Common Drug Review

Subsequent Entry Biologic Review Report

September 2015

Drug	Inflectra (infliximab)
Indication	Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Plaque psoriasis
Listing request	For each indication, list in a similar manner to the public plan listing criteria for Remicade.
Manufacturer	Hospira Healthcare Corporation

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
Asn	asparagine
AUC	area under the curve
AUC_{tau}	area under the curve for a dosing interval
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
bDMARD	biologic disease-modifying antirheumatic drug
BMI	body mass index
$C_{av,ss}$	average concentration at steady state
C_{max}	maximum concentration
$C_{max,ss}$	maximum concentration at steady state
C_{min}	minimum concentration
CD	circular dichroism
CD4	cluster of differentiation 4
CDAI	Clinical Disease Activity Index
CDC	complement-dependent cytotoxicity
CDEC	Canadian Drug Expert Committee
CDR	Common Drug Review
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL_{ss}	clearance at steady state
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events

CTD	Common Technical Document
DAS28	Disease Activity Score 28
DB	double-blind
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
DSC	differential scanning calorimetry
dsDNA	double-stranded deoxyribonucleic acid
EAP	Exceptional Access Program
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	end-of-study
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
F(ab')2	fragment antigen-binding
FTIR	Fourier transform infrared spectroscopy
Fuc	fucose
Gal	galactose
GlcN	glucosamine
GlcNAc	N-acetylglucosamine
HAQ	Health Assessment Questionnaire
HBV	hepatitis B virus
HCP	host cell protein
HIV	human immunodeficiency virus
HPAEC-PAD	high performance anion exchange chromatography with pulsed amperometric detection
hTNF-alpha	human tumour necrosis factor-alpha
hTNF-beta	Human tumour necrosis factor beta
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC-HPLC	ion-exchange chromatography-high performance liquid chromatography
IEF	Iisoelectric focusing
IFT	Inflectra
IgG1	immunoglobulin G1
IgG1-kappa	immunoglobulin G1 kappa
IL	interleukin
ITT	intention-to-treat

KD	dissociation constant
LC	liquid chromatography
Man	mannose
M-CSF	macrophage colony-stimulating factor
MS	mass spectrometry
Nab	neutralizing antibody
NeuGc	N-glycolylneuraminic
NSAID	nonsteroidal anti-inflammatory drug
ODB	Ontario Drug Benefit
PD	pharmacodynamics
pI	isoelectric point
PK	pharmacokinetics
PLANETAS	Program evaLuating the Autoimmune disease iNvIstigational drug cT-p13 in AS patients
PLANETRA	Programme evaLuating the Autoimmune disease iNvEstigational drug cT-p13 in RA patients
PP	per-protocol
ppb	parts per billion
ppm	parts per million
PS	psoriatic spondylitis
PsA	psoriatic arthritis
PsO	plaque psoriasis
QoL	quality of life
RA	rheumatoid arthritis
RANKL	receptor activator of nuclear factor-kappaB ligand
RCT	randomized controlled trial
RF	rheumatoid factor
RMP	reference medicinal product
SI (joint)	sacroiliac (joint)
SAE	serious adverse event
SD	standard deviation
SDAI	Simplified Disease Activity Index
SEB	subsequent entry biologic
SEC-HPLC	size exclusion chromatography-high-performance liquid chromatography
SF-36	Short-Form (36) Health Survey
SJC28	28-joint counts of swelling
SOC	system organ class

SpA	spondyloarthritis
SPR	surface plasmon resonance
sTNF-alpha	soluble tumour necrosis factor-alpha
$T_{1/2}$	terminal elimination half-life
TB	tuberculosis
TEAE	treatment-emergent adverse events
TJC28	28-joint counts of tenderness
T_{max}	time to reach maximum concentration
tmTNF-alpha	transmembrane tumour necrosis factor-alpha
TNFR	tumour necrosis factor receptor
TNF-alpha	tumour necrosis factor-alpha
VAS	visual analogue scale
V_{ss}	volume of distribution at steady state
WDAE	withdrawal due to adverse event
Xab	cross-reacting antibody

EXECUTIVE SUMMARY

Approach to the Review

The CADTH Common Drug Review (CDR) approach to reviewing Inflectra followed the *CDR Procedure and Submission Guidelines for Subsequent Entry Biologics* (March, 2014). The CDR review team validated the information provided by the manufacturer regarding product information (Section 1), the indication under review (Section 2), the rationale for the reimbursement criteria requested by the manufacturer (Section 3), biosimilarity (Section 4), extrapolation of indications (Section 6), and the comparative cost of the new product (Section 7). CDR reviewers provided a critical appraisal of the clinical evidence (Section 5) and cost comparison (Section 7).

Product Information

Inflectra (or CT-P13; infliximab) is a subsequent entry biologic (SEB) based on the innovator infliximab (Remicade). It has been approved in Canada for the following indications:

- 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 (RA).
- Reduction of signs and symptoms and improvement in physical function in patients with active ankylosing spondylitis (AS) who have responded inadequately to, or are intolerant to, conventional therapies.
- 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, Inflectra should be used after phototherapy has been shown to be ineffective or inappropriate.

Inflectra is not approved for the additional Remicade indications, namely Crohn disease and ulcerative colitis. The manufacturer is requesting that Inflectra be reimbursed in a manner similar to Remicade for each of the approved indications.

Clinical Evidence

Two pivotal randomized, double-blinded, multi-centre clinical trials evaluated the efficacy and safety of CT-P13 compared with Remicade. PLANETRA was an equivalence study for which 606 patients with active RA were administered CT-P13 or Remicade at a dose of 3 mg/kg for up to 54 weeks. The primary end point was American College of Rheumatology 20% response (ACR20) at Week 30. Secondary outcomes included ACR50 response, ACR70 response, European League Against Rheumatism (EULAR) response, Disease Activity Score-28 (DAS28) score, Short-Form 36 Health Survey (SF-36) score, safety, and immunogenicity. The equivalence margin for the primary end point was ± 15%. The CT-P13 and Remicade treatment groups were within the equivalence margin for ACR20 response at Week 30 (difference: 0.02; 95% CI: –0.06 to 0.10). Secondary end points, safety, and immunogenicity were similar in both treatment groups through Week 54. PLANETAS was a bioequivalence study for which 250 patients with AS were administered CT-P13 or Remicade at a dose of 5 mg/kg for up to 54 weeks. The primary end points were maximum concentration (C_{max}) at steady state ($C_{max,ss}$) and area under the plasma concentration-time curve over the dosing interval (AUC_{tau}) between Weeks 22 and 30. Additional pharmacokinetic parameters, namely efficacy, safety, and immunogenicity, were evaluated as secondary

end points. The equivalence margin for the primary end points was 80% to 125%. Both primary end points were within the bioequivalence margin, and all secondary end points were similar for both treatment groups.

Long-term, single-arm, extension studies of PLANETRA and PLANETAS were conducted through Week 102. Patients were either maintained on CT-P13 or switched from Remicade to CT-P13. Efficacy, safety, and immunogenicity responses were sustained through Week 102 in [redacted]% of the original study populations.

PLANETRA and PLANETAS both were well designed and executed, with no major biases. The available data for PLANETRA are consistent with the conclusion that Inflectra and Remicade have similar efficacy and safety profiles in patients with RA. The available data for PLANETAS are consistent with the conclusion that Inflectra and Remicade have similar pharmacokinetics and similar efficacy and safety profiles in patients with AS, although this trial was powered for pharmacokinetic parameters rather than for efficacy, and there was no a priori equivalence margin established for the efficacy end points.

Inflectra was approved by Health Canada for the indications for RA and AS based on the similarity between Inflectra and Remicade. Although the manufacturer has indicated that the products are therapeutically equivalent, Health Canada does not consider SEBs to be therapeutically equivalent; instead, Health Canada considers these products to be similar in the absence of any meaningful therapeutic difference.

Extrapolation

The approval in Canada of Inflectra for the indications of PsO and PsA was based on extrapolation due to similarities in the pathology of RA, AS, PsA, and PsO and the mechanism of action of all TNF-alpha-blockers in these indications. In contrast, Health Canada did not recommend extrapolation to Crohn disease and ulcerative colitis, due to differences between the mechanism of action of Inflectra and Remicade in these diseases that might have an effect on the safety and efficacy of these products in these indications.

Cost Comparison

The manufacturer submitted a cost comparison between subsequent entry infliximab (Inflectra) and reference product infliximab (Remicade) for the four indications under review: RA, AS, PsO, and PsA. At the submitted price ($650.00 per 100 mg vial), the annual cost of Inflectra is 34.2% less expensive than Remicade when using the Ontario Drug Benefit (ODB) Formulary Exceptional Access Program (EAP) price of Remicade ($987.56 per vial) as a reference.

Compared with other bDMARDs used for RA (excluding Remicade), for the first year of treatment and assuming a patient body weight of 70 kg, Inflectra was less expensive than all other comparators (abatacept, adalimumab, golimumab, rituximab, certolizumab, etanercept, and tocilizumab IV [8 mg/kg]). When Inflectra was compared with other bDMARDs used for AS or PsA (excluding Remicade), it was the most expensive option except for ustekinumab used for PsA. When used for PsO, Inflectra was more expensive than adalimumab, but it was less expensive than either etanercept or ustekinumab. Patient weight and the proportion of patients requiring dose escalation with infliximab will affect the relative cost of Inflectra compared with other bDMARDs.

Conclusions

Inflectra (infliximab) has been approved in Canada for the indications of RA and AS based on data from two clinical trials (PLANETRA and PLANETAS), which demonstrated similar pharmacokinetics, efficacy, and safety compared with the innovator reference product, Remicade (infliximab). In addition, Inflectra has been approved for the indications of PsO and PsA based on extrapolation, but has not been approved for the indications of Crohn disease and ulcerative colitis. Data from the year-long extension phases of the PLANETRA and PLANETAS studies have not raised any new safety concerns, but there is uncertainty regarding the long-term comparative efficacy and safety between Inflectra and Remicade in real-world patient populations. At the submitted price of $650.00 per vial, Inflectra is a less costly option than Remicade for treating patients with RA, AS, PsO, or PsA.

1. PRODUCT INFORMATION

Information in the following section was provided by the manufacturer and has not been altered by CDR in any way.

1.1 Manufacturer-submitted Overview of the SEB Product

Characteristics	Manufacturer-Provided Details	
	Inflectra	Remicade
Brand name:	*Inflectra*	*Remicade*
Non-proprietary name:	Infliximab	Infliximab
Manufacturer:	Hospira Healthcare Co.	Janssen Inc.
Strength(s):	100 mg/vial	100 mg/vial
Dosage form:	Powder for Solution, Sterile, Lyophilized	Powder for Solution, Sterile, Lyophilized
Route of administration:	Intravenous Infusion	Intravenous Infusion
Drug Identification Number(s):	02419475	02244016
Therapeutic classification:	Biological Response Modifier	Biological Response Modifier
Excipients	Sucrose, sodium dihydrogen phosphate monohydrate, di-sodium hydrogen phosphate dihydrate, polysorbate 80. No preservatives are present.	Dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, polysorbate and sucrose. No preservatives are present.
Impurities[a]	**Product-related** High molecular weight species: [redacted]%-[redacted]% Others: see Table below **Process-related** Residual host cell protein: [redacted] ppm Residual host cell DNA: [redacted]ng (max) Residual Protein A: [redacted] ppm Others: see section below	**Product-related** High molecular weight species: 0.10%-0.37% Others: see Table below **Process-related** Not available, see explanation at the end of this section

Source: Inflectra and Remicade product monographs
[a]Include both product and process-related impurities.

Pharmaceutical form: chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody

Pharmaceutical composition: as the formulation of Inflectra was set identical to that of Remicade, the dosage form for both products contain 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg sodium dihydrogen phosphate monohydrate and 6.1 mg di-sodium hydrogen phosphate dihydrate. No preservatives are present.

Dosage form: both Inflectra and Remicade are identical, namely formulated as white lyophilized powder.

Strength: both Inflectra and Remicade are supplied in 100 mg vials to be reconstituted with 10 mL sterile water resulting in a final concentration of 10 mg/mL. 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 Inflectra and Remicade are administrated via intravenous infusion. (Please be advised that in the Remicade product monograph (p. 3), route of administration is listed as i.v. injection, however, infusion is cited in the remaining of the document).

Purity and impurities:
Product-related impurities: Product-related impurities include: oxidized variants, deamidated variants, C-terminal lysine variants, glyco-variants, high molecular weight (HMW) species as well as molecular fragments.

A detailed description of the results for product-related impurity comparison between Inflectra drug product and Remicade are presented in Appendix 1, Table 1, CTD Module 2.3.R, CTD Module 3.2.R, and *Memorandum of NDS - Evaluation of Chemistry and Manufacturing Information for Inflectra (infliximab) from Celltrion Healthcare* (p.79-85). A summary of results is presented in the table below.

Impurity	Test Method	Results
Oxidized variants	Peptide Mapping (liquid chromatography-mass-spectrometry; LC-MS)	• Based on the available data, it can be concluded that only very low and comparable amounts of oxidized molecular variants are present in IFT drug product and RMP.
Deamidated variants	Ion-exchange chromatography-high performance liquid chromatography (IEC-HPLC)	• [redacted]
C-lysine terminal variants	IEC-HPLC	• It was demonstrated that the difference observed between IFT and RMP with respect to the relative proportion (peak ratio) of the 6 IEC-HPLC peaks is attributable to C-terminal lysine variability. • However, it has been shown that C-terminal lysine variability holds no bearing on biological activity in vitro, and that C-terminal lysine clipping occurs rapidly both in vitro and in vivo, suggesting that nearly all infliximab molecules are fully clipped within several hours following dosing.
Glyco-variants	Site Specific and N-Linked Glycan Analysis by Means of LC-MS Peptide Mapping; Oligosaccharide Profiling; Monosaccharide Analysis;	• Asparagine (Asn)300 was shown to be the only site of N-glycosylation for both IFT and RMP. No O-linked glycans were detected, as one might expect for an IgG1 monoclonal antibody, for IFT or the RMP. • Both IFT drug product and RMP were shown to contain mostly G0F and G1F structures. Minor species including Man5, G2F, G0F minus N-acetylglucosamine (GlcNAc), and G0 were detected.

Impurity	Test Method	Results
	Sialic Acid Analysis	• HPAEC-PAD data reveal that the type and proportion of the uncharged glycans is conserved between IFT and the RMP. • The identified sugars were [redacted]; both IFT and RMP had similar molar ratios for the 4 sugars. • The molar ratio of neutral and amino sugars was observed to be highly similar for IFT drug product and RMP. • IFT samples contain the same type as well as highly similar levels of sialic acid (expressed as molar ratios) when compared to RMP.
High molecular weight species	Size exclusion chromatography (SEC)-HPLC	• IFT drug product and RMP samples contain prominently monomer drug substance within a comparable range ([redacted], respectively). The impurities are high molecular weight species, which are all [redacted]% across both IFT and RMP products.
Molecular fragments	Capillary electrophoresis sodium dodecyl sulfate (CE-SDS) (Reduced/Non-Reduced)	• IFT and RMP display the same types of IgG fragments. • IFT drug product and RMP have similar amount of intact IgG ([redacted], respectively).

IFT=Inflectra; RMP=Reference medicinal product (i.e. Remicade)

Additional information on product-related impurities between Inflectra drug substance and drug product can be found in CTD Module 2.3.S.

Process-related impurities: Process-related impurities include: residual host cell protein (HCP), host cell DNA, residual Protein A, recombinant Insulin-Like Growth Factor 1 (IGF-1), recombinant human insulin and Pluronic F-68. Additional details can be found in *Memorandum of NDS - Evaluation of Chemistry and Manufacturing Information for Inflectra (infliximab)* [redacted].

- In terms of residual host cell protein (HCP), the level that was detected across [redacted] is generally considered as an acceptable level for therapeutic proteins.
- The level of residual host cell DNA, [redacted], below the acceptance criterion of ≤4 ppb (pg/mg) at release.
- The range of residual Protein A across [redacted] ppm, below the limit of ≤4 ppm (ng/mg).
- The ability of the Inflectra purification process to clear **IGF-1** and **recombinant insulin** was evaluated as part of a spiking study. The study demonstrated that the capability of clearance by specific a chromatography ([redacted]) [redacted] (Log_{10} reduction value) for IGF-1 and 4.51 LRV for insulin.
- [redacted].

For Remicade, the process-related impurities and their clearance is specific to each manufacturing process, therefore, Celltrion (manufacturer of Inflectra) does not have information on the manufacturing process of Remicade and the tests used to demonstrate clearance of the impurities in that process. It is also technically inappropriate to apply a Celltrion impurities test to Remicade to generate this data. The approach is therefore for the biosimilar company to develop the manufacturing process and control strategy to remove process-related impurities and to maintain the impurities at the lowest possible level to meet the regulatory requirement. Process-related impurities such as residual host cell protein, residual DNA, and endotoxin all fit this approach. Due to these reasons, there are no regulatory agencies requesting this comparative analysis.

1.2 Manufacturer-submitted Overview of the Reference Product

Please provide a brief description of the reference product that was used to apply for market authorization in Canada. Clearly state if the reference biologic drug is authorized for sale and marketed in Canada. If a non-Canadian reference biologic drug was used, briefly explain the rationale for this choice.

The reference product described in this submission is Remicade (Infliximab; Powder for Solution, Sterile, Lyophilized, 100 mg/vial) (1). Remicade is currently authorized for sale and marketing in Canada (DIN: 02244016). It should be noted that the batches of Remicade used in the clinical trials were manufactured in the EU (CTD Module 2.7.1, Table 2.7.1-2).

The infliximab drug substance is a chimeric IgG1κ antibody 1328 amino acids in length that is composed of human constant and murine variable regions. Infliximab neutralizes the biological activity of human tumour necrosis factor alpha (TNFα) by binding with high affinity to the soluble and transmembrane forms of TNFα (sTNFα, and tmTNFα) and inhibits their binding to TNF receptors (TNFRs).

In Canada, Remicade (infliximab) is indicated for:

1. 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**.
2. 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.
3. 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.
4. 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.
5. treatment of fistulising Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.
6. 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).

7. 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.
8. 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**.
9. 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.

2. INDICATIONS

Information in the following section was provided by the manufacturer and has not been altered by CDR in any way.

2.1 Health Canada-Approved Indications

Indication(s)	Extrapolation
• 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.	No
• 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.	No
• 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.	Yes
• treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, Inflectra 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.	Yes

2.2 Proposed Indications Under Review by Health Canada

Proposed Indication(s)	Anticipated Date of NOC
Not applicable	Not Applicable

3. MANUFACTURER'S REQUESTED LISTING CRITERIA

Information in the following section was provided by the manufacturer and has not been altered by CDR in any way.

3.1 Manufacturer-submitted Requested Listing Criteria

Requested Listing Criteria
• [redacted]
• [redacted]
• [redacted]
• [redacted]

3.2 Manufacturer-submitted Rationale for Requested Listing Criteria

The over-arching rationale for the requested listing criteria for all indications listed below is based on the principle of demonstrated biosimilarity between Inflectra and the currently reimbursed reference medicinal product (RMP), Remicade. First, the formulation of Inflectra has been designed to replicate that of Remicade and both drugs products are identical with respect to strength, pharmaceutical form, route of administration, and composition in excipients (see Section 1.1 above). Second, the active substance of Inflectra, infliximab, has been developed as a similar biological medicinal product to that of Remicade (infliximab). Specifically, an extensive series of orthogonal methods were designed to compare the physiochemical properties as well as the biological activities of Inflectra and Remicade, and results clearly demonstrated that the active substance is highly similar between these two products (see Section 4.1 and Appendix 1 for detailed information).

Therefore, because of the high degree of biosimilarity, Inflectra exhibits a PK profile that is indistinguishable from that of Remicade in ankylosing spondylitis (AS) patients. It is also therapeutically equivalent (as measured by ACR20 at Week 30) to Remicade in rheumatoid arthritis (RA). And is therapeutically similar in AS. Consequently, Inflectra is also expected to have similar efficacy as Remicade in the extrapolated indications of psoriatic arthritis (PsA) and plaque psoriasis (PsO). Additional rationales specific to each of the requested indications are provided below.

3.2.1 Rheumatoid Arthritis

a) Health Canada Indication for RA

From the clinical perspective, Inflectra has been approved by Health Canada 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."*

This indication is identical to that of Remicade, which is 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."*

b) CADTH Therapeutic Review

In July of 2010 (amended November, 2010), CADTH published a therapeutic review titled: "Clinical and Economic Overview: Biological Response Modifier Agents for Adults with Rheumatoid Arthritis." (2) The purpose of the review was to evaluate the comparative efficacy and harms for the available biologic agents (especially TNFα inhibitors) in the treatment of adults with RA. Based on the evidence reviewed by CADTH, the following recommendation was made:

> *"The Therapeutic Review Panel (TRP) recommends that in adult patients with rheumatoid arthritis with an inadequate response on optimal doses of disease-modifying antirheumatic drugs (DMARDs), one of the following biologics: abatacept, adalimumab, etanercept, golimumab, or **infliximab** could be used in combination with methotrexate or other DMARDs."*

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

c) Therapeutic Equivalence between Inflectra and Remicade in RA

In addition to the demonstrated biosimilarity, the approval of Inflectra for treatment of RA was based on the results of the pivotal efficacy study PLANETRA (CT-P13 3.1), which is described in detail in Section 4.2 below. Briefly, in RA patients with active disease treated with MTX for ≥3 months prior to enrolment, **Inflectra was demonstrated to be therapeutically equivalent to the reference product, Remicade** (both groups received concurrent MTX), as determined by the similar American College of Rheumatology 20% (ACR20) response at Week 30 (60.9% vs. 58.6%, respectively; 95% CI: -6% to 10%, which was within pre-defined therapeutic equivalence margin of ±15%) in the all-randomized population. Furthermore, all other efficacy and safety endpoints, as well as immunogenicity were highly similar between both products (3).

d) Reimbursement by CDR-Participating Public Drug Plans

Currently, infliximab (Remicade) is reimbursed by all CDR-participating drug plans across the country (with the exception of NT) for the treatment of RA (see Appendix 2). Consequently, we anticipate that Inflectra will receive generally similar listing decisions as Remicade from these CDR-participating drug plans, assuming that the Canadian Drug Expert Committee issues a positive recommendation for Inflectra.

3.2.2 Ankylosing Spondylitis

a) Health Canada Indication for AS

From the clinical perspective, Inflectra has been approved by Health Canada for:

> *"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."*

This indication is identical to that of Remicade, which is for:

> *"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."*

b) Indistinguishable Pharmacokinetic Profile and Therapeutic Similarity between Inflectra and Remicade in AS

In addition to the demonstrated biosimilarity, the approval of Inflectra for the treatment of AS was based the results of the pivotal PK study PLANETAS (CT-P13 1.1; primary objective was to demonstrate PK equivalence for the primary outcomes of AUC_{tau} and $C_{max,ss}$ between Weeks 22 and 30), which is described in detail in Section 4.2 below. [redacted], thus demonstrating that the **PK of Inflectra could not be distinguished from the reference product Remicade estimated at steady-state using a non-compartmental analysis**. In addition, Inflectra was demonstrated to be similar in efficacy to the reference product, Remicade, as determined by the non-statistically significant differences in ASAS20 and ASAS40 scores at Weeks 14, 30, and 54. Furthermore, all other efficacy and safety endpoints, as well as immunogenicity were highly similar between both products (4, 5).

c) Reimbursement by CDR-Participating Public Drug Plans

Currently, infliximab (Remicade) is reimbursed by the majority of CDR-participating drug plans across the country for the treatment of AS (see Appendix 2). Consequently, we anticipate that Inflectra will receive generally similar listing decisions as Remicade from these CDR-participating drug plans, assuming that the Canadian Drug Expert Committee issues a positive recommendation for Inflectra.

Therefore, based on the totality of the information illustrated above (e.g. demonstrated PK equivalence, clinical similarity, and biosimilarity), the requested listing criteria are reasonable and justified.

3.3.3 Psoriatic Arthritis

a) Health Canada Indication for PsA

From the clinical perspective, Inflectra has been approved by Health Canada for:

> *"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.."*

This indication is identical to that of Remicade, which is for:

> *"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."*

b) Extrapolation of Indication

The detailed justification of extrapolation of Inflectra for the treatment of PsA is described in Section 6 of this document. Briefly, PsA shares similarities with both RA and AS, in that patients with PsA typically present with joint inflammation and bone erosion, and the cytokine expression in the synovial fluid of PsA patients are similar to those seen in RA patients. Furthermore, Remicade has been shown to be clinically efficacious in the treatment of PsA (6, 7).

c) Reimbursement by CDR-Participating Public Drug Plans

Currently, infliximab (Remicade) is reimbursed by several CDR-participating drug plans across the country for the treatment of PsA (see Appendix 2). Consequently, we anticipate that Inflectra will receive generally similar listing decisions as Remicade from these CDR-participating drug plans, assuming that the Canadian Drug Expert Committee issues a positive recommendation for Inflectra. CDR-participating drug plans that do not currently reimburse Remicade may find that the economic advantages of Inflectra make it worthy of reimbursement.

Based on the above and the Health Canada acceptance of evidence supporting extrapolation, the requested listing criteria are reasonable and justified.

3.3.4 Plaque Psoriasis

a) Health Canada Indication for Plaque Psoriasis

From the clinical perspective, Inflectra has been approved by Health Canada for:

> *"treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, Inflectra 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. "*

This indication is identical to that of Remicade, which is for:

> *"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."*

b) CADTH Therapeutic Review

In the July of 2012, CADTH published a Rapid Response Report: Summary with Critical Appraisal titled: "Infliximab versus Methotrexate, Etanercept, Adalimumab, and Ustekinumab for Plaque Psoriasis: A Review of the Comparative Clinical Efficacy, Safety and Cost Effectiveness" (8). The purpose of the review was to examine the comparative clinical efficacy, safety, and cost-effectiveness of infliximab vs. methotrexate (MTX), etanercept, adalimumab, or ustekinumab for the treatment of adults with plaque psoriasis. Based on the evidence reviewed by CADTH, the following conclusion was made:

> *"Infliximab was found to be more effective than methotrexate, etanercept, adalimumab, and ustekinumab through meta-analyses and one randomized controlled trial."*

Therefore, the therapeutic efficacy of infliximab in the treatment of plaque psoriasis has been recognized and supported by CADTH.

c) Extrapolation of Indication

The detailed justification of extrapolation of Inflectra for the treatment of PsO is described in Section 6 of this document. Briefly, PsO is characterized by infiltration of the skin by immune cells, hyper-proliferation of keratinocytes, and subsequent formation of erythematous plaques and increased dermal vascularity. T cells located in the inflamed skin secrete an array of cytokines including TNFα, IFN-γ, and IL-17 (9) and have the capacity to promote the proliferation of keratinocytes in psoriatic skin (10, 11). Furthermore, TNFα-dependent T cell proliferation has been shown to be required for the development of psoriatic skin lesions (12) and blocking of TNFα signalling has been shown to significantly reduce T cell number in lesion skin and attenuate disease development. Therefore, local TNFα/TNFα signalling plays a prominent role in the pathogenesis of this condition.

d) Reimbursement by CDR-Participating Public Drug Plans

Currently, infliximab (Remicade) is reimbursed by several CDR-participating drug plans across the country for the treatment of plaque psoriasis (see Appendix 2). Consequently, we anticipate that Inflectra will receive generally similar listing decisions as Remicade from these CDR-participating drug plans, assuming that the Canadian Drug Expert Committee issues a positive recommendation for Inflectra.

Therefore, based on the totality of information, e.g. the clinical efficacy of infliximab in the treatment of plaque psoriasis as demonstrated by the CADTH Rapid Response Report, and the demonstrated biosimilarity between Inflectra and Remicade based the Health Canada acceptance of evidence supporting extrapolation, the requested listing criteria are reasonable and justified.

4. BIOSIMILARITY

Information in the following section was provided by the manufacturer and has not been altered by CDR in any way.

4.1 Manufacturer-Submitted Quality Information

Inflectra is produced in accordance with ICH guidelines and the manufacturing processes have been extensively validated. An all-encompassing product characterization exercise was conducted, using a range of state-of-the-art methodologies to ensure that Inflectra and Remicade are similar in quality, safety, and efficacy. Finally, similarity of Inflectra before and after manufacturing changes and to Remicade are supported by additional comparability exercises. It should be noted that the results of the following comparability exercises are between Inflectra drug product and Remicade. For those conducted between Inflectra drug substance and Inflectra drug product, please refer to Common Technical Document (CTD) Modules 2.3.S and 3.2.S.

The primary structures of Inflectra and Remicade were confirmed to be identical by amino acid analysis, sequencing using peptide mapping (in combination with MS/MS), N-terminal sequencing and C-terminal sequencing, except for differences in the levels of C-terminal lysine, the latter of which was considered unlikely to impact the efficacy and safety of the proposed biosimilar product.

The higher order structures of Inflectra and Remicade were shown to be comparable. The positions of disulphide bonds matched and the free thiol content per mole IgG was similar. Secondary and tertiary structure analysis did not show any significant difference. Differential scanning calorimetry (DSC) results indicated comparable folding of the proteins between Inflectra and Remicade.

The charged isoforms were also comparable between Inflectra and Remicade as demonstrated by similar ranges of isoelectric point (pI) values. IEC-HPLC results showed that both products contained six peaks with minor differences noted in the relative proportions of each peak compared to Remicade; however, their *in vitro* activities between the products were generally similar with regards to the sTNFα binding/neutralization, and tmTNFα binding activities. The glycosylation of Inflectra was shown to be highly similar to Remicade as demonstrated by sialic acid, monosaccharide, and oligosaccharide analyses. For purities/impurities, the percentage of monomer exceeded 99% in all cases as demonstrated by SEC-HPLC. The above results demonstrated that Inflectra and Remicade are physically highly similar. Results of the key assays are summarized in Table 1; detailed descriptions of these assays and all other relevant assays can be found in Appendix 1, Table 1 as well as CTD Module 3.2.R.

TABLE 1: SUMMARY OF PHYSICOCHEMICAL TEST METHODS FOR COMPARABILITY OF INFLECTRA (IFT) DRUG PRODUCT AND REMICADE (RMP). FOR BREVITY, REFERENCES ARE FROM CTD MODULES WITH ONLY SECTION NUMBERS LISTED.

Test Methods	Summary of Results	References
Primary structure		
Peptide Mapping (LC-MS) with MS/MS	Three separate digestions were employed to ensure 100% sequence coverage for the drug product. IFT drug product and RMP have an identical amino acid sequence, as confirmed by peptide mapping (LC-MS; in combination with MS/MS).	2.3.R, Table 2.3.R-1; 3.2.R.5.2.1
N-terminal Sequencing	The detected N-terminal sequence of the light chain and the heavy chain are identical between IFT drug product and RMP, as confirmed by peptide mapping in combination with MS/MS.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.1
C-terminal Sequencing	The detected C-terminal sequence of the light chain and the heavy chain are identical between IFT drug product and RMP, as confirmed by peptide mapping in combination with MS/MS.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.1
Higher-order structure		
Disulphide Bonds	Eight peaks were identified as disulphide bond linked peptides based on MS and MS/MS sequencing analysis. Positions of the disulphide bonds matched (native and reduced peptide mapping). IFT drug product and RMP exhibit comparable disulphide bond formation, as confirmed by comparing native and reduced peptide maps and MS/MS analysis.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.2
Free Thiol Analysis	The moles of free SH groups per mole IgG were between [redacted] in all IFT drug product batches as well as RMP. These low levels of free sulfhydryl are typically expected for a monoclonal antibody preparation.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.2
FTIR (secondary structure)	For all samples, Fourier transform infrared spectroscopy (FTIR) spectra agree well with respect to shape and location [redacted]. Based on the results obtained, IFT drug product can be considered to be highly similar to RMP in terms of protein secondary structure.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.2
Circular dichroism (CD)	The near (tertiary) and the far (secondary) UV spectrum of IFT drug product and RMP show the typical shape of an antibody with regards to protein structure. No significant differences between the different samples were observed. The data suggest a secondary structure dominated by β-sheet motif.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.2
DSC (thermal stability)	Three endothermic transition temperatures at [redacted], for the IFT drug product were comparable to RMP, indicating similar folding of the proteins.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.2
Charged Isoforms		
Isoelectric focusing (IEF)	The results from IEF analysis show that the calculated pI values of [redacted] are comparable and fall within similar ranges for IFT drug product samples and RMP.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.4
IEC-HPLC	Six IEC-HPLC peaks were observed for all samples analyzed. All peaks have been subjected to structural analysis. IFT drug product and RMP show a similar IEC-HPLC peak distribution, furthermore, the relative proportion of each peak (% area) is conserved from drug substance to drug product. Additionally: • The number and distribution of IEC-HPLC peaks is conserved between IFT and RMP; • The molecular variants and relevant structural identification associated	2.3.R, Table 2.3.R-1; 3.2.R.5.2.4

Test Methods	Summary of Results	References
	with each of the 6 IEC-HPLC peaks is conserved between IFT and RMP; • The biological activity (sTNFα of each of the 6 IEC-HPLC peak factions is conserved between IFT and RMP; • The relative proportion (peak ratio) of the 6 IEC-HPLC peaks displays differences between IFT and RMP. The difference in IEC-HPLC peak ratio was concluded to be the result of C-terminal lysine variability, and, since rapid cleavage of the C-terminal lysine occurs in blood following administration of IFT, thus have no clinically meaningful impact.	
Glycosylation		
Sialic Acid Analysis	Sialic acid was detected in the form of N-glycolylneuraminic acid (NeuGc) in all samples, with no other forms detected. The sialic acid analysis demonstrated that both IFT and RMP contain NeuGc at comparable level. The sialic acid results expressed as molar ratios are summarized in Section 3.2.S.3.1.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.5
Monosaccharide Analysis	The identified sugars were Fuc, GlcNAc, Gal and Man. The monosaccharide content of both IFT and RMP were similar for the neutral and amino sugars (molar ratios).	2.3.R, Table 2.3.R-1; 3.2.R.5.2.5
Oligosaccharide Profiling	Available High Performance Anion Exchange Chromatography with Pulsed Amperometric Detection (HPAEC-PAD) data revealed the presence of G0F, Man5, G0, G1F and G2F structures, which is in agreement with the "typical" oligosaccharide profile of a monoclonal antibody. The HPAEC-PAD data reveal that the type and proportion of the uncharged glycans is conserved between IFT and the RMP.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.5
N-linked Glycan Analysis	Asn300 was shown to be the only site of N-glycosylation for both IFT and RMP with no O-linked glycans detected, as expected for an IgG1 monoclonal antibody. Some differences in the levels of G0, G0F, G2F and the sialic acid containing glycans (higher levels of G1FNeuGc and G2F1NeuGc for IFT finished product compared with RMP) were observed, but in general the glycans were similar in both IFT finished product and the RMP, with no new glycans detected. The main glycans detected in both products are G0F and G1F, typical for IgG.	2.3.R, Table 2.3.R-1; 3.2.R.5.2.5

An extensive series of biological assays were also conducted in order to determine the comparability of Inflectra and Remicade. Specifically, assays were conducted with Inflectra from both pre- and post-changes in manufacturing process and vs. Remicade. Table 2 below summarizes the key results of the biological test that are specifically relevant to the pathophysiology of RA, As, PsA, and PsO, that is, the F(ab')2-dependent sTNFα-binding/neutralizing ability of Inflectra and Remicade. The results clearly demonstrated that, using a wide range of assays, the bioactivity of Inflectra and Remicade were highly comparable. As the blockade of tmTNFα in addition to sTNFα can also prevent the activation of TNFRs, the tmTNFα-binding affinity of Inflectra and Remicade was also tested. The results showed comparable binding between products. A detailed comparison of biological activities between Inflectra and Remicade are presented in Table 2 of Appendix 1 and CTD Module 3.2.R. In addition, comparison of results between two Inflectra manufacturing sites using post-manufacturing change procedures vs. Remicade are presented in the BSEAR Non-Clinical: Toxicology and Pharmacology report. Results showed that their physiochemical properties and biological activities are comparable.

