CADTH

CADTH COMMON DRUG REVIEW

Common Drug Review Subsequent Entry Biologic Review Report

ETANERCEPT (ERELZI)

(Sandoz Canada Inc.)

Indication:

- Treatment of moderately to severely active rheumatoid arthritis (RA) in adults. Treatment is effective in reducing the signs and symptoms of RA, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function. Erelzi can be initiated in combination with methotrexate (MTX) in adult patients or used alone.
- Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients aged 4 to 17 years who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs).
- Reducing signs and symptoms of active ankylosing spondylitis (AS).

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Abbreviations

ADA	anti-drug antibodies
AS	ankylosing spondylitis
AUC	area under the curve
$AUC_{0\text{-}inf}$	area under the serum concentration time curve measured from the time of dosing and extrapolated to infinity
$AUC_{0\text{-}tlast}$	area under the serum concentration time curve measured from the time of dosing to the last measurable concentration
CDR	CADTH Common Drug Review
CI	confidence interval
DMARD	disease-modifying antirheumatic drug
Enbrel/EU	Enbrel (EU-authorized)
Enbrel/US	Enbrel (US-licensed)
GP2015	Erelzi
IGA	investigator's global assessment
JIA	juvenile idiopathic arthritis

Drug	Etanercept (Erelzi)
Indication	• Treatment of moderately to severely active rheumatoid arthritis (RA) in adults. Treatment is effective in reducing the signs and symptoms of RA, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function. Erelzi can be initiated in combination with methotrexate (MTX) in adult patients or used alone. • Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients aged 4 to 17 years who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). • Reducing signs and symptoms of active ankylosing spondylitis (AS).
Listing Request	List in a manner similar to Enbrel, in keeping with the Health Canada–approved indications for Erelzi, for Enbrel-naïve and Enbrel-experienced patients.
Dosage form(s)	Sterile solution for injection 50 mg/mL in a pre-filled syringe (two dosage strengths available: 25 mg/0.5 mL and 50 mg/1.0 mL) Sterile solution for injection 50 mg/mL in a prefilled autoinjector (all dosage forms have one strength: 50 mg/mL)
NOC date	April 06, 2017
Manufacturer	Sandoz Canada Inc.

Executive Summary

Approach to the Review

The CADTH Common Drug Review (CDR) approach to reviewing Erelzi (etanercept biosimilar) 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 the cost comparison (section 7).

Product Information

Erelzi (also known as GP2015) is based on the reference etanercept (Enbrel) and is granted a Notice of Compliance by Health Canada for the following indications:

- treatment of moderately to severely active rheumatoid arthritis (RA) in adults
- reducing signs and symptoms of active ankylosing spondylitis (AS)
- reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients aged four to 17 years who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs).

The reference product, Enbrel, is also indicated for psoriatic arthritis and plaque psoriasis; however, the manufacturer is requesting that Erelzi be reimbursed only for the RA, AS, and polyarticular JIA indications, which are the three indications granted by Health Canada. The manufacturer is requesting that Erelzi be reimbursed in a manner similar to Enbrel. The exact wording of the manufacturer-requested reimbursement criteria are found in section **Error! Reference source not found.**.

Clinical Evidence

The manufacturer provided one phase III, equivalence randomized controlled trial, along with a treatment period in which some patients had a sequence of three treatment switches between Erelzi and Enbrel and an extension period after that, enrolling patients with moderate to severe chronic plaque-type psoriasis (EGALITY study), and a phase I pharmacokinetic study enrolling healthy male volunteers (study GP15-104).

EGALITY was a phase III, randomized, 52-week, double-blind, multi-centre clinical study conducted in Bulgaria, Czech Republic, Estonia, Germany, Hungary, Poland, Romania, Russian Federation, Slovakia, South Africa, Ukraine, and the UK that assessed the efficacy, safety, pharmacokinetics, and immunogenicity of Erelzi (etanercept subsequent entry biologic [SEB]) compared with Enbrel (reference product) in patients with moderate to severe chronic plaque-type psoriasis. The EGALITY study consisted of four periods: screening, treatment period (TP) 1 (weeks 0 to 12), TP2 (weeks 13 to 30), and an extension period (weeks 31 to 52). In TP1, patients were randomized 1:1 to self-administer 50 mg Erelzi or 50 mg Enbrel, twice weekly, subcutaneously. Patients who had achieved at least a 50% improvement on the Psoriasis Area and Severity Index (PASI 50) at week 12 were to proceed to TP2 and were re-randomized either to continue the same treatment or to alternate treatment with GP2015 or Enbrel for periods of six consecutive weeks, i.e., switching to the alternating treatment after week 12 and switching back to the original treatment after week 18 followed by a third switch of treatment regimen after week 24. After the end of TP2, patients continued to be treated for an additional 22 weeks during the extension period. They received the treatment they had last received during TP2. The primary end point was PASI 75 (75% improvement from baseline) at week 12, through which therapeutic equivalence was concluded between Erelzi and Enbrel if the 95% confidence interval (CI) of the adjusted treatment difference was entirely contained within the equivalence margin of −18% to 18%. Additional efficacy, safety, pharmacokinetic, and immunogenicity outcomes were also assessed. Results of the primary end point of PASI 75 response (proportion of patients showing at least 75% improvement in PASI) at week 12 were similar for both the per-protocol set (73.4% vs. 75.7%) and the full analysis set (70.4% vs. 71.6%) between Erelzi and Enbrel, respectively. The 95% CIs of the adjusted difference rates fell within the predefined equivalence margin of ± 18% for both the per-protocol set (−9.85% to 5.30%) and the full analysis set and (−8.77% to 6.45%). In addition, all other efficacy, safety, and pharmacokinetic end points were similar, with fewer injection site reactions in the Erelzi-treated group and comparable immunogenicity in terms of anti-drug antibodies between the treatment groups.

Study GP15-104 was a single-centre, randomized, double-blind, two-way crossover study to compare the pharmacokinetics, safety, and immunogenicity of Erelzi and Enbrel following a single dose of 50 mg subcutaneous injection in healthy male patients. Participants were randomized to receive a single 50 mg subcutaneous injection of Erelzi or European-sourced Enbrel (Enbrel/EU). Participants had a washout period of 35 days before crossing over. After the washout period patients were crossed over and received a single 50 mg subcutaneous injection of the opposite treatment. The primary pharmacokinetic end point was to determine the bioequivalence of Erelzi and Enbrel in terms of maximum observed serum concentration, area under the serum concentration time curve measured from the time of dosing and extrapolated to infinity ($AUC_{0\text{-inf}}$), and AUC measured from the time of dosing to the last measurable concentration ($AUC_{0\text{-tlast}}$), through which pharmacokinetic similarity was concluded between Erelzi and Enbrel if 90% CIs for the geometric mean ratios were entirely contained within the bioequivalence range of 0.80 to 1.25. Additional safety, pharmacokinetic, and immunogenicity outcomes were also assessed. This study demonstrated that the pharmacokinetic profile was equivalent between Erelzi and Enbrel/EU.

In TP2 of the EGALITY study, patients randomized to the switching arms used the other treatment between weeks 12 and 18, the original treatment between weeks 18 and 24, and the other treatment between weeks 24 and 52. The PASI 75 response rates were similar from weeks 18 to 52 across all four arms (Erelzi only, Enbrel only, Erelzi to Enbrel to Erelzi to Enbrel, and Enbrel to Erelzi to Enbrel to Erelzi); however, these results were not compared statistically. Therefore, any

results obtained are considered descriptive and exploratory in nature and offer limited evidence to draw conclusions regarding the appropriateness of switching patients from the reference product to the SEB. In addition, in the treatment arms that switched treatments, there was no washout period before switching treatment, hence it is not clear if the treatment effect was due to the original treatment or the switched treatment. Patients in TP2 who switched treatment groups were exposed to two drugs during the switch periods due to overlapping half-lives, allowing for characterization of the safety and immunogenicity profile when treated with both drugs; comparable safety and immunogenicity were demonstrated in these treatment groups. Also, further comparative data on the safety of Erelzi and Enbrel was obtained from patients who received the initially assigned treatment continuously in TP2, which also showed comparable safety and immunogenicity: the number of patients with at least one treatment-emergent adverse event (TEAE) up to week 52 was 98 (59.8%) in the Erelzi-only treatment group while it was 98 (57.3%) in the Enbrel-only treatment group; and it was 61 (61.0%) and 57 (59.4%) in the switched Erelzi and switched Enbrel treatment groups respectively. The incidences of serious adverse events, study discontinuation due to TEAEs, and treatment-related TEAEs were similar between the two switched treatment groups and the two continued treatment groups. On the other hand, the incidence of adverse events of special interest was higher for the continued Erelzi treatment group (11.0%) than the continued Enbrel treatment group (4.7%) and for the switched Erelzi treatment group (11.0%) compared with the switched Enbrel group (5.2%). In addition, the sample size was too small to detect rare but serious adverse events of etanercept such as pancytopenia and possible malignancies.

The available data for the EGALITY study were consistent with the conclusion that Erelzi and Enbrel have similar efficacy and safety profiles in patients with plaque-type psoriasis. The available data for GP15-104 were consistent with the conclusion that Erelzi and Enbrel have similar pharmacokinetic profiles. The external validity of the results is limited by the lack of North American sites and the lack of racial diversity in the study population.

Erelzi was approved by the European Medical Agency and by the FDA in the US for RA, polyarticular JIA, and AS indications, in addition to psoriatic arthritis and plaque arthritis, based on the similarity between Erelzi and Enbrel.

Extrapolation

The results of a phase III randomized controlled trial suggest similarity in the clinical efficacy, immunogenicity, and safety profile of Erelzi as compared with Enbrel; the consistency of Erelzi's comparable efficacy is further supported by the results of TP2 and the extension period. A phase I, double-blind, randomized, two-way crossover trial on healthy volunteers supports the equivalence in pharmacokinetic profile. The above points suggest that extrapolation of the safety and efficacy results from the plaque psoriasis study to RA, AS, and JIA may be reasonable; however, there is no clinical evidence available in the time being for these indications.

Potential Place in Therapy

The clinical expert indicated that the reference product, etanercept (Enbrel), has been widely used for patients with RA, polyarticular JIA, AS, psoriatic arthritis, and plaque psoriasis for more than 10 years. Etanercept has been one of the most frequently chosen biologics to treat these diseases. Typically, anti–tumour necrosis factor (anti-TNF) agents are used after an inadequate trial of two NSAIDs (nonsteroidal anti-inflammatory drugs) for patients with AS, and after an inadequate trial of DMARD monotherapy or combination therapy in patients with RA or JIA. Etanercept has the advantage of having the longest observation period for safety and efficacy for a subcutaneous anti-TNF. It may be used with or without methotrexate, which is often poorly tolerated.

1. Product Information

The manufacturer provided the information in this section.

1.1 Overview of the SEB Product

An overview of Erelzi, a proposed biological medicinal product similar to Enbrel, is provided in Table 1.

Table 1: Overview of the Biosimilar Product

Characteristics	Manufacturer-Provided Details	
	Erelzi[1]	Enbrel[2]
Brand name:	Erelzi	Enbrel
Non-proprietary name:	etanercept	etanercept
Manufacturer:	Sandoz Canada Inc.	Immunex Corporation, distributed by Amgen Canada Inc.
Strength(s):	• 50 mg (1.0 mL of a 50 mg/mL solution of etanercept) • 25 mg (0.5 mL of a 50 mg/mL solution of etanercept)	• 50 mg/mL • 25 mg/vial
Dosage form:	• Solution for injection in a pre-filled syringe (25 mg of etanercept or 50 mg of etanercept) (with needle guard with finger flange) • Single-use pre-filled SensoReady pen (50 mg)	• Solution for injection in a pre-filled syringe (50 mg) • SureClick autoinjector (50 mg) • Lyophilized powder for reconstitution in a vial (25 mg)
Route of administration:	SC injection	SC injection
Drug Identification Number(s):	N/A	02242903 (25 mg/kit) 02274728 (50 mg/mL)
Therapeutic classification:	DMARD	DMARD
Excipients	50 mg: • 0.786 mg citric acid • 13.52 mg sodium citrate • 1.50 mg sodium chloride • 10 mg sucrose • 4.6 mg lysine 25 mg: • 0.393 mg citric acid • 6.76 mg sodium citrate • 0.75 mg sodium chloride • 5 mg sucrose • 2.3 mg lysine	Pre-filled syringes and SureClick autoinjectors: • 1% sucrose • 100 mM sodium chloride • 25 mM L-arginine hydrochloride • 25 mM sodium phosphate Powder: • Each vial is reconstituted with 1 mL of the supplied sterile bacteriostatic water for injection, USP (containing 0.9% benzyl alcohol), to yield a solution with a pH of 7.4 ± 0.3 containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine
Impurities[b]	See Table 2.	

