial effects of the treatment, specifically:
	  ○ a decrease in the partial Mayo score ≥ 2 from baseline, and
	  ○ a decrease in the rectal bleeding subscore ≥1.
	
	Clinical Notes:
	• Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above.
	• Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented.
	• Patients with severe disease do not require a trial of 5-ASA
	
	Claim Notes:
	• Must be prescribed by a gastroenterologist or physician with a specialty in gastroenterology.
	• Combined use of more than one biologic DMARD will not be reimbursed.
	• Initial Approval: 16 weeks.
	• Renewal Approval: 1 year.

PE	Not a benefit
NL	For the treatment of adult patients with moderately to severely active ulcerative colitis who have a partial Mayo score > 4, and a rectal bleeding subscore ≥ 2 and are: • refractory or intolerant to conventional therapy (i.e. 5-ASA for a minimum of 4 weeks, and prednisone ≥ 40mg daily for two weeks or IV equivalent for one week); or • corticosteroid dependent (i.e. cannot be tapered from corticosteroids without disease recurrence; or have relapsed within three months of stopping corticosteroids; or require two or more courses of corticosteroids within one year.)

Drug Plan	Criteria for Restricted Benefit
	Renewal requests must include information demonstrating the beneficial effects of the treatment, specifically: • a decrease in the partial Mayo score ≥ 2 from baseline, and • a decrease in the rectal bleeding subscore ≥1. Clinical Notes: • Consideration will be given for patients who have not received a four week trial of aminosalicylates if disease is severe (partial Mayo score > 6). • Refractory is defined as lack of effect at the recommended doses and for duration of treatments specified above. • Intolerant is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of intolerance(s) must be clearly documented. Claim Notes: • Must be prescribed by a gastroenterologist or physician with a specialty in gastroenterology. • Combined use of more than one biologic DMARD will not be reimbursed. • All requests will be approved for Inflectra only; requests for Remicade will not be considered. • Initial Approval: 12 weeks. • Renewal Approval: 1 year. • Maximum Quantity Reimbursed: ○ Infliximab: 5 mg/kg at weeks 0, 2 and 6, then every 8 weeks thereafter.
YK	For Ulcerative Colitis on recommendation of a specialist.Consult to be provided. For patients with a Mayo score >6 AND an endoscopic subscore ≥ 2 (within last 12 months) AND failed 2 weeks of oral prednisone ≥ 40mg (or 1 week IV equivalent) AND 3 months of azathioprine or 6-mercaptopurine OR stablizied on prednisone as above but the prednisone dose cannot be tapered despite 3 months of DMARDS. Only one month's dose to be dispensed at a time. Approval for 12 month period. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by expert in gastroenterology • Partial Mayo score > 4 • Inadequate response to conventional therapies: ○ 5-ASA 4grams/day for 6 weeks; PLUS ○ Prednisone 40mg daily for 2 weeks; PLUS ○ Azathioprine 2mg/kg/day for 12 weeks OR 6-mercaptopurine 1mg/kg/day for 12 weeks (unless the use of immunosuppressants is contraindicated). Coverage beyond the initial three doses will be based on improvement in the Partial Mayo Score and discontinuation of systemic corticosteroids.

Drug Plan	Criteria for Restricted Benefit
NIHB	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by expert in gastroenterology • Partial Mayo score > 4 • Inadequate response to conventional therapies: ○ 5-ASA 4grams/day for 6 weeks; PLUS ○ Prednisone 40mg daily for 2 weeks; PLUS ○ Azathioprine 2mg/kg/day for 12 weeks OR 6-mercaptopurine 1mg/kg/day for 12 weeks (unless the use of immunosuppressants is contraindicated). Coverage beyond the initial three doses will be based on improvement in the Partial Mayo Score and discontinuation of systemic corticosteroids.
DND	Not a benefit
VAC	Not a benefit

Restricted Benefit Criteria for Remicade for the treatment of Ulcerative Colitis (Pediatric)

Drug Plan	Criteria for Restricted Benefit
BC	Not a benefit
AB	Information not available
SK	• For treatment of ulcerative colitis in patients unresponsive to high dose intravenous steroids. Clinical response should be assessed after the three-dose induction phase before proceeding to maintenance therapy. Ongoing coverage will only be provided for those who respond to therapy. Patients undergoing this treatment should be reviewed every six months by a specialist in this area.
MB	Information not available
ON	Note that effective November 30, 2016, Infliximab as Remicade for Ulcerative Colitis will only be considered for funding for existing EAP renewals. Infliximab as Inflectra can be considered through Limited Use criteria on the Ontario Drug Benefit Formulary. Initial induction requests for infliximab for patients with mild Ulcerative Colitis (Mayo score < 6) may be considered for Infliximab as Inflectra on a case-by-case basis through EAP but the submission must include the rationale for coverage. Renewal requests for Maintenance therapy of Ulcerative Colitis will be considered for Remicade in patients meeting the following criteria:

Drug Plan	Criteria for Restricted Benefit
	Maintenance Criteria: 1. After 3 loading doses of Remicade: a. Mayo score[1] < 6 AND b. 50% reduction in prednisone from the starting dose Approval: 3 months at 5 mg/kg/dose every 8 weeks If patient is completely off steroids. Approval: 12 months at 5 mg/kg/dose every 8 weeks 2. Subsequent renewals: a. Mayo[1] score < 6; AND b. Must be off steroids (Patients who remain on steroids will be considered on a case-by-case basis) Approval: 12 months at 5 mg/kg/dose every 8 weeks [1]Note that the endoscopy procedure must be done within the last year but does not have to be full endoscopy.
NB	Not a benefit
NS	Information not available
PE	Not a benefit
NL	Not a benefit
YK	Information not available
NT	Information not available
NIHB	Information not available
DND	Not a benefit
VAC	Not a benefit

Restricted Benefit Criteria for Inflectra for the treatment of Ulcerative Colitis (Pediatric)

Drug Plan	Criteria for Restricted Benefit
BC	Treatment of moderate to severe Ulcerative Colitis according to established criteria* when prescribed by a gastroenterologist.
AB	Not a benefit
SK	Not a benefit
MB	Information not available
ON	Not a benefit
NB	Information not available
NS	Information not available
PE	Not a benefit
NL	Information not available
YK	Information not available
NT	Information not available
NIHB	Information not available
DND	Not a benefit
VAC	Not a benefit

Restricted Benefit Criteria for Remicade for the treatment of Psoriatic Arthritis

Drug Plan	Criteria for Restricted Benefit
BC	For patients granted Special Authority prior to Feb. 19, 2016 Treatment of Psoriatic Arthritis according to established criteria* when prescribed by a rheumatologist. *Initial / Switch:* • Not eligible *Renewal:* • Indefinite coverage, 3-5 mg/kg every 8 weeks, OR • Renewal of one year For the criteria originally specified in the request for initial coverage, please provide current status: • Five or more swollen joints • Oligoarthritis • Dactylitis • Tenosynovitis • Enthesitis • Inflammatory spinal symptoms • Daily use of corticosteroids to control active arthritis • Use of narcotics for pain resulting from inflammation
AB	Not eligible for new patients starting April 1, 2016. Special authorization coverage may be provided for use in combination with methotrexate for reducing signs and symptoms and inhibiting the progression of structural damage of active arthritis in adult patients (18 years of age or older) with moderate to severe polyarticular psoriatic arthritis (PsA) or pauciarticular PsA with involvement of knee or hip joint who are refractory or intolerant to: • Methotrexate at 20 mg (PO, SC or IM) or greater total weekly dosage (15 mg or greater if patient is 65 years of age or older) for more than 12 weeks. Patients who do not exhibit a clinical response to PO methotrexate or experience gastrointestinal intolerance to PO methotrexate must have a trial of parenteral methotrexate before being accepted as refractory; AND • An adequate trial of another disease modifying anti-rheumatic agent(s) (minimum 4 month trial). Special authorization coverage of this agent may be provided for use as monotherapy in adult patients for whom methotrexate is contraindicated and/or for those patients who have experienced serious adverse effects. 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs.