TABLE 2: SUMMARY OF STUDIES COMPARING THE BIOLOGICAL ACTIVITIES BETWEEN INFLECTRA (IFT) AND REMICADE (RMP). FOR BREVITY, REFERENCES ARE FROM CTD MODULES WITH ONLY SECTION NUMBERS LISTED.

Test Method(s)	Summary of Results	References
F(ab')2 related		
Comparative binding of IFT and RMP to hTNFα using anti-hTNFα enzyme-linked immunosorbent assay (ELISA)	• The average relative binding affinity [redacted], therefore IFT and RMP can be considered comparable with regards to in vitro TNFα binding affinity as determined by ELISA.	3.2.R.5.2.7, Table 3.2.R-71 (p.132)
Comparative binding of IFT and RMP to hTNFα using Surface Plasmon Resonance (SPR)	• The total mean relative binding affinity of the [redacted], therefore IFT and RMP can be considered comparable in this regard.	3.2.R.5.2.7, Table 3.2.R-70 (p.131)
Comparative hTNFα neutralization assay of IFT and RMP	• The average relative potency of the [redacted], respectively, thus considered comparable with regards to in vitro TNFα neutralizing activity (Table 3.2.R-61).	3.2.R.5.2.7, Table 3.2.R-61 (p.122-123)
Comparative transmembrane hTNFα binding affinity of Inflectra and Remicade using cell-based ELISA	• The total mean relative binding affinities for [redacted], therefore IFT and RMP can be considered comparable in this regard.	3.2.R.5.2.7, Table 3.2.R-65 (p.126)

Source: CTD Module 2.3.R, Table 2.3.R-1; CTD Module 3.2.R

4.2 Manufacturer-sumitted information on Pivotal Clinical Studies

Study Name	Design	Objectives	Population
CT-P13 3.1; PLANETRA (*P*rogramme eva*L*uating the *A*utoimmune disease i*N*v*E*stigational drug c*T*-p13 in *RA* patients)	**Pivotal efficacy**, phase 3, randomized, double-blind, multicentre, multinational, parallel-group study	To compare the efficacy and safety of innovator infliximab (Remicade) and Inflectra, an infliximab biosimilar, in active rheumatoid arthritis patients with inadequate response to MTX treatment.	The therapeutic area is rheumatology. Patients with active RA according to the revised 1987 ACR classification criteria for ≥1 year prior to screening were recruited. Patients had to have ≥6 swollen and ≥6 tender joints and at least two of the following: morning stiffness lasting ≥45 min; serum C-reactive protein (CRP) concentration >2.0 mg/dl and erythrocyte sedimentation rate (ESR) >28 mm/h despite MTX therapy for ≥3 months (stable dose of 12.5–25 mg/week for ≥4 weeks prior to screening). Key characteristics: mostly female (82.7%), Caucasian (72.9%), and median age of 50 years old (range: 18-75).
CT-P13 1.1; Program evaLuating the Autoimmune Disease iNvEstigational Drug cT-p13 in AS Patients (PLANETAS)	**Pivotal PK**, phase 1, randomized, double-blind, multicentre, multinational, parallel-group study	To compare the PK, safety and efficacy of innovator infliximab (Remicade) and Inflectra, a biosimilar to infliximab, in patients with active AS.	The therapeutic area is rheumatology. Patients with active AS according to the 1984 modified New York classification criteria for ≥3 months prior to screening, with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 (range 0–10) and a visual analogue scale score for spinal pain of ≥4 (range 0–10) were eligible for PLANETAS study. Patients were permitted to receive both oral glucocorticoids (equivalent to ≤10mg daily prednisolone) and non-steroidal anti-inflammatory drugs, if they had received a stable dose for ≥4weeks prior to screening. Key characteristics: mostly male (80.8%), Caucasian (75.6%), and median age of 38 years old (range: 18-69).

4.2.1 PLANETRA (CT-P13 3.1)

a) Study Characteristics

Brief description of the study

PLANETRA was a phase 3, randomized, double-blind, multicentre, multinational, parallel-group pivotal study designed to compare the efficacy and safety of innovator infliximab (Remicade) and Inflectra, an infliximab biosimilar, in active rheumatoid arthritis patients with inadequate response to methotrexate treatment. The primary endpoint was the ACR20 response at Week 30. Therapeutic equivalence of clinical response according to ACR20 criteria was concluded if the 95% CI for the treatment difference was within ±15%. Additional efficacy, safety, PK, and immunogenicity outcomes were also assessed.

Characteristics		Details for *PLANETRA*
STUDY DESIGN	**Objective**	Pivotal efficacy and safety study
	Blinding	Double-blind
	Study period	2010-10 to 2012-07
	Study centres	100 centres across 19 countries
	Design	Equivalence
STUDY POPULATION	**Randomized (N)**	606
	Inclusion criteria (major)	1. Patient had a diagnosis of RA according to the revised 1987 ACR classification criteria for at least 1 year prior to Screening. 2. Patients had active disease as defined by the presence of six or more swollen joints, six or more tender joints, and at least two of the following: morning stiffness lasting at least 45 minutes, an ESR greater than 28 mm/h, and a serum CRP concentration greater than 2.0 mg/dL. 3. Patients had completed at least three months of treatment of oral or parenteral dosing with MTX between 12.5 to 25 mg/week and were on stable dosing with MTX between 12.5 to 25 mg/week for at least 4 weeks prior to Screening.
	Exclusion criteria (major)	1. Patients had previously been administered a biological agent for the treatment of RA. 2. Patients had a current or past history of chronic infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus (HIV)-1 or-2 or who had a positive result to the screening test for those infections. 3. Patients had a current diagnosis of tuberculosis (TB) or other severe or chronic infection (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis) or a past diagnosis without sufficient documentation of complete resolution following treatment. 4. Patients had an infection requiring oral antibiotics in the 2 weeks before Screening, parenteral injection of antibiotics in the 4 weeks before Screening, or other serious infection in the 6 months before Screening or who had a history of recurrent herpes zoster or other chronic or recurrent infection.
DRUGS	**Intervention**	Inflectra (infliximab), 3 mg/kg, administered by 2 h intravenous infusion, at weeks 0, 2, and 6, and then q8 weeks up to Week 54. Patients were pre-medicated with anti-histamine (chlorpheniramine 2–4 mg or dose of equivalent anti-histamine) 30–60min prior to the start of infusion at the investigator's discretion. Weekly MTX (12.5–25 mg/week, oral or parenteral dose) and folic acid (≥5 mg/week, oral dose) were co-administered.

Characteristics		Details for *PLANETRA*
	Comparator(s)	Remicade (infliximab), 3 mg/kg, administered by 2 h intravenous infusion, at weeks 0, 2, and 6, and then q8 weeks up to Week 54. Patients were pre-medicated with anti-histamine (chlorpheniramine 2–4 mg or dose of equivalent anti-histamine) 30–60min prior to the start of infusion at the investigator's discretion. Weekly MTX (12.5–25 mg/week, oral or parenteral dose) and folic acid (≥5 mg/week, oral dose) were co-administered.
DURATION	**Run-in**	Not applicable
	Treatment	54-week
	Follow-up	Not applicable
OUTCOMES	**Primary End Point(s)**	ACR20 response at Week 30. Therapeutic equivalence of clinical response according to ACR20 criteria was concluded if the 95% CI for the treatment difference was within ±15%.
	Other End Points	Efficacy endpoints were measured up to 54 weeks • ACR response criteria • Individual components of the ACR criteria comparison with baseline (Week 0) at Weeks 14, 30, and 54 or end-of-study visit [8 weeks after last dose] if different from Week 54 • Time to onset of ACR 20 response • ACR20 at Week 14 and 54 (or the end-of study visit if different from Week 54) • ACR50 and ACR70 at Weeks 14, 30, and 54 (or the end-of study visit if different from Week 54) • European League Against Rheumatism (EULAR) response criteria • Change in Disease Activity Score 28 (DAS28) • Medical Outcomes Study Short-Form Health Survey (SF-36) • Simplified Disease Activity Index (SDAI) • Clinical Disease Activity Index (CDAI) • PK and pharmacodynamic (PD) parameters • Immunogenicity • Safety
NOTES	**Publications**	A randomized, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when co-administered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S, Kovalenko V, Prodanovic N, Abello-Banfi M, Gutierrez-Ureña S, Morales-Olazabal L, Tee M, Jimenez R, Zamani O, Lee SJ, Kim H, Park W, Müller-Ladner U. Ann Rheum Dis. 2013 Oct;72(10):1613-20 (3). Equivalence study comparing CT-P13 with infliximab in active RA: A Phase III, randomized controlled trial to compare CT-P13 with Infliximab (INX) in patients with active rheumatoid arthritis (RA): 54 week results from the PLANETRA STUDY. Yoo D-H, et al. EULAR 2012. Poster available (13). Biosimilars to treat inflammatory arthritis: the challenge of proving identity. Kay J, Smolen JS.

Characteristics		Details for *PLANETRA*
		Ann Rheum Dis. 2013 Oct;72(10):1589-93. doi: 10.1136/annrheumdis-2012-203198. Epub 2013 Jul 29 (14). • Clinicaltrials.gov identification code: NCT01217086

Intervention and Comparators

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

Patients received 2 h intravenous infusion of either 3 mg/kg of Inflectra or Remicade at Weeks 0, 2 and 6 and then q8 weeks up to week 54. Patients were pre-medicated with anti-histamine (chlorpheniramine 2–4 mg or dose of equivalent anti-histamine) 30–60 min prior to the start of infusion at the investigator's discretion.

Reference Product used in the Trial

All batches of the reference product, Remicade, used in the trial, was manufactured in the EU (CTD Module 2.7.1, Table 2.7.1-2).

Placebos and Controls (if applicable)

An active comparator (Remicade) was used in this trial; therefore no placebo was used.

Concomitant Medications

Weekly MTX (12.5–25 mg/week, oral or parenteral dose) and folic acid (≥5 mg/week, oral dose) were co-administered. Rescue therapy was only allowed with tramadol and/or acetaminophen. Salvage therapy was defined as an antirheumatic drug, such as disease-modifying antirheumatic drugs, non-steroidal anti-inflammatory drugs and any biological agent for the treatment of RA, received on or after the day of the first dose of study treatment.

Outcomes (Key Efficacy and Safety Outcomes)

ACR20: The primary efficacy outcome was the ACR20 score at Week 30, through which therapeutic equivalence was to be established if the 95% CI for the treatment difference between Inflectra and Remicade was within ±15%. ACR20 response rate is defined as the percent of patients achieving 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core set measures: patient pain assessment (measured by visual analogue scale [VAS]), patient global assessment (measured by VAS), physician global assessment (measured by VAS), patient self-assessed disability (measured by Health Assessment Questionnaire [HAQ]), and acute-phase reactant (ESR or CRP) (15).

Please note that for the secondary efficacy endpoints listed below, patients were assessed at Weeks 14, 30, and 54 (or the EOS visit if different from Week 54).

Individual components of the ACR criteria (see individual criteria in ACR20 above) were evaluated at Weeks 14, 30, and 54 (or end-of-study [EOS] visit if different from Week 54).

ACR20, ACR50, ACR70: ACR20 at Week 14 and 54 (or the EOS visit if different from Week 54); ACR50 and ACR70 at Weeks 14, 30, and 54 (or the EOS visit if different from Week 54).

Change in Disease Activity Score 28 (DAS28) at Weeks 14, 30, and 54 (or EOS visit if different from Week 54): The DAS28 is a modified version of the DAS. The DAS28 score takes into consideration the 28-joint counts of tenderness (TJC28) and swelling (SJC28), plus the ESR or CRP, and a general health assessment scored on a VAS (16, 17). Score of <2.6 is considered to be remission and score of >5.1 is considered as high disease activity (18). The DAS score may also be more indicative of whether the two treatments are comparable due to its continuous nature.

European League Against Rheumatism (EULAR) response criteria at Weeks 14, 30, and 54 (or EOS visit if different from Week 54): The EULAR was based on the DAS28 scale (19), it requires patients to experience a certain amount of improvement as well as to achieve a particular disease activity state at the time of evaluation (see table below).

Achieved DAS28	DAS28 improvement		
	>1.2	0.6-1.2	<0.6
<3.2	Good	Moderate	No
3.2-5.1	Moderate	Moderate	No
>5.1	Moderate	No	No

Immunogenicity: immunogenicity was tested using both the CT-P13 (Inflectra) tag and infliximab (Remicade) tag. Antibodies against CT-P13 or RMP were measured using an electrochemiluminescent immunoassay method.

Safety: the key safety outcomes included incidence and type of adverse events (AEs) and infection, serious AEs, incidence of infusion-related reactions and changes from baseline in clinical laboratory parameters. AEs were coded using the Medical Dictionary for Regulatory Activities and severity was characterised as mild, moderate or severe.

Statistical Analyses

Statistics Protocol for Equivalence Testing

For the primary analysis of demonstrating therapeutic equivalence, the proportion of patients achieving ACR20 clinical response at Week 30 was analysed by the exact binominal approach, calculating a point estimate and 95% confidence interval (CI) for the difference in proportion between the 2 treatment arms. Therapeutic equivalence was concluded if 95% CI for the treatment difference was entirely within -15% to 15%, which would help further supporting the claim that Inflectra is biosimilar to Remicade. As this method did not allow for stratification, a sensitivity analysis was performed on the primary endpoint, utilizing a logistic regression model, with randomized treatment arm as a fixed effect, and region and CRP category as covariates. The primary efficacy analyses were performed on both the all-randomised and PP populations. For full details, please refer to CTD Module 2.7.3 (p.21).

Rationale for the Equivalence Margins Used

For the development of the pre-specified equivalence margin, the following guidelines have been taken into account: Biostatistical Methodology in Clinical Trials (Directive 75/318/EEC as amended: Guideline on the choice of the non-inferiority margin (ref EMEA/CHMP/EWP/2158/99) (20); Points to consider on switching between superiority and non-inferiority (ref CHMP/EWP/482/99) (21)). Additionally key literature on establishing equivalence margins were identified (22-26). Further, taking into consideration historical response rates of methotrexate and infliximab combination therapy, precision range and European Union regulatory precedents, it is considered that the proposed equivalence margin of 15% is appropriate and should provide adequate assay sensitivity. For full details, please refer to CTD Module

2.7.3 (p.27) and "Response to Clarifax Dated 30 April 2013" located on p.208 of the BSEAR Clinical document (located in Category 1 Folder, under /3_Inflectra_Clinical Information/ 3.10_Inflectra_Health Canada BSEAR).

Historical Response Rates

As recommended in the Guideline on "The choice of the non-inferiority margin" (ref EMEA/CHMP/EWP/2158/99) (20) and ICH E10 (27), a systematic literature review has been conducted to identify studies relevant to the comparison of the reference treatment with placebo in the target indication and population for the proposed trial.

The identification of relevant prospective studies among the results of the literature search took into account the following factors: patient population comparable with the population of the reference ATTRACT trial (i.e. patients with active RA according to the ACR criteria, despite treatment with MTX), stable doses of 3 mg/kg infliximab administered at Weeks 0, 2, 6 and then every 8 weeks, clinical outcome assessed using ACR20 criteria, measurement of ACR20 up to 30 weeks of treatment, controlled studies (control group receiving MTX alone). Except the reference ATTRACT trial, no other clinical trial in which ACR20 response was measured after 30 weeks of treatment could be identified; therefore, ACR20 responses at earlier time points, i.e. after minimum 14 weeks of treatment (corresponding to the administration of the first 3 doses, "loading" phase), have been also considered. Studies conducted in MTX naïve patients or in patients with early RA have been excluded in order to maintain the characteristics of the patient population used in the reference ATTRACT trial.

In the pivotal registration trial performed with infliximab in RA, 50% of the RA patients treated with infliximab in combination with methotrexate reached the primary endpoint ACR20 at Week 30, whereas in the placebo plus methotrexate this was only 20%. Thus the difference between the infliximab plus methotrexate group and control (methotrexate only) group was 30% (28). A 15% equivalence margin represents 50% of this difference.

The proposed sample size will have a power of 80% to demonstrate equivalence if the equivalence margin is 15% (absolute), [redacted], methods of statistical reasoning, and relevance of clinical difference requirement of assay sensitivity for equivalence trials, quality issues of trial management and data from historical response rates.

As per reviewer's assessment in the BSEAR Clinical report (p.213): "The sponsor has identified the relevant historical trials and it has been shown that the effect on the ACR20 of Remicade is approximately 30% over and above MTX alone. Employing a 15% equivalence margin represents [redacted] and ensures that Inflectra produces an effect greater than that of MTX alone (i.e. – greater than 0). A point estimate of the treatment difference that falls within this margin and is bounded by a 95%CI that lies entirely with 15% will provide a reasonable assurance that Inflectra produces an effect on the ACR20 that is not substantially different than the effect produced by Remicade. The response and choice of equivalence bounds are considered acceptable." Therefore, the choice of equivalence margin used was justified and was also considered to be appropriate by Health Canada.

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

All primary efficacy analyses were performed on both the all-randomized and per-protocol (PP) populations. All other efficacy analyses were originally performed on the PP population only. Subsequently, analyses of the results using the all-randomized population were provided per Health

Canada's request (BSEAR Clinical report, p.33) and the results for both populations are provided in this document. The all-randomized population comprised 302 patients in the Inflectra group and 304 patients in the Remicade group. At Week 54, the PP population comprised a total of 496 patients; 246/302 (81.5%) randomized to Inflectra and 250/304 (82.2%) randomized to Remicade (CTD Module 2.7.3.2.1.7, p.34; CTD Module 2.7.3.2.1.8, p.35-37).

The safety population consisted of all patients who received at least one (full or partial) dose of either of the study treatments during any dosing period irrespective of their randomization. The PK–PD population consisted of all patients who received either Inflectra or Remicade during the 30-week blinded study period and had at least one PK–PD concentration data value. A full description of the analysis set can be found in CSR CT-P13 3.1, Section 9.7.1.2 (p.63-64).

Reference Locations

1. For the description of the statistics protocol for therapeutic equivalence testing, please refer to CTD Module 2.7.3 (p.21).
2. For the description of the rationale for the therapeutic equivalence margins used, please refer to CTD Module 2.7.3 (p.27) and "Response to Clarifax Dated 30 April 2013" located on p.208 of the BSEAR Clinical document (located in Category 1 Folder, under /3_Inflectra_Clinical Information/ 3.10_Inflectra_Health Canada BSEAR).
3. For description of the analysis set, please refer to CTD Module 2.7.3.2.1.7 (p.34), CTD Module 2.7.3.2.1.8 (p.35-37), and CSR CT-P13 3.1, Section 9.7.1.2 (p.63-64).

b) Results

Baseline Characteristics

TABLE 3: MAJOR DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR STUDY CT-P13 3.1 (PLANETRA)

	Inflectra 3 mg/kg (N = 302)	Remicade 3 mg/kg (N = 304)
Age (years)	50 (18–75)	50 (21–74)
Gender, no (%)		
Female	245 (81.1)	256 (84.2)
Male	57 (18.9)	48 (15.8)
Ethnicity, no (%)		
Asian	34 (11.3)	37 (12.2)
Black	2 (0.7)	1 (0.3)
White	220 (72.8)	222 (73.0)
Other	46 (15.2)	44 (14.5)
Height (cm)	162.3 (144.0–186.0)	162.0 (124.0–190.0)
Weight (kg)	69.0 (36.5–134.0)	68.0 (36.0–136.0)
BMI (kg/m^2)	26.3 (13.9–49.8)	25.4 (15.0–53.1)
Region, no (%)		
European	179 (59.3)	180 (59.2)
Non-European	123 (40.7)	124 (40.8)
Baseline serum CRP concentration, no (%)		
≤2 mg/dL	163 (54.0)	167 (54.9)
>2 mg/dL	139 (46.0)	137 (45.1)
IgM RF (IU/ml)	74.0 (3.0-4772.8)	97.2 (3.0-10450.2)
Initial MTX dose (mg) (Safety)	15.0 (12.5-25.0)	15.0 (12.5-25.0)

	Inflectra 3 mg/kg (N = 302)	Remicade 3 mg/kg (N = 304)
DAS28-CRP (PP)	5.8 (4.0-7.8)	5.7 (3.1-7.7)
CDAI (PP)	38.8 (17.0-68.9)	38.9 (13.1-72.7)
SDAI (PP)	40.6 (17.7-70.9)	40.5 (13.2-74.6)
Physician global assessment of disease activity	65.0 (5-100)	66.5 (31-100)

Note: Except where indicated otherwise, values are the median (range) and data from all-randomized population is presented. The DAS28-CRP, CDAI, and SDAI are secondary endpoints and therefore were analyzed using per-protocol method as specified in the Statistical and Analytical Plans.
BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; SDAI, Simplified Disease Activity Index; PP, per-protocol population.
Source: CTD Module 2.7.3, Table 2.7.3-10; CSR CT-P13 3.1, Post-text Table 14.2.8.1 (IgM RF), Post-text Table 14.1.8 (MTX), Post-text Table 14.2.5.3 (DAS28-CRP), Post-text Table 14.2.6.2 (CDAI and SDAI), Post-text Table 14.2.1.4 (Physician global assessment of disease activity).

Overall, the study population was well balanced in terms of age, gender, and physical characteristics. There were more females in the study and the population is predominantly European, both of which were balanced between the two arms. Baseline serum CRP concentration as well as disease activity (as measured by DAS28-CRP, CDAI, SDAI, physician global assessment of disease activity) were equally balanced between treatment arms.

Concomitant Conditions and Medications

[redacted]

For both the initial dose of methotrexate (taken at the date of first infusion) and the most recent dose of methotrexate, the mean (standard deviation [SD]) dose taken was similar in the Inflectra and Remicade treatment groups. For the initial dose of methotrexate, the mean (SD) dose was 15.60 (3.08) mg/week and 15.61 (3.16) mg/week in the Inflectra and Remicade treatment groups, respectively. For the most recent dose of methotrexate, the mean (SD) dose was 15.41 (2.92) mg/week and 15.54 (3.19) mg/week in the Inflectra and Remicade treatment groups, respectively. Therefore, Inflectra and Remicade patients were well-balanced in terms of concomitant conditions and medications. Please refer to CTD Module 2.7.3, p.38 for details.

Patient Disposition

1077 patients were screened for enrollment into the study, and 606 were randomized. Of the randomized patients 604 patients initiated study treatment (300 Inflectra; 302 Remicade) (Table 4). 233/302 completed treatment with Inflectra while 222/304 completed treatment with Remicade. 69 Inflectra; 82 Remicade) A similar proportion of patients in each treatment group discontinued the study by Week 54 (69 [22.8%] patients and 82 [27.0%] patients in the Inflectra and Remicade treatment groups, respectively). The most frequently reported reasons for discontinuation from the study by Week 54 were adverse events (31 [10.3%] patients and 41 [13.5%] patients in the Inflectra and Remicade treatment groups, respectively) and withdrawal of consent (16 [5.3%] patients and 21 [6.9%] patients in the Inflectra and Remicade treatment groups, respectively) (Table 4). Overall, similar numbers of patients initiated and completed the study. Please refer to CTD Module 2.7.3, p.35-36 for details.

TABLE 4: SUMMARY OF PATIENT DISPOSITION FOR STUDY CT-P13 3.1 (PLANETRA)

Disposition	PLANETRA	
	Inflectra	Remicade
Screened, N	1077	
Randomized, N	302	304
Discontinued, N (%)	69 (22.8%)	82 (27.0%)
***WDAEs,* N (%)**	31 (10.3%)	41 (13.5%)
***Withdrawal due to SAEs,* N (%)**	N/A	N/A
***Lost to follow-up,* N (%)**	3 (1.0%)	2 (0.7%)
All-randomized, N	302	304
Per-protocol, N	246	250
Safety, N	302	300

SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: CSR CT-P13 3.1, Tables 10-1, 11-1

Efficacy Results

ACR20 at Week 30: The primary efficacy endpoint was the proportion of patients achieving clinical response according to the ACR20 criteria at Week 30 and is summarized for the all-randomized and per-protocol populations.

In the all-randomized population, the proportion of patients achieving clinical response according to the ACR20 criteria at Week 30 was similar in the Inflectra and Remicade treatment groups (184 [60.9%] patients and 178 [58.6%] patients, respectively). In the all-randomized population, the 95% CI for the estimate of treatment difference was entirely contained within the range -15% to 15% (95% CI: [-0.06, 0.10]) indicating therapeutic equivalence between the treatment groups (Table 5). In the per-protocol population, the 95% CI for the estimate of treatment difference was between -0.04 and 0.12, supporting the results of the all-randomized population (Table 5). **Therefore, it can be concluded, based on the primary outcome, that Inflectra is therapeutically equivalent to Remicade.**

The response rate for ACR20, ACR50, and ACR70 at Weeks 14, 30, and 54 in the all-randomized and per-protocol populations are presented in Tables 3 and 4 of Appendix 1, respectively.

TABLE 5: PROPORTION OF PATIENTS ACHIEVING CLINICAL RESPONSE ACCORDING TO ACR20 AT WEEK 30 (EXACT BINOMIAL METHOD): ALL-RANDOMIZED AND PER-PROTOCOL (PP) POPULATION

Population	n/N (%)		Estimate of treatment difference[a]	95% CI of treatment difference[b]
	Inflectra	Remicade		
All-Randomized	184/302 (60.9)	178/304 (58.6)	0.02	(-0.06, 0.10)
Per-Protocol	[redacted]	[redacted]	[redacted]	[redacted]

Note: N=the number of subjects with an assessment, n=the number of subjects with the event, (%)=n/N*100

[a] Estimate of the difference in proportions between the two treatment groups (Inflectra – Remicade) using the exact binomial test.

[b] Therapeutic equivalence was concluded if the 95% CI for the difference in proportions between the 2 treatment groups was entirely contained within the range -15% to 15%.

Source: CTD Module 2.7.3, Table 2.7.3-11; CSR CT-P13 Table 11-3

Individual Components of the ACR Criteria - Comparison with Baseline at Weeks 14, 30, and 54: In the all-randomized population, mean decreases from baseline at Week 14, 30 and 54 were generally similar in the Inflectra and Remicade treatment groups for the following ACR components: mean number of tender joints, mean number of swollen joints, mean VAS scores for the patient assessment of pain, mean VAS scores for the patient global assessment of disease activity, mean VAS scores for the physician global assessment of disease activity, mean score for the health assessment questionnaire estimate of physical ability, CRP, and ESR (the latter two were assessed in PD population including 292 and 290 patients, respectively) (Table 6). Similar results were also seen for the per-protocol population (CSR CT-P13 3.1, Post-text Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, 14.2.1.4, 14.2.1.5, 14.2.1.6, 14.2.1.7).

TABLE 6: CHANGE FROM BASELINE IN INDIVIDUAL ACR COMPONENTS AT WEEKS 14, 30, AND 54 FOR INFLECTRA AND REMICADE: ALL-RANDOMIZED POPULATION

ACR component	Inflectra (N = 302) (Mean±SD)	Remicade (N = 304) (Mean±SD)
Number of tender joints		
Baseline	25.6±13.85	24.0±12.91
Week 14	-14.2±11.65	-14.1±11.60
Week 30	-16.3±11.70	-15.6±12.84
Week 54	-16.7±12.08	-15.4±12.30
Number of swollen joints		
Baseline	16.2±8.67	15.2±8.26
Week 14	-10.6±8.40	-10.0±8.01
Week 30	-12.2±8.84	-11.5±9.06
Week 54	-12.3±8.69	-12.0±8.85
Patient assessment of pain (VAS, 0-100)		
Baseline	65.9±17.45	65.5±17.20
Week 14	-28.5±23.90	-27.1±23.49
Week 30	-29.3±25.75	-27.7±25.17
Week 54	-30.6±23.86	-28.7±26.89
Patient global assessment of disease activity (VAS 0-100)		
Baseline	65.7±17.21	65.4±17.00
Week 14	-28.7±23.20	-25.7±24.70
Week 30	-27.7±26.25	-26.8±25.97
Week 54	-30.6±24.41	-26.8±27.76
Physician global assessment of disease activity (VAS 0-100)		
Baseline	64.8±14.20	65.0±13.46
Week 14	-34.4±21.03	-33.2±20.41
Week 30	-35.8±20.44	-35.4±21.18
Week 54	-37.3±21.52	-35.9±22.51
HAQ Physical Ability (scale 0-3)		
Baseline	1.61±0.55	1.56±0.59
Week 14	-0.56±0.56	-0.50±0.52
Week 30	-0.60±0.59	-0.51±0.57
Week 54	-0.61±0.61	-0.53±0.60
CRP (mg/dL)		
Baseline	1.90±2.51	1.89±2.19
Week 14	-0.60±2.94	-0.80±1.93
Week 30	-0.69±2.33	-0.74±1.95
Week 54	-0.68±2.18	-0.64±2.63
ESR (mm/h)		
Baseline	46.5±22.30	48.5±22.60
Week 14	-13.7±20.85	-16.9±19.51
Week 30	-15.3±20.81	-15.7±21.79
Week 54	-12.0±22.00	-15.1±21.71

VAS=visual analogue scale; HAQ=Health Assessment Questionnaire; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate

Source: CTD Module 2.7.3, Table 2.7.3-13; CSR CT-P13 3.1, Post-text Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, 14.2.1.4, 14.2.1.5, 14.2.1.6, 14.2.1.7 (also see these Post-text Tables for EOS results)

DAS28: The observed adjusted mean DAS28 scores are comparable at all assessment times (Weeks 14, 30, and 54) between Inflectra and Remicade regardless of whether they incorporate CRP or ESR in the all-randomized population (Table 7). In addition, their 95% CIs for the estimates of treatment differences all contained 0; hence there was no evidence of a difference between the Inflectra and Remicade treatment groups at the 5% level of significance (Table 7). Similar results were seen for the analysis in the per-protocol population (Appendix 1, Table 5). These results provided additional evidence that Inflectra and Remicade are therapeutically similar.

TABLE 7: ANALYSIS OF DAS28 (ANCOVA) BETWEEN INFLECTRA AND REMICADE: ALL-RANDOMIZED POPULATION

Population	Adjustment Mean (SE)				Estimate of treatment difference[a]	95% CI of treatment difference
	N	Inflectra	N	Remicade		
ESR						
Week 14	[redacted]		[redacted]		[redacted]	[redacted]
Week 30	[redacted]		[redacted]		[redacted]	[redacted]
Week 54	[redacted]		[redacted]		[redacted]	[redacted]
CRP						
Week 14	[redacted]		[redacted]		[redacted]	[redacted]
Week 30	[redacted]		[redacted]		[redacted]	[redacted]
Week 54	[redacted]		[redacted]		[redacted]	[redacted]

Note: Analysis of covariance (ANOVA) model with DAS28 as the response, treatment as a fixed effect, and baseline DAS28, region, and CRP category as covariates. Adjusted least squares means and SE, estimate of treatment difference (Inflectra – Remicade), and 95% CI calculated from the analysis of covariance model.
CI=confidence interval; CRP=C-reactive protein; DAS28=Disease Activity Score 28; ESR=erythrocyte sedimentation rate; SE=standard error
Source: CSR CT-P13 3.1, Table 2 (33 - CT-P13 3.1_Table 2_DAS28 AR ANCOVA.pdf); also see Table 2 for EOS results

EULAR: Table 8 below shows that there were no statistically significant differences between Inflectra and Remicade in the proportions of patients achieving moderate or good responses at each assessment (Weeks 14, 30 and 54) in the all-randomized population for both EULAR (ESR) and EULAR (CRP) measures. Similar results were seen for the analysis in the per-protocol population (Appendix 1, Table 6). **Therefore, these results indicated that patients treated with Inflectra and Remicade experienced similar amount of disease improvement.**

TABLE 8: ANALYSIS OF THE EULAR RESPONSE CRITERIA (PROPORTIONAL ODDS MODEL) BETWEEN INFLECTRA AND REMICADE: ALL-RANDOMIZED POPULATION

	N	No Response[1] n(%)	Moderate Response[2] n(%)	Good Response[3] n(%)	Proportional Odds Model[4]	
					OR	95% CI of OR
EULAR (ESR)						
Week 14						
Inflectra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remicade	[redacted]	[redacted]	[redacted]	[redacted]		
					Score test (P value [redacted])[5]	
Week 30						
Inflectra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remicade	[redacted]	[redacted]	[redacted]	[redacted]		
					Score test (P value [redacted])[5]	

	N	No Response[1] n(%)	Moderate Response[2] n(%)	Good Response[3] n(%)	Proportional Odds Model[4]	
					OR	95% CI of OR
Week 54						
Inflectra	[redacted]					
Remicade						
Score test (P value [redacted])[5]						
EULAR (CRP)						
Week 14						
Inflectra	[redacted]					
Remicade						
Score test (P value [redacted])[5]						
Week 30						
Inflectra	[redacted]					
Remicade						
Score test (P value [redacted])[5]						
Week 54						
Inflectra	[redacted]					
Remicade						
Score test (P value [redacted])[5]						

CI=confidence interval; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; EULAR=European League Against Rheumatism.

Note: N = the number of subjects with an assessment. n = the number of subjects with the event. (%)= n/N*100

[1] Number and percentage of patients indicating No response according to the EULAR criteria.

[2] Number and percentage of patients indicating Moderate response according to the EULAR criteria.

[3] Number and percentage of patients indicating Good response according to the EULAR criteria.

[4] Proportional odds model with EULAR as response, treatment as a fixed effect, and region and C-reactive protein category as covariates.

[5] The proportional odds assumption was evaluated using the Score test evaluated at the 5% significance level.

Source: CSR CT-P13 3.1, Table 3 (34 - CT-P13 3.1_Table 3_EULAR AR.pdf); also see Table 3 for EOS results

[redacted]

In summary, the PLANETRA study demonstrated that Inflectra was therapeutically equivalent to Remicade up to Week 30 in terms of efficacy as determined by clinical response according to the ACR20 criteria. The efficacy results of Inflectra up to Week 54 were also comparable to Remicade for all secondary endpoints.