DMARD = disease-modifying anti-rhematic drug; N/A = not applicable; SC = subcutaneous.

Erelzi (also known as GP2015) has been developed as a biological medicinal product similar to Enbrel, the reference medicinal product (both the European-authorized and the US-licensed Enbrel were used in the biosimilar development of Erelzi, namely in comparative pharmacokinetics as well as in comparative physicochemical and functional studies). The reference product etanercept is marketed as Enbrel in the European Union, US, and Canada. The Marketing Authorization Holder for the EU-authorized reference product Enbrel is Pfizer Limited, UK (henceforth, EU-authorized Enbrel will be referred to as Enbrel/EU), while in the US and Canada Enbrel is licensed to Immunex Corp, Thousand Oaks, California, and marketed by Amgen Inc. (henceforth, US-licensed Enbrel will be referred to as Enbrel/US).

The serum concentration of the active pharmaceutical ingredient (etanercept) in both dosage forms of Erelzi is the same as for the reference product. The formulations of Erelzi and Enbrel are identical with regard to the concentration of the active pharmaceutical ingredient, etanercept, as well as the pH. The formulations differ with respect to the composition of inactive components due to intellectual property considerations. Specifically, the Erelzi formulation contains citrate and lysine, and the Enbrel formulation contains phosphate and arginine. Long-term stability testing confirmed that the drug product of the chosen composition meets all pre-specified requirements. This final formulation of Erelzi (solution for injection in pre-filled syringes) was used in all nonclinical and clinical studies.

Similar to Enbrel, Erelzi is administered as a subcutaneous injection. In contrast to Enbrel, both the 25 mg and 50 mg strengths of Erelzi are available in a pre-filled syringe (whereas only Enbrel 50 mg is available in this dosage form), and Erelzi is not available as a powder for reconstitution. The recommended dosage is the same for both products: 50 mg per week in patients with rheumatoid arthritis (RA) or ankylosing spondylitis (AS), and 0.8 mg/kg per week (up to a maximum of 50 mg per week) for pediatric patients aged four to 17 years with active polyarticular juvenile idiopathic arthritis (JIA).[1, 2] Erelzi and Enbrel also share similar recommended dosages pertaining to the use of the 50 mg autoinjector; this formulation is only for use in pediatric patients weighing 63 kg (138 pounds) or more who do not require weight-based dosage.[1, 2] Both products are intended for use under the guidance and supervision of a physician. However, patients may self-inject if their physician determines that it is appropriate and if there is medical follow-up, as necessary, after proper training in measurement of the correct dose and injection technique.[1, 2]

Purity:

[redacted]

In case of GP2015, two aged drug product batches (#CS2951 and #DR0917) have been investigated within this comparability exercise, and higher purities compared with the reference product(s) have also been determined for these batches.

Impurities:

Product-Related Impurities

Product-related substances and impurities of the GP2015 drug product are listed in Module 3.2.P.5.5. A detailed description of the results for impurity comparison between GP2015 and Enbrel is presented in Module 3.2.R, Comparability with Reference Product. A brief summary of results is provided in Table 2.

By definition (ICH Q6B), product-related substances of biological products are not impurities, and they are therefore not listed here.

Process-Related Impurities

Process-related impurities, including DNA, residual protein A, and host cell proteins, have been monitored and quantified in the GP2015 drug substance, since no change is expected during the GP2015 manufacturing process. As these impurities are process specific, comparability between GP2015 and Enbrel is not expected. Furthermore, details on the manufacturing process and cell line used for manufacturing of EU-authorized Enbrel and US-licensed Enbrel are not publicly disclosed. Therefore, only DNA and residual protein A have been monitored for GP2015. [redacted] Host cell proteins are routinely controlled for each GP2015 drug substance batch with a release limit determined in concert with health authorities.

Table 2: Comparison of Impurities Between Erelzi and Enbrel

	Manufacturer-Provided Details	
	Impurities	**Comparison Etanercept (GP2015) and Enbrel/EU[a]**
Product-Related Impurities	Aggregation products	[redacted]
	Degradation products	
	Wrongly bridged disulphide variants	[redacted]
	Hydrophobic variants	[redacted]
Product-Related Variant	Free thiols	[redacted]

[a] Enbrel/CA is analytically indistinguishable from the Enbrel/US and Enbrel/EU batches tested.[3]

1.2 Overview of the Reference Product

Enbrel contains the active substance etanercept, a recombinant human tumour necrosis factor (TNF) receptor Fc fusion protein. Enbrel is approved and marketed in Canada.

Enbrel is indicated for:[2]

- treatment of moderately to severely active RA in adults (Treatment is effective in reducing the signs and symptoms of RA, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function. Enbrel can be initiated in combination with methotrexate (MTX) in adult patients or used alone.)
- reducing signs and symptoms of moderately to severely active polyarticular JIA in patients aged four to 17 years who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs) (Enbrel has not been studied in children who are less than four years of age.)
- reducing signs and symptoms, inhibiting the progression of the structural damage of active arthritis, and improving physical function in adult patients with psoriatic arthritis* (Enbrel can be used in combination with MTX in adult patients who do not respond adequately to MTX alone.)
- reducing signs and symptoms of active AS

* Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

- treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*

Enbrel (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 tumour necrosis factor receptor linked to the Fc portion of human immunoglobulin. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system for use as a therapeutic inhibitor of TNF, a pro-inflammatory cytokine. Etanercept is composed entirely of human amino acid sequences. The Fc component of etanercept contains the CH2 and CH3 domains but not the CH1 domain of human imunoglobulin.[2]

Enbrel is available as a clear, colourless, sterile, preservative-free solution, and it is formulated at pH 6.3 ± 0.2. There may be small white particles of protein in the solution, which is not unusual for proteinaceous solutions. Each Enbrel single-use pre-filled syringe and SureClick autoinjector contains a 50 mg/mL solution of etanercept, with 1% sucrose, 100 mM sodium chloride, 25 mM L-arginine hydrochloride, and 25 mM sodium phosphate.[2]

Enbrel is also available as a sterile, white, preservative-free, lyophilized powder in a multiple-use vial. Each vial is to be reconstituted with 1 mL of the supplied sterile bacteriostatic water for injection, USP (containing 0.9% benzyl alcohol), to yield a multiple-use clear and colourless solution with a pH of 7.4 ± 0.3 and containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.[2]

2. Indications

2.1 Health Canada-Approved Indications

The manufacturer provided the information in this section.

Table 3: Health Canada–Approved Indications for Erelzi

Indication(s)	Extrapolation
RA: Treatment of moderately to severely active RA in adults. Treatment is effective in reducing the signs and symptoms of RA, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function. Erelzi can be initiated in combination with MTX in adult patients or used alone.	Yes
Polyarticular JIA: Reducing the signs and symptoms of moderately to severely active JIA in patients aged 4 to 17 years who have had an inadequate response to one or more DMARDs. Erelzi has not been studied in children less than 4 years of age.	Yes
AS: Reducing signs and symptoms of active AS	Yes
RA: Treatment of moderately to severely active RA in adults. Treatment is effective in reducing the signs and symptoms of RA, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function. Erelzi can be initiated in combination with MTX in adult patients or used alone.	Yes

AS = ankylosing spondylitis; CMARD = disease-modifying antirheumatic drug; JIA = juvenile idiopathic arthritis; MTX = methotrexate; RA = rheumatoid arthritis.

2.2 Proposed Indications Under Review by Health Canada

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

NOC = Notice of Compliance.

3. Manufacturer's Requested Listing Criteria

The manufacturer provided the information in this section.

3.1 Requested Listing Criteria

The requested reimbursement criteria for Erelzi are the same for each of the indications under review. Sandoz is requesting the following reimbursement criteria for Erelzi:

- Reimburse in a manner similar to Enbrel, in keeping with the Health Canada–approved indications for Erelzi, for Enbrel-naive and Enbrel-experienced patients.

3.2 Rationale for Requested Reimbursement Criteria

Proof of biosimilarity between Erelzi and Enbrel (Enbrel/EU and Enbrel/US) is based on physicochemical, biological, nonclinical, and clinical data. Erelzi was demonstrated to be bioequivalent to Enbrel/EU (pivotal pharmacokinetic study GP15-104)[4, 5] and was shown to have a comparable safety and efficacy profile to Enbrel/EU in patients with plaque-type psoriasis* (EGALITY study).[6,7] Based on

* Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

the demonstrated biosimilarity of Erelzi to Enbrel (reference product), Sandoz proposes reimbursement criteria for Erelzi that is in line with Enbrel, in keeping with the Health Canada–approved indications for Erelzi.

In addition, Sandoz is proposing that Erelzi be recommended for patients who have not had any previous exposure to Enbrel and for those who are currently being treated with Enbrel. Erelzi is appropriate for use in both Enbrel-naive and Enbrel-experienced patients, as demonstrated in the pivotal phase III EGALITY study.* Results from the EGALITY study demonstrated therapeutic equivalence and similar safety profiles between Erelzi and Enbrel/EU in Enbrel-naive patients with moderate to severe chronic psoriasis* over 52-weeks.[6] In addition, the EGALITY study was designed to evaluate the effects of repeated switching between Erelzi and Enbrel. Similar efficacy, safety, and immunogenicity were demonstrated between patients comprising the "pooled switched" treatment group (i.e., pooled data from patients who switched to and from Erelzi and to and from Enbrel) and the "pooled continued" group (i.e., patients who received either Erelzi or Enbrel throughout the entire 52-week study period).[6] Therefore, patients currently being treated with Enbrel should be considered for switching to Erelzi, in keeping with the Health Canada–approved indications for Erelzi.

4. Biosimilarity

The manufacturer provided the information in this section.

4.1 Quality Information

Table 4: Physicochemical Methods Used to Characterize and Compare GP2015 and Enbrel With Respect to Identity, Purity, and Content

Molecular Parameter	Attribute	Methods for Control and Characterization	Summary of Results		Reference[a]
			Comparison GP2015 to Enbrel/EU	Comparison Enbrel/EU to Enbrel/US	
Primary Structure	Amino acid sequence	[redacted]	[redacted]		**4.1.1.1** **4.1.1.7**
	Degradation product N-terminal heterogeneity	[redacted]	[redacted]	[redacted]	**4.1.1.3**
	Disulphide bridging	[redacted]	[redacted]	[redacted]	**4.1.1.4**
	Free cysteines	[redacted]	[redacted]	[redacted]	**4.1.1.6**
Higher-Order Structure	Secondary and tertiary structure	[redacted]	[redacted]	[redacted]	**4.1.2.1**
		[redacted]	[redacted]	[redacted]	**4.1.2.2**
		[redacted]	[redacted]		**4.1.2.3**
		[redacted]	[redacted]	[redacted]	**4.1.2.4**
		[redacted]	[redacted]		**4.1.2.5**
		[redacted]	[redacted]	[redacted]	**4.1.2.6**

Molecular Parameter	Attribute	Methods for Control and Characterization	Summary of Results		Reference[a]
			Comparison GP2015 to Enbrel/EU	Comparison Enbrel/EU to Enbrel/US	
			[redacted]	[redacted]	
Molecular Mass/Size	Molecular mass	[redacted]	[redacted]	[redacted]	**4.1.3**, **4.1.7.2**
Charge	Charge/Size	[redacted]	[redacted]	[redacted]	**4.1.4.1**
Content	Content	[redacted]	[redacted]	[redacted]	**4.1.11**

[redacted]

Table 5: Physicochemical Characterization of Heterogeneity and Stability Indicating Degradation Products

	Attribute	Methods for Control and Characterization	Summary of Results		Reference[a]
			Comparison GP2015 to Enbrel/EU	Comparison Enbrel/EU to Enbrel/US	
Glycosylation	O-Glycans	[redacted]	[redacted]		[redacted]
	Glycosylation site occupancy and site-specific (e.g., Fc part) N-glycan analysis	[redacted]	[redacted]	[redacted]	Section **4.1.5.2**
	Glycation	[redacted]	[redacted]	[redacted]	Section **4.1.5.3**
	Sialic acids, incl. N-glycolylneura-minic acid	[redacted]	[redacted]	[redacted]	Section **4.1.5.4**
Amino Acid	Variability of	[redacted]	[redacted]	[redacted]	Section **4.1.6.1**

	Attribute	Methods for Control and Characterization	Summary of Results		Reference[a]
			Comparison GP2015 to Enbrel/EU	Comparison Enbrel/EU to Enbrel/US	
Sequence Size Amino Acid Modifications	N- terminus (− Leu, − Leu-Pro) Variability of C-terminus: − Lys, truncation to proline amide Aggregation Fragmentation Oxidation Deamidation	[redacted]	[redacted]	[redacted]	
		[redacted]	[redacted]	[redacted]	Section **4.1.6.2**
		[redacted]	[redacted]		[redacted]
		[redacted]	[redacted]	[redacted]	Section **4.1.7**
		[redacted]	[redacted]		[redacted]
		[redacted]	[redacted]	[redacted]	Section **4.1.8.1**

[a] Section found within Module 3.2.R, Comparability with Reference Product.