Drug Plan	Criteria for Restricted Benefit
	For continued coverage beyond three doses, the patient must meet the following criteria: 1) The patient must be assessed by an RA Specialist after the initial three doses to determine response. 2) The RA Specialist must confirm in writing that the patient is a 'responder' that meets the following criteria: • ACR20 OR an improvement of 1.2 units in the DAS28 score [reported to one (1) decimal place]; AND • An improvement of 0.22 in HAQ score [reported to two (2) decimal places]. It should be noted that the initial score for the DAS28 or HAQ score on record will be rounded to the correct number of decimal places as indicated above. Following this assessment, continued coverage may be approved for one 5 mg/kg dose every 8 weeks, for a period of 12 months. Ongoing coverage may be considered if the following criteria are met at the end of each 12-month period: 1) The patient has been assessed by an RA Specialist to determine response; 2) The RA Specialist must confirm in writing that the patient has maintained a response to therapy as indicated by: • Confirmation of maintenance of ACR20, or • Maintenance of a minimum improvement of 1.2 units in DAS28 score [reported to one (1) decimal place] from baseline. 3) A current HAQ score [reported to two (2) decimal places] must be included with all renewal requests. It should be noted that the initial score for the DAS28 or HAQ score on record will be rounded to the correct number of decimal places as indicated above.
SK	• Psoriatic arthritis in patients who have failed or are intolerant to methotrexate and one other DMARD. Treatment should be combined with an immunosuppressant. Exceptions can be considered in cases where methotrexate or leflunomide are contraindicated. This product should be used in consultation with a specialist in this area.
MB	For treatment of patients over 18 years of age who have active psoriatic arthritis who have failed treatment with at least 3 DMARD therapies, one of which is methotrexate and/or leflunomide unless intolerance or contraindication to these agents is documented. One combination therapy of DMARD must also be tried. Initial application information should include information on disease activity such as the number of tender joins, swollen joints, erythrocyte sedimentation rate and C-reactive protein value. Request for coverage must be made by a specialist in rheumatology. Inflectra will be the preferred infliximab option for all infliximab-naive patients prescribed an infliximab products for Psoriatic Arthritis. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naive patients. Patients will not be permitted to switch from Remicade to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy.
ON	No EAP criteria specified. However, it is stated that: **Note that effective February 25, 2016, Infliximab as Remicade for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis will only be considered for funding for existing EAP renewals. Infliximab as Inflectra can be considered through Limited Use criteria on the Ontario Drug Benefit Formulary.**
NB	Not a benefit
NS	• for patients with active psoriatic arthritis who meet all of the following:

Drug Plan	Criteria for Restricted Benefit
	○ have at least three active and tender joints ○ have not responded to an adequate trial with two DMARDs or have an intolerance or contraindication to DMARDs ○ not used in combination with other TNF antagonists • written request of a rheumatologist or prescriber with a specialty in rheumatology • after initial coverage period, can be reassessed for yearly coverage dependent on patient achieving an • improvement in symptoms of at least 20% • concurrent use of biologics not approved Initial coverage duration and maximum dosage approved: Infliximab: initial period 3 months, maximum dose 5mg/kg 0, 2 and 6 weeks then every 8 weeks For infliximab-naïve patients whose infliximab therapy is initiated after December 1, 2016, Inflectra will be the product approved.
PE	Not a benefit
NL	Not a benefit
YT	For Psoriatic Arthritis patients with moderate to severe disease who are refractroy or intolerant to a 12 week trial of parenteral methotrexate AND an adequate trial (at least 4 months) of at least one other DMARD. Specialist's consult to be provided. Approval for 12 months. After first year, a 24 month approval may be requested. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Not a benefit
NIHB	Not a benefit
DND	Not a benefit
VAC	Case-by-case

Restricted Benefit Criteria for Inflectra for the treatment of Psoriatic Arthritis

Drug Plan	Criteria for Restricted Benefit

BC	For new patients
	
	Treatment of Psoriatic Arthritis according to established criteria* when prescribed by a rheumatologist.
	
	Initial / Switch:
	• Medication is being prescribed by a rheumatologist or medical specialist in rheumatology.
	• Diagnosis of moderate to severe psoriatic arthritis, where patient currently exhibits at least two of the following
	  ○ Five or more swollen joints
	  ○ Oligoarthritis
	  ○ More than one joint with erosion on imaging study
	  ○ Dactylitis
	  ○ Tenosynovitis
	  ○ Enthesitis
	  ○ Inflammatory spinal symptoms
	  ○ Daily use of corticosteroids to control active arthritis
	  ○ Use of narcotics >12 hours per day for pain resulting from inflammation
	• Functional assessment completed by patient (HAQ or BASDAI)
	• Patient has failed two or more DMARDs
	
	Switch:
	• Never achieving a 20% improvement
	• At least 20% improvement in first 12 weeks of a TNF inhibitor but then loss of benefit
	
	Renewal:
	• Indefinite coverage, 3-5 mg/kg every 8 weeks, OR
	• Renewal of one year
	
	For the criteria originally specified in the request for initial coverage, please provide current status:
	• Five or more swollen joints
	• Oligoarthritis
	• Dactylitis
	• Tenosynovitis
	• Enthesitis
	• Inflammatory spinal symptoms
	• Daily use of corticosteroids to control active arthritis
	• Use of narcotics for pain resulting from inflammation

Drug Plan	Criteria for Restricted Benefit
AB	Special authorization coverage may be provided for use in combination with methotrexate for reducing signs and symptoms and inhibiting the progression of structural damage of active arthritis in adult patients (18 years of age or older) with moderate to severe polyarticular psoriatic arthritis (PsA) or pauciarticular PsA with involvement of knee or hip joint who are refractory or intolerant to: • Methotrexate at 20 mg (PO, SC or IM) or greater total weekly dosage (15 mg or greater if patient is 65 years of age or older) for more than 12 weeks. Patients who do not exhibit a clinical response to PO methotrexate or experience gastrointestinal intolerance to PO methotrexate must have a trial of parenteral methotrexate before being accepted as refractory; AND • An adequate trial of another disease modifying anti-rheumatic agent(s) (minimum 4 month trial). Special authorization coverage of this agent may be provided for use as monotherapy in adult patients for whom methotrexate is contraindicated and/or for those patients who have experienced serious adverse effects. 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. For coverage, this drug must be initiated by a Specialist in Rheumatology ("RA Specialist"). • Initial coverage may be approved for three doses as follows: An initial dose of 5 mg/kg, followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion. • Patients will be limited to receiving one dose of infliximab per prescription at their pharmacy. • Patients will be permitted to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy, or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period). • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. • Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. For continued coverage beyond three doses, the patient must meet the following criteria: 1) The patient must be assessed by an RA Specialist after the initial three doses to determine response. 2) The RA Specialist must confirm in writing that the patient is a 'responder' that meets the following criteria: • ACR20 OR an improvement of 1.2 units in the DAS28 score [reported to one (1) decimal place]; AND • An improvement of 0.22 in HAQ score [reported to two (2) decimal places]. It should be noted that the initial score for the DAS28 or HAQ score on record will be rounded to the correct number of decimal places as indicated above. Following this assessment, continued coverage may be approved for one 5 mg/kg dose every 8 weeks, for a period of 12 months. Ongoing coverage may be considered if the following criteria are met at the end of each 12-month period: 1) The patient has been assessed by an RA Specialist to determine response; 2) The RA Specialist must confirm in writing that the patient has maintained a response to therapy as indicated by: • Confirmation of maintenance of ACR20, or • Maintenance of a minimum improvement of 1.2 units in DAS28 score [reported to one (1) decimal place] from baseline. 3) A current HAQ score [reported to two (2) decimal places] must be included with all renewal requests. It should be noted that the initial score for the DAS28 or HAQ score on record will be rounded to the correct number of decimal places as indicated above.