Safety Results

Adverse Events: Overall, comparable rates and types of treatment-emergent adverse events (TEAEs) were observed in the study. TEAEs were experienced by 70.2% of Inflectra patients and 70.3% of Remicade patients. The most commonly observed adverse events in patients receiving Inflectra were latent TB and upper respiratory tract infection (27 [8.9%] patients each), nasopharyngitis (24 [7.9%] patients), and urinary tract infection (18 [6.0%] patients). The TEAEs most frequently reported for patients in the Remicade treatment group were latent TB (25 [8.3%] patients), urinary tract infection (21 [7.0%] patients), bronchitis, alanine transaminase (ALT) increased, and nasopharyngitis (17 [5.7%] patients each), and upper respiratory tract infection and headache (16 [5.3%] patients each).
While the total number of infections was slightly higher in the Remicade arm and infections of the respiratory tract were more prevalent in the Inflectra arm, the majority of TEAEs due to infection were considered to be unrelated to study treatment. In particular, the higher rate of respiratory tract infection in the Inflectra group was likely the result of a medical history of predisposing risk factors such as chronic bronchitis/chronic obstructive pulmonary disease (COPD), allergic disorders, and uncontrolled diabetes mellitus. The TEAEs due to infection considered to be related to the study treatment and most frequently reported for patients in both treatment groups were latent TB (21 patients, 7.0% and 19 patients, 6.3% in the Inflectra and Remicade treatment groups, respectively). No other TEAEs due to infection considered related to study treatment were reported for more than 5% of patients in either treatment group. [redacted]; furthermore, TB is a known risk of treatment with infliximab (and all anti-TNF therapies) and, therefore, this is not considered to be a new risk (29).

The majority of TEAEs were mild or moderate in severity. Treatment-emergent SAEs (in the following SAEs) were reported for 42 (13.9%) patients and 30 (10.0%) patients in the Inflectra and Remicade groups, respectively, and the difference was due to more SAEs occurring in only 1 patient. The SAEs most frequently (i.e. in more than 1 patient) reported in the Inflectra group were [redacted], infusion-related reaction, [redacted]. A summary of TEAEs is provided in Table 9 below.

[redacted]

TABLE 9: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS: SAFETY POPULATION

	Inflectra 3 mg/kg (N=302)	Remicade 3 mg/kg (N=300)	Total (N=602)
Total number of TEAEs	715	722	1437
Number (%) of patients with at least 1 TEAE	212 (70.2)	211 (70.3)	423 (70.3)
Related	131 (43.4)	134 (44.7)	265 (44.0)
Unrelated	161 (53.3)	158 (52.7)	319 (53.0)
Total number of treatment-emergent SAEs	49	38	87
Number (%) of patients with at least one treatment-emergent SAE	42 (13.9)	30 (10.0)	72 (12.0)
Total number of TEAEs leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]
Number (%) of patients with at least 1 TEAE leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]
Total number of TEAEs due to infection	[redacted]	[redacted]	[redacted]
Number (%) of patients with at least 1 TEAE due to infection	[redacted]	[redacted]	[redacted]
Total number of TEAEs due to infusion-related reactions	[redacted]	[redacted]	[redacted]
Number (%) of patients with at least 1 TEAE due to infusion-related reactions	10 (3.3)	11 (3.7)	21 (3.5)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Note: The total number of TEAEs count included all patient events. At each level of summarization, a patient was counted once if he or she reported 1 or more events. Only the most severe event was counted.
The event was considered to be related if the relationship was defined as "possible," "probable," or "definite."
Source: CTD Module 2.7.4, Tables 2.7.4-29 and 2.7.4-32; CSR CT-P13 3.1, Table 12-2

Infusion-related reactions (SOC General disorders and administration site conditions) was similar in the Inflectra and Remicade groups (10 patients, 3.3% vs. 11 patients, 3.7%, respectively). The events were considered serious in 5 patients in the Inflectra group and in 4 patients in the Remicade group, respectively (CTD Module 2.7.4, Table 2.7.4-15) in the Inflectra and Remicade arms, respectively (note: infusion-related reactions were reported with several different prefer terms, including infusion- related reaction, anaphylactic shock, anaphylactic reaction, and drug hypersensitivity). [redacted]

Laboratory Parameters & Electrocardiogram (ECG): The changes from baseline were generally small and there were no concerning differences in the incidence of patients having grade changes in clinical hematology or chemistry parameters observed as measured by Common Terminology Criteria for Adverse Events (CTCAE).

The majority of patients had normal ECG results at baseline, Week 30, and Week 54. The proportion of patients with a shift from normal or abnormal not clinically significant baseline ECG results to abnormal clinically significant ECG results at Weeks 30 and 54, and the EOS visit was low in each treatment group. Overall, [redacted].

In summary, the CT-P13 3.1 study did not identify new risks with Inflectra that are incompatible with those identified for Remicade.

Immunogenicity: For immunogenicity results, please refer to Section 4.4 and Appendix 1, Tables 9 and 11 below.

4.2.2 PLANETAS (CT-P13 1.1)

a) Study Characteristics

Brief description of the study

PLANETAS was a phase 1, randomized, double-blind, multicentre, multinational, parallel-group study designed to compare the pharmacokinetics, safety and efficacy of innovator infliximab (Remicade) and Inflectra, an infliximab biosimilar, in patients with active AS. The primary endpoint was to demonstrate PK equivalence at steady state of area under the concentration-time curve (AUC_{tau}) and observed maximum serum concentration ($C_{max,ss}$) between Inflectra and Remicade between Weeks 22 and 30. Equivalence was demonstrated if the 90% CIs lied within the equivalence margin of 80-125%. Additional PK, efficacy endpoints, and safety outcomes were also assessed.

Characteristics		Details for PLANETAS
STUDY DESIGN	**Objective**	Pivotal pharmacokinetic study
	Blinding	Double-blind
	Study period	2010-10 to 2012-06
	Study centres	46 sites across 10 countries
	Design	Equivalence
STUDY POPULATION	**Randomized (N)**	250
	Inclusion criteria	1. Patient had a diagnosis of AS according to the 1984 modified New York classification criteria [van der Lindenet al 1984] for at least 3 months prior to Screening. 2. Patients had active disease as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 (range 0 to 10) at Screening in spite of following conventional treatment for AS for at least 3 months prior to Screening.
	Exclusion criteria	1. Patients had previously been administered a biological agent for the treatment of AS. 2. Patients had total ankylosis of the spine, as defined by syndesmophytes present on the lateral views of spinal radiographs (cervical, thoracic, and lumbar) at all intervertebral levels from T6 to S1 within 3 months before Screening. 3. Patients had allergies to any of the excipients of infliximab or to any other murine and human proteins, and patients with a hypersensitivity to immunoglobulin product. 4. Patients had a current or past history of chronic infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus (HIV)-1 or -2 or

Characteristics		Details for PLANETAS
		had a positive result to the screening test for those infections.
DRUGS	**Intervention**	Inflectra (infliximab), 5 mg/kg, administered by 2-h IV infusion, at Weeks 0, 2, 6 and then q8 weeks up to week 54. Patients were pre-medicated with anti-histamine (chlorpheniramine 2–4 mg or dose of equivalent anti-histamine, e.g., 10 mg of cetirizine) 30–60 min prior to the start of infusion at the investigator's discretion.
	Comparator(s)	Remicade (infliximab), 5 mg/kg, administered by 2-h IV infusion, at Weeks 0, 2, 6 and then q8 weeks up to week 54. Patients were pre-medicated with anti-histamine (chlorpheniramine 2–4 mg or dose of equivalent anti-histamine, egg, 10 mg of cetirizine) 30–60 min prior to the start of infusion at the investigator's discretion.
DURATION	**Run-in**	Not applicable
	Treatment	54-week
	Follow-up	Not applicable
OUTCOMES	**Primary End Point(s)**	Area under the concentration-time curve (AUC_{tau}) and observed maximum serum concentration ($C_{max,ss}$) between Inflectra and Remicade between Weeks 22 and 30. Bioequivalence was demonstrated if the 90% CIs lied within the equivalence margin of 80-125%.

	Other End Points	• Secondary PK endpoints
		• Efficacy endpoints were assessed at Weeks 14, 30, and 54 (or at the EOS visit [8 week after last dose] if not obtained at Week 54) and included:
		  ○ Proportion of patients achieving Assessment of SpondyloArthritis International Society-20% (ASAS20) or 40% (ASAS40) responses
		  ○ Ankylosing Spondylitis Disease Activity Score (ASDAS) score
		  ○ Change in BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI) scores versus baseline
		  ○ Change in chest expansion score versus baseline
		  ○ Quality of Life (assessed using the Medical Outcomes Study Short-Form Health Survey (SF-36)
		• Safety
		• Immunogenicity

NOTES	**Publications**	A randomized, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, Mikazane H, Gutierrez-Ureña S, Lim M, Lee YA, Lee SJ, Kim H, Yoo DH, Braun J. Ann Rheum Dis. 2013 Oct;72(10):1605-12 (5). A randomized, double-blind, multicentre, parallel-group, phase 1 study comparing the pharmacokinetics, safety and efficacy of CT-P13 and infliximab in patients with active ankylosing spondylitis: 54 week results from the PLANETAS study [Abstract]. Park W, Jaworski J, Brzezicki J, et al. Ann Rheum Dis 2013;72(Suppl. 3):516. Poster available (30)

Characteristics		Details for PLANETAS
		Biosimilars to treat inflammatory arthritis: the challenge of proving identity. Kay J, Smolen JS. Ann Rheum Dis. 2013 Oct;72(10):1589-93. doi: 10.1136/annrheumdis-2012-203198. Epub 2013 Jul 29 (14). • Clinicaltrials.gov identification code: NCT01220518

Intervention and Comparators

Interventions Employed (e.g. dose, route and frequency of administration, duration, etc.): Patients received 2-h Intravenous infusion of either 5 mg/kg of Inflectra or Remicade at Weeks 0, 2, 6 and then q8 weeks up to week 54. Patients were pre-medicated with anti-histamine (chlorpheniramine 2–4 mg or dose of equivalent anti-histamine, e.g., 10 mg of cetirizine) 30–60 min prior to the start of infusion at the investigator's discretion.

Reference Product used in the Trial: All batches of the reference product, Remicade, used in the trial, was manufactured in the EU (CTD 2.7.1).

Placebos and Controls (if applicable): An active comparator (Remicade) was used in this trial; therefore no placebo was used.

Concomitant Medications: Patients were permitted to receive both oral glucocorticoids (equivalent to ≤10mg daily prednisolone) and non-steroidal anti-inflammatory drugs, if they had received a stable dose for ≥4 weeks prior to screening.

Outcomes (Key Efficacy and Safety Outcomes)

Please note that for the secondary efficacy endpoints listed below, patients were assessed at Weeks 14, 30, and 54 (or the EOS visit if different from Week 54).

ASAS20: the ASAS20 response rate is defined as the percent of patients achieving an improvement of at least 20% and an absolute improvement of at least 10 units on a 0 to 100 scale or 1 unit on a 0 to 10 scale from baseline in at least 3 of the following domains:

- Patient global assessment of disease status
- Patient assessment of spinal pain
- Function according to BASFI
- Morning stiffness determined using the last 2 questions of BASDAI

Additionally, ASAS20 responders should not have deterioration (worsening of ≥20% and an absolute worsening of at least 10 units on a 0 to 100 scale or 1 unit on a 0 to 10 scale) of the remaining assessment domain compared to baseline (31).

The BASFI consists of a 1 – 10 scale measuring functional anatomical limitations and the patients' ability to cope with everyday life (1 being no problem and 10 being the worst problem) in to 10 questions asked:

1. Putting on your socks or tights without help or aids (e.g. sock aids)?
2. Bending forward from the waist to pick up a pen from the floor without an aid?
3. Reaching up to a high shelf without help or aids (e.g. helping hand)?
4. Getting up out of an armless dining room chair without using your hands or any other help?

5. Getting up off the floor without any help from lying on your back?
6. Standing unsupported for 10 minutes without discomfort?
7. Climbing 12-15 steps without using a handrail or walking aid (one foot on each step)?
8. Looking over your shoulder without turning your body?
9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports)?
10. Doing a full day activities whether it be at home or work?

The mean of the ten scales gives the BASFI score – a value between 0 and 10 (32).
The BASDAI consists of a 1 - 10 scale measuring discomfort, pain, and fatigue (1 being no problem and 10 being the worst problem) in response to six questions asked of the patient pertaining to the five major symptoms of AS:

- Fatigue
- Spinal pain
- Arthralgia (joint pain) or swelling
- Enthesitis, or inflammation of tendons and ligaments (areas of localized tenderness where connective tissues insert into bone)
- Morning stiffness duration
- Morning stiffness severity

To give each symptom equal weighting, the average of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease (33).

ASAS40: ASAS40 responder are defined as an improvement of at least 40% and an absolute improvement of at least 2 units on a 0 to 10 scale from baseline in at least 3 of the 4 domains of the ASAS20, with no deterioration from baseline in the remaining domain (34).

Immunogenicity: immunogenicity was tested using both the CT-P13 (Inflectra) tag and infliximab (Remicade) tag. Antibodies against CT-P13 or RMP were measured using an electrochemiluminescent immunoassay method.

Safety: the key safety outcomes included incidence and type of adverse events (AEs) and infection, serious AEs, incidence of infusion-related reactions and changes from baseline in clinical laboratory parameters. AEs were coded using the Medical Dictionary for Regulatory Activities and severity was characterised as mild, moderate or severe.

Other efficacy outcomes reported:

- ASDAS score
- Change in BASDAI, BASFI and BASMI scores versus baseline
- Change in chest expansion score versus baseline
- Medical Outcomes Study Short-Form Health Survey (SF-36)

Statistical Analyses

Statistics Protocol for PK Equivalence: The primary outcome in the pivotal PLANETAS was to demonstrate PK equivalence (i.e. bioequivalence), and as such, efficacy outcomes were not subjected to equivalence and/or non-inferiority testing. The statistical protocol for demonstrating bioequivalence is presented in Section 4.3 below. Briefly, the PK parameters used to demonstrate bioequivalence were AUC_{tau} and observed $C_{max,ss}$ between Inflectra and Remicade between Weeks 22 and 30 (at steady state).

Equivalence was demonstrated if the 90% CIs of ratio of geometric means for both parameters contained entirely within the equivalence margin of 80-125%. Please refer to CTD Module 2.5 (Section 2.5.3.1.1, p.23-26) for additional details.

Rationale for the PK Equivalence Margin Used: The rationale for the study design and equivalence margins used for AUC_{tau} and $C_{max,ss}$ are in accordance with the Guideline on the Investigation of Bioequivalence (CHMP/EWP/QWP 1401/98 Rev. 1/Corr **) (35), Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005) (36), and is reflective of the principles set out in the draft Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies (EMA/CHMP/BMWP/403543/2010) (37). In addition, scientific advice from the CHMP and Canadian national regulatory authorities (see CTD Module 2.5.1.4, Table 2.5-5) were taken into account.

AUC is defined as the area under the plasma concentration-time curve over a dosing interval (AUC_{tau}). Equivalence margins of 80 - 125% have been prospectively defined in the protocol for AUC_{tau} as well as for $C_{max,ss}$. A standard acceptance range of 0.80 to 1.25 for AUC_{tau} and $C_{max,ss}$ is considered appropriate from a clinical perspective for infliximab since a broad therapeutic window exists. This is exemplified by the fact that no apparent dose-response relationship has been found for the overall incidence of adverse reactions in the clinical development program as well as post-marketing safety surveillance, even for doses up to 20 mg/kg. Furthermore, although data in AS and PsO patients are limited, the safety profile in AS and PsO patients who receive higher doses is very similar to that observed in patients with RA who receive lower doses of infliximab. Please refer to CTD Module 2.5 (Section 2.5.3.1.1, p.23-26) for additional details.

Analysis Sets (e.g., intention to treat or per-protocol): All randomly assigned patients were included in the all-randomized population. The PK population consisted of all patients who received at least the first five doses of study treatment and provided an end of infusion sample and at least one post-treatment PK sample to facilitate calculation of AUC_{tau} and $C_{max,ss}$. The PK population included only patients who did not have any major protocol deviations. The safety population consisted of all patients who received at least one (full or partial) dose of either of the study treatments during any dosing period irrespective of their randomization. Additional details can be found in CSR CT-P13 1.1, Section 9.7.1.2 (p.60-61).

Reference Locations:

1. For the description of the statistical protocol for PK equivalence (bioequivalence) testing, please refer to CTD Module 2.5 (Section 2.5.3.1.1, p.23-26)
2. For the description of the rationale for the therapeutic equivalence margins used, please refer to CTD Module 2.5 (Section 2.5.3.1.1, p.23-26)
3. For description of the analysis set, please refer to CSR CT-P13 1.1, Section 9.7.1.2 (p.60-61).

b) Results

Baseline Characteristics

TABLE 9: MAJOR/RELEVANT DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR STUDY CT-P13 1.1 (PLANETAS): ALL-RANDOMIZED POPULATION

	Inflectra 5 mg/kg (N = 125)	Remicade 5 mg/kg (N = 125)
Age, years	38.0 (18–69)	38.0 (18–66)
Gender, no (%)		
Male	99 (79.2)	103 (82.4)
Female	26 (20.8)	22 (17.6)
Ethnicity, no (%)		
Caucasian	97 (77.6)	92 (73.6)
Asian	16 (12.8)	13 (10.4)
Other	12 (9.6)	20 (16.0)
Height (cm)	172.0 (148–198)	171.0 (147–193)
Weight (kg)	72.7 (45.0–120.0)	76.0 (45.5–122.7)
BMI (kg/m^2)	24.4 (18.0–38.7)	25.6 (17.5–42.0)
Region, no (%)		
European	81 (64.8)	81 (64.8)
Non-European	44 (35.2)	44 (35.2)
BASDAI (stratification factor), no (%)		
<8	92 (73.6)	95 (76.0)
≥8	33 (26.4)	30 (24.0)
BASDAI score, 0–10	6.8 (3.4–10.0)	6.6 (1.8–10.0)
BASFI score, 0-10	6.3 (0.7–9.8)	6.3 (0.1–10.0)
BASMI score, 0-10	4.0 (0.0–9.0)	4.0 (0.0–9.0)
Chest expansion (cm)	3.0 (0.5-9.0)	2.5 (0.0-7.0)

*Except where indicated otherwise, values are presented as median (minimum, maximum).
BMI=body mass index; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index
Source: CTD 2.7.3, Tables 2.7.3-29 and 2.7.3-30; CSR CT-P13 1.1, Table 11-2, Post-text Table 14.2.2.3 (BASDAI), Post-text Table 14.2.2.4 (BASFI), Post-text Table 14.2.2.5 (BASMI), Post-text Table 14.2.2.6 (Chest expansion)

Demographic and baseline characteristics were similar in the 2 treatment groups. In total, there were a greater percentage of male patients compared with female patients, i.e. 99/125 (79.2%) in the Inflectra group and 103/125 (82.4) in the Remicade group. Mean age was 39.2 years in the Inflectra group and 38.7 years in the Remicade group. The majority of patients were Caucasian (75.6%) and from European region (64.8%).

BASDAI scores were also comparable between groups: the majority of patients (187 [74.8%]) had a baseline BASDAI score of ≤8 (92 [73.6%] patients and 95 [76.0%] patients in the Inflectra and Remicade treatment groups, respectively). The BASDAI score at baseline was >8 in 33/125 (26.4%) and in 30/125 (24.0%) in the Inflectra and Remicade group, respectively.

Concomitant Conditions and Medications: [redacted]

Patient Disposition

Of 370 patients screened in PLANETAS, 250 were randomized to receive Inflectra (N=125) and Remicade (N=125), respectively (Table 10). All patients initiated treatment. By Week 54, 40/250 (16.0%) patients had discontinued, 19/125 (15.2%) in the Inflectra group and 21/125 (16.8%) in the Remicade group. Primary reasons for discontinuations were adverse events occurring in 10/125 (8.0%) in the Inflectra group and in 8/125 (6.4%) in the Remicade group, withdrawal of consent (3/125 [2.4%] in the Inflectra group and 6/125 [4.8%] in the Remicade group), lost to follow-up (2/125 [1.6%] patient in the Remicade group), investigator's decision (1/125 [0.8%] in each group), and sponsor's decision (2/125 [1.6%] in the Inflectra group), lack of efficacy (2/125 [1.6%] in the Inflectra group), malignancy (1/125 [0.8%] in the Inflectra group), death (2/125 [1.6%] patient in the Remicade group), and protocol violation (1/125 [0.8%] patient in the Remicade group). No patient discontinued due to life-threatening infusion-reaction, diabetes mellitus or pregnancy. Overall, similar numbers of patients initiated and completed the study. Please refer to CTD Module 2.7.3, p.52 for details.

TABLE 10: SUMMARY OF PATIENT DISPOSITION FOR STUDY CT-P13 1.1 (PLANETAS)

Disposition	Provide Study Name	
	Inflectra	Remicade
Screened, N	370	
Randomized, N	125	125
Discontinued, N (%)	19 (15.2)	21 (16.8%)
***WDAEs,* N (%)**	10 (8.0%)	8 (6.4%)
***Withdrawal due to SAEs,* N (%)**	N/A	N/A
***Lost to follow-up,* N (%)**	0 (0%)	2 (1.6%)
All-randomized, N	125	125
Pharmacokinetic, N	113	110
Safety, N	128	122

SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: CSR CT-P13 1.1, Tables 10-1, 11-1

Efficacy Results

ASAS20: A highly similar proportion of patients achieved clinical response according to the ASAS20 criteria at Weeks 14, 30, and 54 between Inflectra and Remicade groups. ASAS20 response was achieved by 72/115 (62.6%) patients in the Inflectra group and by 79/122 (64.8%) patients in the Remicade group at Week 14. At Week 30, comparable ASAS20 response was also achieved between Inflectra (79/112 ([70.5%]) and Remicade (84/116 [72.4%]) groups. Finally, at Week 54, ASAS20 response was achieved in 71/106 (67.0%) patients in the Inflectra group and 75/108 (69.4%) patients in the Remicade group. Statistical analysis indicated that there was no significant difference between treatments at Weeks 14, 30, and 54 (Table 11).

ASAS40: At Week 14, ASAS40 response was achieved by 48/115 (41.7%) patients in the Inflectra group and by 56/122 (45.9%) in the Remicade group. At Week 30, ASAS40 response was achieved by 58/112 (51.8%) patients in the Inflectra group and by 55/116 (47.4%) in the Remicade group. At Week 54, ASAS40 response was achieved by 58/106 (54.7%) patients in the Inflectra group and by 53/108 (49.1%) in the Remicade group (see Table 2.7.3-20). Statistical analysis indicated that there was no significant difference between treatments at Weeks 14, 30, and 54 (Table 11).

TABLE 11: PROPORTION OF PATIENTS ACHIEVING CLINICAL RESPONSE ACCORDING TO THE ASAS20 AND ASAS40 CRITERIA (WEEKS 14, 30, AND 54): ALL-RANDOMIZED POPULATION

Visit	Efficacy Parameter	Inflectra Responders	Remicade Responders	OR[1]	95% CI of the OR
Week 14	ASAS20	72/115 (62.9)	79/122 (64.8)	0.91	0.53, 1.54
	Goodness-of-fit test (P=0.819)[2]				
	ASAS40	48/115 (41.7)	56/122 (45.9)	0.85	0.51, 1.42
	Goodness-of-fit test (P=0.875)[2]				
Week 30	ASAS20	79/112 (70.5)	84/116 (72.4)	0.91	0.51, 162
	Goodness-of-fit test (P=0.854)[2]				
	ASAS40	58/112 (51.8)	55/116 (47.4)	1.19	0.70, 2.00
	Goodness-of-fit test (P=0.893)[2]				
Week 54	ASAS20	71/106 (67.0)	75/108 (69.4)	0.89	0.50, 1.59
	Goodness-of-fit test (P=0.360)[2]				
	ASAS40	58/106 (54.7)	53/108 (49.1)	1.26	0.73, 2.15
	Goodness-of-fit test (P=0.543)[2]				

ASAS20, Assessment of SpondyloArthritis International Society 20% improvement scale; ASAS40, Assessment of SpondyloArthritis International Society 40% improvement scale; CI, confident interval
[1] Odds ratio estimated using a logistic regression model with treatment as a fixed effect and region and baseline BASDAI score as covariates.
[2] P value calculated using the Hosmer-Lemeshow test for the goodness-of-fit of the logistic regression model. The test was significant at the 5% level.
Source: CSR Post-text Tables 14.2.2.1 and 14.2.2.2 for EOS results; CTD Module 2.7.3, Table 2.7.3-20

Therefore, the above ASAS20 and ASAS40 results showed that Inflectra and Remicade are therapeutically similar.

BASDAI, BASFI, BASMI, and Chest Expansion : The mean±SD baseline score of Inflectra and Remicade for BADAI, BASFI, BASMI, and chest expansion are 6.74±1.4.13 vs. 6.57±1.636; 6.20±1.928 vs. 6.24±2.207; 4.0±2.07 vs. 4.1±2.05; and 3.16±1.330cm vs. 2.87±1.253cm, respectively, indicating comparable disease activity levels for patients in both groups. **For all 3 scores, the mean decrease from baseline to each of the evaluation time points was comparable between the Inflectra and Remicade treatment groups** (CTD Module 2.7.3, Table 2.7.3-21; CSR CT-P13 1.1 Post-text Tables 14.2.2.3, 14.2.2.4, 14.2.2.5, 14.2.2.6).

Safety Results

Adverse Events: Comparable rates and types of TEAEs were observed in the PLANETAS study. TEAEs were experienced by 93 (72.7%) of Inflectra patients and 82 (67.2%) of Remicade patients (Table 12). The TEAEs most frequently reported for patients in the Inflectra group were ALT increased (19 [14.8%] patients), AST increased (16 [12.5%] patients), and nasopharyngitis (12 [9.4%] patients). The TEAEs most frequently reported for patients in the Remicade treatment group were ALT increased (19 [15.6%] patients), AST increased (13 [10.7%] patients), and upper respiratory tract infection (13 [10.7%] patients) (CSR CT-P13 1.1, Table 12-3). No other TEAEs were reported for more than 10% of patients in either treatment group. The increase in AST and ALT were comparable between the treatment groups.

The proportion of patients who experienced at least 1 TEAE due to infection was similar between groups (Inflectra: [redacted] patients vs. Remicade: [redacted]) (Table 12). The TEAEs due to infection most frequently reported for patients were nasopharyngitis (12 [9.4%] vs. 10 [8.2%]) and upper respiratory tract infection (10 [7.8%] vs. 13 [10.7%] in Inlfectra and Remicade groups, repectively). Other common

TEAEs included urinary tract infection and latent TB (reported for 8 [6.3%] patients each) in the Inflectra group; and upper respiratory tract infection (13 [10.7%] patients), nasopharyngitis (10 [8.2%] patients), and pharyngitis (7 [5.7%] patients) in the Remicade group. The TEAEs due to infection considered by the investigator to be related to the study treatment and most frequently reported for patients in both treatment groups were latent TB (Inflectra: [redacted] and Remicade: [redacted]) (CSR CT-P13 1.1, Table 12-4). No other TEAEs due to infection considered by the investigator to be related to study treatment were reported for more than 4% of patients in either treatment group. At the time of unblinding the study at Week 30 for reporting, [redacted].

The proportion of patients who experienced at least 1 treatment-emergent SAE was similar in the 2 treatment groups (Inflectra: [redacted] patients vs. Remicade: [redacted] patients). No treatment-emergent SAEs were reported for more than 1 patient in the Inflectra group. The most frequently reported treatment-emergent SAE in the Remicade group was infusion-related reaction ([redacted] patients). The most frequently reported treatment-emergent SAEs considered to be related to study treatment were infusion-related reactions in the Remicade group ([redacted] patients). All other drug-related treatment-emergent SAEs occurred in only 1 patient in either treatment group. A summary of TEAEs are provided in Table 12.

Most reported TEAEs were mild or moderate in intensity. Drug-related severe TEAEs occurred in 3 (2.3%) and 5 (4.1%) patients in the Inflectra and Remicade treatment groups, respectively, as determined by investigators. The most frequent severe TEAEs were GGT increased and myocardial infarction, which were reported for patients in each treatment group (each reported for [redacted] patient in both the Inflectra and Remicade treatment groups; only GGT increased were considered drug-related in both groups). No other severe TEAEs were reported for more than 1% of patients in either treatment group.

[redacted].

TABLE 12: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS: SAFETY POPULATION

	Inflectra 5 mg/kg (N=128)	Remicade 5 mg/kg (N=122)	Total (N=250)
Total number of TEAEs	350	365	715
Number (%) of patients with at least 1 TEAE	93 (72.7)	82 (67.2)	175 (70.0)
Related	62 (48.4)	63 (51.6)	125 (50.0)
Unrelated	[redacted]	[redacted]	[redacted]
Total number of treatment-emergent SAEs	[redacted]	[redacted]	[redacted]
Number (%) of patients with at least one treatment-emergent SAE	[redacted]	[redacted]	[redacted]
Total number of TEAEs leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]
Number (%) of patients with at least 1 TEAE leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]

	Inflectra 5 mg/kg (N=128)	Remicade 5 mg/kg (N=122)	Total (N=250)
Total number of TEAEs due to infection	[redacted]	[redacted]	[redacted]
Number (%) of patients with at least 1 TEAE due to infection	[redacted]	[redacted]	[redacted]
Total number of TEAEs due to infusion-related reactions	[redacted]	[redacted]	[redacted]
Number (%) of patients with at least 1 TEAE due to infusion-related reactions	[redacted]	[redacted]	[redacted]

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Note: The total number of TEAEs count included all patient events. At each level of summarization, a patient was counted once if he or she reported 1 or more events. Only the most severe event was counted.
The event was considered to be related if the relationship was defined as "possible," "probable," or "definite."
Source: (CSR: CT-P13 1.1, Table 12-2)

Infusion-related reactions were reported with several different AE terms, including infusion-related reaction and drug hypersensitivity. No patients in the Inflectra group experienced TEAEs due to infusion. In the Remicade group, [redacted] patients that experienced TEAEs due to infusion of drug were permanently discontinued from the study (CTD Module 2.7.4, Table 2.7.4-39).

Laboratory Parameters & ECG: In this study, the majority of patients had no CTCAE grade, CTCAE grade 1, or grade 2 results as their lowest or highest post-baseline laboratory result for each laboratory parameter and time point. [redacted] patients in the Inflectra and Remicade treatment groups, respectively) had grade 4 (life-threatening) results as their lowest or highest post-baseline laboratory result during the study. None of these laboratory results were considered by the investigator to be SAEs. For [redacted] these patients, these laboratory results were reported as AEs.

With respect to ECG, majority of patients were in normal range, and no significant baseline ECG result was found at each time point. No abnormal, clinically significant ECG results were reported in either treatment groups at Week 30, 54, and EOS visit.

In summary, the CT-P13 1.1 study did not identify new risks with Inflectra that are incompatible with those identified for Remicade.

Immunogenicity: For immunogenicity results, please refer to Section 4.4 and Appendix 1, Tables 10 and 12 below.

4.2.3 Summary of Safety

a) Safety Evaluation Plan (CTD Module 2.7.4, Section 2.7.4.1.1)

The objective of the clinical development program for Inflectra was to demonstrate that Inflectra is comparable to the reference medicinal product, Remicade, in terms of its clinical pharmacology, efficacy and safety. In view of the structural, biological, toxicological and PK comparability to the reference drug product Remicade (Section 3.2.R and Section 2.4), Inflectra is expected to display a comparable safety profile. Therefore, the safety evaluation plan was based on the safety profile of Remicade as presented in the SmPC and published data.

The majority of the safety experience reported with Remicade in clinical trials comes from patients with RA and Crohn's disease. In these trials, the most common adverse drug reaction (ADR) reported was upper respiratory tract infection and the most serious ADRs include HBV reactivation, congestive heart failure, and infections (e.g. viral infections such as influenza, herpes). Infusion-related reaction was also

seen with the use of Remicade (18% vs. 5% for placebo-treated patients). Cases of malignancies were also reported from clinical studies and post-marketing surveillance. Anti-dsDNA antibodies were newly detected in infliximab-treated patients but not in placebo-treated patients.

In view of these ADRs, safety-monitoring protocols, in addition to commonly employed procedures, also include hypersensitivity via vital sign, clinical laboratory tests (including ESR and C-reactive protein CRP), signs and symptoms of TB, infections, and infusion-related reactions, were closely monitored. The immunogenicity of Inflectra was assessed by measuring anti-infliximab antibodies, and anti-nuclear anti-double stranded DNA antibodies were measured at pre-defined endpoints. These safety parameters were chosen based on the safety profile of the reference medicinal product Remicade.

b) Safety Populations Evaluated (CTD Module 2.7.4, Section 2.7.4.1.1)

The safety population consisted of 871 patients who were treated with at least 1 dose (full or partial) Inflectra or Remicade during any dosing period. **Study CT-P13 3.1 (PLANETRA)** was a phase 3, pivotal equivalent efficacy and safety study in 606 adults with active RA not receiving adequate response with MTX alone. The safety population included 602 patients (Inflectra: 302 Remicade: 300). In the Inflectra and Remicade groups, the average ages were 48.9 and 48.6 y.o.; predominantly female: 245/302 and 255/300, and predominately Caucasian: 220/302 and 219/300, respectively. **Study CT-P13 1.1 (PLANETAS)** was a phase 1, pivotal equivalent PK study in 250 adults with AS. The safety population included 250 patients (Inflectra: 128 Remicade: 122). In the Inflectra and Remicade groups, the average ages were 39.1 and 38.7 y.o.; predominantly male: 102/128 and 100/122, and predominately Caucasian: 98/128 and 91/122, respectively. **Study CT-P13 1.2** was a pilot study in 19 adults with active RA not receiving adequate response with MTX alone. The safety population included 19 patients (Inflectra: 9 Remicade: 9). In the Inflectra and Remicade groups, the average ages were 51.6 and 47.1 y.o.; predominantly female: 8/9 and 9/9, and all were Asians, respectively.

According to the EMA "Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for Treatment of Rheumatoid Arthritis" report, 300-600 patients should usually be exposed to the proposed marketing dose of a new medicinal product for 6 months and at least 100 patients exposed at this dose or above for a minimum of 12 months. In the case of a biosimilar a smaller data base might be acceptable on the basis of having demonstrated biosimilarity though an orthogonal approach based on demonstrating similarity in terms of physicochemical, biological, non-clinical, PK, PD, and therapeutic clinical data, which has been completed in the case of Inflectra against Remicade. In addition, Delabaye *et al*. (38) demonstrated that the highest numbers of AEs and SAEs were observed during the first 26 weeks of treatment with infliximab. Therefore, it is considered justified to compare the safety profile of Inflectra and Remicade on the basis of data from 233 patients with RA and 106 patients with AS exposed to Inflectra for 54 weeks of treatment.

c) Overview of Safety

The following section includes discussion of safety results from the 2 studies (CT-P13 3.1 and CT-P13 1.1) presented above, as well as those take from a phase 1 pilot RA study (CT-P13 1.2). For study details, please refer to Module 2.7.3, Section 2.7.3.2.2.2.