Table 6: Physicochemical Characterization of Heterogeneity and Stability Indicating Degradation Products

	Test	Method / Cell Line	Summary of Results		Reference[a]
			Comparison GP2015 to Enbrel/EU	Comparison Enbrel/EU to Enbrel/US	
Binding Assays	[redacted]	[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
In Vitro Bioassays	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Test	Method / Cell Line	Summary of Results		Reference[a]
			Comparison GP2015 to Enbrel/EU	Comparison Enbrel/EU to Enbrel/US	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Binding Assays	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
In Vitro Bioassays	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

4.2 Pivotal Clinical Studies

The safety, efficacy, and immunogenicity of Erelzi compared with Enbrel/EU was evaluated in a phase III, multi-centre, double-blind, randomized controlled trial (Table 7). The EGALITY study (GP2015-302; N = 531) was designed to show equivalence in efficacy and similarity in the safety and immunogenicity of Erelzi and Enbrel/EU in patients with moderate to severe chronic plaque-type psoriasis[*] and to evaluate the effects of repeated switching between Erelzi and Enbrel/EU on efficacy, safety, and immunogenicity. The primary

[*] Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

efficacy end point was the proportion of patients showing at least 75% improvement in the Psoriasis Area and Severity Index (PASI 75).

Moderate to severe plaque-type psoriasis* is one of the indications approved for the reference product Enbrel.[2] Sandoz selected psoriasis* for the comparative assessment of GP2015 (Erelzi) and Enbrel/EU in the EGALITY study because it is considered a sensitive indication to detect potential differences between the two products. In addition, the PASI 75 is a clinically meaningful end point commonly used in previous studies of Enbrel in psoriasis,* which allows for comparison of the results of the EGALITY study with those in the literature. Furthermore, etanercept is used as monotherapy in psoriasis*, which reduces confounding factors and the risk of immunosuppression resulting from concomitant medications (e.g., MTX is often used in the treatment of arthritic conditions), thus increasing the likelihood of detecting any potential differences in immunogenicity between the two products. Finally, in psoriasis*, a dose of 50 mg falls into the linear phase of the dose-response curve, in which differences in dose can be seen as a difference in efficacy. In RA, however, a dose of 25 mg falls into the plateau phase of the dose-response curve.

Therefore, psoriasis* is a sensitive indication through which a difference between treatment effects can be easily detected. An overview of the pivotal EGALITY study is provided in Table 7.

Table 7: Summary of the EGALITY Study

Study Name	Design	Objectives	Population
EGALITY (GP15-302)	Phase III, multi-centre, randomized, double-blind	To show equivalence in efficacy and similarity in the safety and immunogenicity profiles of GP2015 and Enbrel by assessing the PASI 75 response rate at week 12 and to evaluate the effects of repeated switching	Adult patients aged ≥ 18 years with active but clinically stable chronic plaque-type psoriasis[a] involving at least 10% of the BSA and having a minimal PASI of 10 (indicating moderate to severe psoriasis) who have previously received phototherapy or systemic therapy at least once for psoriasis or who are eligible to receive such therapy in the opinion of the investigator

BSA = body surface area; PASI = Psoriasis Area and Severity Index; RA = rheumatoid arthritis.

Note: GP15-301 (EQUIRA) is currently an ongoing study in patients with moderate to severe active RA. EQUIRA is a parallel-group, randomized, double-blind study with a treatment duration of up to 48 weeks per patient. GP15-301 is being conducted to obtain additional efficacy and safety data for GP2015 in RA patients to potentially support marketing authorization of GP2015 in other countries where Enbrel has not been approved for plaque psoriasis.

[a] Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

4.2.1 EGALITY (GP15-302)

Study Characteristics

EGALITY is a 52-week, phase III, multi-centre, randomized, double-blind study that assessed the efficacy, safety, and immunogenicity of GP2015 and Enbrel/EU in patients with moderate to severe chronic plaque-type psoriasis*. The EGALITY study also evaluated the effects of repeated switching between GP2015 and Enbrel on efficacy, overall safety, and immunogenicity. Since only Enbrel/EU was utilized in this study, the use of the term “Enbrel” throughout this report describes EU-authorized Enbrel only. An overview of the study is presented in Table 8.

* Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

Table 8: Overview of Study Details for EGALITY

Characteristics		Details for EGALITY
Study Design	Objective	The aim of this pivotal study was to demonstrate equivalence in efficacy, primarily based on the PASI 75 response rate, and similarity in the safety profile of GP2015 and Enbrel/EU in patients with moderate to severe chronic plaque-type psoriasisa and to evaluate the effects of repeated switching between GP2015 and Enbrel/EU on efficacy, overall safety, and immunogenicity.
	Blinding	Double-blind
	Study Period	2013-06 to 2015-03
	Study Centres	74 study centres in 12 countries (Bulgaria, Czech Republic, Estonia, Germany, Hungary, Poland, Romania, Russian Federation, Slovakia, South Africa, Ukraine, and the UK)
	Design	Equivalence
Study Population	Randomized (N)	531
	Inclusion Criteria	Patients ≥18 years with active, but clinically stable chronic plaque-type psoriasisa diagnosed ≥ 6 months prior to baseline with a PASI score ≥ 10 and, IGA score ≥ 3 and, BSA affected by plaque-type psoriasis ≥ 10%. Previous phototherapy or systemic therapy for psoriasisa or eligibility for such therapy in the investigator's opinion
	Exclusion Criteria	Previous exposure to etanercept Exposure to TNF antagonists or other biologic immunomodulating agents in the 6 months prior to randomization Ongoing use of prohibited psoriasisa treatments such as topical corticosteroids or ultraviolet-therapy, or prohibited non-psoriasisa treatments (all other prior non-psoriasisa concomitant treatments had to be on a stable dose for ≥ 4 weeks before baseline) Presence of active systemic infections in the two weeks prior to baseline Latent tuberculosis
Drugs	Intervention	GP2015 50 mg SC twice weekly
	Comparator(s)	Enbrel 50 mg SC twice weekly
Duration	Run-In	NA
	Treatment	TP1 = 12 weeks; TP2 = 18 weeks; extension period: 22 weeks
	Follow-Up	NA
Outcomes	Primary End Point(s)	PASI 75 response rate (proportion of patients showing at least 75% improvement in PASI) after the first 12 weeks of treatment (TP1)
	Other End Points	Key secondary: percentage change from baseline in PASI score up to week 12 Other (assessed at all time points up to week 52): PASI 50, 75, and 90 (proportion of patients showing at least a 50%/75%/90% improvement in PASI score from baseline visit) response rates Observed PASI score Percentage change from baseline in PASI score IGA score
Notes	Publications	Griffiths et al., 2016.7 NCT01891864

BSA = body surface area; GP2015 = Erelzi; IGA = investigator's global assessment; NA = not applicable; PASI = Psoriasis Area and Severity Index; SC = subcutaneous; TNF = tumour necrosis factor; TP = treatment period.

[a] Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

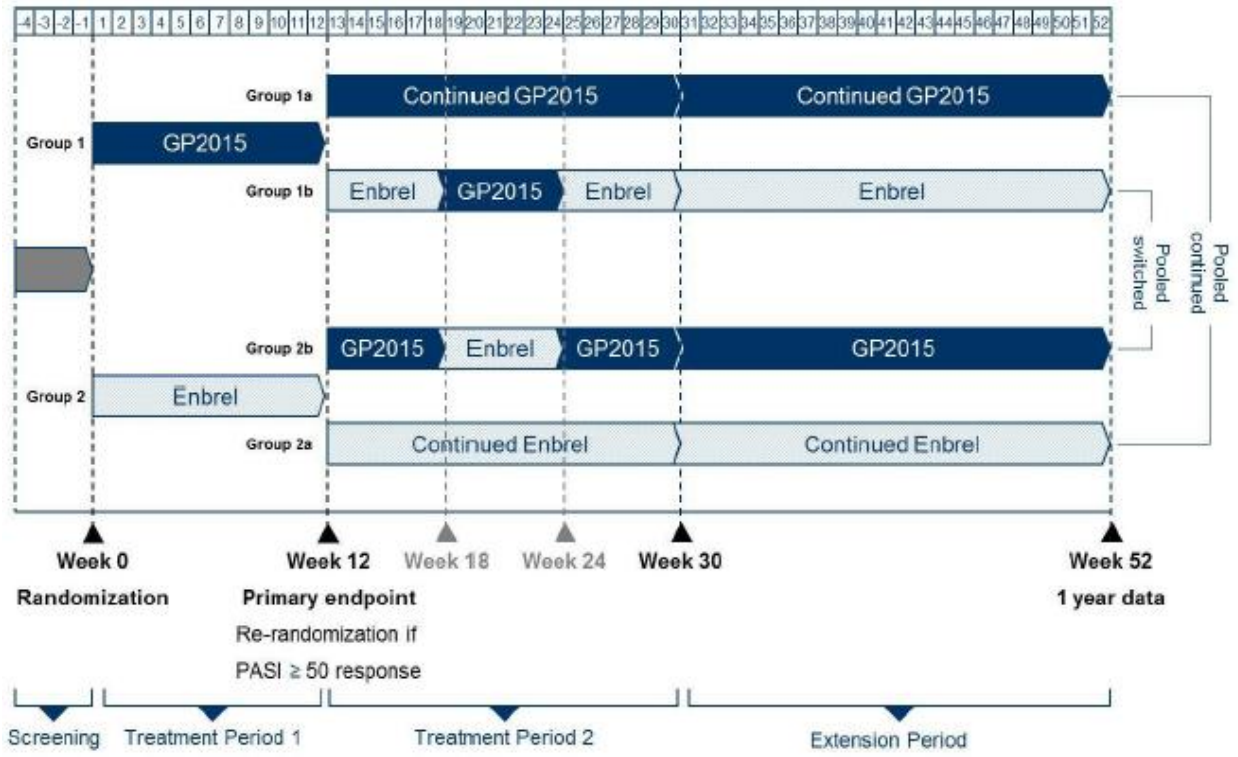
Intervention and Comparators

Enbrel is the comparator in the EGALITY study and is currently marketed in Canada. The specific formulation of Enbrel used to establish equivalency in the EGALITY trials is that authorized in the EU (Enbrel/EU).

Patients were initially randomized 1:1 to receive GP2015 or Enbrel/EU at a dose of 50 mg administered subcutaneously by the patient twice weekly for 12 weeks (treatment period 1 [TP1]). At week 12, patients who achieved a PASI 50 response (≥ 50% improvement in PASI) were re-randomized to continue the same treatment as in TP1 for 18 weeks ("continued GP2015" and "continued Enbrel" groups) or to undergo a sequence of three treatment switches between GP2015 and Enbrel/EU at 6-week intervals until week 30 ("switched GP2015" and "switched Enbrel" groups) (treatment period 2 [TP2]). During TP2, patients were administered either GP2015 or Enbrel/EU at a dose of 50 mg subcutaneous once weekly. At week 30, patients continued the treatment they were receiving at the end of TP2 for an additional 22 weeks (extension period). Patients who had an inadequate response to the study drug at week 30 in the opinion of the investigator or who required treatment with a prohibited agent (Table 9) were discontinued from the study drug and scheduled a follow-up visit.

Figure 1 shows the detailed study design and the flow of treatment periods.

Figure 1: EGALITY Study Design



PASI = Psorisasis Area and Severity Index.

Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomization until final database lock. Unblinding was permitted only in the case of patient emergencies, at the time of the interim primary end point analysis, and at the conclusion of the study.