Drug Plan	Criteria for Restricted Benefit
SK	• Psoriatic arthritis in patients who have failed or are intolerant to methotrexate and one other DMARD Treatment should be combined with an immunosuppressant. Exceptions can be considered in cases where methotrexate or leflunomide are contraindicated. This product should be used in consultation with a specialist in this area.
MB	For treatment of patients over 18 years of age who have active psoriatic arthritis who have failed treatment with at least 3 DMARD therapies, one of which is methotrexate and/or leflunomide unless intolerance or contraindication to these agents is documented. One combination therapy of DMARD must also be tried. Initial application information should include information on disease activity such as the number of tender joins, swollen joints, erythrocyte sedimentation rate and C-reactive protein value. Request for coverage must be made by a specialist in rheumatology. Inflectra will be the preferred infliximab option for all infliximab-naive patients prescribed an infliximab product for Psoriatic Arthritis. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naive patients. Patients will not be permitted to switch from Inflectra to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy
ON	Limited Use Notes: For the treatment of psoriatic arthritis in patients who have severe active disease (greater than or equal to 5 swollen joints and radiographic evidence of psoriatic arthritis) despite: i) treatment with methotrexate (20mg/week) for at least 3 months; AND ii) one of leflunomide (20mg/day) or sulfasalazine (1g twice daily) for at least 3 months. If the patient has documented contraindications or intolerances to methotrexate, then only one of leflunomide (20mg/day) or sulfasalazine (1g twice daily) for at least 3 months is required. Maintenance/Renewal: After 12 months of treatment, maintenance therapy is funded for patients with objective evidence of at least a 20 percent reduction in swollen joint count and a minimum of improvement in 2 swollen joints over the previous year. For funding beyond the second year, the patient must have objective evidence of preservation of treatment effect. Therapy must be prescribed by a rheumatologist or a physician with expertise in rheumatology. The recommended dosing regimen is 5mg/kg/dose at 0, 2 and 6 weeks followed by maintenance therapy of 5mg/kg/dose every 8 weeks.
NB	• For the treatment of moderate to severe psoriatic arthritis in patients who: ○ Have at least three active and tender joints, and ○ Have not responded to an adequate trial of two DMARDs or have an intolerance or contraindication to DMARDs.

Drug Plan	Criteria for Restricted Benefit
	Claim Notes: • Must be prescribed by a rheumatologist. • All requests for coverage of infliximab for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra brand only. • Combined use of more than one biologic DMARD will not be reimbursed. • Initial Approval: 24 weeks. • Renewal Approval: 1 year. Confirmation of continued response is required. • Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions as outlined here.
NS	For infliximab-naïve patients whose infliximab therapy is initiated after December 1, 2016, Infectra will be the product approved for the following indications. • For patients with active psoriatic arthritis who meet all of the following criteria: o have at least three active and tender joints; o have not responded to an adequate trial with two DMARDs or have an intolerance or contraindication to DMARDs; AND o written request of a rheumatologist or prescriber with a specialty in rheumatology. • After initial coverage period, can be reassessed for yearly coverage dependent on patient achieving an improvement in symptoms of at least 20% • Concurrent use of biologics not approved • Initial approval for a maximum of 3 months. Dosage restricted to infliximab 5mg/kg 0, 2 and 6 weeks then every 8 weeks.
PE	Infliximab, injection powder, 100mg/vial (Inflectra-HOS) Approvals will be for a maximum adult dose of 5mg/kg at 0, 2, and 6 weeks then every 8 weeks thereafter. For the treatment of active psoriatic arthritis in patients who meet the following criteria: a) Have at least three active and tender joints AND b) Have not responded to an adequate trial with two DMARDs or have an intolerance or contraindication to DMARDs. Approvals for initial coverage of Psoriatic Arthritis anti-TNF agents will be 4 months. Coverage will NOT be considered in combination with other biologic agents. Reassessment for coverage is dependent on patient achieving an improvement in symptoms of at least 20% (ACR20) or response using the Psoriatic Arthritis Response Criteria. The request for coverage must be made by a rheumatologist or prescriber with a specialty in rheumatology, using the Psoriatic Arthritis Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms Patients must also apply for coverage through the High-Cost Drug Program. The patient application is available from the Drug Programs Office or online at http://healthpei.ca/pharmacareforms
NL	For patients with active psoriatic arthritis who meet all of the following criteria: • Have at least three active and tender joints. • Failure to respond to non-steroidal anti-inflammatory agents and, failure to respond to an adequate trial with two DMARD's (eg, sulfasalazine, methotrexate, leflunomide, cyclosporine) or contraindications to, or intolerance of these agents.

Drug Plan	Criteria for Restricted Benefit
	Coverage will be approved initially for 3 months. Can be reassessed for yearly coverage dependent on achieving improvement in symptoms of at least 20% (20% improvement in the American College of Rheumatology response criteria (ACR 20) or response using the Psoriatic Arthritis Response Criteria). • Approvals will be for a maximum of 5mg/kg at weeks 0, 2 and 6, then every 6 to 8 weeks thereafter. • Not used in combination with other biologic DMARDS. • Written request from a rheumatologist only. Please note: Inflectra is the preferred infliximab therapy for treatment naïve patients (coverage will only be considered for Remicade in patients stabilized prior to June 1, 2016) To facilitate this process specific RA Medication Special Authorization Forms have been developed and can be found at: http://www.health.gov.nl.ca/health/prescription/ra_meds_initiation.pdf http://www.health.gov.nl.ca/health/prescription/ra_meds_continuation_request.pdf
YK	For Psoriatic Arthritis patients with moderate to severe disease who are refractroy or intolerant to a 12 week trial of parenteral methotrexate AND an adequate trial (at least 4 months) of at least one other DMARD. Specialist's consult to be provided. Approval for 12 months. After first year, a 24 month approval may be requested. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a rheumatologist Client who meet at least 2 of the following criteria: • 5 or more swollen joints • if less than 5 swollen joints, at least one joint proximal to, or including wrist or ankle • more than one joint with erosion on imaging study • dactylitis of two or more digits • tenosynovitis refractory to oral NSAIDs and steroid injections • enthesitis refractory to oral NSAIDs and steroid injections (not required for Achilles tendon) • inflammatory spinal symptoms refractory to two NSAIDs (minimum four weeks trial each) and has a BASDAI greater than 4 • daily use of corticosteroids • use of opioids > 12 hours per day for pain resulting from inflammation AND patient is refractory to: • a trial of at least two different NSAIDs at maximum tolerated doses for a combined total duration of four weeks; PLUS a minimum of any two of the following: • methotrexate weekly parenteral (SC or IM) at 20mg or greater (15mg or greater if patient is >65 years of age) for more than 8 weeks; OR • leflunomide: 20mg daily for 10 weeks; OR • sulfasalazine at least 2g daily for 3 months; OR • cyclosporine