Overall, the safety population consisted of 871 patients (1 of which was excluded from analysis, see Table 13 footnote) who were treated with at least 1 dose (full or partial) Inflectra or Remicade during any dosing period across the 3 studies. These were 621 patients with active RA (thereof, 311 treated with Inflectra and 309 with Remicade; 1 patient with protocol violation) as well as 250 patients with acute AS (thereof, 128 treated with Inflectra and 122 with Remicade).

Across the 2 pivotal studies, the most common TEAEs (in ≥4% patients) that are presented in both the RA and AS subjects include latent tuberculosis, nasopharyngitis, urinary tract infection, upper respiratory tract infection, and headache. As expected, the total incidence of these TEAEs across the 3 studies are comparable between the Inflectra and the Remicade treatment groups (Table 13).

TABLE 13: INCIDENCE OF MOST COMMON TEAES (REPORTED IN ≥4% OF PATIENTS) PRESENTED IN BOTH CT-P13 3.1, CT-P13 1.1, AND CT-P13 1.2 FOR INFLECTRA (IFT) AND REMICADE (RMP) – NUMBER (%) OF PATIENTS

	CT-P13 3.1		CT-P13 1.1		CT-P13 1.2		ALL[2]	
	IFT 3 mg/kg	RMP 3 mg/kg	IFT 5 mg/kg	RMP 5 mg/kg	IFT 3 mg/kg	RMP[1] 3 mg/kg	IFT	RMP
	N=302	N=300	N=128	N=122	N=9	N=9	**N=439**	**N=431**
Latent tuberculosis	27 (8.9)	25 (8.3)	8 (6.3)	5 (4.1)	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	24 (7.9)	17 (5.7)	12 (9.4)	10 (8.2)	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	18 (6.0)	21 (7.0)	8 (6.3)	1 (0.8)	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	27 (8.9)	16 (5.3)	10 (7.8)	13 (10.7)	[redacted]	[redacted]	[redacted]	[redacted]
Headache	13 (4.3)	16 (5.3)	10 (7.8)	7 (5.7)	[redacted]	[redacted]	[redacted]	[redacted]

[1]One patient out of the original 10 was excluded from analysis since she received a mislabeled drug but was not discontinued
[2]Sum of patients across 3 studies for Inflectra and Remicade
Source: CTD Module 2.7.4, Tables 2.7.4-9, 2.7.4-10, 2.7.4-11

When examining drug-related TEAEs, across the 2 pivotal studies, mutual TEAEs that were reported in ≥1% patients that are presented in both the RA and AS studies include: latent TB, ALT increased, AST increased, nasopharyngitis, upper respiratory tract infection, urinary tract infection, headache, pyrexia, bronchitis and infusion-related reaction (CTD Module 2.7.4, Tables 2.7.4-12, 2.7.4-14). In addition, across these 2 studies, the majority of the drug-related TEAEs were of mild to moderate severity and their incidences (number of patients experiencing AEs) were comparable between the treatment groups ([redacted]) (CTD Module 2.7.4, Tables 2.7.4-26, 2.7.4-28). Across the 3 studies, drug-related TEAEs leading to premature discontinuation of the study occurred in [redacted] of patients in the Inflectra and Remicade groups, respectively (CTD Module 2.7.4, Tables 2.7.4-35, 2.7.4-36, 2.7.4-37). [redacted] (BSEAR Clinical report, p.268). As with all anti-TNF therapies, TB is a clearly defined safety concern and no concerns exceeding existing knowledge were identified with Inflectra (29). In addition, majority of the patients (Eastern Europeans, South Americans, and Asians) in the pivotal trials were from countries with higher incidence of TB relative to North America (39).

Across the 2 pivotal studies, infusionrelated reactions were reported in 14 patients distributed equally in the two treatment arms (Inflectra = 7: Remicade = 7) (see *Attachment #2: Response to Clinical Clarifax Dated 05 July 2013 – Part I* attached in the BSEAR Clinical report, p.255-262). There were no TEAE reports of systemic lupus erythematosus / lupus-like syndrome or "lymphoproliferative disorders" either in the Inflectra or the Remicade treatment groups across the 3 studies (CTD Module 2.7.4, Sections 2.7.4.2.1.4.2.3 and 2.7.4.2.1.4.2.9). The results of clinical laboratory parameters were comparable

between the treatment groups across all 3 studies (CTD Module 2.7.4, Section 2.7.4.3). With regard to vitals, hypersensitivity monitoring, physical examination, ECG, immunogenicity testing, tuberculosis assessment, and IFN-γ release assay there were no notable differences observed between Inflectra and Remicade across the pivotal studies (CTD Module 2.7.4, Section 2.7.4.4). Overall, across all 3 studies, the types and incidence of AEs were comparable between Inflectra and Remicade.

Safety of Special Interest: Seroconversion

It was noted that a higher proportion of RA patients developed ADAs (i.e. seroconverted) relative to AS patients despite the fact that RA patients received concomitant MTX treatment. Specifically, the proportion of seroconverted AS patients in Study 1.1 was 44/128 (34.4%) in the Inflectra group and 39/122 (32.0%) in the Remicade group; and the proportion of seroconverted RA patients in Study 3.1 was 168/302 (55.6%) in the Inflectra group and 163/300 (54.3%) in the Remicade group. The total numbers of seroconverted patients in each indication were thus 83/250 (33.2%) for AS patients and 331/602 (55.0%) for RA patients. Indeed, in the only direct (i.e. intra-study) evaluation of the effect of MTX-co-administration in RA versus AS infliximab-treated patients, 9/17 (53%) of RA patients and 25/91 (27%) of AS patients received concomitant MTX (40). Infliximab dose was per the approved regimen: RA patients, 3 mg/ kg at Weeks 0, 2, 6 and 14 and every 8 weeks thereafter; AS patients received 5 mg/kg at Weeks 0, 2, 6 and 12 and every 6 Weeks thereafter. Antibodies toward infliximab were noted in 14/91 (15%) AS patients and 7/17 (41%) RA patients. Although this was a relatively small study (RA n=17; AS n=91), the difference in the proportions of antibody-positive AS and RA patients was similar to the two Inflectra trials above.

The reason for the above observations could be two-fold. First, the underlying differences between RA and AS affects susceptibility to antibody formation. Specifically, it has been speculated that genetic predisposition plays a disease-specific role in the development of ADAs (41-44). Second, several studies have found that ADA formation is inversely proportional to dose. For example, In the Remicade registration trial, ATTRACT, 53%, 21%, and 7% of the patients in the cohorts receiving 1 mg/kg, 3 mg/kg, or 10 mg/kg, respectively, developed antibodies to infliximab (and concomitant MTX therapy reduced the rate of antibody formation to 15%, 7%, and 0%, respectively), suggesting a phenomenon resembling tolerance (28, 45, 46). The development of tolerance could partially explain the reduced immunogenicity in AS versus RA; the approved infliximab dose for AS is 5 mg/kg at Week 0, 2, 6 and then every 8 weeks - two-thirds higher than that for RA (3 mg/kg).

Therefore, the observed ADA levels between RA and AS patients in the two Inflectra trials could likely be the balance of several underlying operating mechanisms. A full description of the above can be found in the response to Clarifax portion of the BSEAR Clinical report (p.318-321).

Conclusion

In summary, Inflectra is effective and well tolerated. No new safety issues that have not been previously observed with Remicade were presented in either the RA or AS pivotal studies.

4.3 Manufacturer-submitted information on Pharmacokinetics

The primary objective of the pivotal CT-P13 1.1 (PLANETAS) study was to demonstrate PK equivalence at steady state for the primary outcomes of AUC_{tau} and $C_{max,ss}$ between Inflectra and Remicade between Weeks 22 and 30. “Equivalence” was demonstrated if the 90% CIs of ratio of geometric means for both parameters contained entirely within the equivalence margin of 80-125%.

Table 14 below shows that both AUC_{tau} and $C_{max,ss}$ are essentially identical between Weeks 22 and 30. In addition, the 90% CIs of these parameters' ratios lie entirely with the equivalence margin of 80-125%, thus demonstrating that Inflectra **could not be distinguished from the reference product Remicade estimated at steady-state using a non-compartmental analysis**. For the main secondary PK parameters after Dose 5 (Week 22), including half-life, clearance, volume of distribution, the 90% CIs of the geometric mean ratios also lay within the 80% - 125% limits, further supporting the PK similarity of both products. Mean serum PK parameters (C_{max}, C_{min}, T_{max}) between Weeks 0 and 54 (Doses 1 to 9) are presented in Table 7 of Appendix 1. Secondary PK parameters between Weeks 22 and 30 are presented in Table 8 in Appendix 1.

TABLE 14: SERUM PK PARAMETERS OF THE PK POPULATION BETWEEN WEEKS 22 AND 30 (AT STEADY-STATE) FROM STUDY CT-P13 1.1 (PLANETAS)

Pharmacokinetics	Inflectra (5 mg/kg)		Remicade (5 mg/kg)		Comparison of SEB versus Reference Product
	n	Geometric Mean	n	Geometric Mean	Ratio (%) of geometric means [90% CI of ratio (%)]
AUC_{tau} (µgh/ml)	112	32751.0	110	31366.0	104.4 [94.3 – 115.7]
$C_{max,ss}$ (µg/ml)	113	147.0	110	144.8	101.5 [94.7 – 108.9]
$T_{1/2}$ (h)	102	280.0	98	286.1	97.9 [90.8 – 105.5]
$C_{min,ss}$ (µg/ml)	108	2.5	108	2.3	109.2 [85.7 – 139.1]

AUC_{tau} = area under the curve at steady-state between dosing at Weeks 22 and 30; CI = confidence interval;
$C_{max,ss}$, $C_{max,ss}$ = maximum and minimum concentration at steady-state, respectively; $T_{1/2}$ = terminal elimination half-life
Source: CTD Module 2.5.3.1.1, Table 2.5-9; CSR CT-P13 1.1, Table C41

Study CT-P13 3.1 provided supportive PK information in its secondary endpoints. The geometric means of C_{max} and T_{max} appeared similar between both products in the PK population at Weeks 30 and 54 as shown in Table 15 below. Additional PK parameters between Weeks 0 and 54 are presented in CSR CT-P13 3.1 Table 11-14 and Post-text Table 14.2.7.3A. Further conclusions regarding the PK similarity between Inflectra and Remicade can be found on p.66 of the BSEAR PK/PD report.

TABLE 15: GEOMETRIC MEAN (%CV) OF C_{MAX} AND MEDIAN (RANGE) OF T_{MAX} AT WEEKS 30 AND 54 BETWEEN INFLECTRA AND REMICADE: PK POPULATION (CT-P13 3.1, PLANETRA)

Pharmacokinetics	Inflectra (3 mg/kg) (N = 290)		Remicade (3 mg/kg) (N =288)	
Week 30				
C_{max} (µg/ml)	n = 241	83.5 (38.1)	n = 244	83.8 (34.9)
T_{max} (h)*	n = 241	2.08 (2.00, 3.50)	n = 244	2.22 (0.10, 3.33)
Week 54				
C_{max} (µg/ml)	n = 211	75.3 (37.6)	n = 208	69.2 (32.5)
T_{max} (h)*	n = 211	2.12 (2.00 3.18)	n = 208	2.08 (1.92, 3.32)

$C_{max,ss}$ = Maximum serum concentration at steady state, *T_{max}=Time to reach maximum concentration; reported as median (minimum, maximum)
Source: CTD 2.5.3.1.2, Tables 2.5-13 and 2.5-14; CSR CT-13 3.1 Table 11-14 and Post-text Table 14.2.7.3A

4.4 Manufacturer-submitted Information On Immunogenicity

Immunogenicity testing in both CT-P13 3.1 and CT-P13 1.1 was conducted using both the CT-P13 (Inflectra) tag and INX (Remicade) tag. Antibodies against CT-P13 or RMP were measured using an electrochemiluminescent immunoassay method using the Meso Scale Discovery platform (MSD, Rockville, Maryland, USA).

In study CT-P13 3.1, highly similar proportions of patients in the Inflectra (52.0%) and Remicade (50.0%) arms developed anti-drug antibodies (ADAs) at Week 54, with the majority being neutralizing antibody (Nab) in both groups (≥98%). Similar observations were seen in the PLANETAS study, with a comparable proportion of patients between treatment arms developing ADA (Inflectra: 32.0%; Remicade: 28.7%); over 95% of the ADAs are NAb (Table 16). For the proportion of RA and AS patients with ADAs at Weeks 14, 30, and EOS, please refer to Tables 9 and 10 in Appendix 1, respectively. In both trials, ADA titres were measured up to Week 30. ADA titres increased over time in comparable fashion between treatment arms (Appendix 1, Tables 11 and 12 for RA and AS, respectively). **Therefore, the above results suggested that Inflectra elicited similar immunogenic response as Remicade in each of the patient populations.**

TABLE 16: SUMMARY OF IMMUNOGENICITY TESTING - SAFETY POPULATION (STUDIES CT-P13 3.1 AND CT-P13 1.1)

CT-P13 3.1			
	Inflectra 3 mg/kg (N = 302) n (%)	**Remicade 3 mg/kg (N = 300) n (%)**	**Total (N = 602) n (%)**
Screening			
ADA Positive	9 (3.0)	6 (2.0)	15 (2.5)
Nab Positive (as % of ADA positive)	4 (44.4)	2 (33.3)	6 (40.0)
Xab Positive (as % of ADA positive)	Not measured	Not measured	Not measured
ADA Negative	292 (96.7)	292 (97.3)	584 (97.0)
Week 54			
ADA Positive	123 (40.7)	107 (35.7)	230 (38.2)
Nab Positive (as % of ADA positive)	122 (99.2)	103 (96.3)	225 (97.8)
Xab Positive (as % of ADA positive)	Not measured	Not measured	Not measured
ADA Negative	114 (37.7)	111 (37.0)	225 (37.4)
CT-P13 1.1			
	Inflectra 5 mg/kg (N = 128) n (%)	**Remicade 5 mg/kg (N = 122) n (%)**	**Total (N = 250) n (%)**
Screening			
ADA Positive	2 (1.6)	1 (0.8)	3 (1.2)
Nab Positive (as % of ADA positive)	1 (50.0)	0	1 (33.3)
Xab Positive (as % of ADA positive)	Not measured	Not measured	Not measured
ADA Negative	125 (97.7)	119 (97.5)	244 (97.6)
Week 54			
ADA Positive	25 (19.5)	27 (22.1)	52 (20.8)
Nab Positive (as % of ADA positive)	25 (100.0)	27 (100.0)	52 (100.0)
Xab Positive (as % of ADA positive)	Not measured	Not measured	Not measured
ADA Negative	84 (65.6)	78 (63.9)	162 (64.8)

ADA = Anti-drug antibodies; Nab = Neutralizing antibody; Xab = Cross-reacting antibody
Note: The immunogenicity ADA test involved both a screening and confirmatory assay to confirm positive results. Samples that were positive in the screening assay were spiked with excess drug to determine if they are a true positive. Percentages for the neutralizing antibody result are based on the number of positive ADA results at that visit.
Sources: CSRs CT-P13 3.1 and CT-P13 1.1, Table 14.3.6.

5. CADTH COMMON DRUG REVIEW CRITICAL APPRAISAL OF CLINICAL STUDIES

5.1 CADTH Common Drug Review Reviewer Comments on Internal Validity

PLANETRA and PLANETAS were two pivotal clinical trials that evaluated the efficacy and safety of subsequent entry infliximab, Inflectra (CT-P13), against innovator infliximab (Remicade). A review of the grey literature and abstracts from database searches identified no additional relevant studies that had not already been identified by the manufacturer. The information presented below is based on the manufacturer's submission and published reports.

1. PLANETRA (Study CT-P13 3.1)

Description:

PLANETRA was a phase 3, randomized, double-blind, multi-centre, and multinational trial in patients with active rheumatoid arthritis (RA) for ≥ one year, despite at least three months of treatment with methotrexate 12.5 mg to 25 mg per week. Participants were randomized to receive 3 mg/kg of CT-P13 (N = 302) or Remicade (N = 304) as a 2-hour infusion on Weeks 0, 2, 6, and then every eight weeks. In both study groups, patients also received oral or parenteral methotrexate (12.5 mg to 25 mg/week) and oral folic acid (≥ 5 mg/week). In addition, patients were permitted to receive oral glucocorticoids (≤ 10 mg equivalent daily prednisolone) or NSAIDs if patients had been on a stable dose for at least four weeks prior to screening. Treatment was administered over 54 weeks and follow-up was done up to eight weeks after the last dose.

The primary end point was a 20% improvement in the American College of Rheumatology criteria (ACR20 response) at Week 30. Secondary outcomes were 20%/50%/70% improvements to ACR response criteria (ACR20/ACR50/ACR70), time to onset of ACR20, European League Against Rheumatism (EULAR) response criteria, the Disease Activity Score based on 28 joints (DAS28), the Short-Form 36 Health Survey (SF-36), the Simplified Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI), pharmacokinetic maximum concentration (Cmax), minimum concentration (Cmin), average concentration at steady state (Cav,ss), peak to trough fluctuation ratio, time to reach maximum concentration (Tmax) and pharmacodynamic parameters (serum C-reactive protein [CRP], rheumatoid factor [RF], anti-cyclic citrullinated peptide [anti-CCP], erythrocyte sedimentation rate [ESR]), safety and immunogenicity.

Outcomes were assessed at baseline, Week 14, Week 30, and Week 54. The equivalence margin was pre-specified as a treatment difference of ± 15% for the primary outcome (ACR20 at Week 30). The primary end point was assessed in both the intention-to-treat (ITT) and per-protocol (PP) populations, whereas all other efficacy end points were assessed in the PP population only. Health Canada requested ITT data for all efficacy end points from the manufacturer and this data is included in the Health Canada report1 and by the manufacturer in this submission. In addition, the results of a logistic regression sensitivity analysis for ACR20 at Week 30 are presented below. Non-responder imputation for the primary efficacy end point was used for patients with missing or incomplete data. The safety population included patients who received at least one full or partial dose of study treatment during any dosing period.

Summary of results:

- ACR20 Week 30: Equivalence demonstrated in ITT population (95% CI: –6 to 10%) (Table 5)
- Other efficacy end points: Study groups comparable (Tables 6, 7, and 8, and Table 3 in Appendix 1)
- Safety: Study groups comparable (one death in Remicade group at Week 54) (Tables 9 and 13)
- Immunogenicity (development of antibodies to drug): Study groups comparable (Table 16)
- Pharmacokinetic/pharmacodynamic parameters: Study groups comparable (Table 15).

ACR20 (week 30) – Data extracted from Health Canada Review (sensitivity analysis)

Group	n/N (%)	Difference (95% CI)	Goodness-of-fit test (p-value)*
CT-P13	184/302 (60.9)	0.02 (-0.05, 0.10)	0.999
Remicade	178/304 (58.6)		

* Sensitivity analysis is based on a logistic regression model with treatment group as a fixed effect and region + CRP as covariates. P-value for goodness-of-fit generated from Hosmer-Lemeshow test (rejection at 5% significance level indicates model is not a good fit).

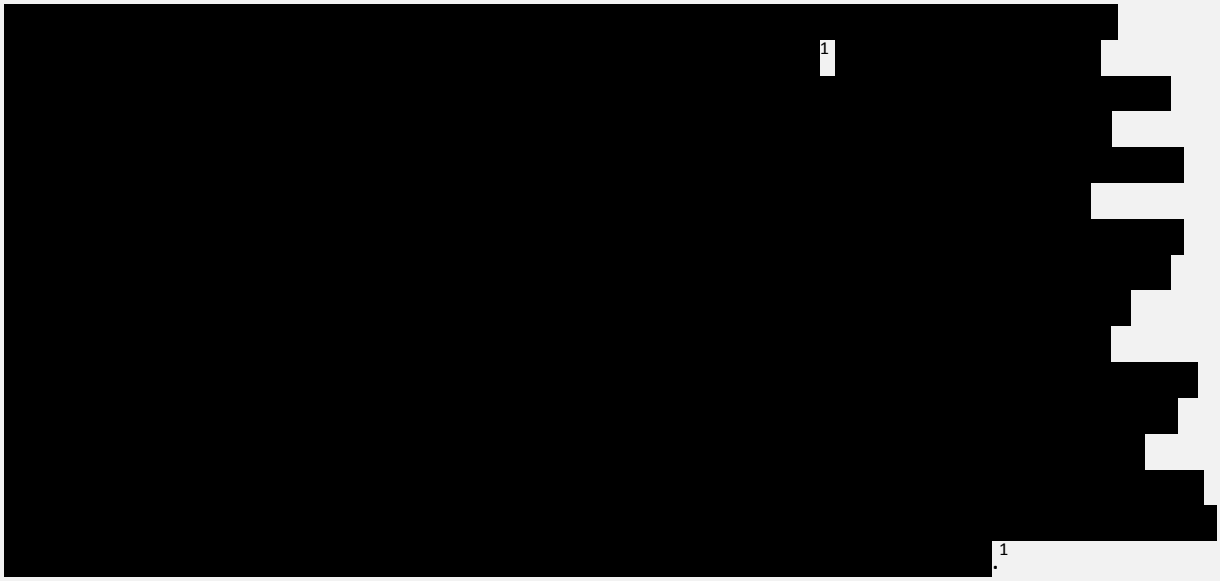
ACR = American College of Rheumatology; CI = confidence interval; CRP = C-reactive protein.

Appraisal:

PLANETRA was a well-designed, randomized clinical trial with sufficient power (N = 606), with patients recruited from several countries. CT-P13 and Remicade were administered for RA at the recommended doses (3 mg/kg IV infusion) and dosing schedules (at Weeks 0, 2, and 6, followed by every eight weeks) in combination with methotrexate, as indicated. Participants were well balanced in demographic characteristics, body mass index (BMI), and disease severity as shown by CRP, ESR, CDAI, SDAI, Health Assessment Questionnaire (HAQ) responses, DAS28, patient assessment of pain and global disease activity, and physician global assessment of disease activity.[2] It is unclear whether groups were comparable with respect to disease duration. A higher percentage of patients in the CT-P13 group than in the Remicade group had a medical history of gastrointestinal disorders (24.8% versus 15.1%, respectively) and had taken systemic corticosteroids (70.5% versus 61.7%, respectively). While concomitant corticosteroid use may influence disease outcomes, a stratified analysis based on corticosteroid use for ACR20 presented in the Health Canada review found no significant difference between users and non-users of corticosteroids at Weeks 30 and 54. In addition, corticosteroid use was added as a covariate in a logistic regression model of ACR20, which also included region and CRP as covariates; the result at Week 30 was consistent with the main finding of similar efficacy of CT-P13 and Remicade. The balance in treatment groups suggests that randomization procedures were properly performed. The random allocation sequence was implemented with an interactive voice recognition system that linked sequential patient randomization numbers to treatment codes.[3]

The trial was double-blinded and the randomization code was broken only for reporting purposes once all clinical data had been collected and entered at Week 30. The study remained blinded to investigators and patients until the end of the study.[3] Specific procedures for blinding were not described by the manufacturer in this submission or in the published report. It is important to note also that infusion-related reactions were numerically lower in the CT-P13 group than in the Remicade group (6.6% versus 8.3%, respectively), with a more pronounced difference in the anti-drug antibody-positive (ADA-positive) group (6.7% versus 13.3%, respectively).[2]

The primary outcome (ACR20) was assessed after 30 weeks and follow-up was done up to 54 weeks. While this provides some evidence of longer-term efficacy, maintenance of sustained response and development of long-term adverse events (AEs), such as malignancy, are still unclear. The primary outcome, ACR20, is defined as at least 20% improvement in tender and swollen joint counts and meeting three of the five remaining ACR core set measures (i.e., global assessments, pain, disability, acute phase reactant, ESR, or CRP). In the corresponding study that compared Remicade with placebo (ATTRACT),[4] ACR20 at Week 30 was also the primary end point. The equivalence margin of 15% was established as 50% of the treatment difference between Remicade and placebo (effect estimate was 30%) in the ATTRACT trial. The equivalence demonstrated with ACR20 is supported by similar findings with ACR50, ACR70, and actual value of the hybrid ACR score. Several other clinically important end points, including DAS28,[5] quality of life (QoL), safety, and immunogenicity were evaluated. Pharmacokinetic parameters were also assessed as secondary end points.


[1]
[1].

The primary end point was assessed in the ITT population and safety end points were assessed in patients who had received at least one dose of treatment. In the published report, other efficacy outcomes were based on the PP population, which excluded about 18% of the starting population and potentially introduced bias in the effect estimates. However, ITT data for secondary efficacy outcomes are available in Health Canada's review and in this submission. These data support product comparability, although they were not evaluated in the context of an equivalence margin as was done with ACR20. Although the manufacturer has indicated that the products are "therapeutically equivalent," it is important to note that Health Canada does not consider SEBs to be therapeutically equivalent but, rather, comparable with respect to "no meaningful therapeutic difference."[6]

Overall, PLANETRA provides evidence that CT-P13 and innovator infliximab have similar efficacy and safety profiles in patients with RA taking concomitant methotrexate and folic acid over a 54-week course of treatment.

2. PLANETAS (Study CT-P13 1.1)

Description:
PLANETAS was a phase 1, randomized, double-blind, multi-centre, and multinational trial in patients with active ankylosing spondylitis (AS) for three or more months prior to screening. It was the pivotal trial to demonstrate bioequivalence between CT-P13 and Remicade. Participants were randomized to receive 5 mg/kg of CT-P13 (N = 125) or innovator infliximab (N = 125) as a two-hour infusion on Weeks 0, 2, 6, and then every eight Weeks. In addition, patients were permitted to receive oral glucocorticoids (≤ 10 mg equivalent daily prednisolone) or NSAIDs if patients had been on a stable dose for at least four weeks prior to screening. Treatment was administered over 54 weeks and follow-up was done up to eight weeks after the last dose.

The primary end point was area under the curve for a dosing interval (AUC_{tau}) and maximum concentration at steady state ($C_{max,ss}$) between weeks 22 and 30 (doses 5 and 6). The bioequivalence margin was 80% to 125% based on 90% CIs of geometric mean ratios. The secondary objective of the trial was to assess long-term efficacy and safety up to Week 54. Secondary outcomes included additional pharmacokinetic parameters (C_{max}, C_{min}, and T_{max} up to Week 30; comparison from Week 22 to 30 of $C_{av,ss}$; minimum concentration at steady state ($C_{min,ss}$); swing; degree of fluctuation; mean residence time; terminal elimination half-life [$t_{1/2}$]; clearance at steady state [CL_{ss}]; volume of distribution at steady state [V_{ss}]); efficacy (ASAS20, ASAS40, Ankylosing Spondylitis Disease Activity [ASDAS] score, Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], Bath Ankylosing Spondylitis Functional Index [BASFI], Bath Ankylosing Spondylitis Metrology Index [BASMI], chest expansion score, and QoL); safety; and immunogenicity.[7] Efficacy outcomes were assessed at Weeks 14, 30, and 54. Non-responder imputation was used for patients with missing or incomplete data for Assessment of SpondyloArthritis International Society-20 (ASAS20) and Assessment of SpondyloArthritis International Society-40 (ASAS40). The manufacturer indicates that ITT analyses are presented for ASAS20 and ASAS40 in Table 11; however, the full sample population has not been included based on the denominators. In the Health Canada report, it has been clarified that a complete case analysis, rather than an ITT analysis, was conducted (i.e., if all components for ASAS20 or ASAS40 evaluation were missing, then the participant was excluded from the analysis). The ITT data and logistic regression sensitivity analysis, as presented in the Health Canada report, with effect estimate of difference (rather than odds ratio) in treatment groups are displayed below. The safety population included all patients who had received at least one full or partial dose of study treatment. The pharmacokinetic population included all patients who received at least the first five doses of study treatment and who had had an end of infusion sample and at least one post-treatment pharmacokinetic sample (89% of the total study population were analyzed).[7]

Summary of results:
- Primary pharmacokinetic parameters: Study groups comparable (90% CIs for AUC_{tau} and $C_{max,ss}$ fell within the 80% to 125% range) (Table 14)
- Other pharmacokinetic parameters: Study groups comparable (Table 14; Appendix 1, Tables 7 and 8)
- ASAS20: Study groups comparable (Table 11)
- ASAS40: Study groups comparable (Table 11)

- BASDAI/BASFI/BASMI: Study groups comparable
- Chest expansion: Study groups comparable
- QoL: Study groups comparable (published report)
- Safety: Study groups comparable (two deaths) (Tables 12 and 13)
- Immunogenicity (development of antibodies to drug): Study groups comparable (Table 16).

Proportion of patients achieving response according to ASAS20/40 criteria: All-randomized population with non-responder imputation — Exact Binomial Method

ASAS20 and ASAS40 - Data extracted from Health Canada Review

Visit	Group	n/N (%)	Difference (95% CI)
ASAS20			
Week 14	CT-P13 Remicade	72/125 (57.6) 79/125 (63.2)	-0.06 (-0.18, 0.07)
Week 30	CT-P13 Remicade	79/125 (63.2) 84/125 (67.2)	-0.04 (-0.16, 0.08)
Week 54	CT-P13 Remicade	71/125 (56.8) 75/125 (60.0)	-0.03 (-0.15, 0.09)
ASAS40			
Week 14	CT-P13 Remicade	48/125 (38.4) 56/125 (44.8)	-0.06 (-0.19, 0.06)
Week 30	CT-P13 Remicade	58/125 (46.4) 55/125 (44.0)	0.02 (-0.10, 0.15)
Week 54	CT-P13 Remicade	58/125 (46.4) 53/125 (42.4)	0.04 (-0.08, 0.16)

ASAS20 and ASAS40 - Data extracted from Health Canada Review (sensitivity analysis)

Visit	Group	n/N (%)	Difference (95% CI)	Goodness-of-fit test (p-value)*
ASAS20				
Week 14	CT-P13 Remicade	72/125 (57.6) 79/125 (63.2)	-0.06 (-0.18, 0.06)	0.683
Week 30	CT-P13 Remicade	79/125 (63.2) 84/125 (67.2)	-0.04 (-0.16, 0.08)	0.178
Week 54	CT-P13 Remicade	71/125 (56.8) 75/125 (60.0)	-0.03 (-0.15, 0.09)	0.453
ASAS40				
Week 14	CT-P13 Remicade	48/125 (38.4) 56/125 (44.8)	-0.06 (-0.19, 0.06)	0.573
Week 30	CT-P13 Remicade	58/125 (46.4) 55/125 (44.0)	0.02 (-0.10, 0.15)	0.974
Week 54	CT-P13 Remicade	58/125 (46.4) 53/125 (42.4)	0.04 (-0.08, 0.16)	0.438

* Sensitivity analysis is based on a logistic regression model with treatment group as fixed effect and region + BASDAI score as covariates. P-value for goodness-of-fit generated from Hosmer-Lemeshow test (rejection at 5% significance level indicates model is not a good fit).

ASAS = Assessment of SpondyloArthritis International Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval.

Appraisal:
PLANETAS followed a similar design to PLANETRA. It was a well-designed, randomized clinical trial, powered for a pharmacokinetic equivalence margin of 80% to 125% (N = 250), which recruited patients from several countries. CT-P13 and Remicade were administered at the recommended doses (5 mg/kg IV infusion) and dosing schedules (at Weeks 0, 2, and 6, then every eight weeks) for AS. Participants were well balanced in demographic characteristics (with some imbalance in ethnicity), BMI, and disease severity (baseline ASDAS, BASDAI, BASFI, BASMI, chest expansion, QoL, CRP, and ESR).[7] The random allocation sequence was implemented with an interactive voice recognition system that linked sequential patient randomization numbers to treatment codes. Randomization was stratified by region and baseline BASDAI score.[8] The balance in treatment groups suggests that randomization procedures were properly performed.

The trial was double-blinded and the randomization code was broken only for reporting purposes once all clinical data had been collected and entered at Week 30. The study remained blinded to investigators and patients until the end of the study.[8] Specific procedures for blinding were not described by the manufacturer in this submission or in the published report.

Compared with PLANETRA, PLANETAS provides better evidence that CT-P13 and Remicade have similar pharmacokinetic profiles because there was no concomitant administration of methotrexate. Participants were permitted to receive oral glucocorticoids and NSAIDs; the percentage of patients taking these medications was balanced between groups (the most frequently reported concomitant medications were anti-inflammatory and antirheumatic products [97.7% and 91.8%, respectively]). Although the manufacturer stated that the products are bioequivalent, Health Canada noted that while the products have comparable pharmacokinetics, bioequivalency has not been established.[1] Efficacy and safety were assessed up to Week 54. While this provides some evidence of longer-term efficacy, maintenance of sustained response and development of long-term adverse effects, such as malignancy, are still unclear. It must be noted that the trial was powered for the primary pharmacokinetic parameters and not for efficacy. In addition, an equivalence margin was not established for efficacy end points, thus precluding any formal conclusions about therapeutic equivalence.

3. Summary of Long-Term Follow-up Studies
Open-label, single-arm, extension studies of PLANETRA and PLANETAS have been conducted to assess the efficacy and safety of CT-P13 administered up to Week 102. Participants receiving Remicade were switched to CT-P13, which was administered at similar dosing and administration schedules as the main trials.

[redacted][9]

[redacted][10]

4. List of Relevant Ongoing Studies

(i) CT-P13 3.4 (phase 3 study): Randomized, double-blind, parallel-group study to demonstrate noninferiority in the efficacy and safety of CT-P13 compared with Remicade in patients with active Crohn disease. [redacted]

(ii) CT-P13 4.1 (phase 4 study): An open-label, single-arm study to evaluate the efficacy and safety of CT-P13 in Korean patients with inflammatory bowel disease (Crohn disease or ulcerative colitis). [redacted]

(iii) CT-P13 4.2: Observational prospective cohort study to evaluate the long-term efficacy and safety of CT-P13 in patients with RA over five years. [redacted]

(iv) CT-P13 4.3: Observational, prospective cohort study to evaluate the long-term efficacy and safety of CT-P13 in patients with Crohn disease or ulcerative colitis over five years. [redacted]

(v) CT-P13 4.4: Observational, prospective cohort study to evaluate the long-term efficacy and safety of CT-P13 in patients with AS over five years. [redacted]

(vi) NCT02148640 (phase 4 study): Randomized, double-blind, parallel-group study to evaluate the efficacy and safety of switching from Remicade to CT-P13 compared with continued treatment with Remicade in patients with RA, spondyloarthritis, PsA, ulcerative colitis, Crohn disease, or chronic PsO. [redacted]

5.2 External Validity

1. PLANETRA (Study CT-P13 3.1)
The trial recruited patients from 100 centres across 19 countries in Europe, Asia, Latin America, and the Middle East. The population was clinically relevant. Participants had active RA according to the revised 1987 ACR classification criteria and were taking concomitant methotrexate plus folic acid. In addition, patients were permitted to continue on oral glucocorticoids or nonsteroidal anti-inflammatories (NSAIDs). The majority (80%) of patients were female, which reflects general practice in Canada where about 60% of those with RA are female (Statistics Canada).