Since the EGALITY study employs an active-comparator, and since Erelzi and Enbrel were administered in an identical manner, the use of matched placebos or double-dummy controls was not necessary.

The use of any treatments that could confound the efficacy analyses was not permitted after randomization for any indication, including psoriasis.[*6] These treatments had to be washed out before randomization. Further details, including the washout periods for these treatments before randomization, are presented in Table 9. Patients who were using topical treatments during the screening period had to stop use of these topical corticosteroids the day before the baseline visit (visit 2) and were not allowed to use these topical corticosteroids for any indication at any time after randomization.[6]

Table 9: Treatments Prohibited During the EGALITY Study[6]

Prohibited Treatments	Washout Period
Washout Period Relative to Randomization	
Etanercept	No prior use allowed
TNF antagonists (investigational or approved), e.g., adalimumab, and infliximab	6 months
Biological immunomodulating agents other than above, e.g., alefacept, briakinumab, ustekinumab, abatacept, and anakinra	6 months
Other systemic immunomodulating treatments (e.g., MTX, cyclosporine A, and corticosteroids[3])	4 weeks
Cyclophosphamide	6 months
Leflunomide	8 weeks (unless a cholestyramine washout has been performed)
Other systemic psoriasis[a] treatments (e.g., retinoids, fumarates)	4 weeks
Photochemotherapy (e.g., PUVA)	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks
Topical treatment that is likely to impact signs and symptoms of psoriasis[a] (e.g., vitamin D analogues, pimecrolimus, retinoids, salicyl vaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, alpha-hydroxy acid, or fruit acids	2 weeks
Live vaccinations	6 weeks
Prohibited regimen of topical corticosteroids:	
• Topical corticosteroids with higher than moderate potency on any body location	2 weeks
• Topical corticosteroids with mild to moderate potency on any body location other than the face, scalp, and/or genitoanal area	2 weeks
• Topical corticosteroids with mild to moderate potency on the face, scalp, and/or genitoanal area.	1 day
Washout Period Relative to Screening	
Any investigational treatment (other than those mentioned above) or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)

MTX = methotrexate; PUVA = psoralen ultraviolet between 320 and 400 nanometers; TNF = tumour necrosis factor; UVA = ultraviolet between 320 and 400 nanometers; UVB = ultraviolet B.

Notes: If the prohibited treatment was used during the study for any indication, the patient had to discontinue use of the prohibited treatment if he/she wished to continue in the study. In the case of an undue safety risk for the patient, the patient had to discontinue study treatment at the discretion of the investigator. If the patient received a live vaccination during the study, the patient had to discontinue study treatment. Inhalative corticosteroids with only a topical effect (e.g., to treat asthma) were not considered systemic immunomodulating treatments and were therefore acceptable as co-medication.

[a] Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

[*] Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

Outcomes

The key efficacy and safety outcomes for the EGALITY study are briefly described below.

The primary efficacy variable was the PASI 75 response rate (i.e., the proportion of patients showing at least a 75% improvement in PASI) after the first 12 weeks of treatment (TP1).[6, 7]

The key secondary end point was the percentage change in the PASI score from week 2 to week 12.[6, 7]

Other secondary efficacy end points for TP1, TP2, the extension period, and the overall analysis included the following measurements:[6, 7]

- PASI 50, 75, and 90 response rates
- Observed PASI score
- Percentage change from baseline in PASI scores
- Investigator's global assessment (IGA), i.e., the proportion of patients achieving clear (0) or almost clear (1) disease state (scale of 0 to 4). Those patients were IGA responders according to the definition
- Change from baseline in IGA
- Health-related quality of life as assessed by relative changes in the Dermatology Life Quality Index, the EuroQol 5-Dimensions questionnaire, and the proportion of patients achieving a Dermatology Life Quality Index score of 0 or 1.
- Functional ability in patients with a medical history of psoriatic arthritis[*] as assessed by relative changes in the Health Assessment Questionnaire — Disability Index and pain visual analogue scale.

Safety end points included treatment-emergent adverse events (TEAEs), injection site reactions, laboratory parameters, immunogenicity, vital signs, electrocardiogram, and physical examination.[6, 7]

Statistical Analyses

The analysis of the primary variable was based on the per-protocol set, which consisted of all patients who completed the study until week 12 without major protocol deviations.[6, 7]

Therapeutic equivalence in terms of PASI 75 was concluded if the exact 95% confidence interval (CI) for the difference in the PASI 75 rates at week 12 was completely contained within the interval (−18% to 18%). This is statistically equivalent to calculating two independent one-sided tests at a 2.5%-alpha level (one in each direction), of which both had to be successful. As a key secondary end point, the percentage change in PASI score over all time points from week 2 to week 12 was analyzed using two methods: a mixed-effects model for repeated measures analysis and a mean averaged treatment effect analysis.[6] In both models, treatment group (GP2015 or Enbrel), visit, body weight category (< 90 kg or ≥ 90 kg), and prior systemic therapy (no prior systemic therapy or any prior systemic therapy, including biologic immunomodulating agents or prior treatment with a TNF antagonist) were fitted as factors, and the baseline score for the PASI was fitted as a continuous covariate. All secondary efficacy, safety, and immunogenicity parameters were analyzed using descriptive statistics for continuous or categorical variables, as appropriate.

A mixed-effects model for repeated measures was performed at week 12 with the percentage change of the PASI score as the end point. The mixed-effects model for repeated measures is a standard approach to longitudinal analysis of continuous end points. Its roots bear into linear mixed modelling methodology, and it was specified as a multivariate normal model of the longitudinal data. More specifically, this model included a saturated visit-by-treatment structure for the mean, and all variance and covariance parameters were estimated. This analysis was performed on the TP1 full analysis set and the TP1 per-protocol set.

The averaged treatment effect was derived for each patient and then analyzed as a stand-alone end point to capture the overall difference between treatment groups. This analysis was performed on the TP1 full analysis set (all randomized patients to whom study treatment was assigned) and the TP1 per-protocol set (patients who completed the study until week 12 without major protocol

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deviations). The averaged treatment effect analysis was performed at week 12 using analysis of covariance. Missing values were not imputed. Summary statistics for continuous variables were presented for averaged treatment effect by treatment groups.[6]

The secondary variables and comparisons detailed below were analyzed separately for TP1, TP2, and the extension period, as well as combined for the entire study (overall analysis: baseline to week 52) at the following respective time points:[6]

- TP1 variables were measured at weeks 2, 4, 8, and 12.
- TP2 variables were measured at weeks 18, 24, and 30.
- Extension period variables were measured at weeks 36, 42, 48, and 52.
- Overall analysis variables were measured at each time point from week 2 to week 52.

All safety evaluations were performed on the TP1 safety set for TP1, TP2 safety set for TP2, extension period safety set for the extension period, and the overall analysis safety set for the baseline to week 12, baseline to week 30, and baseline to week 52 analyses. Each safety set included all patients who took at least one dose of study treatment during the specified treatment period. For TP1, all safety data were presented by treatment (GP2015 or Enbrel).[6]

Results

Data are reported as per specified objectives for each treatment period (i.e., TP1, TP2, and extension period) and for combined data (baseline to week 52) as follows:

- For TP1, the comparison is between GP2015 and Enbrel.
- For TP2, extension period, and baseline to week 52, the comparison is between continued GP2015 and continued Enbrel. Also, the data from the continued treatment groups (i.e., GP2015 and Enbrel) were pooled and presented as a pooled continued group. This pooled continued group was directly compared with a pooled switched group (data from switched GP2015 and switched Enbrel groups pooled).

Baseline Characteristics

The baseline demographics and disease characteristics of patients were similar across the two treatment groups for each treatment period.

In TP1, the treatment groups were well balanced in demographic characteristics. The mean (± standard deviation [SD]) age across treatment groups was 42.4 ± 12.57 years, and 62.0% of patients were male. The mean (± SD) body weight was 86.1 ± 19.93 kg, and the mean (± SD) body mass index was 28.509 ± 5.7809 kg/m^2. The majority of patients were Caucasian (n = 527 [99.2%]).[6]

In TP2, treatment groups were well balanced based on demographic characteristics at baseline. The mean (± SD) age across treatment groups was 42.4 ± 12.52, years, and 62.2% of patients were male.

The mean (± SD) body weight was 86.9 ± 20.07 kg, and the mean (± SD) body mass index was 28.692 ± 5.8192 kg/m^2. The majority of patients were Caucasian (494 [99.4%] patients).[6] The extension period was a continuation of TP2, without any re-assignment, and was not considered as a new population; therefore, demographic data were not summarized separately for the extension period.

In the combined analysis (baseline to week 52), demographic characteristics at baseline were well balanced between the continued GP2015 and continued Enbrel groups and between the pooled continued and pooled switched groups (Table 10).[6]

Table 10: Baseline Demographics and Disease Characteristics From Baseline to Week 52 (Overall Analysis, Full Analysis Set)[6]

Parameter	Continued GP2015 N = 164	Continued Enbrel N = 71	Pooled Continued Treatment N = 335	Pooled Switched Treatment N = 196
Age, mean (SD)	42.1 (12.20)	43.5 (13.09)	42.8 (12.66)	41.7 (12.42)
Sex, n (%)				
Male	103 (62.8)	109 (63.7)	212 (63.3)	117 (59.7)
Female	61 (37.2)	62 (36.3)	123 (36.7)	79 (40.3)
Race, n (%)				
Caucasian	163 (99.4)	170 (99.4)	333 (99.4)	194 (99.0)
Black	1 (0.6)	0	1 (0.3)	0
Asian	0	1 (0.6)	1 (0.3)	0
Unknown	0	0	0	1 (0.5)
Other	0	0	0	1 (0.5)
Duration since initial diagnosis of plaque-type psoriasis[a] (years), mean (SD)	18.485 (11.0412)	17.711 (12.0907)	18.090 (11.5780)	17.001 (11.5325)
Prior systemic therapy[a]				
No prior systemic therapy	114 (69.5)	117 (68.4)	231 (69.0)	135 (68.9)
Any prior systemic therapy	49 (29.9)	52 (30.4)	101 (30.1)	59 (30.1)
Prior systemic therapy with TNF antagonist	1 (0.6)	2 (1.2)	3 (0.9)	2 (1.0)
IGA of psoriasis[a]				
2 = Mild	0	1 (0.6)	1 (0.3)	0
3 = Moderate	118 (72.0)	120 (70.2)	238 (71.0)	139 (70.9)
4 = Severe	46 (28.0)	50 (29.2)	96 (28.7)	57 (29.1)
PASI score, Mean (SD)	22.41 (8.577)	22.57 (9.478)	22.49 (9.035)	22.54 (9.546)
BSA affected, Mean (SD)	30.76 (13.467)	30.47 (15.284)	30.61 (14.403)	30.84 (14.172)
Psoriatic arthritis, n (%)				
Present	39 (23.8)	39 (22.8)	78 (23.3)	29 (14.8)
Absent	125 (76.2)	132 (77.2)	257 (76.7)	167 (85.2)

BSA = body surface area; IGA = investigator's global assessment; PASI = Psoriasis Area and Severity Index; SD = standard deviation; TNF = tumour necrosis factor.

[a] Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

Patient Disposition

Treatment Period 1

The majority of randomized patients (n = 511 [96.2%]) completed TP1. The most common reasons for discontinuation during TP1 were adverse events and patient decision (1.3% each, total). All other reasons for discontinuation were reported by fewer than one patient (0.2% total), and no patients discontinued due to lack of efficacy (Table 11).

Table 11: Summary of Patient Disposition for Treatment Period 1 in the EGALITY Study[6]

Disposition	EGALITY	
	GP2015	Enbrel
Screened, N	774	
Randomized, N	264	267
Discontinued, N (%)	8 (3.0)	12 (4.5)
WDAEs, N (%)	4 (1.5)	3 (1.1)
Death	0	1 (0.4)
Lost to follow-up, N (%)	1 (0.4)	0
Non-compliance with study treatment	0	1 (0.4)
Physician decision	0	1 (0.4)
Protocol deviation	1 (0.4)	0
Patient decision	2 (0.8)	5 (1.9)
Injection site reaction	0	1 (0.4)
Full analysis set, N	264	267
Per-protocol, N	239	241
Safety, N	264	267
Immunogenicity set, N	264	267
PK set, N	72	75

PK = pharmacokinetics; WDAE = withdrawal due to adverse event.