Drug Plan	Criteria for Restricted Benefit
	OR Axial disease with both of the following: • Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4; AND • Patient is refractory to a trial of at least two different NSAIDs at maximum tolerated doses for a combined total duration of four weeks. Coverage beyond one year will be based on improvement according to the Psoriatic Arthritis Response Criteria (PsARC). • Improvement in at least two of the four PsARC criteria, one of which has to be joint tenderness or swelling score, with no worsening in any of the four criteria. A response in joint count is determined by a reduction of ≥ 30%. A response in the Physician or Patient Global Assessment scale is determined by a reduction of 1 point.
NIHB	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 weeks. • Prescribed by a rheumatologist Client who meet at least 2 of the following criteria: • 5 or more swollen joints • if less than 5 swollen joints, at least one joint proximal to, or including wrist or ankle • more than one joint with erosion on imaging study • dactylitis of two or more digits • tenosynovitis refractory to oral NSAIDs and steroid injections • enthesitis refractory to oral NSAIDs and steroid injections (not required for Achilles tendon) • inflammatory spinal symptoms refractory to two NSAIDs (minimum four weeks trial each) and has a BASDAI greater than 4 • daily use of corticosteroids • use of opioids > 12 hours per day for pain resulting from inflammation AND patient is refractory to: • a trial of at least two different NSAIDs at maximum tolerated doses for a combined total duration of four weeks; PLUS a minimum of any two of the following: • methotrexate weekly parenteral (SC or IM) at 20mg or greater (15mg or greater if patient is >65 years of age) for more than 8 weeks; OR • leflunomide: 20mg daily for 10 weeks; OR • sulfasalazine at least 2g daily for 3 months; OR • cyclosporine OR Axial disease with both of the following: • Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4; AND • Patient is refractory to a trial of at least two different NSAIDs at maximum tolerated doses for a combined total duration of four weeks. Coverage beyond one year will be based on improvement according to the Psoriatic Arthritis Response Criteria (PsARC). • Improvement in at least two of the four PsARC criteria, one of which has to be joint tenderness or swelling score, with no worsening in any of the four criteria. A response in joint count is determined by a reduction of ≥ 30%. A response in the Physician or Patient Global Assessment scale is determined by a reduction of 1 point.
DND	Not a benefit
VAC	Not a benefit

Restricted Benefit Criteria for Remicade for the treatment of Plaque Psoriasis

Drug Plan	Criteria for Restricted Benefit

BC	For patients granted Special Authority prior to Feb. 19, 2016
	
	Treatment of moderate to severe Psoriasis, according to established criteria*, when prescribed by a dermatologist.
	
	Initial / Switch:
	• Not eligible
	
	Renewal:
	• 5 MG/KG EVERY 8 WEEKS FOR 1 YEAR
	• Pre-Biologic PASI score
	• Current PASI score
	• First Renewal after the initial 12 to 16 week trial of biologic
	  ○ Patient has obtained a PASI ≥ 75 from the baseline biologic naive PASI score
	• Subsequent Renewals for Maintenance Therapy
	  ○ Patient has maintained a PASI ≥ 50 from the baseline biologic naive PASI score

AB	Not eligible for new patients starting April 1, 2016. Special authorization coverage may be provided for the reduction in signs and symptoms of severe, debilitating plaque psoriasis in patients who: • Have a total PASI of 10 or more and a DLQI of more than 10, OR • Who have significant involvement of the face, palms of the hands, soles of the feet or genital region; AND • Who are refractory or intolerant to: • Methotrexate at 20 mg (PO, SC or IM) or greater total weekly dosage (15 mg or greater if patient is 65 years of age or older) for more than 12 weeks. Patients who experience gastrointestinal intolerance to PO methotrexate must have a trial of parenteral • methotrexate before being accepted as refractory, OR • Cyclosporine (6 weeks treatment); AND • Phototherapy (unless restricted by geographic location) Patients who have a contraindication to either cyclosporine or methotrexate will be required to complete an adequate trial of the other pre-requisite medication prior to potential coverage being considered. 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. For continued coverage beyond three doses, the patient must meet all of the following criteria: 1) The patient must be assessed by a Dermatology Specialist after the initial three doses to determine response. 2) The Dermatology Specialist must confirm, in writing, that the patient is a 'responder' that meets the following criteria: • Greater than or equal to 75% reduction in PASI score, or

Drug Plan	Criteria for Restricted Benefit
	• Greater than or equal to 50% reduction in PASI score AND improvement of greater than or equal to 5 points in the DLQI. Following this assessment, continued coverage may be considered for one 5 mg/kg dose of infliximab every 8 weeks for a period of 12 months. Ongoing coverage may be considered if the patient is re-assessed by a Dermatology Specialist every 12 months and is confirmed to be continuing to respond to therapy by meeting criteria as outlined in (2) above. PASI and DLQI scores are required for all requests for Plaque Psoriasis including those requests for patients that have significant involvement of the face, palms, soles of feet or genital region.
SK	• For treatment of adult patients with severe debilitating plaque psoriasis who meet all of the following criteria: i) failure to respond to, contraindications to, or intolerant of methotrexate and cyclosporine; AND ii) failure to respond to, intolerant to or unable to access phototherapy. Coverage will be approved initially for the induction phase of up to 16 weeks. Coverage can be renewed in patients who have responded to therapy. This product should be used in consultation with a specialist in this area.
MB	For the treatment of adult patients with severe plaque psoriasis with one or more of the following: • Psoriasis Area and Severity Index (PASI) ≥ 10; • Body Surface Area (BSA) > 10 percent; • Dermatology Life Quality Index (DLQI) > 10; • Significant involvement of the face, hands, feet or genital region; AND • Failure to respond to, contraindications to, intolerant of or unable to access methotrexate, cyclosporine and/or phototherapy. The initial request is approved for a maximum of 4 months. For continued coverage the physician must confirm the patient's response to treatment and demonstration of treatment clinical benefits: ≥ 50 percent reduction in the PASI score with ≥ point improvement in the DLQI; OR ≥ 75 percent reduction in the PASI score; OR ≥ 50 percent reduction in the BSA with significant improvement of the face, hands, feet or genital region. Request for coverage must be made by a specialist in dermatology. Inflectra will be the preferred infliximab option for all infliximab-naive patients prescribed an infliximab product for Psoriasis. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naive patients. Patients will not be permitted to switch from Remicade to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy
ON	No EAP criteria specified. However, it is stated that: **Note that effective February 25, 2016, Infliximab as Remicade for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis will only be considered for funding for existing EAP renewals. Infliximab as Inflectra can be considered through Limited Use criteria on the Ontario**