However, the applicability of study results is limited based on some characteristics of included patients. First, the applicability of results to men with RA requires further study. Second, therapeutic equivalence remains to be evaluated in people of different ethnicities. Most patients (more than 79%) were Caucasian, with Asian and Black patients comprising only about 12% and under 1% of the population respectively. Also, no patients were recruited from North America. Third, equivalence of the two treatments in the elderly (older than 75 years of age) has not been established. The median age of patients was 50 years of age and patients older than 75 years of age were excluded. Fourth, the applicability to patients with multiple diseases and more complex medication regimens requires further investigation. The following patients were excluded from the study: obese, having other inflammatory or rheumatic diseases, asthma, and taking DMARDs other than methotrexate. Such situations could be encountered in clinical practice and patients, especially the elderly, may be taking several concomitant medications. Investigation of potential differences between CT-P13 and Remicade in patients with comorbid diseases and concomitant medications is needed. In addition, further investigation of CT-P13 and Remicade with respect to specific drug interactions (e.g., cytochrome P450 (CYP) enzyme-inducing potential) would be worthwhile. Lastly, no information was provided on disease duration.

In PLANETRA, an analysis of efficacy criteria at Week 30 according to ADA status (positive or negative) was performed.[3] Although no major differences were observed, this was a post-hoc analysis. Therefore, more clinical trial data are needed to investigate potential differences among CT-P13 and innovator infliximab in ADA-positive patients.

Infliximab may be administered at doses higher than 3 mg/kg for RA, with doses up to 10 mg/kg being a possibility.[11] The implications of such higher dosing regimens on equivalence require evaluation.

2. PLANETAS (Study CT-P13 1.1)
As with PLANETRA, PLANETAS recruited a clinically relevant population from multiple centres in Europe, Asia, and Latin America, although no patients were from North America. Participants had active AS according to the 1984 modified New York classification criteria, and the majority were male (about 80%) and Caucasian (about 75%). The study reflects the higher prevalence of AS in males. However, the applicability of results to patients with conditions other than AS, females, and other ethnicities is limited. Similar concerns with respect to applying the results to patients with comorbid conditions and taking concomitant medications, as described above for PLANETRA, also are present for PLANETAS. Pharmacokinetic analyses were stratified by ADA status and results were similar for ADA-positive and ADA-negative patients. Efficacy end points were also stratified by ADA status, but on a post-hoc basis. Therefore, more clinical data on the efficacy and safety of CT-P13 are needed in ADA-positive patients with AS.

6. EXTRAPOLATION OF INDICATIONS

Information in the following section was provided by the manufacturer and has not been altered by CDR in any way.

6.1 Manufacturer's Rationale for Extrapolation

The complete details for the information provided below are located in Manufacturer's Response to Screening Deficiency Notice issued on 14 Jan 2013 (p.4-68), and BSEAR Clinical report (p.162-189,196-207 [latter is *Attachment #1: Response to Clarifax Dated 30 April 2013*]).

6.1.1 Pathophysiology – Rheumatoid Arthritis

RA is a chronic inflammatory condition that affects synovial joints and is characterised by chronic synovial inflammation, bone erosion and cartilage damage. Considerable evidence demonstrates that TNFα plays a prominent role in all three processes (47). Inflammation of the synovial joint causes an increase in vascularity and cellularity, the latter of which is due in part to an influx of inflammatory cells such as T cells, B cells and macrophages into the joint (48). Recruitment of these cells is mediated by the TNFα-dependent expression of adhesion molecules and chemokines (48, 49). The pro-inflammatory cytokine TNFβ is responsible for the recruitment of macrophages into the synovial joint and the subsequent elevated production of TNFα by these cells.

Synovial fibroblasts increase proliferation in RA, and act in concert with TNFα in another feed-forward loop that promotes sustained synovial inflammation. Activation of synovial fibroblasts, by cytokines such as TNFα and interleukin (IL)-1β, has been shown to induce these cells to release further pro-inflammatory mediators including TNFα, IL-1β, VEGF and matrix-degrading enzymes (50). IL-1β also induces chrondrocytes within the cartilage to release matrix-degrading enzymes (50). This self-perpetuating cycle of cytokine-induced cytokine release, in the absence of robust feedback mechanisms, is also associated with cartilage damage.

Bone erosion is also associated with TNFα. Under normal conditions, homeostasis is achieved through the balance between the activities of osteoclasts (resorption) and osteoblasts (formation). With elevated TNFα, osteoclast precursor cells are driven, in part, by TNFα and the interaction of osteoclast precursor cells with synovial mesenchymal cells and lymphocytes. Interactions between osteoclast precursor cells and T helper 1 cells and activated synovial fibroblasts are of particular importance as the latter two cell types express receptor activator of nuclear factor-κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) in a TNFα-dependent manner, and both RANKL and M-CSF are essential for the differentiation of osteoclast precursor cells into mature osteoclasts that are responsible for bone erosion (47, 50).

6.1.2 Pathophysiology – Ankylosing Spondylitis

AS is characterized by back pain, new bone formation, and joint inflammation (51). The primary site of inflammation is the axial skeleton and predominantly the sacroiliac joints at the entheses (the cartilage/bone interface) (52, 53). In AS, especially at early time points, mononuclear infiltrates (primarily T cells and macrophages) invade the collagen at these sites and secrete TNFα (54, 55). Localization of TNFα to sites of inflammation in AS suggests that this molecule plays a pathogenic role in this disorder. This hypothesis has been tested in several studies utilizing anti-TNFα therapies (e.g. infliximab (56), etanercept (57), adalimumab (58)), and there is convincing data that indicates that blocking TNFα in AS robustly attenuates the signs and symptoms of disease.

6.1.3 Pathophysiology – Psoriatic Arthritis

PsA shares similarities with both RA and AS, in that patients with PsA typically present with joint inflammation and bone erosion. However, in contrast to RA, new bone formation is also a characteristic feature of PsA demonstrating that this disease shares further similarities with AS (51). In PsA, increased levels of TNFα, other proinflammatory cytokines and activated T-cells are found in synovial tissue (59-61). In addition, the cytokine profile and the levels of cytokine expression in the synovial fluid of PsA patients are similar to those seen in RA patients, indicating potentially similar process in the inflammation and bone erosion process between conditions (62). This is supported by evidence indicating that osteoclastogenesis in PsA is similarly dependent on both TNFα and RANKL (63). Furthermore, the role of TNFα in PsA has been directly tested in randomized, placebo controlled studies of anti-TNFα therapies and convincing data now indicate that these therapies demonstrate strong clinical efficacy in patients with PsA (6, 64).

6.1.4 Pathophysiology – Psoriasis

PsO is characterized by infiltration of the skin by immune cells, hyper-proliferation of keratinocytes, and subsequent formation of erythematous plaques and increased dermal vascularity. Patients with PsO also have higher prevalence of PsA, suggesting the two conditions may have similar pathophysiological mechanisms. This is supported by evidence of activated T cells and elevated levels of TNFα in both the skin (65, 66) and joints of patients with PsO and PsA (59-61). In addition, clinical studies utilizing monoclonal antibodies specific for cluster of differentiation 4 (CD4) have demonstrated that the selective antagonism of T cells is able to attenuate clinical symptoms in patients with severe PsO, indicating the pivotal role of T cells in the pathogenesis of PsO (67, 68). T cells, and CD4-positive T-helper cells in particular, located in the inflamed skin, secrete an array of cytokines including TNFα, IFN-γ, and IL-17 (9), and these cells have been shown to have the capacity to promote the proliferation of keratinocytes in psoriatic skin (10, 11). Furthermore, TNFα-dependent T cell proliferation has been shown to be required for the development of psoriatic skin lesions (12) and blocking of TNFα signalling has been shown to significantly reduce T cell number in lesioned skin and attenuate disease development.

Therefore, although other cell types and signalling molecules, such as dendritic cells and IL-23 are clearly important mediators in the development of PsO, it is also clear that local TNFα/TNFα signalling plays a prominent role in the pathogenesis of this condition. On the basis of this evidence a broad range of structurally different anti-TNFα therapies have been utilised in the treatment of PsO and have been shown to be highly effective in the management of this disease (69, 70).

In summary, considerable evidence indicates that TNFα signalling is pivotal in the pathogenesis of a number of chronic inflammatory conditions, including RA, AS, PsA, and PsO. Evidence indicates that in all of these conditions the expression of TNFα is high and the predominant source of TNFα is immune cells and in particular macrophages. The pathogenic nature of TNFα in the above indications seems to stem predominantly from its critical role in driving the pro-inflammatory cytokine network.

The above conclusion is also supported by the Health Canada reviewer's comment in the BSEAR Clinical document (p.164): "in RA, AS, PsA and PsO, there is a consistent finding of activated T-cells in the joint (and skin in PsO). Elevated levels of TNFα a have also been observed to be present at these sites. These findings support a common disease pathophysiology between each of these inflammatory diseases."

6.1.5 Mechanism of Action of Infliximab

Infliximab is a chimeric IgG1 mAb composed of a variable murine Fab region linked to a human IgG1κ constant region. Infliximab can bind to both the monomer and trimer forms of soluble TNFα (sTNFα). Furthermore, infliximab can bind simultaneously to two TNFα trimers, and up to three molecules of infliximab have been shown to bind to each TNFα trimer, and is thus proposed to be able to form multimeric complexes (Scallon et al. 2002).

The high affinity of infliximab towards sTNFα supports its use in inflammatory diseases such as RA, PsA, AS and PsO, in which sTNFα signalling through binding to TNFR1 and TNFR2 plays a dominant role in the pathogenesis of these indications. Infliximab has been shown to have highly effective anti-inflammatory effects in the above indications (71).

In RA, antagonists of TNFα have been shown to induce the following: reduced levels of rheumatoid factor and markers of systemic inflammation, attenuated angiogenesis, decreased cytokine (e.g. IL-6, IL-1β, TNFα and VEGF), chemokine and adhesion molecule expression in synovial tissue and fluid, diminished serum levels of chemokines and cytokines and inhibit damage to cartilage and bone (71, 72). Inhibition of cytokine production (IL-1, IL-6 and IL-8) by TNFα antagonists has been replicated in cell culture (73). Furthermore, the suppression of cytokine levels by infliximab seems to be directly related to the neutralization of sTNFα as serum levels of IL-6 have been shown to be reduced within 24 hours of drug administration (74).

The ability of TNFα antagonists to attenuate angiogenesis and adhesion molecule expression is particularly relevant to RA, PsA and PsO. Angiogenesis is a prominent feature of all of these indications, and in association with increased expression of specific adhesion molecules leads to increased trafficking of inflammatory cells into the inflamed tissue. The attenuation of cellularity in inflamed tissues is a characteristic feature of TNFα antagonists. Infliximab has been shown to decrease the number of macrophages and T cells in synovial tissue of patients with RA and to decrease the number of leucocytes (predominantly T cells) in both synovial tissue and psoriatic lesions in patients with PsA (75, 76).

TNFα signalling is not limited to the soluble form of the molecule, as the transmembrane form of TNFα (tmTNFα) is also biologically active (77). The tmTNFα is expressed on monocytes/macrophages and T cells (78) and interacts with its receptors, TNFR1 and TNFR2, through cell-to-cell contact. Consequently, conventional signalling through tmTNFα is thought to play an important role in local inflammation and in indications such as Crohn's disease, in which granulomatous (aggregates of macrophages) inflammation in typically evident. As the main difference between the arthritis indications and the inflammatory bowel indications appears to be the involvement of membrane bound TNFα in irritable bowel diseases, this mechanism, and the downstream events (i.e. complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and reverse signalling) will not be discussed in this document. Please refer to the Response to Notice of Screening Deficiency and BSEAR for further information.

6.1.6 Clinical Efficacy of Infliximab in RA and AS

For the RA indication, the approval of Inflectra as a therapy was based on the results of the pivotal efficacy study PLANETRA (CT-P13 3.1), which is described in detail in Section 4.2 above. Briefly, in RA patients with active disease treated with MTX for ≥3 months prior to enrolment, Inflectra was demonstrated to be therapeutically equivalent to the reference product, Remicade, (both groups received concurrent MTX), as determined by the similar ACR20 response at Week 30 (60.9% vs. 58.6%, respectively; 95% CI: -6% to 10%, which was within pre-defined therapeutic equivalence margin of

±15%). Furthermore, all other efficacy and safety endpoints, as well as immunogenicity were highly similar between both products.

For the AS indication, efficacy results for the all-randomized population (N= 250; Inflectra: n=125; Remicade: n=125) indicated the proportion of patients achieving clinical response according to the ASAS20 and ASAS40 criteria at Weeks 14, 30, and 54 was similar in the Inflectra and Remicade treatment groups.

Therefore, based on the above clinical evidence demonstrating that Inflectra is as effective as Remicade in diseases where TNFα plays a predominant role in disease pathophysiology, Inflectra is expected to have similar efficacy in diseases with similar mechanism, namely PsA and PsO.

In Vitro Comparability Between Inflectra and Remicade With Respect To The Mechanisms Of Action
A multitude of state-of-the-art physicochemical and biological analytical methodologies using multiple batches of Inflectra drug product and Remicade were employed, and demonstrated comparability in the primary and higher order structures, glycan structures, charged variants and impurity profile between products. These results are highlighted in Section 4.1 above and additional details are presented in Appendix 1 (Tables 1 and 2); further data is located in CTD Module 3.2.R. Similar analysis comparing Inflectra drug substance and drug product can be found in CTD Module 3.2.S.3.1.

Similarly, Table 2 in Section 4.1 outlined the qualified *in vitro* methodologies employed as means to assess the biological activity of Inflectra and Remicade. The *in vitro* biological techniques utilized to evaluate TNFα-infliximab binding/neutralization include cell-based TNFα neutralization assay, TNFα binding affinity as determined by SPR, TNFα binding affinity as determined by ELISA, and TNFα binding as determined by means of a cell-based system (see CTD Module 3.2.R for an overview of these assays).

6.1.7 Justification For Extrapolation – Biosimilarity

A comprehensive quality, non-clinical and clinical data package provided demonstrates Inflectra drug product and Remicade to be biosimilar. By undertaking an extensive quality physicochemical and biological testing program using sensitive, state-of-the-art methods and evaluating multiple batches of Inflectra and Remicade in parallel, the two products were clearly demonstrated to be comparable with respect to primary and higher order structure, charge distribution and biological activity. The biological testing program was also expansive and utilized a combination of biochemical and biological assays to address the primary and secondary mechanisms of action of Inflectra and Remicade. The results demonstrated comparable results in assays that are relevant to the pathophysiology of RA, AS, PsA, and Ps, namely, TNFα binding affinity (using ELISA and SPR), TNFα neutralization, and tmTNFα binding affinity using cell-based ELISA. Finally no trends in differences in efficacy and safety are discernible following completion of two pivotal studies in a total of 860 patients. Thus it can be concluded that Inflectra is biosimilar to Remicade.

6.1.8 Justification For Extrapolation – Efficacy and Safety

Based on the submission dossier, the trial data suggests that no clear differences in the drugs' safety and efficacy profile exist. In AS, the mean response in ASAS20 is similar to Remicade e.g. for Week 30 (ASAS20 is 72.4% and 70.5 % for Remicade and Inflectra, respectively). In RA, the ACR20 response rate at Week 30 is also similar in the all-randomized population (58.6% and 60.9% for Remicade and Inflectra, respectively). No statistical differences are observed for any efficacy endpoints with the exception of time to onset, which favours Inflectra, but is likely a random occurrence in view of the high number of endpoints tested.

6.1.9 Justification For Extrapolation – Dosage and Regimen

Inflectra has established comparability in therapeutic efficacy and PK equivalence in the indications of RA and AS, respectively, at two dosages, 3 mg/kg and 5 mg/kg. Specifically, both of these doses are given as a loading dose at Weeks 0, 2, 6 followed by administrations every 8 Weeks. In addition, the dose used in AS of 5 mg/kg at every 6 to 8 weekly intervals is the same posology as indicated for treatment of PsA and PsO (both at every 8 weeks).

6.1.10 Justification for Extrapolation – Pharmacokinetics

The rationale to extrapolate from AS to the other indications is further supported by the fact that the available data and published literature on Remicade, indicate on balance that there are no significant differences in pharmacokinetic profiles for Remicade in patients with RA and PsO (79-81) and there are no data to indicate that the pharmacokinetic profile in these two indications differ from the pharmacokinetic profile in AS patients.

6.2 Health Canada's Conclusion on Extrapolation

As per Health Canada BSEAR Clinical report's *Summary of Extrapolation Assessment* (p.186-187):

> *"The principles for extrapolation discussed above, and outlined in the SEB guidance document, were taken into account in the review of this submission, and extrapolation of data from the settings of rheumatoid arthritis and ankylosing spondylitis to plaque psoriasis and psoriatic arthritis are considered acceptable. Extrapolations to these indications are supported by similar pathophysiologies between these diseases and the diseases in which CT-P13 has been tested. Also, the efficacy of a variety of anti-TNFs in these four indications indicates that binding and neutralization of soluble TNFalpha is sufficient to elicit significant clinical benefit. Since no differences were identified in the ability of CT-P13 and Remicade to bind and neutralize TNFalpha, and since CT-P13 and Remicade demonstrated similar clinical benefit, safety and immunogenicity in RA and in AS, it follows that CT-P13 will also provide similar benefit to patients with PsA and Ps. Further, the dosage and schedule tested in the AS population is identical to that recommended for PsA and Ps, both of which receive infliximab as monotherapy, which allows for the extrapolation of the PK comparability data and immunogenicity data from the AS trial.*
>
> *As described above extrapolation to PsA and Ps is supported. It is noted that the differences observed in the FcγRIIIa binding and, subsequently, ADCC, do not preclude extrapolation from the settings of RA and AS to the other requested indications of psoriatic arthritis and plaque psoriasis. In these diseases, ADCC is not considered to be an important mechanism for generating a response to infliximab. This is supported by the observation that certolizumab pegol and etanercept are both capable of producing clinical responses of the same order as infliximab in patients with psoriatic arthritis and plaque psoriasis despite their inability (certolizumab pegol) or possible impaired ability (etanercept) to induce ADCC."*

6.3 International Regulatory Conclusions on Extrapolation

As per EMA CHMP Assessment Report's Extrapolation of Efficacy and Safety (p.95-96):

> *"It is currently believed that neutralisation of sTNF and tmTNF is responsible of its efficacy in RA by preventing TNF from inducing TNFR-mediated cellular functions. It can also be accepted that the effects of infliximab blockade on synovial inflammation are comparable in different forms of arthritis [i.e. psoriatic arthritis]. Such effects are also believed to play a role in psoriasis plaques…"*

Inflectra has not yet been approved by the US Food and Drug Administration and the Australian Therapeutic Goods Administration.

In summary, the totality of evidence from extensive characterization processes demonstrated that Inflectra is highly similar from both the chemistry & manufacturing and *in vitro* biological activities perspectives, to the RMP Remicade. In addition, the indications for which reimbursement is requested, RA, AS, PsA, and PsO, all share a common disease pathway, that is, the predominant involvement of sTNFα in the pathophysiology of these diseases. This is in part supported by evidence that infliximab is effective in the treatment of RA, AS, PsA, and PsO. Finally, efficacy and PK studies demonstrated that Inflectra is therapeutically equivalent to (ACR20 at Week 30) and pharmacokinetically indistinguishable from Remicade in RA and AS patients, respectively. Together, this evidence suggests that Inflectra will have similar efficacy to Remicade in the extrapolated indications of PsA and PsO.

6.4 CDR Comments on Extrapolation

Of the six indications approved in Canada for the use of Remicade (rheumatoid arthritis, ankylosing spondylitis, adult and pediatric Crohn's disease, adult and pediatric ulcerative colitis, plaque psoriasis, and psoriatic arthritis), Health Canada has granted approval to CT-P13 for the following four indications: rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis. Clinical trial data are available only for rheumatoid arthritis and ankylosing spondylitis (PLANETRA and PLANETAS), therefore the approval for plaque psoriasis and psoriatic arthritis was based on extrapolation. Health Canada deemed that extrapolating data from rheumatoid arthritis and ankylosing spondylitis to adult or pediatric Crohn's disease and ulcerative colitis could not be supported at this time. Below is a brief discussion of the process followed by Health Canada to arrive at decisions of extrapolation. Other jurisdictions, such as the European Medicines Agency (EMA), have arrived at difference conclusions for extrapolating indications of CT-P13 – this is also addressed briefly.

Health Canada – Principles of Extrapolation

Extrapolation means extending use of a product to other, related indications, in the absence of clinical studies. Health Canada considers the following factors when making decisions about extrapolation:[6]

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

Health Canada will review quality information of the biosimilar compared with the innovator, assess that the "most sensitive" population and best endpoints were included in clinical trials, and evaluate whether the biosimilar and innovator have similar safety and immunogenicity (>100 patients and sufficiently long duration).

Health Canada – CT-P13 Extrapolation Decisions

The following reasons were provided by Health Canada for extrapolating to plaque psoriasis and psoriatic arthritis:[1]

- Observations support common disease pathology among rheumatoid arthritis, ankylosing spondylitis, psoriasis, and psoriatic arthritis. In all conditions, activated T-cells are present in the joint (skin in psoriasis) and elevated levels of TNFα are present at these sites.
- The differences observed in afucosylation, FcyRIIIa receptor binding, and ADCC do not support extrapolation to diseases where ADCC is a mechanism of action. ADCC is likely not an important mechanism of action in plaque psoriasis and psoriatic arthritis.
- Similarities in efficacy and safety have been observed between infliximab, adalimumab, and etanercept in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, which suggests a common mechanism of action of TNF blockers in these conditions. These three molecules all bind to and inhibit sTNF. Despite differences in molecular structure, they exhibit similar effects and therefore, CT-P13 can be extrapolated to psoriasis and psoriatic arthritis.
- Similarity in product quality, safety, pharmacokinetics, and dosage regimens (5 mg/kg IV infusion for plaque psoriasis and psoriatic arthritis)

The following reasons were provided by Health Canada for not extrapolating to inflammatory bowel diseases and pediatric patients:[1,12]

- The treatment of inflammatory bowel diseases with TNF blockers may be through additional mechanisms of action than those of rheumatic diseases. In rheumatoid arthritis and ankylosing spondylitis, sTNF is the predominant form involved, whereas trans membrane TNF has a role in Crohn's disease.
- Pharmacokinetics of Remicade differ between adults and children with ulcerative colitis and, therefore, extrapolation from adult studies of rheumatoid arthritis to inflammatory bowel diseases and pediatrics is not supported.
- The differences observed in afucosylation, FcyRIIIa receptor binding, and ADCC do not support extrapolation to diseases where ADCC is a mechanism of action, such as bowel diseases.
- Safety profile of infliximab is different between rheumatic and inflammatory bowel diseases. For example, risk of hepatosplenic T-cell lymphoma is uniquely associated with inflammatory bowel diseases.

European Medicines Agency

The EMA has granted approval to CT-P13 for all the six indications of Remicade, including pediatric and adult Crohn's disease and ulcerative colitis. Whereas Health Canada highlighted the differences observed between CT-P13 and Remicade in ADCC assay, the EMA questioned the physiological relevance of the results that used natural killer cells.[13]

Special Considerations for Extrapolation

Immunogenicity: Concerns have been raised that the assessment of immunogenicity in patients with rheumatoid arthritis taking concomitant methotrexate and in patients with ankylosing spondylitis is not ideal. Patients taking methotrexate will have a lowered immune response and, therefore, ADA formation will be inhibited. In addition, patients with ankylosing spondylitis may have lower ADA formation than patients with psoriasis or inflammatory bowel diseases.[13]

Sensitive Model: The comparison between a biosimilar and innovator product should be conducted in the most sensitive population, so that differences are more likely to be detected. It has been suggested that rheumatoid arthritis and ankylosing spondylitis are not the most sensitive populations. One reason is due to lower potential for generating ADA, as described above. In addition, Lee et al. indicated that of the six indications of Remicade, the greatest placebo-adjusted response was observed in plaque psoriasis and the smallest in rheumatoid arthritis.[14] The greater the placebo-adjusted response, the more likely that differences between a treatment and comparator will be detected. Therefore, according to this criterion, rheumatoid arthritis is the least sensitive model.

Summary: Considering all available evidence, Health Canada and the EMA have accepted the rheumatoid arthritis and ankylosing spondylitis models to be sensitive and suitable for evaluating immunogenicity. Together with the accepted evidence of: (a) high degree of similarity in the physicochemical characteristics between Inflectra and Remicade; (b) high degree of similarity in *in vitro* (binding and function) characteristics and common disease pathology of rheumatoid arthritis, ankylosing spondylitis, psoriasis, and psoriatic arthritis; and (c) pharmacokinetic profile that could not be distinguished from the reference product Remicade; and comparable clinical benefit, safety and immunogenicity profiles between Inflectra and Remicade. The acceptability of these observations sufficiently allowed both regulatory agencies to accept extrapolation of data from the settings of rheumatoid arthritis and ankylosing spondylitis to plaque psoriasis and psoriatic arthritis."

7. COST COMPARISON

The Inflectra 100 mg/vial drug product will carry a 30.85% lower price ($650.0000) relative to the currently lowest-listed price of Remicade 100 mg/vial, which is at $940.0000 per the RAMQ. Consequently, the 30.85% cost differential equates to $290.0000 savings per 100 mg vial.

COST COMPARISON OF INFLECTRA AND REMICADE FOR RHEUMATOID ARTHRITIS (FIRST YEAR)

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose[c]	Average Drug Cost ($)/Year
Inflectra	100 mg/vial	Lyophilized power	$650.0000[a]	3 mg/kg	$10,920
Remicade	100 mg/vial	Lyophilized power	$940.0000[b]	3 mg/kg	$15,792

[a] Public price
[b] RAMQ List of Medications, updated 2014-04-24
[c] Inflectra and Remicade product monograph

COST COMPARISON OF INFLECTRA AND REMICADE FOR RHEUMATOID ARTHRITIS (SUBSEQUENT YEAR)

Drug / Comparator	Strength	Dosage Form	Price ($)	Expected Dose[c]	Average Drug Cost ($)/Year
Inflectra	100 mg/vial	Lyophilized power	$650.0000[a]	4.45 mg/kg	$13,161
Remicade	100 mg/vial	Lyophilized power	$940.0000[b]	4.45 mg/kg	$19,033

[a] Public price
[b] RAMQ List of Medications, updated 2014-04-24
[c] Inflectra and Remicade product monograph

COST COMPARISON OF INFLECTRA AND REMICADE FOR ANKYLOSING SPONDYLITIS (FIRST YEAR)

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose[c]	Average Drug Cost ($)/Year
Inflectra	100 mg/vial	Lyophilized power	$650.0000[a]	5 mg/kg	$18,200
Remicade	100 mg/vial	Lyophilized power	$940.0000[b]	5 mg/kg	$26,320

[a] Public price
[b] RAMQ List of Medications, updated 2014-04-24
[c] Inflectra and Remicade product monograph

COST COMPARISON OF INFLECTRA AND REMICADE FOR ANKYLOSING SPONDYLITIS (MAINTENANCE AT EVERY 7 WEEKS[*]), (SUBSEQUENT YEAR)

Drug / Comparator	Strength	Dosage Form	Price ($)	Expected Dose[c]	Average Drug Cost ($)/Year
Inflectra	100 mg/vial	Lyophilized power	$650.0000[a]	5.5 mg/kg	$17,518
Remicade	100 mg/vial	Lyophilized power	$940.0000[b]	5.5 mg/kg	$25,333

[*] To reflect the maintenance intervals of 6-8 weeks as per Inflectra product monograph for AS.
[a] Public price
[b] RAMQ List of Medications, updated 2014-04-24
[c] Inflectra and Remicade product monograph

COST COMPARISON OF INFLECTRA AND REMICADE FOR PSORIATIC ARTHRITIS AND PLAQUE PSORIASIS (FIRST YEAR)

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose[c]	Average Drug Cost ($)/Year
Inflectra	100 mg/vial	Lyophilized power	$650.0000[a]	5 mg/kg	$20,800
Remicade	100 mg/vial	Lyophilized power	$940.0000[b]	5 mg/kg	$30,080

[a] Public price
[b] RAMQ List of Medications, updated 2014-04-24
[c] Inflectra and Remicade product monograph

COST COMPARISON OF INFLECTRA AND REMICADE FOR PSORIATIC ARTHRITIS AND PLAQUE PSORIASIS (MAINTENANCE AT EVERY 8 WEEKS) (SUBSEQUENT YEAR)

Drug / Comparator	Strength	Dosage Form	Price ($)	Expected Dose[c]	Average Drug Cost ($)/Year
Inflectra	100 mg/vial	Lyophilized power	$650.0000[a]	5.5 mg/kg	$16,900
Remicade	100 mg/vial	Lyophilized power	$940.0000[b]	5.5 mg/kg	$24,480

[a] Public price
[b] RAMQ List of Medications, updated 2014-04-24
[c] Inflectra and Remicade product monograph

CADTH Common Drug Review Reviewer Comments Regarding Cost Information

Summary of the Manufacturer's Analysis

Inflectra is available in 100 mg vials for infusion. The manufacturer submitted a price of $650.00 per vial. The manufacturer submitted a cost comparison between Inflectra and reference infliximab (Remicade) for the four indications under review: RA, AS, PsO, and PsA. The manufacturer assumed an adult patient weight of 70 kg for all indications. Other assumptions regarding dosing and the number of annual treatments for new users (first year of treatment) and retained patients (subsequent years of treatment) are presented in Table 1 below.

TABLE 1: INFLIXIMAB DOSING BASED ON THE MANUFACTURER'S COST COMPARISON[A]

Indication	Patient History	Mg/Treatment	Treatments/Year	Annual Mg
Rheumatoid arthritis	New Patients	210	8	1680
	Retained Patients	311.5[b]	6.5	2025
Psoriatic arthritis and plaque psoriasis	New Patients	400	8	3200
	Retained Patients	400[c]	6.5	2600
Ankylosing spondylitis	New Patients	400	8	3200
	Retained Patients	400[c]	7	2800

[a] Wastage was accounted for in the cost, based on a threshold of 35% (defined as the percentage of product remaining in vial, below which the manufacturer assumed that the provider would not use the vial for the next patient).
[b] The manufacturer assumed that 40%, 50%, and 10% of retained patients would receive 3 mg/kg, 5 mg/kg, and 7.5 mg/kg, respectively, in the subsequent years.
[c] The manufacturer assumed that 80% and 20% of retained patients would receive 5 mg/kg and 7.5 mg/kg, respectively, in the subsequent years.
Source: Adapted from the manufacturer's budget impact analysis.

According to the manufacturer-submitted annual cost comparisons for new and retained patients, the annual cost of Inflectra is 30.85% less than the cost of Remicade when used for RA, AS, PsO, or PsA. Of note, the manufacturer used the Quebec Régie de l'assurance maladie du Québec (RAMQ) list price for Remicade ($940 per vial), which is lower than the Ontario Drug Benefit (ODB) Formulary Exceptional Access Program (EAP) price ($987.56 per vial).

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

- Using the ODB EAP price of Remicade as a reference instead of RAMQ list price, the annual cost of Inflectra is 34.2% less than the cost of Remicade (See CDR Cost Comparison Tables, Appendix 4).
- The manufacturer's analysis accounted for drug wastage only if the unused product in the opened vial was more than 35 mg. In case of unused product less than 35 mg, the manufacturer included the price of the used portion only. Based on CDR analysis (Appendix 4), any unused amount remaining in an opened vial was considered as wastage and was included in the drug cost. This difference in wastage estimation did not have an impact on the relative cost difference between Inflectra and Remicade.

Issues for Consideration

- Inflectra can be used either for patients who would otherwise have initiated Remicade or other biologic disease-modifying antirheumatic drugs (bDMARDs). Compared with other less expensive bDMARDs, the use of Inflectra would result in an incremental cost. (See CDR Cost Comparison Tables with other bDMARDs, in Appendix 4).
- Other drug plans, such as Alberta Health and Saskatchewan formularies, have lower list prices for Remicade ($962.68 and $976.00 per vial, respectively) compared with Ontario. Therefore, the expected savings may vary among public drug plans. Furthermore, the projected savings do not account for any confidential pricing of Remicade.
- A CADTH therapeutic review of biologics in RA reported that infliximab dose escalation — i.e., increasing individual doses up to 10 mg/kg or increasing the frequency of infusions — is common in clinical practice.[15] The clinical expert consulted for this review indicated that dose escalation can include both increasing the dose and the frequency. Dose escalation would affect both Inflectra and Remicade, but it would not affect their relative cost difference. However, this would have a considerable impact when comparing the cost of Inflectra with other bDMARDs.
- The dosage of infliximab products is based on patient weight, and the manufacturer's comparisons for rheumatology indications were based on an average patient weight of 70 kg. Inflectra and Remicade share the same dosing strategies; variations in patients' weight would not affect the relative cost difference between the two, but would have an impact when Inflectra is compared with other bDMARDs.
- The indications under review are chronic in nature. The relative cost difference of Inflectra and Remicade is not expected to vary with a longer time horizon, but would affect the comparison with other bDMARDs because of the loading doses used in the first year for some biologic therapies.

CDR Exploratory Analysis

To estimate the impact of the aforementioned issues for consideration, CDR conducted a sensitivity analysis, using the following conservative assumptions (for the RA indication):

- a three-year time horizon
- a patient weight of 70 kg

- an average dose of infliximab of 5 mg/kg; 75% of patients on IV tocilizumab would receive a dose of 8 mg/kg (while the dose of other bDMARDs would remain stable)
- an annual discount rate of 5%.

Based on the scenario described above, the price of Inflectra would need to be reduced by 13% to equal the average three-year cost of other bDMARDs, and by 38% to equal the average three-year cost of the lowest-priced bDMARD (IV tocilizumab, $42,336) (See CDR Price Reduction Analysis, Appendix 5).

Conclusion

At the manufacturer-submitted price, the annual cost of Inflectra is 34.2% less expensive than the innovator infliximab (Remicade) when using the ODB EAP price of Remicade ($987.56 per vial) as a reference. Compared with other bDMARDs used for RA (excluding Remicade), for the first year of treatment and a patient weight of 70 kg, Inflectra was less expensive than all other comparators (abatacept, adalimumab, golimumab, rituximab, certolizumab, etanercept, and tocilizumab IV [8 mg/kg]). When Inflectra was compared with other bDMARDs used for AS or PsA (excluding Remicade), it was the most expensive option, with the exception of ustekinumab used for PsA. When used for PsO, Inflectra was more expensive than adalimumab, but it was less expensive than etanercept and ustekinumab. Patient weight and the proportion of patients requiring dose escalation with infliximab will impact the relative cost of Inflectra compared with other bDMARDs.