Treatment Period 2

Of the 511 patients who completed TP1, 497 patients were re-randomized in TP2 as follows:[6]

- 150 patients continued to receive GP2015 from TP1.
- 151 patients continued to receive Enbrel from TP1.
- 100 patients who received GP2015 during TP1 switched to the treatment sequence Enbrel to GP2015 to Enbrel.
- 96 patients who received Enbrel during TP1 switched to the treatment sequence GP2015 to Enbrel to GP2015.

Apart from direct comparisons between GP2015 and Enbrel, these first two groups (i.e., GP2015 and Enbrel) were pooled and presented as pooled continued groups. Similarly, the last two groups were pooled and presented as pooled switched groups (Table 12).

The majority of re-assigned patients (n = 472 [95.0%]) completed TP2. The most common reasons for discontinuation during TP2 were patient decision (1.8% total) and adverse events (1.4% total).[6] A total of five patients (1.0%) were discontinued in Ukraine as the war situation resulted in closure of the study site. All other reasons for discontinuation were reported by not more than one patient in each group.

There was no notable difference in the rate of discontinuation between the continued GP2015 and

continued Enbrel groups (4.7% versus 6.0%, respectively) or in the rate of discontinuation between the pooled continued and pooled switched groups (5.3% versus 4.6%, respectively).[6]

Table 12: Summary of Patient Disposition for the EGALITY Study in Treatment Phase II[6]

Disposition	EGALITY			
	Continued GP2015	Continued Enbrel	Pooled Continued Treatment	Pooled Switched Treatment
Re-Randomized, N	150	151	301	196
Discontinued, N (%)	7 (4.7)	9 (6.0)	16 (5.3)	9 (4.6)
WDAEs, N (%)	1 (0.7)	2 (1.3)	3 (1.0)	4 (2.0)
Patient decision, N (%)	3 (2.0)	4 (2.6)	7 (2.3)	2 (1.0)
Study terminated by sponsor, N (%)	1 (0.7)	2 (1.3)	3 (1.0)	2 (1.0)
Lack of efficacy	1 (0.7)	0	1 (0.3)	1 (0.5)
Physician decision	1 (0.7)	0	1 (0.3)	0
Protocol deviation	0	1 (0.7)	1 (0.3)	0
Full analysis set, N	150	151	301	196
Per-protocol, N	138	129	267	179
Safety, N	150	151	301	196
Immunogenicity set, N	150	151	301	196

WDAE = withdrawal due to adverse event.

Extension Phase

A total of 467 patients were treated in the extension period as follows:[6]

- 140 patients continued to receive GP2015 from TP2.
- 142 patients continued to receive Enbrel from TP2.
- 95 patients who switched to the treatment sequence Enbrel to GP2015 to Enbrel in TP2 continued treatment with Enbrel in the extension period.
- 90 patients who switched to the treatment sequence GP2015 to Enbrel to GP2015 in TP2 continued treatment with GP2015 in the extension period.

The majority of patients (95.7%) treated in the extension period completed this period. As shown in Table 13, the most common reasons for discontinuation during the extension period were adverse events (1.7% total) and patient decision (1.5% total). The rate of discontinuation was marginally higher in the continued GP2015 group than in the continued Enbrel group. There was no notable difference in the rate of discontinuation between the pooled continued and pooled switched groups.[6]

Table 13: Summary of Patient Disposition for the EGALITY Study in the Extension Phase[6]

Disposition	EGALITY			
	Continued GP2015	Continued Enbrel	Pooled Continued Treatment	Pooled Switched Treatment
Treated in EP, N	140	142	282	185
Discontinued, N (%)	8 (5.7)	5 (3.5)	13 (4.6)	7 (3.8)
WDAEs, N (%)	4 (2.9)	2 (1.4)	6 (2.1)	2 (1.1)
Patient decision, N (%)	1 (0.7)	2 (1.4)	3 (1.1)	4 (2.2)
Lost to follow-up	2 (1.4)	0	2 (0.7)	0
Lack of efficacy	0	1 (0.7)	1 (0.4)	1 (0.5)
Pregnancy	1 (0.7)	0	1 (0.4)	0
Full analysis set, N	140	142	282	185
Per-protocol, N	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N	140	142	282	185
Immunogenicity set, N	140	142	282	185

EP = extension period; WDAE = withdrawal due to adverse event.

Overall Analysis (Baseline to Week 52)

For the overall disposition of the 531 randomized patients from baseline to week 52, the disposition of patients in TP2 and the extension period was taken, and those patients who did not receive treatment in TP2 and the extension period were included in the continued treatment groups in the overall analysis set, because these patients received treatment only during TP1.

Therefore, the overall analysis set consisted of all 531 randomized patients subgrouped as follows:[6]

- 164 patients received only GP2015 at least once during the study.
- 171 patients received only Enbrel at least once during the study.
- 196 were re-randomized at week 12 to the switched treatment sequences in TP2 and the extension period.

The rate of discontinuation was similar between the continued GP2015 and the continued Enbrel groups (Table 14). There was a higher rate of discontinuation in the pooled continued group than in the pooled switched group.[6]

Table 14: Summary of Patient Disposition for the EGALITY Study From Baseline to Week 52[6]

	EGALITY			
Disposition	**Continued GP2015**	**Continued Enbrel**	**Pooled Continued Treatment**	**Pooled Switched Treatment**
Completed TP1, N (%)	154 (93.9)	158 (92.4)	312 (93.1)	196 (100)
Completed TP2, N (%)	141 (86.0)	142 (83.0)	283 (84.5)	186 (94.9)
Completed EP, N (%)	132 (80.5)	137 (80.1)	269 (80.3)	178 (90.8)
Completed study, N (%)	132 (80.5)	137 (80.1)	269 (80.3)	178 (90.8)
Discontinued, N (%)	28 (17.1)	30 (17.5)	58 (17.3)	18 (9.2)
WDAEs, N (%)	10 (6.1)	7 (4.1)	17 (5.1)	7 (3.6)
Patient decision, N (%)	8 (4.9)	14 (8.2)	22 (6.6)	6 (3.1)
Lost to follow-up	4 (2.4)	1 (0.6)	5 (1.5)	0
Physician decision	2 (1.2)	1 (0.6)	3 (0.9)	0
Study terminated for site by sponsor, N (%)	1 (0.6)	2 (1.2)	3 (0.9)	2 (1.0)
Lack of efficacy, N (%)	1 (0.6)	1 (0.6)	2 (0.6)	3 (1.5)
Protocol deviation	1 (0.6)	1 (0.6)	2 (0.6)	0
Pregnancy	1 (0.6)	0	1 (0.3)	0
Death	0	1 (0.6)	1 (0.3)	0
Injection site reaction	0	1 (0.6)	1 (0.3)	0
Non-compliance with study drug	0	1 (0.6)	1 (0.3)	0
OA full analysis set, N	164	171	335	196
Per-protocol, N	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N	164	171	335	196

EP = extension period; OA = overall analysis; TP = treatment period; WDAE = withdrawal due to adverse event.

Efficacy Results

Treatment Period 1

Primary Efficacy Results: PASI 75 at Week 12: The 95% CI for the proportion of patients achieving PASI 75 at week 12 in the TP1 per-protocol set (GP2015 to Enbrel) was contained within the specified interval of −18% to 18%, thereby showing therapeutic equivalence between the GP2015 and Enbrel groups (Table 15).[7] The results of the supportive analysis on the TP1 full analysis set closely mirror those in the per-protocol set, with a difference (GP2015 to Enbrel) in the PASI 75 adjusted rates of −1.2 (95% CI, −8.77% to 6.45%) between the groups.[6]

Table 15: Logistic Regression Analysis on PASI 75 Response at Week 12 (TP1 Per-Protocol Set)[6, 7]

PASI 75 Response	N	n	Adjusted Response Rate (%)	Adjusted Response Rate Difference (%) (GP2015 vs. Enbrel)	95% CI (%)
GP2015	239	176	73.4	−2.3	−9.85 to 5.30
Enbrel	241	182	75.7		

CI = confidence interval; PASI = Psoriasis Area and Severity Index; SE = standard error; TP1 = treatment period 1.

Note: The adjusted response rates for the treatment groups were derived from the logistic regression analysis, which included treatment, BW strata, and prior systemic therapy in the model; the 95% CI for the rates difference was derived based on the normal approximation; the SE was computed using the delta method.

Key Secondary End Points: Absolute and Percentage Changes From Baseline in PASI Score up to Week 12: Equivalence between GP2015 and Enbrel was also demonstrated with respect to the secondary end points. Similar profiles were observed between the treatment groups for both absolute and percentage changes from baseline in PASI score over time. The 95% CI for the percentage

change from baseline in PASI score (GP2015−Enbrel/EU) up to week 12, using both the mixed-effects model for repeated measures and averaged treatment effect approaches (as measured by analysis of covariance), were contained within the specified interval of −15% to 15%, thereby corroborating equivalence between the GP2015 and Enbrel/EU groups (Table 16).[6, 7] Both of these analyses are supported by the outcome of the respective analyses on the full analysis set (Table 16).

Table 16: Statistical Analysis of Per Cent Change From Baseline in PASI Score up to 12 weeks of Treatment[6, 7]

End Point	GP2015 N = 239	Enbrel N = 241	Main Analysis in PPS: LSMD, GP2015 vs. Enbrel, % (95% CI)	Supportive Analysis in FAS: LSMD, GP2015 vs. Enbrel, % (95% CI)
% Change from baseline in PASI score[a] (MMRM approach)	−56.11	−55.48	−0.64 (−3.474 to 2.204)	−1.59 (−4.367 to 1.178)
ATE of % change from baseline in PASI score[b] (ANCOVA approach)	−52.99	−52.11	−0.88 (−3.610 to1.845)	−2.14 (−4.966 to 0.686)

ANCOVA = analysis of covariance; ATE = averaged treatment effect; BW = body weight; CI = confidence interval; FAS = full analysis set; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; PASI = Psoriasis Area and Severity Index; PPS = treatment period 1 per-protocol set; vs. = versus.

[a] Per cent change from baseline in PASI score is analyzed by employing an MMRM, with treatment, visit, treatment-by-visit interaction, BW strata, and prior systemic therapy as fixed factors and baseline PASI score as covariate. An unstructured covariance matrix is used to model the within-patient variance-covariance matrix.

[b] The ATE of per cent change from baseline in PASI score is analyzed by employing an ANCOVA model, with treatment, BW strata, and prior systemic therapy as fixed effects and baseline PASI score as covariate. ATE is the weighted average of the per cent change from baseline in PASI scores at weeks 2, 4, 8, and 12 (weights based on the time intervals between two consecutive visits in days).

Other Objectives: Other secondary efficacy objectives in TP1 were also achieved with no evidence of any differences between the GP2015 and Enbrel groups for mean PASI score; mean change in PASI score (%) from baseline; and adjusted PASI 50, 75, and 90 response rates. In addition, the proportion of IGA responders (0 or 1) increased over time, with a numerically higher response rate observed in the GP2015 group than in the Enbrel group at week 8 and week 12.[6]

[redacted] (Table 17).

Table 17: Summary of Actual and Per Cent Change From Baseline in DLQI Overall Scores up to 12 Weeks of Treatment — Full Analysis Set[6]

DLQI Total Score	GP2015 N = 264	Enbrel N = 267
Baseline values		
n	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]
Week 12		
n	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]
% Change from baseline	[redacted]	[redacted]

DLQI = Dermatology Life Quality Index; HRQoL = health-related quality of life; SD = standard deviation.

Note: The DLQI total score range from 0 to 30, and higher scores indicate greater HRQoL impairment.