Drug Plan	Criteria for Restricted Benefit
	Drug Benefit Formulary.
NB	• For the treatment of patients with severe, debilitating chronic plaque psoriasis who meet all of the following criteria: ○ Body surface area (BSA) involvement of >10% and/or significant involvement of the face, hands, feet or genital region; ○ Failure to respond to, contraindications to or intolerance to methotrexate and cyclosporine; ○ Failure to respond to, intolerance to or unable to access phototherapy. • Requests for renewal must include information demonstrating an adequate response, defined as: ○ ≥75% reduction in the Psoriasis Area and Severity Index (PASI) score from when treatment started (PASI 75), or ○ ≥50% reduction in the PASI score (PASI 50) with a ≥5 point improvement in the Dermatology Life Quality Index (DLQI) from when treatment started, or ○ A quantitative reduction in BSA affected with qualitative consideration of specific regions such as face, hands, feet, or genital region. Claim Notes: • Must be prescribed by a dermatologist. • Combined use of more than one biologic DMARD will not be reimbursed. • All requests for coverage of infliximab for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra brand only. • Approvals will be for a maximum of 5mg/kg at weeks 0, 2, and 6, then every 8 weeks thereafter. • Initial Approval: 12 weeks. • Renewal Approval: 1 year. • Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions as outlined here.
NS	• for patients with severe, debilitating chronic plaque psoriasis (PsO) who meet all of the following criteria: ○ Body Surface Area (BSA) involvement of >10% and/or significant involvement of the face, hands, feet or genital region ○ failure to respond to, contraindications to or intolerant of methotrexate and cyclosporine ○ failure to respond to, intolerant of or unable to access phototherapy • written request of a dermatologist or prescriber with a specialty in dermatology continued coverage is dependent on evidence of improvement, specifically: ○ ≥ 75% reduction in the Psoriasis Area and Severity Index (PASI) score, or ○ ≥ 50% reduction in PASI with a ≥ 5 point improvement in DLQI (Dermatology Life Quality Index), or ○ significant reduction in BSA involved, with consideration of important regions such as the face, hands, feet or genitals • concurrent use of biologics not approved Initial duration and maximum dosage approved: Infliximab • initial approval for a maximum of 12 weeks • dosage restricted to infliximab 5mg/kg 0, 2 and 6 weeks then every 8 weeks For infliximab-naïve patients whose infliximab therapy is initiated after June 1, 2016, Inflectra will be the product approved.

Drug Plan	Criteria for Restricted Benefit
PE	Initial approval will be for a maximum adult dose of 5mg/kg at 0, 2, and 6 weeks then every 8 weeks for 12 weeks. If response criteria is met at 12 weeks, approval will be continued at 5mg/kg every 8 weeks up to one year. For treatment of patients with severe, debilitating chronic plaque psoriasis who meet all of the following criteria: Body surface area (BSA) involvement of >10% and/or significant involvement of the face, hands, feet or genital region AND Failure to respond to, contraindications to or intolerance to methotrexate and cyclosporine AND Failure to respond to, intolerance to or unable to access phototherapy. Clinical Notes: 1. Continuation of therapy beyond initial approval will be based on response. Patients not responding adequately at these time points should have treatment discontinued with no further treatment with the same agent recommended. 2. An adequate response is defined as either: >/= 75% reduction in the Psoriasis Area and Severity Index (PASI) score from when treatment started (PASI 75), OR >/= 50% reduction in the PASI score (PASI 50) with a >/= 5 point improvement in the Dermatology Life Quality Index (DLQI) from when treatment started, OR A quantitative reduction in BSA affected with qualitative consideration of specific regions such as face, hands, feet, or genital region. Concurrent use of biologics will not be approved. Must be prescribed by a dermatologist. Renewal of coverage will require reassessment of the patient and submission of a new Special Authorization form. Requests for Plaque Psoriasis Biologic Agents must be requested by a dermatologist using the Anti-TNF Agents for Psoriasis Special Authorization form which is available from the Drug Programs office or on-line at http://healthpei.ca/pharmacareforms Patients must also apply for coverage by the High-Cost Drug Program. The patient application is available from the Drug Program Office or online at http://healthpei.ca/pharmacareforms
NL	For patients with severe, debilitating PsO who meet all of the following criteria: • Body Surface Area (BSA) involvement of > 10% and/or significant involvement of the face, hands, feet or genital region. • Failure to respond to, contraindications to or intolerant of methotrexate and cyclosporine. • Failure to respond to, intolerant of or unable to access phototherapy. Clinical Notes: 1. Continuation of therapy beyond 12 weeks will be based on response. Patients not responding adequately at these time points should have treatment discontinued with no further treatment with the same agent recommended. 2. An adequate response is defined as either: • ≥75% reduction in the Psoriasis Area and Severity Index (PASI) score from when treatment started (PASI 75),

Drug Plan	Criteria for Restricted Benefit
	OR • ≥50% reduction in the PASI score (PASI 50) with a ≥5 point improvement in the Dermatology Life Quality Index (DLQI) from when treatment started, OR • A quantitative reduction in BSA affected with qualitative consideration of specific regions such as face, hands, feet, or genital region. 3. Concurrent use of >1 biologic will not be approved 3. Combined use of more than one biologic DMARD will not be reimbursed. 4. Patients will not be permitted to switch from Inflectra™ to another infliximab product or vice versa, if previously trialed and deemed unresponsive to therapy. Claim Notes: • Initial approval limited to 12 weeks. Patients not responding adequately at 12 weeks should have treatment discontinued with no further treatment recommended. • Must be prescribed by a dermatologist • Approval limited to a dose of 5 mg/kg administered at 0, 2, and 6 weeks, then every 8 weeks up to a year (if response criteria met at 12 weeks) Please note: Inflectra is the preferred infliximab therapy for treatment naïve patients (coverage will only be considered for Remicade in patients stabilized prior to June 1, 2016) To facilitate this process a specific Chronic Plaque Psoriasis Special Authorization Form has been developed and can be found at: http://www.health.gov.nl.ca/health/prescription/chronic_plaque_psoriasis_meds_coverag e_request.pdf
YK	For Plaque Psoriasis on recommendation of Dermatologist. Consult to be provided. For patients with body surface involvement (BSA) of > 10%, OR significant involvement of face, hands, feet or genitals, AND have a PASI > 12. For patients who are refractory or intolerant to a 12 week trial of parenteral methotrexate AND a 12 week trial of cyclosporine. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Not a benefit
NIHB	Not a benefit
DND	• when prescribed by a dermatologist and meets all of the following criteria: • A diagnosis of severe, debilitating psoriasis • BSA (Body Surface Area)>10% and /or significant involvement of face, hand, feet or genital area • Failure to respond to, contraindications to, or intolerant of methotrexate and cyclosporine (methotrexate PO,SC,IM 20mg weekly) (cyclosporine 4mg/kg daily) each for 12 weeks. • Failure to respond to, intolerant to or unable to access phototherapy
VAC	Case-by-case

Restricted Benefit Criteria for Inflectra for the treatment of Plaque Psoriasis

Drug Plan	Criteria for Restricted Benefit

BC	For new patients
	
	Treatment of moderate to severe Psoriasis, according to established criteria*, when prescribed by a dermatologist.
	