8. DISCUSSION

Biological agents are important treatment options for rheumatic diseases, psoriasis, and bowel diseases. According to the EULAR recommendations for the management of RA, biological treatments should be considered if conventional DMARD strategies have not achieved remission or low disease activity.[16] A biosimilar product is designed to be comparable to an innovator that is already part of clinical practice. While such products provide potentially cost-effective treatment options for patients, the molecular complexity of biologics compared with other drugs requires close scrutiny of their pharmacokinetics, efficacy, safety, and immunogenicity.

The Canadian Rheumatology Association, the Ontario Rheumatology Association, the Canadian Dermatology Association, and the Canadian Association of Gastroenterology have released position statements on SEBs. While they are supportive of the potential benefits of SEBs with respect to cost and patient choice, they have also voiced several common concerns pertaining to issues of interchangeability and the need for ongoing post-marketing surveillance.[17-20] The automatic substitution of an SEB by dispensing pharmacies, as is done with non-biologics, is not recommended by those associations or by Health Canada. Also, post-marketing surveillance data are needed to monitor for long-term, unanticipated AEs.

Infliximab (Remicade) has been used in clinical practice for several years and has a demonstrated efficacy profile in RA, AS, PsO, PsA, Crohn disease, and ulcerative colitis. The clinical trials PLANETRA and PLANETAS provided evidence that the biosimilar, CT-P13, is comparable to Remicade in patients with RA and AS. In addition, single-arm extension studies have demonstrated the maintenance of efficacy and safety up to two years. However, uncertainties remain regarding the applicability of these results to real-world patients who will be routinely encountered in clinical practice. Therefore, it will be essential to evaluate CT-P13 post-marketing data and accumulated clinical experience in the coming years.

Health Canada's decision to limit the extrapolation of CT-P13 to PsA and PsO —a more cautious approach than the EMA has taken — seems reasonable at this time. Results from ongoing studies, such as clinical trials in Crohn disease and ulcerative colitis and five-year observational studies, will provide more data on which to base clinical and regulatory decisions for using CT-P13 in inflammatory bowel diseases.

APPENDIX 1: ADDITIONAL DATA

TABLE 1: DETAILED METHODS AND RESULTS OF PHYSICOCHEMICAL TEST METHODS FOR COMPARABILITY OF INFLECTRA (IFT) DRUG PRODUCT VS. REMICADE (RMP)

Test Method(s)	Summary of Results	Reference(s)
Primary structure (CTD Module 3.2.R.5.2.2, p. 19–53)		
Amino Acid Analysis	• Amino acid analysis was performed, which involved hydrolysis of peptide bonds followed by analysis using RP-HPLC with fluorescence detection. • The molar ratio of the amino acids for multiple batches of each of the IFT and RMP were analyzed. • For all robust amino acids (% deviation between observed and expected results ≤ 5%) that were not subjected to conversion or degradation during acid hydrolysis, their **molar ratios for both IFT and RMP matched the expected ratios**. These amino acids include aspartic acid, glutamic acid, histidine, glycine, threonine, arginine, alanine, phenylalanine, isoleucine, proline and leucine (Table 3.2.R-4).	CTD Module 3.2.R.5.2.1, Table 3.2.R-4 (p. 19–20)
Peptide Mapping (LC-MS) in combination with MS/MS	• Peptide mapping were analyzed by LC-MS after reduction and alkylation. After incubation of both IFT and RMP with trypsin or Asp-N (see Figure 3.2.R-1 for digestion sites), the digested peptides was then separated by RP-HPLC. An online mass spectrometer with an electrospray source was used in-line after the UV detector to collect mass spectra of the intact peptide as well as to fragment the peptides for sequencing (MS/MS analysis). • The peptide sequence coverage was 100% for heavy chain and 100% for light chain for all samples tested. • **The detected peptides of IFT drug product and RMP matched the expected peptides from the amino acid sequence (Tables 3.2.R-5 through 3.2.R-16)**. The data support the notion that the primary structure of IFT and RMP are identical.	CTD Module 3.2.R.5.2.1, Figure 3.2.R-1, Tables 3.2.R-5 thru 3.2.R-16 (p. 21–40)
Peptide Mapping by HPLC	• In addition to the peptide mapping analysis by LC-MS described above, IFT drug product and RMP were analyzed by HPLC peptide mapping after tryptic digestion. • The resulting peptide maps (chromatograms) were visually compared between samples. • **Visual inspection of the chromatograms indicated there is no significant difference (missing peaks or additional peaks) between samples (Figure 3.2.R-2)**. These data further confirm the similarity of primary structure between samples. • The validated method employed for QC stability testing was employed for this purpose. Validated UV based tryptic peptide map results showed comparable chromatograms for IFT drug product and RMP.	CTD Module 3.2.R.5.2.1, Figure 3.2.R-1, Figure 3.2.R-2 (p. 22,41–44)
Post-translational Modifications by Peptide Mapping	• Peptide mapping was also used as a means to identify the post-translational modifications to which IFT and RMP are subject. • **Glycosylation:** the level of aglycosylated protein (Asn300) was shown to be below the limit of quantitation for all IFT drug product and RMP batches tested (see below and Module 3.2.R.5.2.5). • **Deamidation** of asparagine, deamidation was detected at [redacted] (see below and Module 3.2.R.5.2.4).	CTD Module 3.2.R.5.2.1 (p. 45)

Test Method(s)	Summary of Results	Reference(s)
	• **Peptide mapping confirmed that C-terminal lysine variability is a feature of infliximab** (see below and Module 3.2.R.5.2.1 and Module 3.2.R.5.2.4).	
N-Terminal Sequencing	• The N-terminal sequences of IFT drug product and RMP were subjected to peptide mapping in combination with MS/MS, a state-of-the-art for protein sequencing. • Trypsin was employed for proteolytic digestion, and the peptides were separated by RP-HPLC. An online mass spectrometer with an electrospray source was used in-line after the UV detector to collect mass spectra of the intact peptide as well as to fragment the peptides for sequencing (MS/MS analysis). • The identities of peptides from heavy and light chains were confirmed by interpretation of corresponding MS/MS spectra. For each peptide, a representative MS/MS spectrum was selected and matched against that of the expected fragmented peptide. • **For IFT drug product and RMP, the N-terminal of light chain ([redacted]) and the heavy chain (residues 1-19) matched the expected sequence (Table 3.2.R-17).**	CTD Module 3.2.R.5.2.1 Table 3.2.R-17 (p. 46–48)
C-Terminal Sequencing	• The C-terminal sequences of IFT drug product and RMP were subjected to peptide mapping in combination with MS/MS. • Lys-C was employed for proteolytic digestion, and the peptides were separated by RP-HPLC. An online mass spectrometer with an electrospray source was used in-line after the UV detector to collect mass spectra of the intact peptide as well as to fragment the peptides for sequencing (MS/MS analysis). • The identities of peptides from heavy and light chains were confirmed by interpretation of corresponding MS/MS spectra. For each peptide, a representative MS/MS spectrum was selected and matched against that of the expected fragmented peptide. • **For IFT drug product and RMP, the C-terminal of light chain (residues 208-214) and the heavy chain ([redacted]) matched the expected sequence (Table 3.2.R-18).**	CTD Module 3.2.R.5.2.1 Table 3.2.R-18 (p. 46, 49)
Reduced Mass	• Cysteine bonds of the IFT drug product and RMP were reduced with DTT followed by LC-ES-MS analysis. • For all samples tested, IFT drug product and RMP, reduced mass analysis yielded a single prominent mass for the light chain and the observed mass closely match with the expected mass (Table 3.2.R-19, Figure 3.2.R-4). Moreover, the data further confirm that the light chain is not glycosylated. The differences in mean masses for the light chain are within the analytical variation of the method. • Reduced mass analysis yielded all six possible masses for the heavy chain corresponding to [redacted] (Table 3.2.R-19, Figure 3.2.R-3). • [redacted].	CTD Module 3.2.R.5.2.1, Table 3.2.R-19, Figure 3.2.R-3, Figure 3.2.R-4 (p. 50–53)

Test Method(s)	Summary of Results	Reference(s)
	• Further discussion in relation to IFT and RMP C-terminal lysine variability is provided below.	
Higher Order Structure (CTD Module 3.2.R.5.2.2, p. 54–72)		
Positioning of Disulphide Bonds	• IFT drug product and RMP were analyzed by comparing native and reduced peptide maps. Samples were reduced with DTT and alkylated with sodium iodoacetate for the reduced peptide mapping analysis, but no reduction was carried out for the non-reduced mapping analysis. • The samples were digested using trypsin and the resulting peptides were separated by RP-HPLC. An online mass spectrometer with an electrospray source was used in-line after the UV detector to collect mass spectra of the intact peptide as well as to fragment the peptides for sequencing (MS/MS analysis). • Based on the MS and MS/MS sequencing analysis, [redacted] were identified as disulphide bond linked peptides. **These [redacted] linked peptides were matched in all samples (Tables 3.2.R-21, 3.2.R-23, and 3.2.R-23)** and the disulphide bond linkages of all samples were assigned as in Figure 3.2.R-5.	CTD Module 3.2.R.5.2.2, Table 3.2.R-21, Table 3.2.R-22, Table 3.2.R-23, Figure 3.2.R-5 (p. 54–56)
Free Thiol Analysis	• The free thiol groups (SH) in IFT drug product and RMP batches were determined by means of the DTNB method (Ellman's assay). • **The moles of free SH groups per mole IgG were between [redacted] for all IFT drug product batches subjected to analysis and is highly similar to the RMP batches that fell with a range of [redacted]** (Table 3.2.R-24).	CTD Module 3.2.R.5.2.2, Table 3.2.R-24 (p. 57)
Fourier Transform Infrared Spectroscopy (FTIR)	• Secondary structure of IFT drug product ([redacted]) and RMP ([redacted]) was evaluated by FTIR analysis. • FTIR spectra were analyzed by comparison of the location and shape of the amide I and amide II bands and of four other bands between 1,000 and 1,500 cm^{-1}. • For all samples, FTIR spectra agreed well with respect to shape and location of the [redacted] (Table 3.2.R-25, Figure 3.2.R-6). • **Thus, IFT is considered to be highly similar to RMP with regards to secondary structure, as determined by FTIR.** • Note: The amide I and amide II bands are the two most prominent vibrational bands of the protein backbone. The most sensitive spectral region of the protein secondary structural components is the amide I region. The frequencies of the amide I band components are known to be correlated closely to the secondary structural elements of a protein. In contrast, the amide II region is much less sensitive than the amide I region, and therefore provides less insight into secondary structural elements. Thus, usually the amide I FTIR spectrum alone is considered sufficient to provide confirmation of the overall structural integrity of a monoclonal antibody. In this regard, the minor differences seen in Amide II FTIR spectra between IFT and the RMP are not considered meaningful.	CTD Module 3.2.R.5.2.2, Table 3.2.R-25, Figure 3.2.R-6 (p. 58–60)
Circular Dichroism (CD)	• CD spectroscopy was performed to compare protein secondary and tertiary structure between IFT and RMP samples. • The near UV spectrum of IFT and RMP shows the typical shape of an antibody with a high maximum around [redacted] and the fine structure	CTD Module 3.2.R.5.2.2, Table 3.2.R-26, Figure 3.2.R-7,

Test Method(s)	Summary of Results	Reference(s)
	between [redacted] resulting from the aromatic amino acids and cysteines **in the tertiary structure of the protein (Figure 3.2.R-7)**. **No significant differences between the samples were observed**. The variability in the duplicate measurements was in the same magnitude as the variability between the samples (Table 3.2.R-26). • The far UV spectrum of IFT and RMP shows the typical shape of an antibody with a minimum at [redacted] and a maximum at [redacted], **suggesting a secondary structure dominated by ß-sheet motif (Figure 3.2.R-8). No significant differences between the different samples were observed**. The variability in the duplicate measurement was in the same magnitude as the variability between the samples (Table 3.2.R-26).	Figure 3.2.R-8 (p. 61–65)
Differential Scanning Calorimetry (DSC)	• The thermal stability of IFT drug product and RMP samples were evaluated by measuring their melting temperature values by means of DSC. • Three transitions temperatures were identified (at about [redacted]) for both IFT and RMP, and these temperatures agreed well with their respective thermograms (Table 3.2.R-27, Figure 3.2.R-9). • According to a relevant literature, those three transition temperatures are related with CH2, Fab, and CH3 domains of IgG proteins, respectively. • The similar thermal unfolding profiles and thermal transition midpoint temperatures indicate that **the thermal stability and conformation of IFT batches are comparable to those for RMP**. • Note: [redacted]	CTD Module 3.2.R.5.2.2, Table 3.2.R-27, Figure 3.2.R-9 (p. 66–72)
Purity/Impurity (CTD Module 3.2.R.5.2.3, p. 72–79)		
SEC-HPLC	• SEC-HPLC was performed under non-denaturing conditions for IFT drug product and RMP. • **All IFT drug product and RMP samples tested showed prominent monomer peaks within a comparable range ([redacted])(Table 3.2.R-28).** • All batches of IFT drug product and RMP showed only a single peak for high molecular weight (HMW) species, which were all below 0.7% for both IFT ([redacted]) and RMP ([redacted]) batches. • It is noted that the RMP European Public Assessment Report (EPAR) provides some insight into the batch-to-batch monomer content variability that was considered acceptable for the RMP at the time of licensing. Specifically, the RMP EPAR states that the product specification for monomer content by gel filtration (GF)-HPLC was set at ≥98.0%. **Therefore, all batches of IFT drug substance and drug product tested fall well within this range.**	CTD Module 3.2.R.5.2.3, Table 3.2.R-28 (p. 72–73)
CE-SDS (Reduced/Non-Reduced)	**NON-REDUCING** • CE-SDS was performed under both non-reducing and reducing conditions for analysis of purity/impurities, an overview of the CE-SDS results are shown in Table 3.2.R-29. Results indicated that the under reducing condition, the amount of intact IgG is slightly lower for IFT drug product ([redacted]) relative to RMP ([redacted]). • Non-reducing conditions were used for determination of levels of	CTD Module 3.2.R.5.2.3, Table 3.2.R-29, Figure 3.2.R-10, Figure 3.2.R-11, Figure 3.2.R-12, Figure 3.2.R-13, Table

Test Method(s)	Summary of Results	Reference(s)
	intact IgG (H2L2) and any detectable non-assembled antibody species. Under this condition, 6 bands were identified for IFT and RMP in SDS-PAGE gel (Figure 3.2.R-10). Each of the bands were extracted and purified and the purity was further confirmed by means of SDS-PAGE analysis (Figure 3.2.R-11). • Each band was then excised and subject to LC/MS analysis. As infliximab is subject to post-translational modifications such as glycosylation, and presents with C-terminal lysine variability (as described above), therefore multiple peaks corresponding to each band were detected for both IFT (Figure 3.2.R-12) and RMP (Figure 3.2.R-13), as expected. [redacted]; and **results indicated that IFT and RMP display the same types of IgG fragments (Table 3.2.R-30).** • In relation to these data, the fragment is composed of two heavy chains and one light chain, which constitutes the "main" non-assembled IFT form. To investigate the biological activity of this fragment, 3 samples with differing amounts of H2L1 fragment were tested. The results of this study demonstrated that up to [redacted] difference in the amount of H2L1 fragment has no detectable effect on TNF-alpha binding affinity (ELISA) or in vitro TNF-alpha neutralization activity. ***Assessment of Amount of Intact IgG and IgG Fragments*** • Available data show that both products display the same "array" of six IgG molecular variants (fragments). Specifically, the six molecular variants detected for both IFT drug product and RMP are: (1) two heavy chains and two light chains, H2L2 [the intact IgG monomer]; (2) two heavy chains and one light chain, H2L1; (3) two heavy chains, H2; (4) one heavy chain and one light chain, H1L1; (5) one heavy chain, H1; (6) one light chain, L1. In relation to these data (and as discussed in Module 3.2.S.3.2), the H2L1 fragment constitutes the "main" non-assembled IFT form (> 50% of all fragments and non-assembled forms) and is responsible for much of the aforementioned difference in intact IgG content between IFT and the RMP. • With regard to the above noted difference between IFT drug product and RMP with respect to the amount of intact IgG ([redacted], respectively), CHMP/437/04 (Guideline on Similar Biological Medicinal Products) states the following: *"Any differences between the similar biological medicinal product and the reference medicinal product will have to be justified by appropriate studies on a case-by-case basis."* Therefore, in order to investigate the implications of differing amounts of this infliximab molecular variant (H2L1), the Applicant prepared three samples with differing amounts of H2L1 from IFT ([redacted], respectively; refer to Module 3.2.S.3.2 for details). Their TNF-alpha binding affinity (as determined by ELISA) and potency by means of in vitro TNF-alpha neutralization was then assessed.	3.2.R-30 (p. 73–79) CTD Module 3.2.R.5.3, Figure 3.2.R-28, Figure 3.2.R-29, Figure 3.2.R-30, Table 3.2.R-82, Table 3.2.R-83 (p. 136–152)

Test Method(s)	Summary of Results	Reference(s)
	TNF-alpha Binding Affinity (ELISA) • ELISA results showed that the following for each of the sample: [redacted] • Therefore, no discernible trend between H2L1 content and TNF-alpha binding affinity in samples with a difference of up to 3.1% H2L1 fragment. In Vitro TNF-alpha neutralization • In the case of potency as measured by in vitro TNF-alpha neutralization, results showed that the following for each of the sample: [redacted] • Therefore no discernible trend between H2L1 content and in vitro TNF-alpha neutralization in samples with a difference of up to [redacted] H2L1 fragment. Conclusion • [redacted] • [redacted] • [redacted] • [redacted] (82). [redacted] • [redacted] • [redacted]	

Test Method(s)	Summary of Results	Reference(s)
	[redacted]. • In relation to this, the PK of IFT at off target models in rats was comparable to that of RMP (refer to Module 4.2.2.2, available upon request), and the non-reduced CE-SDS profiles of antibody was not changed after 1 day of administration in humans (83) therefore, H2L1 is stable in vivo. • Furthermore, immunogenicity testing (CTD Module 5 and Module 2.7.2.4.1.1 for further information) revealed minor difference in intact IgG fragment content but does not have discernible impact on immunogenicity using the sensitive assay applied in the clinical study program, which showed roughly an equivalent incidence of antibodies against IFT and RMP. • Finally, IFT drug product is entirely stable when stored at 5±3°C, and the amount of H2L1 fragment does not increase during storage (Module 3.2.P.8). • **In conclusion, the difference of intact IgG level documented above does not impact safety or efficacy, and therefore IFT and RMP can be considered comparable in this regard.** **REDUCING** • Reducing CE-SDS was performed for determination of purity by sum of heavy and light chain (H+L). It is noteworthy that the validated method employed for QC product release and stability testing was employed for this purpose. **Under reduced conditions, comparable results were obtained for IFT and RMP; all samples were within a similar range of [redacted].**	
Charged Isoforms (CTD Module 3.2.R.5.2.4, p. 80–97) • Within this sub-section, discussion pertaining to IFT and RMP charged molecular variants is provided. There are a number of post-translational modifications that have the potential to influence IFT charge heterogeneity, notably, C-terminal lysine variability, product deamidation, oxidation and sialidation, all of which (with the exception of glycosylation which is discussed in a separate sub-section) is summarized below.		
IEF	• Isoelectric focusing (IEF) gel analysis was used to determine pI values of charge variants in IFT drug product and RMP samples. • **The results from IEF analysis in show that all samples resulted in 7 bands (Figure 3.2.R-14), and that the calculated pI values of the seven bands are comparable and fall within similar ranges for IFT samples compared with RMP (3.2.R-14).** • It is noteworthy that the seven bands (from band 1 to band 7) are the part of quality control for routine IEF analysis. • [redacted].	CTD Module 3.2.R.5.2.4, Figure 3.2.R-14, Table 3.2.R-31 (p. 80–83)
IEC-HPLC	• The IEC-HPLC method was used to evaluate distribution of charge variants using cation exchange chromatography; a total of six charge variants were separated and detected by this method (Table 3.2.R-32). • Peaks in the IEC-HPLC chromatogram were integrated and percentage peak areas of each peak were calculated. Results	CTD Module 3.2.R.5.2.4, Table 3.2.R-32, Figure 3.2.R-15, Figure 3.2.R-16, Table 3.2.R-33, Table

Test Method(s)	Summary of Results	Reference(s)
	indicated that the relative proportion (peak ratio) of the 6 IEC-HPLC peaks displays some differences between IFT and RMP (Table 3.2.R-32), and these differences led to additional investigation below. • In order to characterize these 6 IEC-HPLC peaks, and to understand the relationship between the seven bands observed by IEF (above) and the six peaks observed by IEC-HPLC, a peak fractionation study using IFT and RMP was performed; these data serve as a means to confirm that the IEC-HPLC peak assignment made for IFT is also applicable to the RMP; **results demonstrated that each of the peaks eluted at the same time between IFT and RMP (Figure 3.2.R-15).** • Each of the 6 IEC-HPLC fractions were then assessed by means of IEF (Figure 3.2.R-16); the **resulting pI value(s) of each peak are comparable to those presented in the IEC section above (Tables 3.2.R-33 and 3.2.R-34).** For both IFT and RMP, tryptic peptide mapping was then performed on the six peaks separated by IEC-HPLC in order to determine the structure of the infliximab molecular variant(s) associated with each of the 6 IEC-HPLC fractions (peaks); the results indicated that the relative amount of the peaks displayed differences (Table 3.2.R-35) (and further studies to elucidate the difference are found at the bottom). • [redacted] • Given that IEC-HPLC is routinely performed during IFT drug substance and drug product QC release, in order to develop an appropriate control strategy for IFT, the biological activity of the 6 IEC-HPLC peak fractions with respect to TNFα neutralization activity and TNFα binding affinity by ELISA were assessed against RMP (see Table 2, Appendix 1 below for description of these assays). • The biological activities between IFT and RMP were found to be comparable in the TNFα neutralization assay (Table 3.2.R-36) and TNFα binding affinity by ELISA (Table 3.2.R-37). ***Assessment of Peak Differences Observed in IEC-HPLC*** • With regard to the above noted difference between IFT and RMP in the relative proportion (peak ratio) of the 6 IEC-HPLC peaks, CHMP/437/04 (Guideline on Similar Biological Medicinal Products)	3.2.R-34, Table 3.2.R-35, Figure 3.2.R-17, Table 3.2.R-36, Table 3.2.R-37 (p. 84–95) CTD Module 3.2.R.5.3, Figure 3.2.R-25, Table 3.2.R-75, Figure 3.2.R-26, Table 3.2.R-76, Table 3.2.R-77, Table 3.2.R-80, Table 3.2.R-81, Figure 3.2.R-27 (p. 136–146)

Test Method(s)	Summary of Results	Reference(s)
	states the following: *'Any differences between the similar biological medicinal product and the reference medicinal product will have to be justified by appropriate studies on a case-by-case basis.'* • Therefore, 3 separate approaches were adopted to investigate whether or not C-terminal variability was responsible for the observed difference: <u>Carboxypeptidase B</u> • The first approach involved incubation of IFT and RMP with the enzyme CPB in order to eliminate C-terminal lysine variability that might be responsible for said difference. • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • Results indicated that the TNFα neutralizing activity did not differ between pre- and post-CPB samples for either IFT and RMP (Table 3.2.R-77). <u>C-Terminal Lysine Clipping by IgG-Free Serum</u> • The second approach involved incubation of IFT and RMP with IgG-free human serum in order to eliminate C-terminal lysine variability that might be responsible for the observed peak proportion difference. • [redacted] • [redacted] • [redacted] • The rate of C-terminal clipping was highly similar for IFT and RMP. • The effect of C-terminal lysine clipping on TNFα binding affinity was measured by ELISA and results indicate that intact samples and the C-	

Test Method(s)	Summary of Results	Reference(s)
	terminal lysine truncated samples showed similar TNFα binding affinity (data available upon request). <u>C-Terminal Lysine Clipping In Vivo</u> • The third approach involved the analysis of clinical blood samples to monitor the rate of C-terminal lysine clipping in vivo in order to confirm the in vitro human serum experiment presented above. • 12 blood samples taken from patients of Study IFT 1.2: 8 patients immediately and 1 h post infusion, following Doses 1, 3, and 6. Samples from 5 and 3 patients treated with IFT and RMP, respectively, were pooled for each time point and were assayed for C-terminal lysine content. • C-terminal lysine was not detected in most samples, with only minor levels being detected in samples from patients treated with IFT Dose 1 (namely 3.11% and 0.4% immediately and 1 h post infusion). • This indicates rapid cleavage of the C-terminal lysine residues in blood following administration. <u>Conclusion</u> • Based on the sum of data presented above, it was demonstrated that the difference observed between IFT and RMP with respect the relative proportion (peak ratio) of the 6 IEC-HPLC peaks is attributable to C-terminal lysine variability. • More importantly, it has been shown that C-terminal lysine variability holds no bearing on biological activity in vitro, and that C-terminal lysine clipping occurs rapidly both in vitro and in vivo, suggesting that nearly all infliximab molecules are fully clipped within several hours following dosing. • [redacted]. • **Taking all of these data into account, the difference in the relative proportion of the 6 IEC-HPLC peaks can be considered as having no implications for product safety or efficacy, and therefore, IFT and RMP can be considered comparable in this regard.**	
Product Oxidation	• As part of the extended characterization exercise, analysis of the oxidized species in IFT and RMP has been undertaken for the purpose of demonstrating comparability utilizing peptide mapping. • Peptide mapping were analyzed by LC-MS after reduction and alkylation; which involved incubation of both IFT with trypsin or Asp-N, the digested peptides is then separated by RP-HPLC. An online mass spectrometer with an electrospray source was used in-line after the UV detector to collect mass spectra of the intact peptide as well as to fragment the peptides for sequencing (MS/MS analysis). • In order to gauge the amount of molecular variants with oxidation at methionine 255, multiple batches of IFT drug products and RMP were analyzed following approximately 1–13 months storage at 2–8oC. Results indicated low level of oxidation ([redacted]) for both IFT drug	CTD Module 3.2.R.5.2.4, Table 3.2.R-41, Table 3.2.R-42, Table 3.2.R-43 (p. 95–97)

Test Method(s)	Summary of Results	Reference(s)
	product and RMP (Table 3.2.R-41). • Oxidization following storage of IFT and the RMP under various conditions, and for various storage periods were also test. IFT drug product stability samples (long-term, accelerated, stress) and RMP samples (long-term, accelerated, stressed) were analyzed by LC-MS peptide mapping after reduction, alkylation and digestion with trypsin and separated by reversed-phase HPLC. Selected ion chromatograms (SIC) were used to quantify the amount of oxidized species. The samples analyzed are outlined in Table 3.2.R-42. • **In terms of a comparability assessment between IFT and the RMP, both products showed highly similar amounts of oxidized molecular variants (Table 3.2.R-43)**. Any minor differences observed between IFT and the RMP could be impacted by differences in the 'age' of the product at the time of testing, or the start of the respective stability study. However, the results are consistent for the [redacted] tested. Additional data and discussion in respect of product oxidation can be located in Module 3.2.P.8 as part of the forced degradation study.	
Glycosylation (3.2.R.5.2.5, p.98-109)		
Site Specific and N-Linked Glycan Analysis by Means of LC-MS Peptide Mapping	• LC-MS analysis of the peptides generated during peptide mapping was employed as a means to identify all sites of glycosylation. • Samples were prepared as described in the peptide mapping section using reduction, alkylation and tryptic digestion. Selected ion chromatograms were used to quantify each oligosaccharide species. The percentage calculation was based on each glycosylation site. For that site, all the detectable oligosaccharide structures were counted. • It is noteworthy that the level of aglycosylated protein was below the limit of quantitation (<1.0%) for all IFT drug substance and drug product samples. • **Asn300 was shown to be the only site of N-glycosylation for both IFT and RMP. No O-linked glycans were detected, as one might expect for an IgG1 monoclonal antibody, for IFT or the RMP.** • **Both IFT drug product and RMP were shown to contain mostly G0F and G1F structures. Minor species including Man5, G2F, G0F minus GlcNAc, and G0 were detected (Table 3.2.R-44 and Table 3.2.R-45).** • The glycan micro-heterogeneity associated with IFT closely reflects the heterogeneity observed with respect to RMP. [redacted], the types as well as the relative proportion of the various glycan species were shown to be highly conserved between IFT and the RMP. • The two charged glycan species identified by this method were G1F1NeuGc and G2F1NeuGc; analysis of sialic acid content is discussed below under Sialic Acid Analysis.	CTD Module 3.2.R.5.2.5, Table 3.2.R-44, Table 3.2.R-45 (p. 98–100)
Oligosaccharide Profiling	• To further characterize the glycan micro-heterogeneity associated with this single site of N-glycosylation (Asn300), glycans were enzymatically cleaved from IFT and RMP and resolved using chromatography and the released glycans were analyzed by HPAEC-PAD. • Typical oligosaccharide profiles of monoclonal antibodies show five peaks which include: G0F (absence of terminal Gal), G1F+G1'F (one	CTD Module 3.2.R.5.2.5, Table 3.2.R-46, Figure 3.2.R-18 (p. 100–104)

Test Method(s)	Summary of Results	Reference(s)
	terminal Gal, in one of two positions, G1 or G1'), G2F (two terminal Gals), Man5 and G0 structures. • **HPAEC-PAD data reveal that the type and proportion of the uncharged glycans is conserved between IFT and the RMP (Table 3.2.R-46; representative chromatograms: Figure 3.2.R-18).** • [redacted]	
Monosaccharide Analysis	• Monosaccharide analysis of neutral and amino sugars was performed by hydrolyzing the samples followed by chromatography analysis of the contents. • **The identified sugars were Fuc, GlcNAc, Gal and Man; both IFT and RMP had similar molar ratios for the four sugars (Table 3.2.R-47; Figure 3.2.R-19).** • **The molar ratio of neutral and amino sugars was observed to be highly similar for IFT drug product and RMP.**	CTD Module 3.2.R.5.2.5, Table 3.2.R-47, Figure 3.2.R-19 (p. 104–106)
Sialic Acid Analysis	• Sialic acid is the collective name for neuraminic acid, and its derivatives. The most commonly occurring forms of neuraminic acid are N-acetylneuraminic acid (NANA) and N-glycolylneuraminic acid (NGNA). Glycoproteins expressed by mammalian cell lines may have glycans capped by sialic acids. In this regard, the peptide mapping LC-MS data above revealed the presence of G2F1NeuGc. • In order to further investigate the proportion of charged glycans associated with IFT and RMP, sialic acid analysis was conducted. • For the analysis of sialic acid species (e.g., NANA and NGNA), sialic acids were released from antibody by mild acid hydrolysis and pulsed amperometric detection (HPAEC-PAD) was used for the analysis. • Sialic acid was detected in the form of NGNA (N-glycolylneuraminic acid) in all samples; whereas NANA was not detected. • **The data confirm that IFT samples contain the same type as well as highly similar levels of sialic acid (expressed as molar ratios) when compared to RMP (Table 3.2.R-48, Figure 3.2.R-20).**	CTD Module 3.2.R.5.2.5, Table 3.2.R-48, Figure 3.2.R-20 (p. 107–109)
Content (Module 3.2.R.5.2.6, p.120-121)		
Protein Concentration	• The protein content IFT drug product and RMP samples were determined spectrophotometrically by measuring absorbance at UV 280 nm with background correction at 320nm to 350 nm. • Product specific ELISA analysis was also employed as an orthogonal methodology. TNFα coated plates and anti-human kappa light chain secondary antibody were used for this ELISA analysis. • The protein content of IFT drug product and RMP batches was comparable as demonstrated by both UV 280 nm and ELISA (Table 3.2.R-60).	CTD Module 3.2.R.5.2.6, Table 3.2.R-60 (p. 120–121)

Source: CTD 2.3.R, Table 2.3.R-1; CTD Module 3.2.R.

TABLE 2: SUMMARY OF STUDIES COMPARING BIOLOGICAL ACTIVITY BETWEEN INFLECTRA (IFT) DRUG PRODUCT AND REMICADE (RMP)

Test Method(s)	Summary of Results	Reference(s)
In Vitro TNF-alpha Neutralization Activity	• In vitro human TNF-alpha neutralization assay was developed to investigate the effects of the anti-TNF-alpha monoclonal antibody upon the viability of [redacted] cell line treated with hTNF-alpha. • It is noteworthy that the validated method employed for QC product release and stability testing was employed for this purpose. • **The average relative potency of the [redacted], respectively, thus considered comparable with regards to in vitro TNFα neutralizing activity (Table 3.2.R-61).**	CTD Module 3.2.R.5.2.7, Table 3.2.R-61 (p. 122–123)
Cell-Based Binding Affinity	• ELISA was used to measure the TNF-alpha binding affinity of IFT and RMP batches to the transmembrane (tm) TNF-alpha expressing cell line, tmTNF-alpha Jurkat cells. • The cells were immobilized onto the plate and incubated with IFT drug product or RMP. Binding affinity to tmTNF-alpha Jurkat cell line was measured using an HRP-labelled anti-human IgG (gamma) antibody followed by TMB (3, 3', 5, 5' tetramethylbenzidine) mediated detection. • The relative potency of samples was determined from the comparison of the mean EC50 (effective concentration yielding a 50% response) of the reference standard to the mean EC50 of the sample. • **The total mean relative binding affinities for [redacted], respectively (Table 3.2.R-65), therefore IFT and RMP can be considered comparable in this regard.**	CTD Module 3.2.R.5.2.7, Table 3.2.R-65 (p. 126)
TNF-alpha Binding Affinity (SPR)	• The binding affinity of IFT and RMP to TNFα was measured using SPR (surface plasmon resonance). • As IFT and RMP bind to the TNF-alpha fixed on the chip, the accumulation of protein results in an increase in the refractive index, which are measured as a KD value relative to a reference standard. • **The total mean relative binding affinity of the [redacted] (Table 3.2.R-70), therefore IFT and RMP can be considered comparable in this regard.**	CTD Module 3.2.R.5.2.7, Table 3.2.R-70 (p. 131)
TNF-alpha Binding Affinity (ELISA)	• A direct ligand-binding assay to determine antibody binding affinity was used to support the biological comparability of IFT and RMP. The binding affinity of IFT drug product and RMP batches was measured by ELISA using TNF-alpha protein as the coating antigen. • The relative potency of each test article was determined from the comparison of the mean EC50 (effective concentration yielding a 50% response) of the reference standard to the mean EC50 of the infliximab test article. • **The average relative binding affinity [redacted]; and for the [redacted] RMP examined, the average relative binding affinity was [redacted] (Table 3.2.R-71), therefore IFT and RMP can be considered comparable with regards to in vitro TNF-alpha binding affinity as determined by ELISA.**	CTD Module 3.2.R.5.2.7, Table 3.2.R-71 (p. 132)

Test Method(s)	Summary of Results	Reference(s)
Comparative TNF-alpha binding affinity from different species using SPR	• For IFT drug product and RMP, neither product displayed binding affinity for mouse, rat, canine, porcine, or rhesus monkey TNF-alpha.	BSEAR Non-Clinical: Tox & Pharm, p. 8–9; vii)
Human TNF-beta binding specificities	• Neither IFT drug product nor RMP had binding affinity toward hTNF-beta.	BSEAR Non-Clinical: Tox & Pharm, p. 11; xii)
Human tissue cross-reactivity using immunohisto-chemistry	• The tissue cross-reactivity of biotinylated IFT and biotinylated RMP were shown to be comparable using a panel of human tissues.	BSEAR Non-Clinical: Tox & Pharm, p. 11–12; xiii)

Source: CTD 2.3.R, Table 2.3.R-1; CTD Module 3.2.R.5.