Treatment Period 2

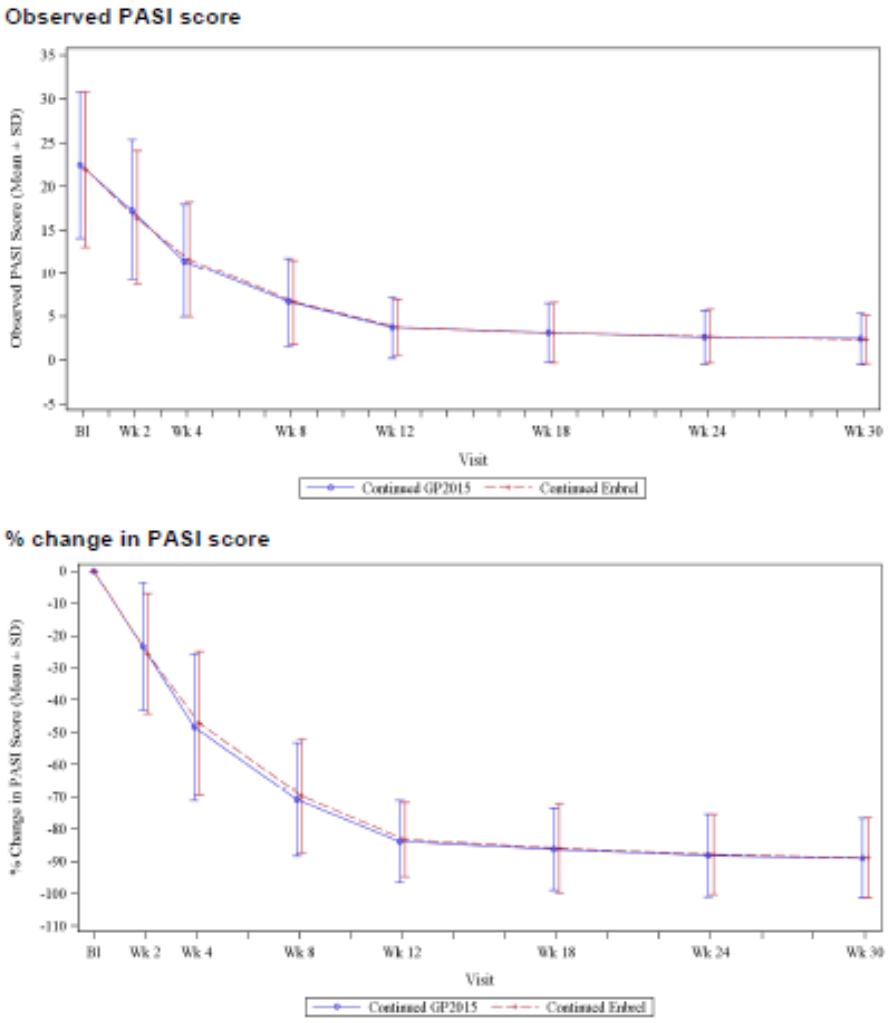
In TP2, the pooled continued group consists of patients receiving continued GP2015 and patients receiving continued Enbrel/EU. The pooled switched group consists of patients who switched from GP2015 to Enbrel/EU and back to GP2015, and patients who

switched from Enbrel/EU to GP2015 and back to Enbrel/EU. Re-randomization into continued and switched groups occurred at week 12.

All secondary efficacy objectives in TP2 were achieved with no evidence of any differences between the continued GP2015 and continued Enbrel treatment groups, or between the pooled continued and pooled switched treatment groups.[6]

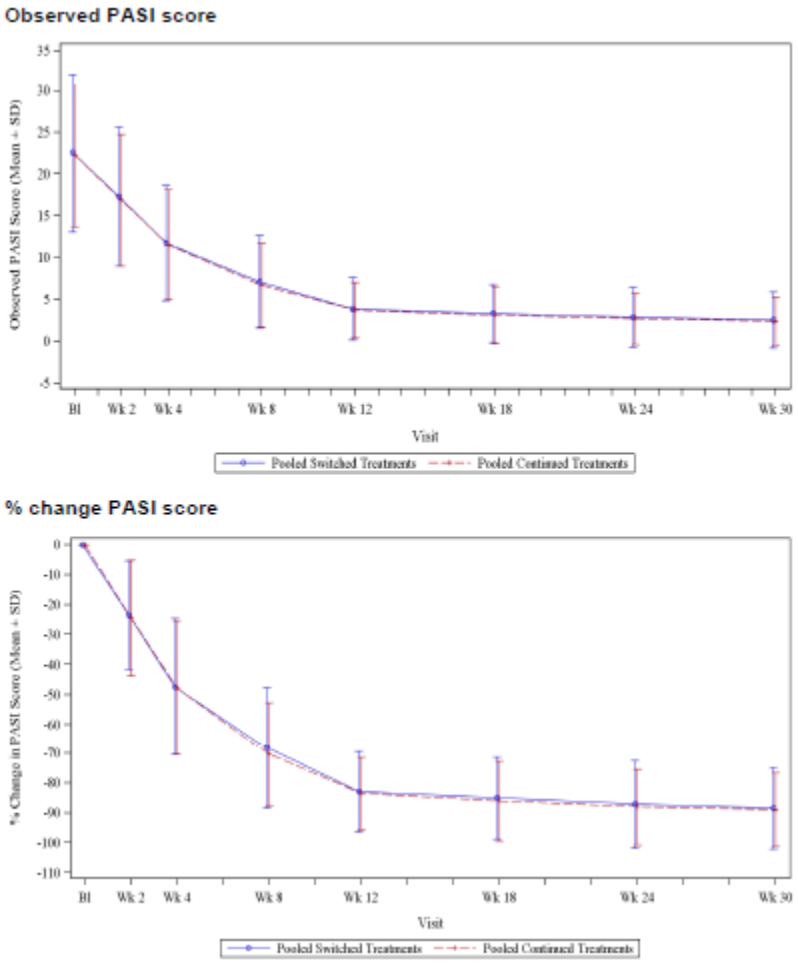
The mean score and the percentage change from baseline in mean PASI score showed a steep decline (improvement) up to week 12 and remained steady thereafter up to week 30 for all treatment groups (continued GP2015 versus continued Enbrel and pooled continued versus pooled switched; Figures 2 and 3, respectively).[6]

Figure 2: Mean (SD) PASI Score and Per Cent Change from Baseline in Mean PASI Score in Continued GP2015 vs. Continued Enbrel Groups[6]



PASI = Psoriasis Area and Severity Index; SD = standard deviation; vs. = versus.

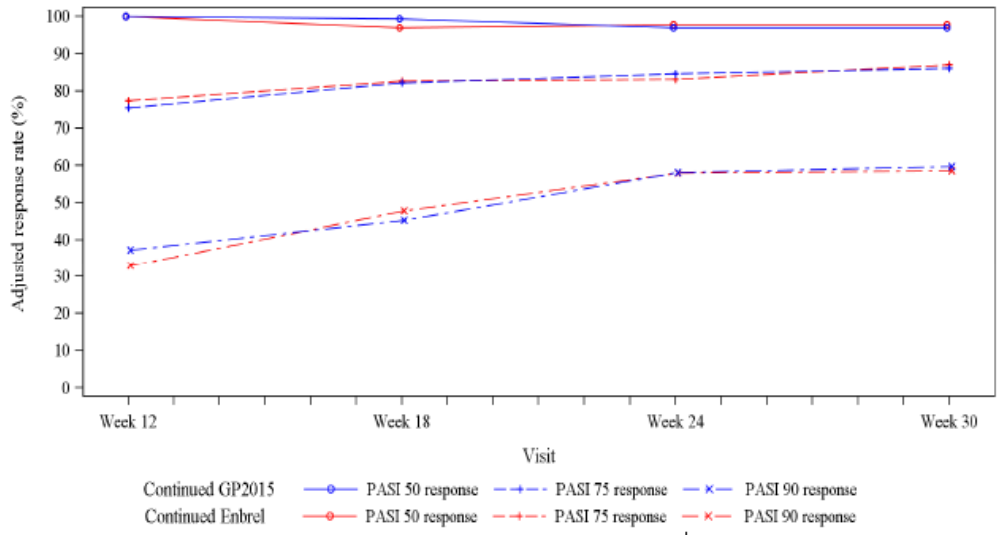
Figure 3: Mean (SD) PASI Score and Per Cent Change From Baseline in Mean PASI Score in Pooled Continued vs. Pooled Switched Groups[6]



PASI = Psoriasis Area and Severity Index; SD = standard deviation; vs. = versus.

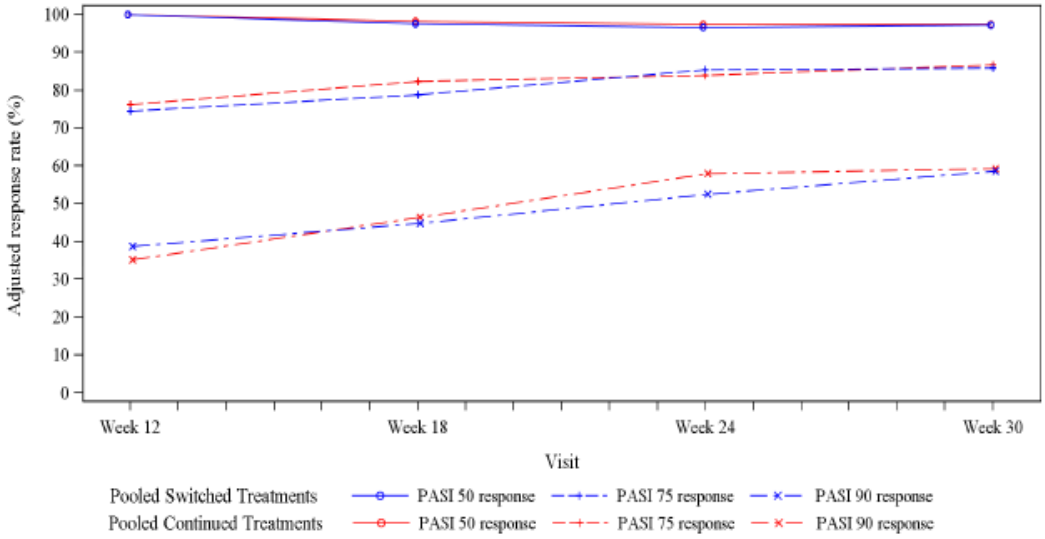
In addition, the proportion of patients achieving PASI 50, PASI 75, and PASI 90 in TP2 was similar between the continued GP2015 and continued Enbrel treatment groups (Figure 4), and between the pooled continued and pooled switched treatment groups (Figure 5).[6] While the adjusted PASI 50 response rate remained steady from week 12 up to week 30, the adjusted PASI 75 and PASI 90 response rates gradually increased over time from week 12 up to week 30 for all groups (the change over time was not tested statistically). The IGA response rate also gradually increased from week 12 up to week 30 in all treatment groups (the change over time was not tested statistically).[6]

Figure 4: Plot for Adjusted Response Rate (%) for PASI 50, PASI 75, and PASI 90 by Visit and Continued Treatment Group (TP2 Per-Protocol Set)[6]



PASI = Psoriasis Area and Severity Index; TP2 = treatment period 2.

Figure 5: Plot for Adjusted Response Rate (%) for PASI 50, PASI 75, and PASI 90 by Visit and Pooled Treatment Group (TP2 Per-Protocol Set)[6]



PASI = Psoriasis Area and Severity Index; TP2 = treatment period 2.

There was no difference between the continued GP2015 and the continued Enbrel treatment groups, nor between the pooled continued and pooled switched groups, for any of the adjusted response rates at each time point in TP2 (week 12 to week 30).[6]

Results for TP2 included the time points in TP1; however, they were organized based on the TP2 group assignments, i.e., data up to week 12 from TP1 were displayed according to the group the patients were assigned to in TP2, and not the initial group they were

assigned to in TP1. Health-related quality-of-life end points were found to be similar in all treatment groups in TP2 (continued GP2015 versus continued Enbrel and pooled continued versus pooled switched). There was an improvement (reduction) in Dermatology Life Quality Index total score over time up to week 18, after which the score remained stable up to week 30 (Table 18). The EuroQol 5-Dimensions questionnaire individual question responses also remained stable from week 12 up to week 30. In patients with psoriatic arthritis,[*] both the Health Assessment Questionnaire — Disability Index scores and the pain visual analogue scale scores were steady from week 12 up to week 30 for all treatment groups.

Table 18: Summary of Actual and Per Cent Change From Baseline in DLQI Overall Scores by Constant and Pooled Treatment — TP2 Full Analysis Set[6]

	EGALITY			
DLQI Total Score	Continued GP2015	Continued Enbrel	Pooled Continued Treatment	Pooled Switched Treatment
Baseline values				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Week 12				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
% Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 18				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
% Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 30				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
% Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Baseline is defined as the day of first study drug dose administration (day 1) in TP1. The DLQI overall score ranges from 0 to 30, and higher scores indicate greater HRQoL impairment.

DLQI = Dermatology Life Quality Index; HRQoL = health-related quality of life; TP2 = treatment period 2.

Extension Phase

All secondary efficacy objectives in the extension period were achieved with no evidence of any differences between the continued GP2015 and continued Enbrel treatment groups, or between the pooled continued and pooled switched treatment groups.