	Initial:
	• First approval (induction period): 3 doses (5 MG/KG AT 0, 2 AND 6 WEEKS)
	• Patient is 18 years of age or older
	• Patient has a body surface area (BSA) involvement of >10% and/or significant involvement of the face, hands, feet or genital region
	• Patient failed to respond, is intolerant, or is unable to access UV phototherapy
	• Patient has a baseline pre-biologic PASI of >12
	• Patient has failed to respond, or experienced a specific intolerance, or has a specific contraindication to methotrexate and cyclosporine
	
	Switch:
	• Patient failed to achieve a PASI > 75 from baseline biologic naive PASI score after initial trial of previous biologic
	• Patient failed to maintain a PASI > 50 from baseline biologic naive PASI score while on maintenance therapy of previous biologic
	• Other
	
	Renewal:
	• 5 MG/KG EVERY 8 WEEKS FOR 1 YEAR
	• Pre-Biologic PASI score
	• Current PASI score
	• First Renewal after the initial 12 to 16 week trial of biologic
	  ○ Patient has obtained a PASI ≥ 75 from the baseline biologic naive PASI score
	• Subsequent Renewals for Maintenance Therapy
	  ○ Patient has maintained a PASI ≥ 50 from the baseline biologic naive PASI score

AB	Special authorization coverage may be provided for the reduction in signs and symptoms of severe, debilitating plaque psoriasis in patients who: • Have a total PASI of 10 or more and a DLQI of more than 10, OR • Who have significant involvement of the face, palms of the hands, soles of the feet or • genital region; AND • Who are refractory or intolerant to: • Methotrexate at 20 mg (PO, SC or IM) or greater total weekly dosage (15 mg or greater if patient is 65 years of age or older) for more than 12 weeks. Patients who experience gastrointestinal intolerance to PO methotrexate must have a trial of parenteral • methotrexate before being accepted as refractory, OR • Cyclosporine (6 weeks treatment); AND • Phototherapy (unless restricted by geographic location)

Drug Plan	Criteria for Restricted Benefit

	Patients who have a contraindication to either cyclosporine or methotrexate will be required to complete an adequate trial of the other pre-requisite medication prior to potential coverage being considered.
	
	'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above.
	'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs.
	
	For coverage, this drug must be prescribed by a Specialist in Dermatology ("Dermatology Specialist").
	
	• Initial coverage may be approved as follows: An initial dose of 5 mg/kg, followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion.
	• Patients will be limited to receiving one dose of infliximab per prescription at their pharmacy.
	• Patients will be permitted to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy, or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period).
	• Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy.
	• Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed.
	
	For continued coverage beyond three doses, the patient must meet all of the following criteria:
	1) The patient must be assessed by a Dermatology Specialist after the initial three doses to determine response.
	2) The Dermatology Specialist must confirm, in writing, that the patient is a 'responder' that meets the following criteria:
	  • Greater than or equal to 75% reduction in PASI score, or
	  • Greater than or equal to 50% reduction in PASI score AND improvement of greater than or equal to 5 points in the DLQI.
	
	Following this assessment, continued coverage may be considered for one 5 mg/kg dose of infliximab every 8 weeks for a period of 12 months. Ongoing coverage may be considered if the patient is re-assessed by a Dermatology Specialist every 12 months and is confirmed to be continuing to respond to therapy by meeting criteria as outlined in (2) above.
	
	PASI and DLQI scores are required for all requests for Plaque Psoriasis including those requests for patients that have significant involvement of the face, palms, soles of feet or genital region.

SK	• For treatment of adult patients with severe debilitating plaque psoriasis who meet all of the following criteria: i) failure to respond to, contraindications to, or intolerant of methotrexate and cyclosporine; AND ii) failure to respond to, intolerant to or unable to access phototherapy. Coverage will be approved initially for the induction phase of up to 16 weeks. Coverage can be renewed in patients who have responded to therapy. This product should be used in consultation with a specialist in this area.
MB	For the treatment of adult patients with severe plaque psoriasis with one or more of the following: • Psoriasis Area and Severity Index (PASI) ≥ 10; • Body Surface Area (BSA) > 10 percent; • Dermatology Life Quality Index (DLQI) > 10;

Drug Plan	Criteria for Restricted Benefit
	• Significant involvement of the face, hands, feet or genital region; AND • Failure to respond to contraindications to intolerant of or unable to access methotrexate to respond to, contraindications to, intolerant of or unable to access methotrexate, cyclosporine and/or phototherapy. The initial request is approved for a maximum of 4 months. For continued coverage the physician must confirm the patient's response to treatment and demonstration of treatment clinical benefits: ≥ 50 percent reduction in the PASI score with ≥ point improvement in the DLQI; OR ≥ 75 percent reduction in the PASI score; OR ≥ 50 percent reduction in the BSA with significant improvement of the face, hands, feet or genital region. Request for coverage must be made by a specialist in dermatology. Inflectra will be the preferred infliximab option for all infliximab-naive patients prescribed an infliximab productsfor Psoriasis. Preferred means the first infliximab product to be considered for reimbursement for infliximab-naive patients. Patients will not be permitted to switch from Inflectra to another infliximab product or vice versa, if: 1. Previously trialed and deemed unresponsive to therapy.
ON	Limited Use Notes: For the treatment of severe (see Note 1 below) plaque psoriasis in patients 18 years of age or older who have experienced failure, intolerance, or have a contraindication to adequate trials of several standard therapies (see Note 2 below). Claims for the first 6 months must be written by a dermatologist. Monitoring of patients is required to determine if continuation of therapy beyond 12 weeks is required. Patients not responding adequately at 12 weeks should have treatment discontinued. Note 1: Definition of severe plaque psoriasis: • Body Surface Area (BSA) involvement of at least 10 percent, or involvement of the face, hands, feet or genital regions, AND • Psoriasis Area and Severity Index (PASI) score of at least 10 (not required if there is involvement of the face, hands, feet or genital regions), AND • Dermatology Life Quality Index (DLQI) score of at least 10. Note 2: Definition of failure, intolerance or contraindication to adequate trials of standard therapies: • 6 month trial of at least 3 topical agents including vitamin D analogues and steroids, AND • 12 week trial of phototherapy (unless not accessible), AND • 6 month trial of at least 2 systemic, oral agents used alone or in combination • Methotrexate 15 to 30mg/week • Acitretin (could have been used with phototherapy) • Cyclosporine

Drug Plan	Criteria for Restricted Benefit
NB	• For the treatment of patients with severe, debilitating chronic plaque psoriasis who meet all of the following criteria: o Body surface area (BSA) involvement of >10% and/or significant involvement of the face, hands, feet or genital region; o Failure to respond to, contraindications to or intolerance to methotrexate and cyclosporine; o Failure to respond to, intolerance to or unable to access phototherapy. • Requests for renewal must include information demonstrating an adequate response, defined as: o ≥75% reduction in the Psoriasis Area and Severity Index (PASI) score from when treatment started (PASI 75), or o ≥50% reduction in the PASI score (PASI 50) with a ≥5 point improvement in the Dermatology Life Quality Index (DLQI) from when treatment started, or o A quantitative reduction in BSA affected with qualitative consideration of specific regions such as face, hands, feet, or genital region. Claim Notes: • Must be prescribed by a dermatologist. • Combined use of more than one biologic DMARD will not be reimbursed. • All requests for coverage of infliximab for infliximab-naïve patients (including those on induction therapy) will be approved for Inflectra brand only. • Initial Approval: 12 weeks. • Renewal Approval: 1 year. • Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions as outlined here.
NS	For infliximab-naïve patients whose infliximab therapy is initiated after June 1, 2016, Infectra will be the product approved for the following indications. • For patients with severe, debilitating chronic plaque psoriasis (PsO) who meet all of the following criteria: o Body Surface Area (BSA) involvement of >10% and/or significant involvement of the face, hands, feet or genital region; o failure to respond to, contraindications to or intolerant of methotrexate and cyclosporine; o failure to respond to, intolerant of or unable to access phototherapy; AND o written request of a dermatologist or prescriber with a specialty in dermatology. • Continued coverage is dependent on evidence of improvement, specifically: o ≥ 75% reduction in the Psoriasis Area and Severity Index (PASI) score; OR o ≥ 50% reduction in PASI with a ≥ 5 point improvement in DLQI (Dermatology Life Quality Index); OR o significant reduction in BSA involved, with consideration of important regions such as the face, hands, feet or genitals. • Concurrent use of biologics not approved. • Initial approval for a maximum of 12 weeks. Dosage restricted to infliximab 5mg/kg 0, 2 and 6 weeks then every 8 weeks.
PE	Initial approval will be for a maximum adult dose of 5mg/kg at 0, 2, and 6 weeks then every 8 weeks for 12 weeks. If response criteria is met at 12 weeks, approval will be continued at 5mg/kg every 8 weeks up to one year. For treatment of patients with severe, debilitating chronic plaque psoriasis who meet all of the following criteria: Body surface area (BSA) involvement of >10% and/or significant involvement of the face, hands, feet or genital region AND Failure to respond to, contraindications to or intolerance to methotrexate and cyclosporine AND Failure to respond to, intolerance to or unable to access phototherapy.