TABLE 3: PROPORTION OF PATIENTS ACHIEVING CLINICAL RESPONSE ACCORDING TO ACR20, ACR50, AND ACR70 AT WEEKS 14, 30 AND 54 (EXACT BINOMIAL METHOD) BETWEEN INFLECTRA AND REMICADE: ALL-RANDOMIZED POPULATION (STUDY CT-P13 3.1, PLANETRA)

ACR Scores	n/N (%)		Estimate of treatment difference[a]	95% CI of treatment difference
	Inflectra	Remicade		
Week 14 – ACR20	192/302 (63.6)	175/304 (57.6)	0.06	–0.02, 0.14
Week 14 – ACR50	100/302 (33.1)	91/304 (29.9)	0.03	–0.04, 0.11
Week 14 – ACR70	42/302 (13.9)	37/304 (12.2)	0.02	–0.04, 0.07
Week 30 – ACR20	184/302 (60.9)	178/304 (58.6)	0.02	–0.06, 0.10
Week 30 – ACR50	107/302 (35.4)	103/304 (33.9)	0.02	–0.06, 0.09
Week 30 – ACR70	50/302 (16.6)	47/304 (15.5)	0.01	–0.05, 0.07
Week 54 – ACR20	172/302 (57.0)	158/304 (52.0)	0.05	–0.03, 0.13
Week 54 – ACR50	100/302 (33.1)	96/304 (31.6)	0.02	–0.06, 0.09
Week 54 – ACR70	49/302 (16.2)	46/304 (15.1)	0.01	–0.05, 0.07

[a] Estimate of the difference in proportions between the two treatment groups (Inflectra – Remicade) using the exact binomial test.

Source: CSR CT-P13 3.1, Table C48 (35 - CT-P13 3.1_Table C48_ACR AR)

TABLE 4: PROPORTION OF PATIENTS ACHIEVING CLINICAL RESPONSE ACCORDING TO ACR20, ACR50, AND ACR70 AT WEEKS 14, 30 AND 54 (EXACT BINOMIAL METHOD) BETWEEN INFLECTRA AND REMICADE: PER-PROTOCOL POPULATION (STUDY CT-P13 3.1, PLANETRA)

ACR Scores	n/N (%)		Estimate of treatment difference[a]	95% CI of treatment difference
	Inflectra	Remicade		
Week 14 – ACR20	[redacted]	[redacted]	[redacted]	[redacted]
Week 14 – ACR50	[redacted]	[redacted]	[redacted]	[redacted]
Week 14 – ACR70	[redacted]	[redacted]	[redacted]	[redacted]
Week 30 – ACR20	[redacted]	[redacted]	[redacted]	[redacted]
Week 30 – ACR50	[redacted]	[redacted]	[redacted]	[redacted]
Week 30 – ACR70	[redacted]	[redacted]	[redacted]	[redacted]
Week 54 – ACR20	[redacted]	[redacted]	[redacted]	[redacted]
Week 54 – ACR50	[redacted]	[redacted]	[redacted]	[redacted]
Week 54 – ACR70	[redacted]	[redacted]	[redacted]	[redacted]

[a] Estimate of the difference in proportions between the two treatment groups (Inflectra – Remicade) using the exact binomial test.
Source: CTD Module 2.7.3, Tables 2.7.3-11 and 2.7.3-18

TABLE 5: ANALYSIS OF DAS28 (ANCOVA) BETWEEN INFLECTRA AND REMICADE: PER-PROTOCOL POPULATION (STUDY CT-P13 3.1, PLANETRA)

Population	Adjustment Mean (SE)				Estimate of treatment difference[a]	95% CI of treatment difference
	N	Inflectra	N	Remicade		
ESR						
Week 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRP						
Week 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score 28; ESR, erythrocyte sedimentation rate; SE, standard error.
Note: Analysis of covariance model with DAS28 as the response, treatment as a fixed effect, and baseline DAS28, region, and CRP category as covariates. Adjusted least squares means and SE, estimate of treatment difference (Inflectra – Remicade), and 95% CI calculated from the analysis of covariance model.
Source: CTD 2.7.3, Table 2.7.3-16

TABLE 6: ANALYSIS OF THE EULAR RESPONSE CRITERIA (PROPORTIONAL ODDS MODEL) BETWEEN INFLECTRA AND REMICADE: PER-PROTOCOL POPULATION (STUDY CT-P13 3.1, PLANETRA)

	N	No Response[1] n(%)	Moderate Response[2] n(%)	Good Response[3] n(%)	Proportional Odds Model[4]	
					OR	95% CI of OR
EULAR (ESR)						
Week 14						
Inflectra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remicade	[redacted]	[redacted]	[redacted]	[redacted]		
Score test (*P* value [redacted])[5]						
Week 30						
Inflectra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remicade	[redacted]	[redacted]	[redacted]	[redacted]		
Score test (*P* value 0.[redacted])[5]						
Week 54						
Inflectra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remicade	[redacted]	[redacted]	[redacted]	[redacted]		
EULAR (CRP)						
Week 14						
Inflectra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remicade	[redacted]	[redacted]	[redacted]	[redacted]		
Score test (P value 0.[redacted])[5]						
Week 30						
Inflectra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remicade	[redacted]	[redacted]	[redacted]	[redacted]		
Score test (*P* value [redacted])[5]						
Week 54						
Inflectra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remicade	[redacted]	[redacted]	[redacted]	[redacted]		

CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism.

[1] Number and percentage of patients indicating No Response according to the EULAR criteria.

[2] Number and percentage of patients indicating Moderate Response according to the EULAR criteria.

[3] Number and percentage of patients indicating Good Response according to the EULAR criteria.

[4] Proportional odds model with EULAR as response, treatment as a fixed effect, and region and C-reactive protein category as covariates.

[5] The proportional odds assumption was evaluated using the Score test evaluated at the 5% significance level.

Source: CTD 2.7.3, Table 2.7.3-17

TABLE 7: MEAN (CV) SERUM PK PARAMETERS FOR INFLECTRA AND REMICADE: PHARMACOKINETIC POPULATION (CT-P13 1.1, PLANETAS)

		Inflectra (N=113)		Remicade (N=110)
Dose 1 (Week 0)				
C_{max} (mcg/mL)	n=109	155.79 (37.2)	n=107	145.29 (25.3)
C_{min} (mcg/mL)	n=109	29.10 (40.1)	n=108	29.77 (40.8)
T_{max} (h)	n=109	2.03 (1.92, 3.20)	n=107	2.08 (1.95, 3.50)
Dose 2 (Week 2)				
C_{max} (mcg/mL)	n=112	175.62 (20.9)	n=108	181.39 (23.8)
C_{min} (mcg/mL)	n=110	20.11 (56.1)	n=108	22.78 (72.0)
T_{max} (h)	n=112	2.08 (1.75, 3.08)	n=108	2.08 (1.83, 3.17)
Dose 3 (Week 6)				
C_{max} (mcg/mL)	n=113	172.34 (26.8)	n=110	166.34 (22.8)
C_{min} (mcg/mL)	n=112	6.93 (80.2)	n=110	7.06 (77.6)
T_{max} (h)	n=113	2.05 (2.00, 3.22)	n=110	2.08 (2.00, 3.17)
Dose 4 (Week 14)				
C_{max} (mcg/mL)	n=113	158.35 (24.0)	n=110	153.62 (27.5)
C_{min} (mcg/mL)	n=112	4.50 (83.6)	n=110	4.80 (75.2)
T_{max} (h)	n=113	3.00 (1.97, 3.32)	n=110	2.08 (1.95, 4.83)
Dose 5 (Week 22)				
C_{max} (mcg/mL)	n=113	153.52 (27.4)	n=110	150.39 (26.9)
C_{min} (mcg/mL)	n=108	4.23 (139.5)	n=108	3.59 (88.1)
T_{max} (h)	n=113	3.00 (2.00, 359.08)	n=110	3.00 (1.98, 168.00)
Dose 6 (Week 30)				
C_{max} (mcg/mL)	n=108	152.54 (31.8)	n=108	147.79 (26.4)
C_{min} (mcg/mL)	n=106	3.44 (91.7)	n=105	3.37 (86.5)
T_{max} (h)	n=108	2.08 (1.85, 3.25)	n=108	2.19 (2.00, 4.00)
Dose 7 (Week 38)				
C_{max} (mcg/mL)	n=109	137.00 (25.9)	n=104	134.28 (21.4)
C_{min} (mcg/mL)	n=102	3.57 (96.0)	n=103	3.59 (93.5)
T_{max} (h)	n=109	2.13 (2.00, 3.30)	n=104	2.08 (1.95, 3.20)
Dose 8 (Week 46)				
C_{max} (mcg/mL)	n=103	137.59 (26.3)	n=102	150.41 (44.9)
C_{min} (mcg/mL)	n=98	4.51 (274.7)	n=100	3.41 (91.0)
T_{max} (h)	n=103	2.08 (0.75, 3.23)	n=102	2.07 (2.00, 5.08)
Dose 9 (Week 54)				
C_{max} (mcg/mL)	n=102	137.53 (29.0)	n=100	130.22 (24.3)
C_{min} (mcg/mL)	n=0	N/A	n=0	NA
T_{max} (h)	n=102	2.08 (1.90, 3.23)	n=100	2.16 (2.00, 3.20)

CV=coefficient of variation; C_{max}=maximum concentration, C_{min}=minimum concentration; T_{max}=time at maximum concentration
Source: CTD Module 2.7.2, Table 2.7.2-11

TABLE 8: SECONDARY SERUM PK PARAMETERS (MEAN [%CV]) FOR INFLECTRA AND REMICADE BETWEEN DOSE 5 (WEEK 22) AND DOSE 6 (WEEK 30): PK POPULATION (STUDY CT-P13 1.1, PLANETAS)

Parameter	Inflectra 5 mg/kg (N=[redacted])	Remicade 5 mg/kg (N=[redacted])
$C_{av,ss}$ (mcg/mL)	[redacted]	[redacted]
$C_{min,ss}$ (mcg/mL)	[redacted]	[redacted]
Swing	[redacted]	[redacted]
Degree of fluctuation	[redacted]	[redacted]
Mean residence time (h)	[redacted]	[redacted]
$T_{1/2}$ (h)	[redacted]	[redacted]
CL_{ss} (mL/h)	[redacted]	[redacted]
V_{ss} (mL)	[redacted]	[redacted]

CV=coefficient of variation; $C_{av,ss}$=average concentration at steady state, $C_{min,ss}$=trough concentration at steady-state; $T_{1/2}$=half-life; CL_{ss}=clearance at steady-state; V_{ss}=volume of distribution at steady-state
Source: CTD Module 2.7.2, Table 2.7.2-9

TABLE 9: SUMMARY OF IMMUNOGENICITY TESTING FOR INFLECTRA AND REMICADE - SAFETY POPULATION (CT-P13 3.1, PLANETRA)

	Inflectra 3 mg/kg (N = 302) n (%)	Remicade 3 mg/kg (N = 300) n (%)	Total (N = 602) n (%)
Screening			
ADA positive	9 (3.0)	6 (2.0)	15 (2.5)
Nab positive (as % of ADA positive)	4 (44.4)	2 (33.3)	6 (40.0)
ADA negative	292 (96.7)	292 (97.3)	584 (97.0)
Week 14			
ADA positive	[redacted]	[redacted]	[redacted]
Nab positive (as % of ADA positive)	[redacted]	[redacted]	[redacted]
ADA negative	[redacted]	[redacted]	[redacted]
Week 30			
ADA positive	[redacted]	[redacted]	[redacted]
Nab positive (as % of ADA positive)	[redacted]	[redacted]	[redacted]
ADA negative	[redacted]	[redacted]	[redacted]
Week 54			
ADA positive	[redacted]	[redacted]	[redacted]
Nab positive (as % of ADA positive)	[redacted]	[redacted]	[redacted]
ADA negative	[redacted]	[redacted]	[redacted]
End-of-Study			
ADA positive	157 (52.0)	150 (50.0)	307 (51.0)
Nab positive (as % of ADA positive)	155 (98.7)	147 (98.0)	302 (98.4)
ADA negative	112 (37.1)	119 (39.7)	231 (38.4)

ADA = anti-drug antibodies; N = Number of all patients in this group; Nab = neutralizing antibody
Source: CSR CT-P13 3.1, Post-text Table 14.3.6.5

TABLE 10: SUMMARY OF IMMUNOGENICITY TESTING FOR INFLECTRA AND REMICADE: SAFETY POPULATION (CT-P13 1.1, PLANETAS)

	Inflectra 5 mg/kg (N = 128) n (%)	Remicade 5 mg/kg (N = 122) n (%)	Total (N = 250) n (%)
Screening			
ADA positive	2 (1.6)	1 (0.8)	3 (1.2)
Nab positive (as % of ADA positive)	1 (50.0)	0	1 (33.3)
ADA negative	125 (97.7)	119 (97.5)	244 (97.6)
Week 14			
ADA positive	[redacted]	[redacted]	[redacted]
Nab positive (as % of ADA positive)	[redacted]	[redacted]	[redacted]
ADA negative	[redacted]	[redacted]	[redacted]
Week 30			
ADA positive	[redacted]	[redacted]	[redacted]
Nab positive (as % of ADA positive)	[redacted]	[redacted]	[redacted]
ADA negative	[redacted]	[redacted]	[redacted]
Week 54			
ADA positive	[redacted]	[redacted]	[redacted]
Nab positive (as % of ADA positive)	[redacted]	[redacted]	[redacted]
ADA negative	[redacted]	[redacted]	[redacted]
End-of-Study			
ADA positive	41 (32.0)	35 (28.7)	76 (30.4)
Nab positive (as % of ADA positive)	39 (95.1)	35 (100)	74 (97.4)
ADA negative	81 (63.3)	78 (63.9)	159 (63.6)

ADA = anti-drug antibody; N = Number of all patients in this group; Nab = neutralizing antibody
Source: CSR CT-P13 1.1, Post-text Table 14.3.6.5

TABLE 11: DESCRIPTIVE STATISTICS OF ADA TITRE BETWEEN INFLECTRA AND REMICADE: SAFETY POPULATION (STUDY CT-P13 3.1; PLANETRA)

		Inflectra 3 mg/kg (N=302)		Remicade 3 mg/kg (N=300)		Total (N=602)	
Visit		n		n		n	
Screening	Mean (SD)	12	3.4 (1.00)	7	4.0 (1.91)	19	3.6 (1.38)
	Median (range)		3.0 (3-6)		3.0 (3-8)		3.0 (3-8)
Week 14	Mean (SD)	72	6.9 (2.40)	70	6.6 (2.31)	142	6.8 (2.35)
	Median (range)		3 (7.0-13)		6.5 (3-14)		7.0 (3-14)
Week 30	Mean (SD)	126	8.0 (2.90)	120	8.4 (3.06)	246	8.2 (2.98)
	Median (range)		8.0 (3-15)		8.0 (3-18)		8.0 (3-18)

Note: The CT-P13 tag was used for this summary. Statistics displayed are those of the transformed values of the titre results. The transformation [log2(x/5)]+1 was used.
Source: CSR CT-P13 3.1, Table 54 (37 - CT-P13 3.1_Table 54_D120 ADA Titre.pdf)

TABLE 12: DESCRIPTIVE STATISTICS OF ADA TITRE: SAFETY POPULATION (STUDY CT-P13 1.1; PLANET AS)

		Inflectra 5 mg/kg (N = 128)		Remicade 5 mg/kg (N = 122)		Total (N = 250)	
Visit		n		n		n	
Screening	Mean (SD)	2	3.5 (0.71)	2	5.0 (2.83)	4	4.3 (1.89)
	Median (range)		3.5 (3 to 4)		5.0 (3 to 7)		3.5 (3 to 7)
Week 14	Mean (SD)	10	8.6 (3.20)	13	8.9 (2.36)	23	8.8 (2.70)
	Median (range)		9.0 (5 to 13)		9.0 (5 to 14)		9.0 (5 to 14)
Week 30	Mean (SD)	31	8.5 (2.97)	24	8.5 (1.82)	55	8.5 (2.51)
	Median (range)		8.0 (3 to 17)		8.0 (6 to 12)		8.0 (3 to 17)

Note: The CT-P13 tag was used for this summary. Statistics displayed are those of the transformed values of the titre results. The transformation [log2(x/5)]+1 was used.
Source: CSR CT-P13 1.1, Table 21 (33 - CT-P13 1.1_Table 21_D120 ADA Titre.pdf)

APPENDIX 2: DRUG PLAN LISTING STATUS FOR REFERENCE PRODUCT

Listing Status for Remicade

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	NB	RES	RES	RES
Ankylosing spondylitis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	NB	EX	RES	EX
Psoriatic arthritis	RES	RES	RES	RES	EX	NB	NB	NB	NB	RES	NB	EX	EX	EX
Plaque psoriasis	RES	RES	RES	RES	EX	RES	RES	EX	RES	RES	NB	EX	RES	EX

AB = Alberta; BC = British Columbia; CDR = CADTH Common Drug Review; DND = Department of National Defence; EX = Exception item for which coverage is determined on a case-by-case basis; MN = Manitoba; NB = not a benefit; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; RES = Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit); SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

Restricted Benefit Criteria for Remicade for the Treatment of Rheumatoid Arthritis

Drug Plan	Criteria for Restricted Benefit
BC	Treatment of RA according to established criteria when prescribed by a rheumatologist by Special Authority Request. Initial or switching (1 year): must demonstrate lack of effect or intolerance to: • methotrexate (parenteral 25 mg [15 mg for patients > 65 years], minimum 8 weeks required) **plus two or more** of the following: • leflunomide (20 mg daily for 10 weeks) • gold (weekly injections for 20 weeks) • sulfasalazine (> 2 gm daily for 3 months) • azathioprine (2 mg to 3 mg/kg/day for 3 months) • other **plus at least one** DMARD combination (NOTE: antimalarial in combination with one other DMARD is not acceptable): • methotrexate with cyclosporine (minimum 4 months) • methotrexate with hydroxychloroquine and sulfasalazine (O'Dell protocol) (minimum 4 months) • methotrexate with gold (minimum 20-week trial) • methotrexate with leflunomide (minimum 10-week trial) • other. Renewal (1 year to indefinite).
AB	Special authorization coverage may be provided for use in combination with methotrexate for the reduction in signs and symptoms of severely active RA in adult patients (≥ 18 years of age) who are refractory[a] or intolerant to[b]: • methotrexate at ≥ 20 mg (PO, SC, or IM) or greater total weekly dosage (≥ 15 mg if patient is ≥ 65 years of age) for more than 12 weeks. Patients who do not exhibit a clinical response to PO methotrexate or who experience gastrointestinal intolerance to PO methotrexate must have had a trial of parenteral methotrexate before being accepted as refractory. **and** • methotrexate with other DMARD(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"). • Initial coverage may be approved for 3 doses as follows: an initial dose of 3 mg/kg, followed by additional 3 mg/kg doses at 2 weeks and 6 weeks after the first infusion. • Patients will: ▪ be limited to receiving one dose of infliximab per prescription at their pharmacy ▪ be permitted to switch from one biologic agent to another (with the exception of anakinra) following an adequate trial[c] of the first biologic agent if unresponsive to therapy, or due to SAEs or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g., initial coverage period). ▪ not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy ▪ not be permitted to switch from anakinra to other biologic agents except under exceptional circumstances ▪ be 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: • The patient must be assessed by an RA specialist after the initial 3 doses to determine response. • The RA specialist must confirm in writing that the patient is a "responder" who meets the following criteria: o ACR20 or an improvement of 1.2 units in the DAS28 score (reported to one [1] decimal place) **and** o 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 to up to 10 mg/kg and/or treating as often as every 4 weeks). Ongoing coverage may be considered only if the following criteria have been met at the end of each 12-month period: • The patient has been assessed by an RA specialist to determine response. • The RA specialist must confirm in writing that the patient has maintained a response to therapy as indicated by: o confirmation of maintenance of ACR20 **or** o maintenance of a minimum improvement of 1.2 units in DAS28 score [reported to one (1) decimal place] from baseline. • 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.

	All requests (including renewal requests) for infliximab for RA must be completed using the Abatacept/Adalimumab/Anakinra/Etanercept/Golimumab/Infliximab/Tocilizumab for Rheumatoid Arthritis Special Authorization Request Form (ABC 30902).
SK	Active RA in patients who: • have failed treatment with methotrexate and leflunomide • are intolerant to methotrexate and leflunomide. Treatment should be combined with an immunosuppressant. This product should be used in consultation with a specialist in this area. (Note: Exceptions can be considered in cases where methotrexate or leflunomide are contraindicated.)
MB	For the treatment of patients over 18 years of age who have moderate to severe active RA and 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 have been tried. Initial application information should include information on disease activity such as the number of tender joints, the number of swollen joints, ESR, and CRP value. Request for coverage must be made by a physician who is a specialist in rheumatology.
ON	For the treatment of RA in patients who have severe, active disease (≥ 5 swollen joints and RF-positive and/or radiographic evidence of RA) despite the optimal use of various formulary 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 tral(s) of methotrexate and/or leflunomide due to contraindication(s) or intolerance(s), the nature of the contraindication(s) or intolerance(s) must be provided along with details of trials of other DMARDs or a clear rationale of why other DMARDs cannot be considered. 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 the 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 RA are as follows: infliximab 3 mg/kg/dose at 0, 2, and 6 weeks followed by maintenance therapy of 3 mg/kg/dose every 8 weeks up to a maximum of 6 maintenance doses per year.
NB	For patients with moderately to severely active RA who:

	• have not responded to, or have had intolerable side effects with, an adequate trial of combination therapy of at least two traditional DMARDs. Combination DMARD therapy must include methotrexate unless contraindicated or not tolerated. **or** • are not candidates for combination DMARD therapy but who have had an adequate trial of at least three traditional DMARDs in sequence, one of which must have been methotrexate unless contraindicated **and** • have had an adequate trial of leflunomide unless it is contraindicated or not tolerated. The drug must be prescribed by a rheumatologist.
NS	For patients with a diagnosis of active RA who: • have not responded, or who have had intolerable toxicity to, an adequate trial[d] of combination therapy of at least two traditional DMARDs[e] **or** • if combination therapy is not an option, an adequate trial[d] of at least 3 traditional DMARDs[e] in sequence as monotherapy **and** • must have had an adequate trial[d] of leflunomide. Exceptions can be considered in cases where leflunomide is contraindicated or not tolerated. Therapy must include methotrexate alone or in combination unless contraindicated or not tolerated. The written request of a rheumatologist or prescriber with a specialty in rheumatology is needed. After the initial coverage period, patients can be reassessed for yearly coverage, dependent on the patient achieving at least a 20% improvement in symptoms. Initial coverage duration and maximum dosage approved: Initial coverage period is 6 months. Notes: • An adequate trial is 5 months for IM gold, 6 months for penicillamine, 4 months for hydroxychloroquine, and 3 months for all other traditional DMARDs as well as leflunomide, infliximab and etanercept. • Traditional agents include methotrexate, IM gold, sulfasalazine, hydroxychloroquine, azathioprine, chloroquine, penicillamine, and cyclosporine.
PE	Initial approval for adults is for infliximab is for 3 mg/kg/dose given at 0, 2, and 6 weeks.

	For the treatment of RA in patients who: • have not responded to a trial of at least 3 months of leflunomide **and** • have not responded to, or have had an intolerable toxicity to, an adequate trial of methotrexate and at least one of the following DMARDs: IM gold, sulfasalazine, hydroxychloroquine, azathioprine, chloroquine, or penicillamine **or** • are intolerant to, or have a contraindication to methotrexate, and are refractory to at least two of the following DMARDs: IM gold, sulfasalazine, hydroxychloroquine, azathioprine, chloroquine, or penicillamine **or** • are not candidates for combination DMARD therapy but who 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.[f] (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 25 mg/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[d] will be for a 6-month period.
NL	For the treatment of RA, in combination with methotrexate in patients who: • have not responded or who have had intolerable toxicity to an adequate trial[d] of combination therapy of at least two traditional DMARDs[g] **or/and** • have had an adequate trial[d] of leflunomide. Exceptions can be considered in cases where leflunomide is ineffective or contraindicated. Therapy must include methotrexate[h] alone or in combination unless contraindicated or not tolerated.Unless limited by toxicity, methotrexate dosage should be increased up to 25 mg/wk unless response is achieved at a lower dose. Coverage will be approved initially for 6 months. Can be reassessed for yearly coverage dependent on patient achieving an improvement in symptoms (ACR) of at least 20%. Written request of a rheumatologist only.
YK	For severely active RA on the recommendation of RA specialist. Specialist's consult to be provided. For patients who are: • refractory, or intolerant to, parenteral methotrexate after at least a 12-week trial **and** • who have taken methotrexate with other DMARD(s) after at least a 4-month trial (e.g., methotrexate with hydroxychloroquine or methotrexate with sulfasalazine) **and** • who have had a minimum 10-week trial of leflunomide at 20 mg daily.

NT	Non-benefit
NIHB	Criteria for initial 12 weeks of coverage for infliximab for RA: • prescribed by a rheumatologist • for use in combination with methotrexate for the treatment of severely active RA. (Note: Initial coverage is provided for 3 doses of 3 mg/kg of infliximab ONLY.) Patient is refractory to: • methotrexate: oral therapy at ≥ 20 mg total weekly dosage (≥ 15 mg or greater if patient is < 65 years of age) for more than 8 weeks **and** • methotrexate: weekly parenteral (SC or IM) at ≥ 20 mg (≥ 15 mg if patient is > 65 years of age) for more than 8 weeks **plus** • leflunomide: 20 mg daily for 10 weeks **plus** • gold: weekly injections for 20 weeks **or** • sulfasalazine: at least 2 gm daily for 3 months **or** • azathioprine: 2 mg/kg/day to 3 mg/kg/day for 3 months **plus** one of the following combinations: • methotrexate with cyclosporine (minimum 4-month trial on both) **or** • methotrexate with hydroxychloroquine and sulfasalazine (minimum 4-month trial on triple therapy) **or** • methotrexate with gold (minimum 12-week trial) **or** • methotrexate with leflunomide (minimum 8-week trial) **or** • in patients who are intolerant or who have contraindications to, methotrexate therapy, refractory to a combination of a least 2 DMARDs **plus** • etanercept or adalimumab (minimum of a 12-week trial). Criteria for continued coverage for infliximab beyond 12 weeks Patient must meet all of the following criteria: • Initially prescribed by a rheumatologist • Previous failure to etanercept or adalimumab. • Patient has been assessed after the 8th to 12th week of infliximab therapy and meets the following response criteria: o > 20% reduction in the number of tender and swollen joints **plus** o > 20% improvement in physician global assessment scale **plus either** - > 20% improvement in the patient global assessment scale **or** - > 20% reduction in the acute phase as measured by ESR or CRP.

DND	When prescribed by a rheumatologist or a prescriber with a specialty in rheumatology for patients with moderately to severely active RA despite treatment with at least 2 DMARDs (including methotrexate unless contraindicated) in monotherapy or combination therapy after 3 months at target dose **and one or more** of the following: ○ leflunomide 20 mg daily for 10 weeks ○ gold: weekly injections for 20 weeks ○ sulfasalazine ≥ 2 gm daily for 3 months ○ azathioprine 2 mg/kg/day to 3 mg/kg/day for 3 months. Note: Methotrexate at ≥ 20 mg (PO, SC, IM) 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 being refractory to methotrexate.
VAC	Prescribed by a rheumatologist. Tried and failed on, or been proven intolerant to, adalimumab.[i] Note: the above criteria are based on information provided from Medavie Bluecross on behalf of VAC (see reference for details).

AB = Alberta; ACR = American College of Rheumatology; BC = British Columbia; CRP = C-reactive protein; DAS28 = Disease Activity Score-28; DMARD = disease-modifying antirheumatic drugs; DND = Department of National Defence; ESR = erythrocyte sedimentation rate; EX = exception item for which coverage is determined on a case-by-case basis; IM = intramuscular; MN = Manitoba; NB = not a benefit; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NSAID = nonsteroidal anti-inflammatory drug; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; PO = by mouth; RA = rheumatoid arthritis; RES = restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit); SC = subcutaneous; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] "Refractory to" is defined as a lack of effect at the specified recommended doses and for the specified duration of treatments.

[b] "Intolerant to" is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs.

[c] An adequate trial is defined as at a minimum the completion of induction dosing (i.e., initial coverage period).

[d] An adequate trial is defined as 5 months for IM gold, 6 months for penicillamine, 4 months for hydroxychloroquine, and 3 months for all other traditional DMARDs as well as leflunomide, infliximab, and etanercept.

[e] Traditional agents include methotrexate, IM gold, sulfasalazine, hydroxychloroquine, azathioprine, chloroquine, penicillamine, and cyclosporine.

[f] 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.

[g] Traditional agents include methotrexate, IM gold, sulfasalazine, hydroxychloroquine, azathioprine, chloroquine, D-penicillamine and cyclosporine.

[h] Unless limited by toxicity, methotrexate dosage should be increased up to 25 mg/week unless response is achieved at a lower dose.

[i] These two criteria are based on information provided from Medavie Bluecross on behalf of VAC (see reference for details).

Restricted Benefit Criteria for Remicade for the Treatment of Ankylosing Spondylitis

Drug Plan	Criteria for Restricted Benefit
BC	Treatment of AS according to established criteria when prescribed by a rheumatologist by Special Authority Request. Initial or Switching (1 year): • diagnosis of moderate to severe AS • active AS with a BASDAI score ≥ 4 • for predominantly axial disease: treatment failure with, or intolerance, to 3 NSAIDS for a minimum of 2 weeks each at the accepted maximum dosage

Drug Plan	Criteria for Restricted Benefit

	or
	• for predominantly peripheral disease: patient is refractory to minimum 3-month trials of each of the following:
	  ○ methotrexate up to 25 mg parenterally, weekly (15 mg for patients > 65 years)
	  ○ sulfasalazine up to 3 g daily.
	
	Renewal (1 year to indefinitely):
	• medication is being prescribed by a rheumatologist or medical specialist in rheumatology
	• extra-articular manifestations
	• axial disease
	  ○ spinal pain (worse to resolved)
	• peripheral disease
	  ○ active joints (worse to resolved)
	  ○ active tenosynovitis and/or enthesitis (worse to resolved)

AB	"Special authorization coverage may be provided for the reduction in the signs and symptoms and improvement in physical function of severely active AS, as defined by the modified New York criteria for AS, in adult patients (≥ 18 years of age) who have active disease as demonstrated by: • a BASDAI ≥ 4 units, demonstrated on 2 occasions at least 8 weeks apart **and** • a Spinal Pain VAS of ≥ 4 cm (on a 0 cm to 10 cm scale), demonstrated on 2 occasions at least 8 weeks apart **and** • who are refractory[a] or intolerant to[b] treatment with two or more NSAIDS each taken for a minimum of 4 weeks at maximum tolerated or recommended doses. For coverage, this drug must be initiated by a specialist in rheumatology ("RA Specialist"). Initial coverage may be approved for 3 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 • be permitted to switch from one biologic agent to another following an adequate trial[c] 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., e.g. initial coverage period) • not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy • be limited to receiving one biologic agent at a time, regardless of the condition for which it is being prescribed. For continued coverage beyond 3 doses, the patient must meet the following criteria: 1. The patient must be assessed by an RA specialist after the initial 3 doses to determine response.

Drug Plan	Criteria for Restricted Benefit
	2. The RA specialist must confirm, in writing, that the patient is a "responder" who 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. 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 reassessed 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. All requests (including renewal requests) for infliximab for AS must be completed using the "Adalimumab/Etanercept/Golimumab/Infliximab for Ankylosing Spondylitis Special Authorization Request Form" (ABC 31195).
SK	For treatment of AS according to the following criteria: For patients who • have already been treated conventionally with two or more NSAIDS taken sequentially at maximum tolerated or recommended doses for 4 weeks without symptom control **and** • Satisfy the New York diagnostic criteria: a score > 4 BASDAI and a score of > 4 cm on the 0 cm to 10 cm Spinal Pain VAS on two occasions at least 12 weeks apart without any change of treatment **and** • Have adequate response to treatment assessed at 12 weeks, defined as at least 50% reduction in pre-treatment baseline BASDAI score or by > 2 units and a reduction of > 2 cm in the Spinal Pain VAS. NOTE: Coverage will not be provided when a patient switches to another anti-TNF agent, if the patient fails to respond, or if there is a loss of response to the first agent.Requests for coverage for this indication must be made by the rheumatologist. A second application would also be required after 12 weeks to assess and would need to show an improvement to the patient's condition on either of these medications. Please refer to the Formulary website for the application form. Subsequent annual renewal requests (beyond 15 months) will be considered for patients whose BASDAI scores do not worsen (i.e., remain within 2 points of the second assessment). This product should be used in consultation with a specialist in this area.
MB	For the treatment of patients with active AS who have failed to respond to an adequate trial of at least 3 different nonsteroidal anti-inflammatory drugs (NSAIDs) and in patients with peripheral joint involvement who have failed to respond to methotrexate or sulfasalazine. Request for coverage must be made by a physician who is a specialist in rheumatology.
ON	For the treatment of AS or psoriatic spondylitis (PS) in patients who have severe active disease with:

Drug Plan	Criteria for Restricted Benefit
	• age of disease onset ≤ 50 **and** • low back pain and stiffness for > 3 months that improves with exercise and that is not relieved by rest **and** • failure to respond to, or documented intolerance to, adequate trials of two 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 "sacroiliac (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. 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: • adalimumab 40 mg every other week. • etanercept 25 mg twice weekly or 50 mg once weekly • golimumab 50 mg once a month • infliximab 3 mg/kg 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 AS (e.g. 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' observation or in whom NSAIDs are contraindicated

Drug Plan	Criteria for Restricted Benefit
	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. *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. • Must be prescribed by a rheumatologist or internist • Approval will be for a maximum of 6 months • 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"). • Approvals will be for a maximum of 5 mg/kg at weeks 0, 2, and 6, then every 6 to 8 weeks thereafter. • Infliximab will not be reimbursed in combination with other anti-TNF agents.
NS	• For the treatment of patients with moderate to severe AS (e.g., 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. • 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). *Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication of axial disease do not require a trial of two NSAIDs. Initial coverage duration and maximum dosage approved: • initial coverage period of 6 months, maximum dose 5 mg/kg at 0, 2, and 6 weeks, then every 6 to 8 weeks thereafter, and not in combination with other anti-TNF agents.