The mean score and the per cent change from baseline in mean PASI score, and the adjusted PASI 50, PASI 75, and PASI 90 response rates, all remained stable from week 36 to week 52 for all treatment groups (continued GP2015 versus continued Enbrel and pooled continued versus pooled switched). In addition, the IGA response rate showed a slight downward trend from week 36 to week 52, which was similar in all treatment groups.

[redacted]

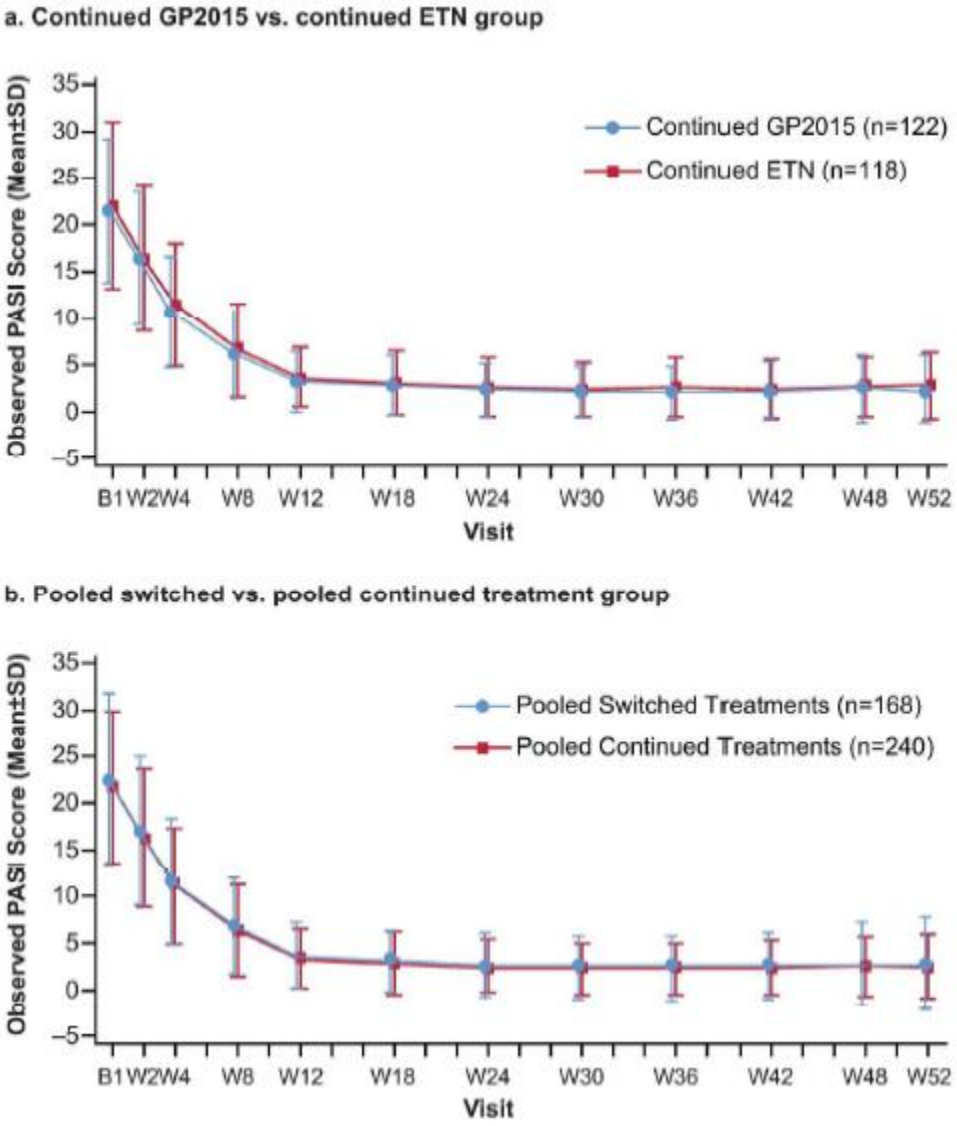
[*] Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

Overall Analysis (Baseline to Week 52)

There was no evidence of any differences between the continued GP2015 and continued Enbrel treatment groups, or between the pooled continued and pooled switched treatment groups throughout the study.

From baseline to week 52, the mean scores and per cent changes in PASI score from baseline at all time points were comparable between the continued GP2015 and Enbrel groups in the per-protocol set and between the pooled continued and pooled switched treatment groups (Figures 6 and 7, respectively).[7]

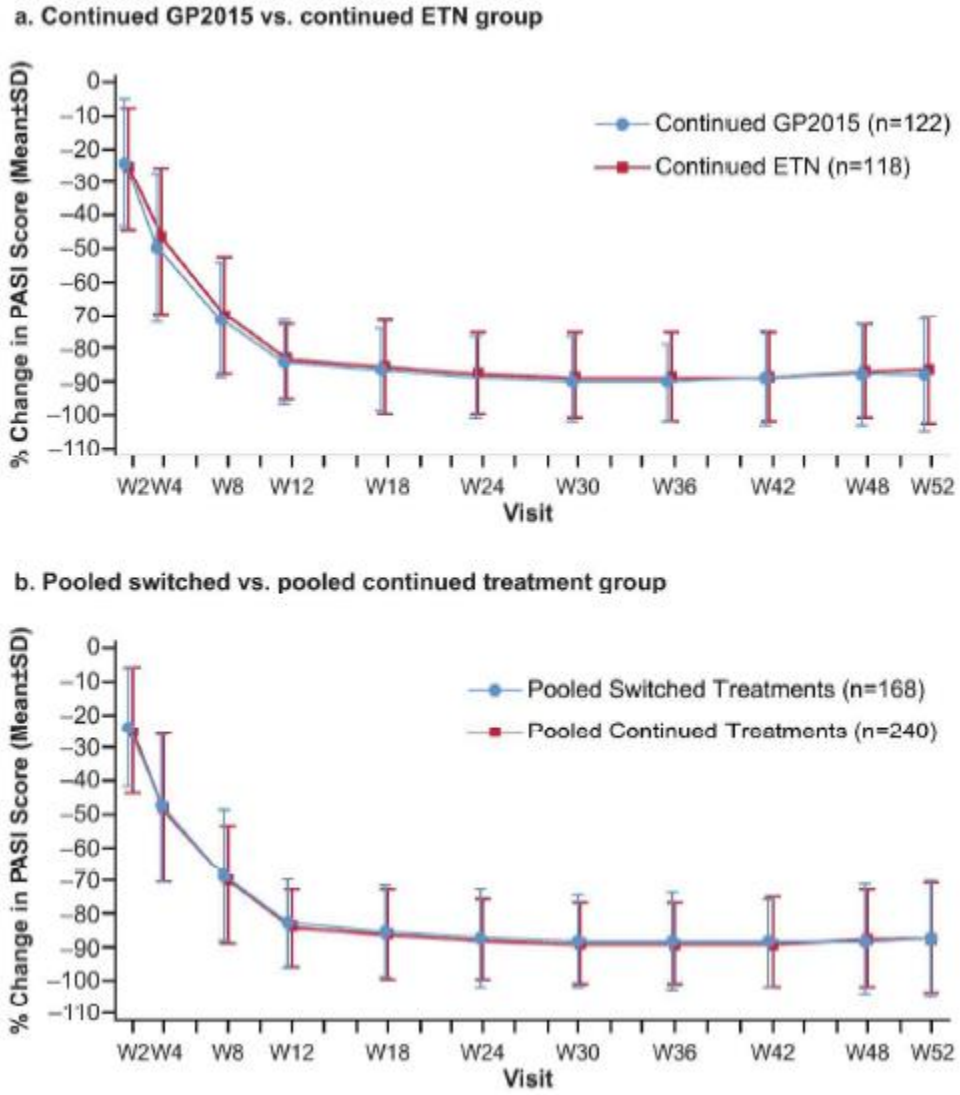
Figure 6: Mean Observed PASI Scores from Baseline to Week 52 (Overall Analysis Per-Protocol Set)[7]



B1 = baseline; ETN = etanercept originator product (Enbrel); PASI = Psoriasis Area and Severity Index; SD = standard deviation; TP = treatment period; W = week.

Note: The pooled continued treatment group includes patients who received GP2015 or Enbrel continuously from TP1. Patients in TP1 who did not continue to TP2 are considered under pooled continued treatments (under continued GP2015 or ETN). The pooled switched treatment group includes patients who switched to treatment sequences Enbrel to GP2015 to Enbrel or GP2015 to Enbrel toGP2015 in TP2.

Figure 7: Per Cent Change in PASI Scores from Baseline to Week 52 (Overall Analysis Per-Protocol Set)[7]

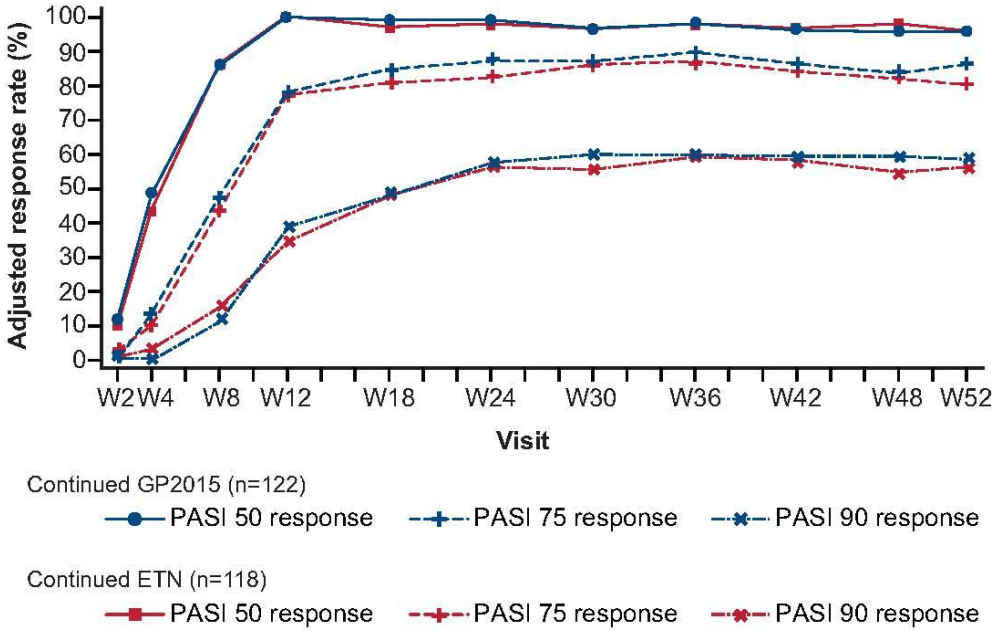


B1 = baseline; ETN = etanercept originator product (Enbrel); PASI = Psoriasis Area and Severity Index; SD = standard deviation; W = week.

Note: The pooled continued treatment group includes patients who received GP2015 or Enbrel continuously from TP1. Patients in TP1 who did not continue to TP2 are considered under pooled continued treatments (under continued GP2015 or ETN). The pooled switched treatment group includes patients who switched to treatment sequences Enbrel to GP2015 to Enbrel or GP2015 to Enbrel to GP2015 in TP2.