Drug Plan	Criteria for Restricted Benefit
	Clinical Notes: 1. Continuation of therapy beyond initial approval will be based on response. Patients not responding adequately at these time points should have treatment discontinued with no further treatment with the same agent recommended. 2. An adequate response is defined as either: >/= 75% reduction in the Psoriasis Area and Severity Index (PASI) score from when treatment started (PASI 75), OR >/= 50% reduction in the PASI score (PASI 50) with a >/= 5 point improvement in the Dermatology Life Quality Index (DLQI) from when treatment started, OR A quantitative reduction in BSA affected with qualitative consideration of specific regions such as face, hands,feet, or genital region. Concurrent use of biologics will not be approved. Must be prescribed by a dermatologist. Renewal of coverage will require reassessment of the patient and submission of a new Special Authorization form. Requests for Plaque Psoriasis Biologic Agents must be requested by a dermatologist using the Plaque Psoriasis Special Authorization form which is available from the Drug Programs office or on-line at http://healthpei.ca/pharmacareforms . Patients must also apply for coverage by the High-Cost Drug Program. The patient application is available from the Drug Program Office or online at http://healthpei.ca/pharmacareforms
NL	For patients with severe, debilitating PsO who meet all of the following criteria: • Body Surface Area (BSA) involvement of > 10% and/or significant involvement of the face, hands, feet or genital region. • Failure to respond to, contraindications to or intolerant of methotrexate and cyclosporine. • Failure to respond to, intolerant of or unable to access phototherapy. Clinical Notes: 1. Continuation of therapy beyond 12 weeks will be based on response. Patients not responding adequately at these time points should have treatment discontinued with no further treatment with the same agent recommended. 2. An adequate response is defined as either: • ≥75% reduction in the Psoriasis Area and Severity Index (PASI) score from when treatment started (PASI 75), OR • ≥50% reduction in the PASI score (PASI 50) with a ≥5 point improvement in the Dermatology Life Quality Index (DLQI) from when treatment started, OR • A quantitative reduction in BSA affected with qualitative consideration of specific regions such as face, hands, feet, or genital region. 3. Concurrent use of >1 biologic will not be approved 3. Combined use of more than one biologic DMARD will not be reimbursed. 4. Patients will not be permitted to switch from Inflectra™ to another infliximab product or vice versa, if previously trialed and deemed unresponsive to therapy.

Drug Plan	Criteria for Restricted Benefit
	Claim Notes: • Initial approval limited to 12 weeks. Patients not responding adequately at 12 weeks should have treatment discontinued with no further treatment recommended. • Must be prescribed by a dermatologist • Approval limited to a dose of 5 mg/kg administered at 0, 2, and 6 weeks, then every 8 weeks up to a year (if response criteria met at 12 weeks) Please note: Inflectra is the preferred infliximab therapy for treatment naïve patients (coverage will only be considered for Remicade in patients stabilized prior to June 1, 2016) To facilitate this process a specific Chronic Plaque Psoriasis Special Authorization Form has been developed and can be found at: http://www.health.gov.nl.ca/health/prescription/chronic_plaque_psoriasis_meds_coverag e_request.pdf
YK	For Plaque Psoriasis on recommendation of Dermatologist. Consult to be provided. For patients with body surface involvement (BSA) of > 10%, OR significant involvement of face, hands, feet or genitals, AND have a PASI > 12. For patients who are refractory or intolerant to a 12 week trial of parenteral methotrexate AND a 12 week trial of cyclosporine. NB: All new infliximab patients will be covered for Inflectra brand only.
NT	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 week. • Prescribed by a dermatologist • Body surface area (BSA) involvement greater than 10% and/or significant involvement of the face, hands, feet or genital region; AND • Intolerance or lack of response to phototherapy; OR • Inability to access phototherapy; AND • Intolerance or lack of response to methotrexate (MTX) weekly oral or parenteral (SC or IM) at 20 mg or greater (15 mg or greater if patient is > 65 years of age) for more than 8 weeks; AND • Intolerance or lack of response to cyclosporine; OR • A contraindication to methotrexate or cyclosporine. Coverage beyond the initial three doses will be based on a significant reduction in the Body Surface Area (BSA) involved and improvements in the Psoriasis Area Severity Index (PASI) score and the Dermatology Life Quality Index (DLQI): • A 75 % reduction in Psoriasis Area Severity Index (PASI) score; OR • A ≥ 50 % reduction in the Psoriasis Area Severity Index (PASI) score with a ≥ 5-point improvement in the Dermatology Life Quality Index (DLQI); OR • A significant reduction in Body Surface Area (BSA) involved, with consideration of important areas such as the face, hands, feet or genital regions.
NIHB	Coverage is provided for an initial three doses of 5 mg/kg, administered at 0, 2 and 6 week. • Prescribed by a dermatologist • Body surface area (BSA) involvement greater than 10% and/or significant involvement of the face, hands, feet or genital region; AND

Drug Plan	Criteria for Restricted Benefit
	• Intolerance or lack of response to phototherapy; OR • Inability to access phototherapy; AND • Intolerance or lack of response to methotrexate (MTX) weekly oral or parenteral (SC or IM) at 20 mg or greater (15 mg or greater if patient is > 65 years of age) for more than 8 weeks; AND • Intolerance or lack of response to cyclosporine; OR • A contraindication to methotrexate or cyclosporine. Coverage beyond the initial three doses will be based on a significant reduction in the Body Surface Area (BSA) involved and improvements in the Psoriasis Area Severity Index (PASI) score and the Dermatology Life Quality Index (DLQI): • A 75 % reduction in Psoriasis Area Severity Index (PASI) score; OR • A ≥ 50 % reduction in the Psoriasis Area Severity Index (PASI) score with a ≥ 5-point improvement in the Dermatology Life Quality Index (DLQI); OR • A significant reduction in Body Surface Area (BSA) involved, with consideration of important areas such as the face, hands, feet or genital regions.
DND	when prescribed by a dermatologist and meets all of the following criteria: • A diagnosis of severe, debilitating psoriasis • BSA (Body Surface Area)>10% and /or significant involvement of face, hand, feet or genital area • Failure to respond to, contraindications to, or intolerant of methotrexate and cyclosporine, methotrexate PO,SC,IM 20mg weekly) (cyclosporine 4mg/kg daily) each for 12 weeks. • Failure to respond to, intolerant to or unable to access phototherapy Duration of Therapy: Long-term.
VAC	Not a benefit

Appendix 3: Summary of Patient Input

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patient groups provided input: Arthritis Consumer Experts (ACE) and The Arthritis Society. ACE is a national, patient-led organization that provides information, education, and support programs to people with arthritis. The Arthritis Society is a health charity that provides education, programs, and support to more than 4.6 million Canadians with arthritis. It is the largest non-government funder of arthritis research in Canada.