Drug Plan	Criteria for Restricted Benefit
PE	Approvals will be for a maximum adult dose of 5 mg/kg at 0, 2, and 6 weeks, then every 6 to 8 weeks. For the treatment of patients with moderate to severe AS (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. *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 AS anti-TNF agents will be for a maximum of 6 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 decrease of at least 2 points on the BASDAI scale, compared with 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). The request for coverage must be made by a rheumatologist or prescriber with a specialty in rheumatology, using the AS 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 AS (e.g., 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 • 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. Must be prescribed by a rheumatologist or internist. Approval will be for a maximum of 6 months.

Drug Plan	Criteria for Restricted Benefit
	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** Approvals will be for a maximum dose of 5 mg/kg at 0, 2, 6 weeks, then every 6 to 8 weeks thereafter and will NOT be reimbursed in combination with other anti-TNF agents.
YK	For AS patients with a BASDAI score ≥ 4 who are refractory or intolerant to a minimum 4-week trial of 3 NSAIDs **or** who are refractory to a 3-month trial of parenteral methotrexate and a 3-month trial of sulfasalazine. Rheumatologists' consult to be provided.
NT	Non-benefit
NIHB	Case-by-case
DND	When prescribed by a rheumatologist or a prescriber with a specialty in rheumatology and meets the following criteria: • a diagnosis of moderate to severe AS as demonstrated by a BASDAI ≥ 4 units • treatment failure or intolerance to 3 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

AB = Alberta; ACR = American College of Rheumatology; BC = British Columbia; CRP = C-reactive protein; DAS28 = Disease Activity Score-28; DMARD = disease-modifying antirheumatic drugs; DND = Department of National Defence; ESR = erythrocyte sedimentation rate; EX = Exception item for which coverage is determined on a case-by-case basis; IM = intramuscular; MN = Manitoba; NB = not a benefit; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NSAID = nonsteroidal anti-inflammatory drug; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; PO = by mouth; PS = psoriatic spondylitis; RA = rheumatoid arthritis; RES = Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit); SC = subcutaneous; SK = Saskatchewan; TNF = tumour necrosis factor; VAC = Veterans Affairs Canada; YK = Yukon.

[a] "Refractory" is defined as lack of effect at the specified recommended doses and for the specified duration of treatments.

[b] "Intolerant to" is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs.

[C] An adequate trial is defined as at a minimum the completion of induction dosing (i.e., initial coverage period).

Restricted Benefit Criteria for Remicade for the Treatment of Psoriatic Arthritis

Drug Plan	Criteria for Restricted Benefit
BC	Treatment of PsA according to established criteria when prescribed by a rheumatologist by Special Authority Request: Initial or Switching (1 year): Diagnosis of moderate to severe PsA, where patient currently exhibits at least 2 of the following (please indicate all that apply): • 5 or more active joints • if oligoarticular (less than 5 joints), at least 1 active joint proximal to, or including, wrist or ankle • more than 1 joint with erosion on imaging study • dactylitis of 2 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 2 NSAIDs (minimum 4-week trial each) and submit a BASDAI with a score > 4 • daily use of corticosteroids to control active arthritis • use of narcotics > 12 hours per day for pain resulting from inflammation. Functional assessment (HAQ or BASDAI) completed by patient and attached. Patient has failed 2 or more DMARDs: • sulfasalazine (if allergic, must have failed 2 of the medications listed below) • methotrexate: up to 25 mg (15 mg for > 65 years)parenteral weekly • IM gold • chloroquine and/or hydroxychloroquine • azathioprine • cyclosporine • other (specify). Renewal (1 year to indefinite): Medication is prescribed by a rheumatologist or medical specialist in rheumatology **and** For the criteria originally specified in the request for initial coverage, please provide current status: • 5 or more swollen joints • oligoarthritis • dactylitis

Drug Plan	Criteria for Restricted Benefit
	• tenosynovitis • enthesitis • inflammatory spinal symptoms • daily use of corticosteroids to control active arthritis • use of narcotics for pain resulting from inflammation
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) with moderate to severe polyarticular PsA or pauciarticular PsA with involvement of knee or hip joint who are refractory[a] or intolerant[b] to: • methotrexate at ≥ 20 mg (PO, SC, or IM) total weekly dosage (15 mg or greater if patient is ≥ 65 years of age) for more than 12 weeks. Patients who do not exhibit a clinical response to PO methotrexate or who experience gastrointestinal intolerance to PO methotrexate must have a trial of parenteral methotrexate before being accepted as refractory **and** • an adequate trial of another DMARD(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 SAEs. "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 3 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 1 dose of infliximab per prescription at their pharmacy ▪ 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). ▪ not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy ▪ be limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. For continued coverage beyond 3 doses, the patient must meet the following criteria: • The patient must be assessed by an RA specialist after the initial 3 doses to determine response. • The RA specialist must confirm in writing that the patient is a "responder" who meets the following criteria: o ACR20 or an improvement of 1.2 units in the DAS28 score (reported to one [1] decimal place) **and** o an improvement of 0.22 in HAQ score (reported to two [2] decimal places).

Drug Plan	Criteria for Restricted Benefit
	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: • The patient has been assessed by an RA specialist to determine response. • The RA specialist must confirm in writing that the patient has maintained a response to therapy as indicated by: o confirmation of maintenance of ACR20 **or** o maintenance of a minimum improvement of 1.2 units in DAS28 score (reported to one [1] decimal place) from baseline. • 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." All requests (including renewal requests) for infliximab for psoriatic arthritis must be completed using the "Adalimumab/Etanercept/Golimumab/Infliximab for Psoriatic Arthritis Special Authorization Request Form (ABC 30964)."
SK	PsA in patients who have failed or are intolerant to methotrexate and one other DMARD. Note: Exceptions can be considered in cases where methotrexate or leflunomide are contraindicated. Treatment should be combined with an immunosuppressant. This product should be used in consultation with a specialist in this area.
MB	For the treatment of patients older than 18 years who have active PsA and 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 have been tried. Initial application information should include information on disease activity such as the number of tender joints, swollen joints, ESR, and CRP value. Request for coverage must be made by a physician who is a specialist in rheumatology.
ON	Case-by-case
NB	Non-benefit
NS	Non-benefit
PE	Non-benefit
NL	Non-benefit
YK	For PsA patients with moderate to severe disease:

Drug Plan	Criteria for Restricted Benefit
	• who are refractory[a] or intolerant to[b] a 12-week trial of parenteral methotrexate **and** • an adequate trial (at least 4 months) of at least one other DMARD. Specialists consult to be provided.
NT	Non-benefit
NIHB	Case-by-case
DND	Case-by-case
VAC	Case-by-case

AB = Alberta; ACR = American College of Rheumatology; BC = British Columbia; CRP = C-reactive protein; DAS28 = Disease Activity Score-28; DMARD = disease-modifying antirheumatic drugs; DND = Department of National Defence; ESR = erythrocyte sedimentation rate; EX = Exception item for which coverage is determined on a case-by-case basis; IM = intramuscular; MN = Manitoba; NB = not a benefit; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NSAID = nonsteroidal anti-inflammatory drug; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; PO = by mouth; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RES = Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit); SC = subcutaneous; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] "Refractory" is defined as lack of effect at the specified recommended doses and for the specified duration of treatments.

[b] "Intolerant" is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs.

Restricted Benefit Criteria for Remicade for the Treatment of Plaque Psoriasis

Drug Plan	Criteria for Restricted Benefit

BC	Treatment of moderate to severe psoriasis, according to established criteria, when prescribed by a dermatologist.
	
	Initial (induction three doses) — **All of the following criteria have to be met:**
	• Patient is ≥ 18 years of age.
	• Patient has a 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. (Specify current PASI score or attach copy of completed PASI form.)
	• Patient has failed to respond, or experienced a specific intolerance, or has a specific contraindication to both of the following medications:
	  ○ methotrexate (oral/parenteral 20 mg weekly [15 mg for ages > 65] for 3 months)
	  ○ cyclosporine (4 mg/kg daily for 3 months)
	For intolerance or contraindication:
	• significant liver disease (abnormal liver biopsy, chronic hepatitis, or liver enzymes 3X ULN)
	• significant kidney disease (serum creatinine elevation > 30% over baseline on two or more occasions, known kidney disease)
	• persistent hypertension uncontrolled by antihypertensive therapy
	• other
	
	Renewal (1 year)
	• First renewal after the initial 12-week 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 PsO in patients who:
	• have a total PASI of ≥ 10 and a DLQI > 10
	or
	• who have significant involvement of the face, palms of the hands, soles of the feet, or genital region
	and
	• who are refractory[a] or intolerant to[b]:
	  ○ methotrexate at 20 mg (PO, SC, or IM) or greater total weekly dosage (≥ 15 mg if patient is ≥ 65 years of age) 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 prerequisite 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 ○ will be permitted to switch from one biologic agent to another following an adequate trial[c] of the first biologic agent if unresponsive to therapy, or due to serious adverse effects or contraindications ○ will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy ○ are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. For continued coverage beyond 3 doses, the patient must meet all of the following criteria: 1. The patient must be assessed by a dermatology specialist after the initial 3 doses to determine response. 2. The dermatology specialist must confirm, in writing, that the patient is a “responder” who meets the following criteria: • ≥ 75% reduction in PASI score **or** • ≥ 50% reduction in PASI score and improvement of ≥ 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 reassessed 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 PsO including those requests for patients who have significant involvement of the face, palms, soles of feet, or genital region. All requests (including renewal requests) for infliximab for PsO must be completed using the “Adalimumab/Etanercept/Infliximab/Ustekinumab for Plaque Psoriasis Special Authorization Request Form” (ABC 31192).
SK	For the treatment of adult patients with severe debilitating PsO who meet all of the following criteria: • failure to respond to, contraindications to, or intolerant of methotrexate and cyclosporine **and**

Drug Plan	Criteria for Restricted Benefit
	• 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 PsO with one or more of the following: • PASI ≥ 10 • BSA > 10% • 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% reduction in the PASI score with ≥ point improvement in the DLQI **or** • ≥ 75% reduction in the PASI score **or** • ≥ 50% reduction in the BSA with significant improvement of the face, hands, feet, or genital region. Request for coverage must be made by a physician who is a specialist in dermatology.
ON	Case-by-case
NB	Requests will be considered for the treatment of patients with severe, debilitating chronic PsO who meet all of the following criteria: • 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. An adequate response is defined as either: • ≥ 75% reduction in the PASI score from when treatment started (PASI 75) **or** • ≥ 50% reduction in the PASI score (PASI 50) with a ≥ 5 point improvement in the 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. must be prescribed by a dermatologist.

Drug Plan	Criteria for Restricted Benefit
	Concurrent use of > 1 biologic will not be approved. 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 are met at 12 weeks).
NS	For patients with severe, debilitating chronic PsO who meet all of the following criteria: • 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. The written request of a dermatologist or prescriber with a specialty in dermatology is required. Continued coverage is dependent on evidence of improvement, specifically: • ≥ 75% reduction in the PASI score **or** • ≥ 50% reduction in PASI with a 5-point improvement in DLQI **or** • significant reduction in BSA involved, with consideration of important regions such as the face, hands, feet, or genitals The concurrent use of biologics will not be approved. Initial duration and maximum dosage approved: • initial approval for a maximum of 12 weeks • dosage restricted to infliximab 5 mg/kg 0, 2, and 6 weeks, then every 8 weeks.
PE	Case-by-case
NL	For patients with severe, debilitating PsO who meet all of the following criteria: • 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 Coverage will be initially approved for 12 weeks. Continuation of therapy beyond 12 weeks will depend on response. Patients not responding adequately at 12 weeks should have treatment discontinued with no further treatment recommended. An adequate response is defined as either: • a 75% reduction in the PASI score (PASI 75) from when treatment started **or** • a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.

Drug Plan	Criteria for Restricted Benefit
	Written request of dermatologist only. Two biologicals cannot be given concurrently. Dosage restricted to infliximab 5 mg/kg ay 0, 2, and 6 weeks, then every 8 weeks.
YK	• For PsO on the recommendation of dermatologist. Consult to be provided. For patients with BSA of > 10% **or** • significant involvement of face, hands, feet, or genital region **and** • 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.
NT	Non-benefit
NIHB	Case-by-case
DND	When prescribed by a dermatologist and the patient meets all of the following criteria: • a diagnosis of severe, debilitating psoriasis • BSA > 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, or IM 20 mg weekly; cyclosporine 4 mg/kg daily) each for 12 weeks • failure to respond to, intolerant to, or unable to access phototherapy.
VAC	Case-by-case

AB = Alberta; ACR = American College of Rheumatology; BC = British Columbia; BSA = body surface area; CRP = C-reactive protein; DAS28 = Disease Activity Score-28; DLQI = Dermatology Life Quality Index; DMARD = disease-modifying antirheumatic drugs; DND = Department of National Defence; ESR = erythrocyte sedimentation rate; EX = Exception item for which coverage is determined on a case-by-case basis; IM = intramuscular; MN = Manitoba; NB = not a benefit; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NSAID = nonsteroidal anti-inflammatory drug; NT = Northwest Territories; ON = Ontario; PASI = Psoriasis Area and Severity Index; PE = Prince Edward Island; PO = by mouth; PsO = plaque psoriasis; RA = rheumatoid arthritis; RES = Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit); SC = subcutaneous; SK = Saskatchewan; ULN = upper limit of normal; UV = ultraviolet; VAC = Veterans Affairs Canada; YK = Yukon.

[a] "Refractory to" is defined as lack of effect at the specified recommended doses and for the specified duration of treatments.

[b] "Intolerant to" is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs.

[c] An adequate trial is defined as at a minimum the completion of induction dosing (i.e., initial coverage period).

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. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Information About the Inflectra Patient Input Summary

Inflectra has been approved by Heath Canada for the following indications:

- Use in combination with methotrexate for the reduction of 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).
- The reduction of signs and symptoms and improvement in physical function in patients with active ankylosing spondylitis (AS) who have responded inadequately to, or are intolerant to, conventional therapies.
- Reduction of signs and symptoms, induction of major clinical response, 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, Inflectra should be used after phototherapy has been shown to be ineffective or inappropriate.

While, in most cases, submitting patient groups provided individual submissions for each indication—AS, PsA, and RA — CADTH has collated and summarized all of the received input for all indications in one summary for inclusion in the CDR Subsequent Entry Biologic Clinical Review Report. No patient input was received regarding the use of Inflectra for PsO, although it was referred to in some patient input submissions. Each patient input submission is available in its entirety to the CDR Review Team and Canadian Drug Expert Committee (CDEC) members.

2. Brief Description of Patient Groups Supplying Input

Six patient groups provided input regarding Inflectra.

Arthritis Consumer Experts (ACE) is a national organization that strives to inform, educate, and empower those living with arthritis by providing support, educational programs, and science-based information (in reader-friendly language) to them. ACE has received unrestricted grants-in-aid from AbbVie Corporation, Amgen Canada, the Arthritis Research Centre of Canada, BIOTECanada, Bristol-Myers Squibb Canada, the Canadian Rheumatology Research Consortium, the Canadian Institutes of Health Research, Celgene Inc., GlaxoSmithKline, Hoffman-La Roche Canada Ltd., Janssen Inc., Pfizer Canada, Purdue Pharma L.P., St. Paul's Hospital, and the University of British Columbia.

The Arthritis Society provides education, programs, and support to Canadians living with arthritis. It is accredited under Imagine Canada's Standards Program, and also funds arthritis research. In the last 12 months, The Arthritis Society has received funding from AbbVie, Amgen, Bayer, Bristol-Myers Squibb, Celgene, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Pfizer, Roche, and UCB.

The Canadian Arthritis Patient Alliance (CAPA) is a national, patient-driven, grass-roots advocacy organization that educates, supports, and provides links to Canadians living with arthritis. Sources of grants and support received by CAPA in the last year include AbbVie, Amgen Canada, Arthritis Alliance of Canada, The Arthritis Society, the Canadian Rheumatology Association, Janssen, Novartis, the Ontario Rheumatology Association, and UCB Pharma. Additionally, CAPA has also received grants and donations in the past from the Canadian Institutes for Health Research, Hoffman-La Roche, Pfizer Canada, Rx&D, Schering Canada, the Scleroderma Society, and STA Communications.

The Canadian Spondylitis Association (CSA) is a volunteer-run, patient support, and advocacy association that advocates nationally and provincially for patients living with spondyloarthritis (SpA) (including AS and PsA), supports and advocates for research for SpA, provides a national resource centre and a national patient and medical forum, participates in the international SpA community, and promotes public awareness of SpA. The CSA has received both unrestricted and restricted grants from AbbVie and restricted grants from Janssen and UCB Canada.

The Consumer Advocare Network (Advocare) aims to provide education and support to patient groups. Advocare created the Canadian Expert Patients in Health Technology in 2012 to promote informed patient engagement in all levels of health policy. In the past five years, it has received unrestricted educational grants to develop materials and workshops on SEBs from BIOTECanada, Janssen-Ortho Amgen, Sanofi, Wyatt Health Management, and Health Canada.

Patient Commando Productions aims to amplify the patient experience as a guide to improving health care practice through an online collection of patient stories, accredited Continuing Medical Education for health care professionals on narrative competency, collaborations between patients and health care professionals, and advocating for patient experience. Patient Commando Productions declares no conflict of interest with respect to corporate members and joint working, sponsorship, or funding arrangements.

ACE, Advocare, The Arthritis Society, CAPA, CSA, and Patient Commando Productions declared no conflicts of interest in the preparation of their respective submissions.

3. Condition and Current Therapy-Related Information

Patient groups obtained information for their submissions through interactions in patient forums, discussions with patients (in person or by telephone), newsletters, websites, surveys, Facebook, and from personal experiences of CAPA Board members living with inflammatory arthritis.

AS, PsA, RA, and PsO are chronic autoimmune diseases. AS, PsA and RA are different types of inflammatory arthritis with unique characteristics; however, swelling, stiffness and joint pain are common to all. Joint pain is due to inflammation that occurs around the joint, damage to the joint from disease, daily wear and tear of the joint, muscle strains, and fatigue. Joint pain is a major complaint of individuals with arthritis and is often constant. Patients with PsA or PsO experience scaly patches on the skin surface which can also occur in other areas such as the mouth or genital area.

Symptoms and Disease Impacts in Common for Patients With AS, PsA, RA, or Psoriasis

With AS, PsA, and RA being progressive diseases with no cure, controlling the inflammation early in the disease is the best hope a patient can have to ward off the devastating effects. In addition to the

physical aspects of the disease, these patients (and those with PsO) can also experience fatigue, depression, and fear of flare-ups, which often compound the effects of the disease itself and result in a poor quality of life. The unpredictable nature of AS, PsA, and RA can have a negative effect on a patient's life. They are unable to plan ahead. Damage to the hips can sometimes be so severe that hip replacement is required. Patients also have to use modified tools to assist them in completing daily activities because their disease affects their range of motion.

Patients report that the control of their arthritis ranged from well controlled to poorly controlled. In those cases where the disease is not well controlled, patients with AS, PsA, and RA have difficulties performing day-to-day activities such as bathing, cooking, dressing, driving, exercising, getting into and out of bed, parenting, sitting, sleeping, using the toilet, and walking. Additionally, participating in post-secondary education, being physically active, becoming and staying employed, being intimate with one's significant other, socialization with friends and family, and taking care of either oneself or one's family are often limited by the disease.

Caregiver Experiences for Patients With AS, PsA, or RA

Depending on a person's ability to cope with activities of daily living and his or her ability to remain employed, caregivers of people living with AS, PsA, or RA are relied upon in varying capacities. In some cases, caregivers are required to assist with simple tasks such as bathing, getting in and out of bed, getting dressed, even using the toilet. When a patient is experiencing extreme pain, fatigue, or depression, especially on a regular basis, it may then be necessary for the caregiver to not only help the patient with day-to-day activities, but also to take over the patient's usual household and financial responsibilities. Additionally, a caregiver may have to take time off to care for the patient. The emotional toll on both patients and caregivers in this type of situation cannot be underscored enough. In other situations, a caregiver's burden may not be as great, perhaps giving the patient their injection or taking the patient to receive their infusion. The psychological impact of living with a potentially debilitating chronic condition can affect the patient and his or her caregiver profoundly. When patients do not have drug coverage options, the cost of the drugs, particularly the biologics, adds to the burden of disease.

Treatment Experiences for Patients With AS, PsA, RA, or PsO

While there are numerous treatments available — nonsteroidal anti-inflammatories (NSAIDs), analgesics, methotrexate, cyclosporine, and biologic disease-modifying antirheumatic drugs (DMARDs) — patients with AS, PsA, and RA often have to try a number of these drugs, singly or in combination, to find the most suitable treatment. When they work, current treatments can be extremely effective. For others, current treatments are not at all effective, or are not effective enough. One patient noted, "Current treatment is effective, to a point. I will never be able to run across the street or live in a house with stairs, and I'm not yet 40." In addition, a drug may work well for a while and then it may lose its effectiveness as the patient's immune system adapts to it. There is no specific method to help physicians predict which patients will respond to which treatment. Each of the pharmaceutical treatments has adverse effects that range in severity and that can affect patients differently, from minimal impact to requiring discontinuation of the agent.

As this submission is for a subsequent entry biologic (SEB), experiences with the originator drug, Remicade, are informative. Just as the other drugs, Remicade works well for some patients, but it does not work as well, or does not work at all, for others. The most common adverse events (AEs) for biologics, including Remicade, include infections, allergic reactions, cold-like symptoms, and infusion-related reactions. Patients have experienced intolerance of methotrexate in combination with the originator and other biologic therapies, including side effects such as stomach problems and nausea. Some patients develop vein scarring and scar tissue from numerous infusions and injections.

Other issues related to using Remicade or biologics include the need to take time off work, the need to travel to clinics for infusions, the high costs for those without coverage, the significant paperwork required by some plans to apply for coverage, and delays in the processing of the paperwork. In addition, the mode of administration (IV or self-injection) for each medication also influences overall medication experience. Patients believe that the best treatment is one that has the fewest adverse effects.

Patients reported that patient support programs for patients taking Remicade and other biologics are very helpful. The support programs provide services that range from providing pre-infusion health checks, regular communication between the program and the patient's physician that allow patients to stay informed regarding treatment results, to providing a safe and comfortable environment in which to receive these medications. It is uncertain whether these support programs will be available with the SEB treatments.

4. Related Information About Inflectra

No patients contacted by any of the patient groups had had direct experience with Inflectra, although some were aware of SEBs.

Patients' expectations for Inflectra include the following:

- It will be less costly and thus could potentially lower health care costs and increase access.
- It provides another treatment option, and an option for those who have not responded to the originator.
- Its adverse events are expected to be the same as with Remicade; therefore, the uncertainty about what to expect is eliminated.

Patients expressed the following concerns:

- Not knowing if patient support programs like those already existing for the originator drug will be available
- Potentially a less-established, post-marketing surveillance program will be in place; hence, there are safety concerns
- Potentially less scientifically rigorous clinical trials for the SEB than for the originator
- Uncertainty that the SEB will work as well as the originator
- Potential confusion at the pharmacy since these drugs have the same INN number and this could lead to accidental switching and subsequent AEs
- Potential to be switched to the SEB by one's insurer to minimize cost.

5. Key Messages

Key messages followed the following themes:

- Therapeutic options are required for patients who live with arthritis, and SEBs offer another biologic drug therapy that is not identical to the originator drug, but that may be effective for patients who are biologic-naive or who have failed on other biologic drugs.
- There should be no interchangeability or substitutability at the pharmacy or payer level — the decision should be made by the physician and the patient. CDR's recommendations should include advising against public payers listing Inflectra as being interchangeable with its originator.
- This SEB molecule has the identical INN to the originator drug; there are significant issues and concerns for patients regarding this, including the potential for a patient to be inadvertently exposed to the wrong drug.
- Patient support programs are an important part of biologic therapies, and it is not clear that the manufacturers of SEBs will offer them.

APPENDIX 4: CADTH COMMON DRUG REVIEW COST COMPARISON TABLES

Cost comparison tables of biologic disease-modifying antirheumatic drugs (bDMARDs) used for the management of rheumatoid arthritis.

COST COMPARISON TABLE OF INFLIXIMAB FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Price per Dose ($)	Recommended Dose	Cost in Year 1 ($)
Infliximab (Inflectra)	100 mg	Vial for infusion	650.0000[a]	1,950	3 mg/kg Week 0, 2, and 6, then every 8 weeks thereafter	15,600[b]
Infliximab (Remicade)	100 mg	Vial for infusion	987.5600	2,963	3 mg/kg Week 0, 2 and 6, then every 8 weeks thereafter	23,701[b]
Other Biologics indicated for the treatment of Rheumatoid Arthritis in Canada						
Abatacept (Orencia)	250 mg/15 mL	Vial for infusion	480.4100	1,441	500 mg to 1,000 mg Weeks 0, 2, and 4, then every 4 weeks thereafter	20,177
	125 mg/mL	Pre-filled syringe	358.9000	359	A single 500 mg to 1,000 mg IV loading dose, then 125 mg SC within one day and once weekly	20,104 includes IV loading dose
Adalimumab (Humira)	40 mg/0.8 mL	Pre-filled syringe or pen	740.3600	740	40 mg SC every other week	19,249
Certolizumab (Cimzia)	200 mg/mL	Pre-filled syringe	664.5100	665	400 mg SC Weeks 0, 2, and 4, then 200 mg SC every 2 weeks or 400 mg every 4 weeks	19,271
Etanercept (Enbrel)	25 mg	Vial for injection	194.2450	194	50 mg SC weekly or 25 mg SC twice weekly	20,201
	50 mg/mL	Pre-filled syringe or	388.6050	389		20,207
Golimumab (Simponi)	50 mg/0.5 mL 100 mg/1.0 mL	Pre-filled syringe or auto-injector	1,520.2100 1,649.4300[c]	1,520	50 mg SC once monthly	18,243
	50 mg/4.0 mL	Vial for infusion	897.1500[c]	2,691	2 mg/kg Weeks 0 and 4, then every 8 weeks thereafter	18,840
Rituximab (Rituxan)	100 mg/10 mL 500 mg/50 mL	Vial for infusion	453.1000 2,265.5000	4,531	1,000 mg in Week 0 and 1,000 mg Week 2; reassess for re-treatment at Week 26, no sooner than 16 weeks after previous course	18,124 (assumes two courses)

Drug/ Comparator	Strength	Dosage Form	Price ($)	Price per Dose ($)	Recommended Dose	Cost in Year 1 ($)
Tocilizumab (Actemra)	80 mg/4.0 mL 200 mg/10.0 mL 400 mg/20.0 mL	Vial for infusion	179.2000 448.0000 896.0000	627 (4 mg/kg) 1,254 (8 mg/kg)	4 mg/kg every 4 weeks, increasing to 8 mg/kg based on clinical response	8,153 (4 mg/kg) 15,680 (8 mg/kg)
	162 mg/0.9 mL	Pre-filled syringe	385.175[c]	1,541	162 mg SC every other week, increasing to weekly based on clinical response	Biweekly: 10,014 Weekly: 20,029

IV = intravenous; SC = subcutaneous.
[a] Manufacturer's submitted price.
[b] Based on 8 doses in the first year.
[c] McKesson Canada wholesale price (September 2014), includes markup.
Notes: All prices are from the Ontario Drug Benefit Formulary Exceptional Access Program (September 2014) unless otherwise indicated. Costs include wastage of unused medication, but do not include administration. Patient weight is assumed to be 70 kg.

Cost comparison tables of bDMARDs used for the management of ankylosing spondylitis.

COST COMPARISON TABLE OF INFLIXIMAB FOR THE MANAGEMENT OF ANKYLOSING SPONDYLITIS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Price per Dose ($)	Recommended Dose	Cost in Year 1 ($)
Infliximab (Inflectra)	100 mg	Vial for infusion	650.0000[a]	2,600	5 mg/kg Weeks 0, 2, and 6, then every 8 weeks thereafter	20,800[b]
Infliximab (Remicade)	100 mg	Vial for infusion	987.5600	3,950	5 mg/kg Weeks 0, 2, and 6, then every 8 weeks thereafter	31,601[b]
Other biologics indicated for the treatment of ankylosing spondylitis in Canada						
Adalimumab (Humira)	40 mg/0.8 mL	Pre-filled syringe or pen	740.3600	740	40 mg SC every other week	19,249
Certolizumab (Cimzia)	200 mg/mL	Pre-filled syringe	664.5100	665	400 mg SC Weeks 0, 2, and 4, then 200 mg SC every 2 weeks or 400 mg every 4 weeks	19,271
Etanercept (Enbrel)	25 mg	Vial for injection	194.2450	194	50 mg SC weekly or 25 mg SC twice weekly	20,201
	50 mg/mL	Pre-filled syringe or auto-injector	388.6050	389		20,207

Drug/ Comparator	Strength	Dosage Form	Price ($)	Price per Dose ($)	Recommended Dose	Cost in Year 1 ($)
Golimumab (Simponi)	50 mg/0.5 mL 100 mg/1.0 mL	Pre-filled syringe or auto-injector	1,520.2100 1,649.4300[c]	1,520	50 mg SC once monthly	18,243

SC = subcutaneous.
[a] Manufacturer's submitted price.
[b] Based on 8 doses in the first year.
[c] McKesson Canada wholesale price (September 2014).
Notes: All prices are from the Ontario Drug Benefit Formulary Exceptional Access Program (September 2014) unless otherwise indicated.
Costs include wastage of unused medication, but do not include administration.
Patient weight is assumed to be 70 kg.

Cost Comparison Tables of bDMARDs Used for the Management of Psoriatic Arthritis

COST COMPARISON TABLE OF INFLIXIMAB FOR THE MANAGEMENT OF PSORIATIC ARTHRITIS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Price per Dose ($)	Recommended Dose	Cost in Year 1 ($)
Infliximab (Inflectra)	100 mg	Vial for infusion	650.0000[a]	2600	5 mg/kg Weeks 0, 2, and 6, then every 8 weeks thereafter	20,800[b]
Infliximab (Remicade)	100 mg	Vial for infusion	987.5600	3,950	5 mg/kg Weeks 0, 2, and 6, then every 8 weeks thereafter	31,601[b]
Other biologics indicated for the treatment of psoriatic arthritis in Canada						
Adalimumab (Humira)	40 mg/0.8 mL	Pre-filled syringe or pen	740.3600	740	40 mg SC every other week	19,249
Certolizumab (Cimzia)	200 mg/mL	Pre-filled syringe	664.5100	665	400 mg SC Weeks 0, 2, and 4, then 200 mg SC every 2 weeks or 400 mg every 4 weeks	19,271
Etanercept (Enbrel)	25 mg	Vial for injection	194.2450	194	50 mg SC weekly or 25 mg SC twice weekly	20,201
	50 mg/mL	Pre-filled syringe or auto-injector	388.6050	389		20,207
Golimumab (Simponi)	50 mg/0.5 mL 100 mg/1.0 mL	Pre-filled syringe or auto-injector	1,520.2100 1,649.4300	1,520	50 mg SC once monthly	18,243
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/1.0 mL	Pre-filled syringe	4,593.15	4,593	45 mg SC Weeks 0 and 4, then every 12 weeks thereafter	22,966

SC = subcutaneous.
[a] Manufacturer's submitted price.
[b] Based on 8 doses in the first year.
Notes: All prices are from the Ontario Drug Benefit Formulary Exceptional Access Program (July 2014) unless otherwise indicated.
Costs include wastage of unused medication, but do not include administration.
Patient weight is assumed to be 70 kg.

Cost Comparison Tables of bDMARDs Used for the Management of Plaque Psoriasis

COST COMPARISON TABLE OF INFLIXIMAB FOR THE MANAGEMENT OF PLAQUE PSORIASIS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Price per Dose ($)	Recommended Dose	Cost in Year 1 ($)
Infliximab (Inflectra)	100 mg	Vial for infusion	650.0000[a]	2,600	5 mg/kg Weeks 0, 2, and 6, then every 8 weeks thereafter	20,800[b]
Infliximab (Remicade)	100 mg	Vial for infusion	976.0000	3,904	5 mg/kg Weeks 0, 2, and 6, then every 8 weeks thereafter	31,232[b]
Other biologics indicated for the treatment of plaque psoriasis in Canada						
Adalimumab (Humira)	40 mg/0.8 mL	Pre-filled syringe or pen	740.3600	740	80 mg SC Week 0, then 40 mg Week 1, then every other week thereafter	20,730
Etanercept (Enbrel)	25 mg	Vial for injection	195.3200	391	50 mg SC twice weekly for 3 months, then once weekly thereafter	25,001
	50 mg/mL	Pre-filled syringe or auto-injector	390.7500	391		25,008
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/1.0 mL	Pre-filled syringe	4,593.15	4,593	45 mg SC Weeks 0 and 4, then every 12 weeks thereafter	22,966

SC = subcutaneous.
[a] Manufacturer's submitted price.
[a] Manufacturer's submitted price.
[b] Based on 8 doses in the first year.
Note: Prices are from the Saskatchewan Online Formulary Exceptional Drug Status Program (July 2014) unless otherwise indicated.
The Ontario Drug Benefit Formulary Exceptional Access Program does not routinely reimburse bDMARDs for the treatment of plaque psoriasis.

APPENDIX 5: PRICE REDUCTION ANALYSIS

The CADTH Common Drug Review (CDR) calculated the price reduction required for Inflectra to be equivalent to (a) the average cost of other biologic disease-modifying antirheumatic drugs (bDMARDs) and (b) the lowest-priced bDMARD currently reimbursed by public plans in Canada. The analysis was based on RA dosing (eight doses in the first year and 6.5 doses in the subsequent years), a patient weight of 70 kg, and the assumption that the average dose of infliximab would be 5 mg/kg and that 75% of patients on IV tocilizumab would receive 8 mg/kg. As shown in the table below, the price of Inflectra would need to be reduced by 13% to equal the average cost of other bDMARDs, and the price of Inflectra would need to be reduced by 38% to equal the lowest bDMARD (intravenous [IV] tocilizumab over three years, total cost $42,336).

CADTH COMMON DRUG REVIEW ANALYSIS OF PRICE REDUCTION SCENARIOS FOR INFLECTRA

Scenario	Estimated 3-Year Total Cost of Inflectra ($)	Inflectra Current Price ($)	Price Reduction Needed (%)	Reduced Price ($)
Price reduction needed to equal the average 3-year cost of alternatives ($59,394)[a]	68,250	650.00	13.0	566
Price reduction needed to equal the least costly alternative (IV tocilizumab) — 3-year total cost estimated at $42,336)	68,250	650.00	38.0	403

IV = intravenous.

[a] Alternatives included infliximab (Remicade), abatacept, adalimumab, certolizumab, etanercept, rituximab , SC golimumab, , and IV tocilizumab (innovative infliximab was not included).

Note: Prices were based on an average patient weight of 70 kg when used for RA.

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