ACE has received grants-in-aid or research funding from Canadian Biosimilars Forum, Merck Canada, and other pharmaceutical companies. The patient input submission was prepared by ACE staff without influence from any outside party. The Arthritis Society has received funding by Merck, Janssen, and other pharmaceutical companies. The patient input submission was prepared independently by the Society.

2. Condition-Related Information

ACE gathered information by issuing a call for patient experiences on August 14, 2017; detailing day-to-day interactions with people living with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and plaque psoriasis; working with clinical researchers in Canada; and having discussions with consumers and scientific members of the ACE advisory board. The Arthritis Society issued a request for information on social media and gathered responses from 19 patients with RA (four with experience with infliximab), 27 patients with AS (12 with experience with infliximab), and 21 patients with PsA (eight with experience with infliximab).

RA, AS, PsA, and plaque psoriasis affect all aspects of patients' lives. People with these conditions must plan out their activities carefully and always keep in mind the state of their disease, what types of activities they can handle, and what help they may need. All four conditions can significantly restrict the ability to perform day-to-day chores, work, exercise, and recreational activities, and adversely affect emotional health. Patients may also require the assistance of caregivers to help with management of the condition.

Patients with RA report a variety of symptoms, such as swollen and stiff hands, fingers, feet, and toes; joint pain; morning stiffness; and a weakened immune system. One patient reported having ear and eye problems, in addition to getting lumps on her buttocks and neck. For those with AS, pain, fatigue, and stiffness greatly affect day-to-day life. Pain and stiffness occurred in the low back, hand, foot, and neck. Simple activities, such as walking, sitting, or standing for periods of time, can be problematic. This can lead to difficulties in studying and at work. Other troubling symptoms include spasms, hunched posture, difficulty expanding chest to breathe, sleep disruption, uveitis, and bowel issues. Patients with PsA report pain, fatigue, stiffness, loss of function, and limited range of motion. These symptoms may make it difficult to perform simple tasks, such as house chores, getting in and out of a bath tub, walking, writing, or holding a phone. Plaque psoriasis can cause skin sensitivity, redness, flaking, and pain. One patient with plaque psoriasis indicated feelings of distress and embarrassment related to the symptom of flaking. Another patient reported experiencing joint pain in the hip, knee, ankle, elbow, and spine.

3. Current Therapy-Related Information

Patients reported improvement of symptoms with different types of treatments. Biologics, such as Enbrel, Orencia, Rituxan, Remicade, Humira, Actemra, and Cosentyx were specifically mentioned as providing some benefit. Other treatment options that have provided benefits, according to patients, are Xeljanz, MTX, and hydroxychloroquine. One patient indicated using Tylenol Arthritis because of her allergies to NSAIDs (nonsteroidal anti-inflammatory drugs). Improvements included less itchiness, decrease in the number of joints with inflammation, and better control over psoriasis. However, patients also mentioned that treatments were associated with troubling side effects, such as infections, gastrointestinal upsets, nausea, and fatigue. In addition, the efficacy of treatments often waned over time, requiring a change of treatment. For example, a patient with AS indicated that Enbrel worked for 1.5 years, but then stopped working; the patient subsequently switched to another biologic, Cimzia. Another patient with PsA indicated that Remicade was beneficial for the first four doses, but also stopped working.

Patients want to have as many treatment options available as possible, as this provides alternatives in the event of treatment failure, waning of efficacy over time, side effects, or lack of coverage. Patients would like to see treatments that confer better control of pain and fatigue, have fewer side effects (e.g., immunosuppressive effects, nausea, fatigue), that are less costly, and that are available in different administration routes (e.g., oral or self-injections versus infusion at a clinic). One patient mentioned that better follow-up care was needed to help with managing the side effects of medications. Another individual highlighted that approvals for drug coverage should take less time.

4. Expectations About the Drug Being Reviewed

No comments were made about the specific biosimilar under review. Patients discussed Remicade; one described the use of Inflectra, another infliximab biosimilar. For some patients, infliximab has helped with symptom control and disease progression, but for others, the treatment stopped working or had side effects. Although some side effects, such as tiredness and infusion-site reactions, were manageable, patients also mentioned developing allergic reactions that required them to discontinue the medication. The impact of the drug over time was identified as a concern. For example, one patient observed that they would *"…still have the same concerns as with regular biologics, and that is: what is the long-term effect?"*

Although the lower cost of biosimilars was welcomed by some, a need for more clinical trial data about their safety was also stated. For example, in describing the conflict, one patient said: *"I have concerns about drug effectiveness over time for biosimilars…quality control methods may not be as rigorous. A less expensive drug would be good for me financially.*" In addition, patient groups emphasized that a switch to a biosimilar should be made cautiously, especially if a patient has been stabilized for several years on the reference product, and that the decision to initiate or switch a medication should not be forced by insurers.

5. Additional Information

The position of The Arthritis Society is summarized in the following statements:

- Biosimilars have a role to play in the care and management of those living with inflammatory arthritis.
- Biosimilars will offer more choice for those living with inflammatory arthritis and have the potential to lower health care costs and increase access to treatment.
- Biosimilars, while similar to the innovator biologic, are not identical and cannot be considered generic versions of innovator biologics.
- Consistent, universal, unique biosimilar naming practices should be implemented to facilitate tracking of what specific medication is received by a patient.
- A process for post-market surveillance must be put in place to track the long-term safety and efficacy of biosimilars.
- All producers of biologic medications — whether innovator or biosimilar — should provide a robust program of patient and physician support.
- Until conclusive evidence determines that switching is safe, switching should not be permitted for patients who are stable on an existing course of biologic treatment, except at the express discretion of the physician in consultation with their patient.

ACE's mandate is to continue to provide the latest research-based education and information on biosimilars to its members, subscribers, and the public, and our guiding principle has been, and continues to be, to follow the scientific evidence in our therapeutic area. Based on peer reviewed, well-designed research studies and current meta-analysis, our organization's views are:

- Patients living with inflammatory arthritis should ask for and expect the best care possible through shared decision-making between themselves, their rheumatologist, and other health care providers.
- Biosimilars may have advantages over their originators due to improvements in manufacturing processes and delivery devices, among others.
- This new class of biologics is delivering significant drug plan savings without compromising safety and efficacy in thousands of patients in many European countries.
- The evidence acquired over 10 years of clinical experience shows that biosimilars approved through the European Medicines Agency can be used as safely and effectively in all their approved indications as other biological medicines.

- Policy development related to biosimilars to treat inflammatory arthritis should include unbiased and credible patient and rheumatologist participation who fully disclose their sources of funding from the manufacturers of the drug products affected by the policy.
- Patients should be fully informed about policy decisions that transition them to a biosimilar in advance of the transition; patients should be able to assess treatment (or no treatment) risk against benefit; and patients should have tools that enable them to discuss the pros and cons of all treatments with their health care teams.
- Policy transition is appropriate if the prescribing physicians and their patient have sufficiently supportive education and information tools related to all aspects of accessing their biosimilar, from “care coaching” to help with formulary or private insurance paperwork to infusion clinic and pharmacy orientation as well as adherence.
- Government should reinvest policy transition savings in a timely manner into innovative medicines on formularies for unmet patient needs, list biologics, and tsdisease-modifying antirheumatic drugs (DMARDs) with revised or relaxed reimbursement criteria to make access more efficient, and implement other important aspects of inflammatory arthritis models of care, such as instituting rheumatology nursing billing codes.
- Policy-transitioned patients should be monitored as part of their routine care.
- Outcomes data should be collected on patients who make multiple transitions between biosimilars and originators.

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