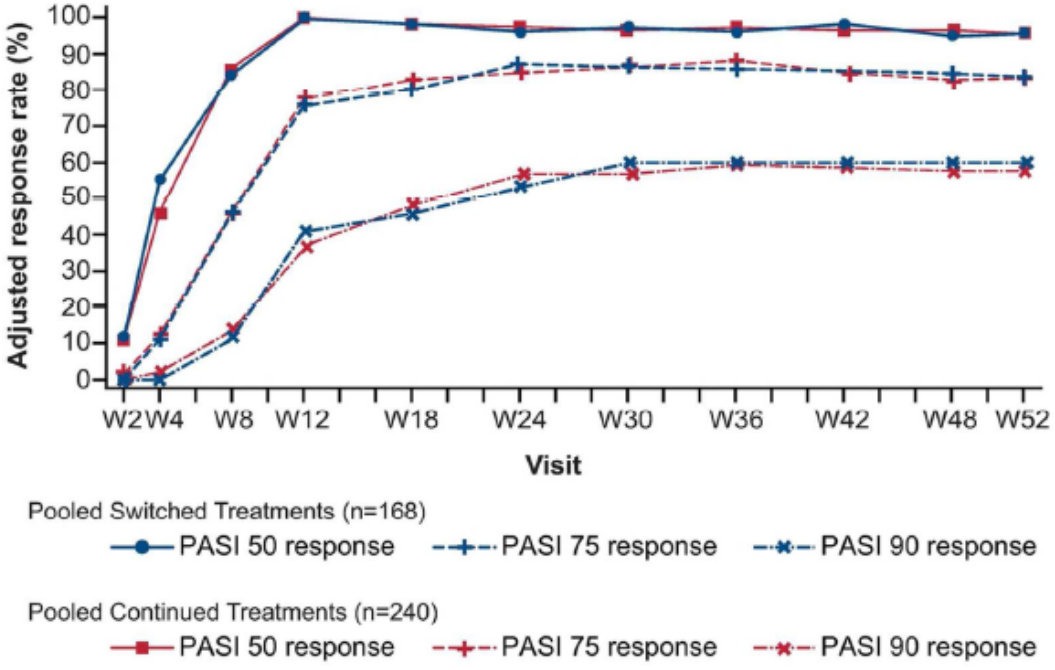
In all treatment groups, the adjusted PASI 75 and PASI 90 response rates gradually increased over time until week 30 and thereafter remained stable until week 52 (Figures 8 and 9). The adjusted PASI 50 response rate increased until week 12, at which time PASI 50 nonresponders were discontinued from the study (Figure 8). The PASI 50 response rate remained stable from week 18 until week 52 in all treatment groups (Figures 8 and 9).[7]

Figure 8: Adjusted PASI 50, 75, and 90 Response Rates for Continued Treatment Groups from Baseline to Week 52 (Overall Analysis Per-Protocol Set)[7]



ETN = etanercept originator product (Enbrel); PASI = Psoriasis Area and Severity Index; W = week.

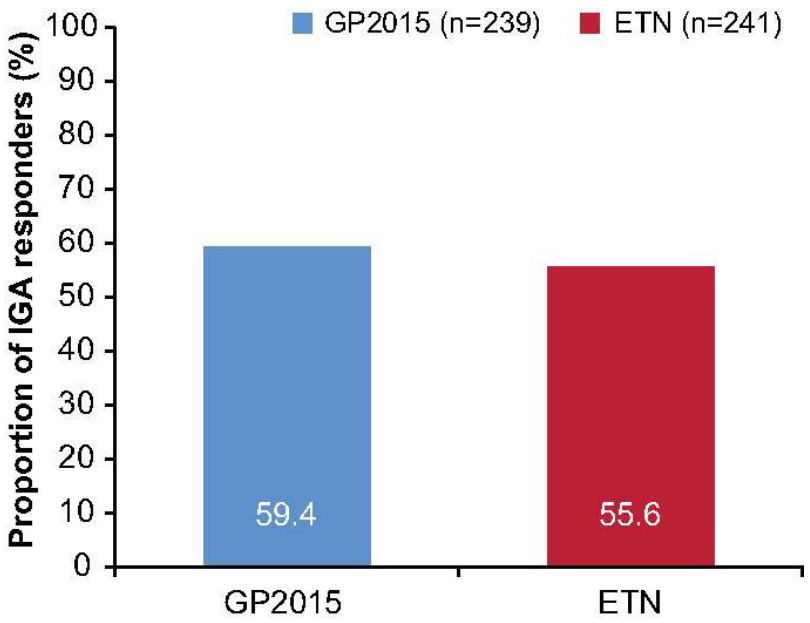
Figure 9: Adjusted PASI 50, 75, and 90 Response Rates for Continued vs. Switched Treatment Groups from Baseline to Week 52 (Overall Analysis Per-Protocol Set)[7]



PASI = Psoriasis Area and Severity Index; W = week.

At baseline, the majority of patients in the GP2015 (72.0% [n = 172/239]) and Enbrel (68.9% [n = 166/241]) groups had an IGA mod 2011 score of 3. At week 12, the proportion of IGA mod 2011 responders (score of 0 or 1) was numerically higher in the GP2015 group than in the Enbrel group (Figure 10).[7]

Figure 10: Proportion of IGA Responders at Week 12 (Per-Protocol Set)[7]



ETN = etanercept originator product (Enbrel); IGA = investigator's global assessment.

Note: An IGA responder was defined as a patient who achieved a score of 0 ("clear") or 1 ("almost clear") and improved by at least 2 points of the IGA scale compared with baseline.

[redacted] (Table 19).[6]

Table 19: Summary of Actual and Per Cent Change From Baseline in DLQI Overall Scores by Constant and Pooled Treatment — Extension Period Full Analysis Set[6]

	EGALITY			
DLQI Total Score	Continued GP2015	Continued Enbrel	Pooled Continued Treatment	Pooled Switched Treatment
Baseline values				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Week 36				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
% Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 42				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
% Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
% Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]

DLQI = Dermatology Life Quality Index; EP = extension period; HRQoL = health-related quality of life; SD = standard deviation; TP1 = treatment period 1.

Notes: Baseline is defined as day (day 1) of first study drug dose administration in TP1. The DLQI overall score ranges from 0 to 30, and higher scores indicate greater HRQoL impairment.

Safety Results

EGALITY is a phase III clinical trial supporting similarity of safety between Erelzi and Enbrel, thus forming the basis of the safety analysis. Safety results from this study are presented in section 4.2.2 of the present document.

4.2.2 Summary of Safety

a) Safety Evaluation Plan

All safety analyses were based on the safety analysis set defined in the individual studies as all patients or subjects who had received at least one dose of investigational medicinal product (IMP; i.e., GP2015, Enbrel/EU, or Enbrel/US) and provided safety data. All analyses were presented by treatment group (GP2015, Enbrel/EU, or Enbrel/US, unless otherwise specified). Subjects were analyzed in the safety analysis set according to the study treatment they had actually received. The safety data for healthy volunteers in the pharmacokinetic studies are described in section 2.1.1.1. of Module 2.7.4, Summary of Clinical Efficacy.

Given that EGALITY is a phase III study evaluating the safety of Erelzi, the safety evaluation plan is identical to that described previously in section 4.2.1 of the current document.

b) Safety Populations Evaluated

In the EGALITY study, safety was assessed by treatment period:[6]

- **TP1 safety set:** The TP1 safety set included all patients who took at least one dose of study treatment during the treatment period. Patients were analyzed according to treatment received.
- **TP2 safety set:** The TP2 safety set included all patients who took at least one dose of study treatment during TP2. Patients were analyzed according to treatment received.

- **Extension period safety set:** The extension period safety set included all patients who took at least one dose of study treatment during the extension period. Patients were analyzed according to treatment received.
- **Overall analysis safety set:** The overall analysis safety set included all patients who took at least one dose of study treatment during the study. Patients were analyzed according to treatment received.

In the EGALITY study, the median duration of exposure until 12 weeks was the same in both the GP2015 and Enbrel groups (81 days) and was similar between the continued GP2015 and Enbrel groups (358 days) until 52 weeks.[6]

c) Overview of Safety

The number of patients with at least one TEAE up to week 52 was similar between the continued GP2015 (n = 98 [59.8%]) and the continued Enbrel groups (n = 98 [57.3%]), and between the switched GP2015 (n = 61 [61.0%]) and switched Enbrel groups (n = 57 [59.4%], Table 20).[7] The incidence of serious adverse events, study discontinuation due to TEAEs (Table 20), and treatment-related TEAEs was similar between the two continued treatment groups and between the two switched treatment groups (Table 27 in Appendix 1).[7]

Table 20: Summary of Safety Results up to Week 52 for Continued and Switched Treatment Groups (Overall Safety Set)[7]

	Continued GP2015 N = 164 n (%)	Continued Enbrel N = 171 n (%)	Switched GP2015[a] N = 100 n (%)	Switched Enbrel[b] N = 96 n (%)
Any TEAE	98 (59.8)	98 (57.3)	61 (61.0)	57 (59.4)
Any SAE	7 (4.3)	7 (4.1)	6 (6.0)	6 (6.3)
Any treatment-related TEAE	34 (20.7)	33 (19.3)	22 (22.0)	20 (20.8)
Discontinuations due to TEAE	11 (6.7)	8 (4.7)	2 (2.0)	5 (5.2)
Deaths	0	1 (0.6)	0	0

ETN = etanercept originator product (Enbrel); SAE = serious adverse event; TEAE = treatment-emergent adverse event; TP2 = treatment period 2.

[a] Switched GP2015: Switched to treatment sequence ETN to GP2015 to ETN in TP2 and continued with ETN in extension period.

[b] Switched ETN: Switched to treatment sequence GP2015 to ETN to GP2015 in TP2 and continued with GP2015 in extension period.

The incidence and types of TEAEs reported across TP1 (comparing GP2015 with Enbrel), TP2, and from baseline to week 12, baseline to week 30, and baseline to week 52, were generally similar between the treatment groups (comparing continued GP2015 with continued Enbrel and pooled continued with pooled switched). The most commonly reported TEAEs were in the infections and infestations, skin and subcutaneous tissue disorders, and musculoskeletal and connective tissue disorders SOCs (system organ classes), with a similar incidence between treatment groups. The majority of TEAEs were mild or moderate in severity, with a low proportion of severe TEAEs reported in any treatment group across all treatment periods and a similar incidence between treatment groups (Appendix 1, Table 28).

The incidence of TEAEs was higher in the continued GP2015 group than in the continued Enbrel group during the extension period but was similar between the pooled continued and pooled switched groups. This difference was not caused by an increased number of TEAEs in any specific SOC but rather was due to a slightly higher incidence of events in the GP2015 group across several separate SOCs. This difference did not have an impact on the overall similarity in incidence and types of TEAEs observed between the continued GP2015 and Enbrel groups from baseline to week 52. A consistent and similar accumulation of reported TEAEs was present for the two treatment groups throughout the 52 weeks of the study.

TEAEs with a suspected causal relationship to study treatment occurred with similar incidences in all treatment groups (GP2015 versus Enbrel and pooled continued versus pooled switched) and in all treatment periods, with the most commonly affected SOC being “infections and infestations.”

The total incidence of TEAEs leading to study drug discontinuation was low and generally similar across all treatment groups. There was no clustering of events in any particular SOC.

Few patients were reported to have serious adverse events. The total incidence of serious adverse events was generally similar across all treatment groups but was higher in the pooled switched group than in the pooled continued group in TP2. There was no clustering of specific serious adverse events. One patient in the Enbrel group died of cardiopulmonary failure during this study (TP1); the death was not considered to be related to study treatment.

The incidence of adverse events of special interest was higher for continued GP2015 versus continued Enbrel (11.0% versus 4.7%) and for switched GP2015 (n = 11 [11.0%]) versus switched Enbrel (n = 5 [5.2%]) groups (Table 29, Appendix 1). Malignant melanoma in situ was reported in one patient in the continued GP2015 group. One patient died during the study due to cardiopulmonary failure (in the ETN group in TP1). The death was suspected to be due to concomitant conditions such as type 2 diabetes mellitus and not suspected to be treatment related.[7]

Adverse events of special interest, defined according to the special warnings and precautions of the Enbrel label, occurred infrequently, with the most commonly affected SOCs including [redacted]. The frequency of adverse events of special interest was higher in the GP2015 group than in the Enbrel group during each treatment period and from baseline to week 12, baseline to week 30, and baseline to week 52, but it was similar across the pooled continued and pooled switched groups. The differences in adverse events of special interest frequency between the continued GP2015 and Enbrel groups were not caused by an increased number of events in any specific SOC but rather were due to a slightly higher incidence of reported events in the GP2015 group across several SOCs [redacted]. Most of these events occurred in just one patient each in the continued GP2015 group versus none in the continued ETN group and, upon detailed analysis, were not considered to be medically relevant.

Injection site reactions were reported in 13 (4.9%) patients in the GP2015 group and in 38 (14.2%) patients in the Enbrel group until week 12. Most injection site reactions were mild in both treatment groups (11 [4.2%] and 32 [12.0%] patients, respectively). In the continued GP2015 and continued Enbrel groups, injection site reactions were reported in 14 (8.5%) and 27 (15.8%) patients, respectively, until week 52; most were mild (13 [7.9%] versus 23 [13.5%], respectively).[7]

A lower proportion of patients in the GP2015 group (8.5%) versus the Enbrel group (15.8%) reported injection site reactions from baseline to week 52, a difference that is attributable to the large difference in injection site reaction frequency between the groups in TP1. The incidence of injection site reactions was similar across all treatment groups (continued GP2015 versus continued Enbrel and pooled continued versus pooled switched) in TP2 and the extension period. Overall, the pooled continued and pooled switched groups were similar with regard to the incidence of injection site reactions.

Clinical laboratory parameters, vital signs, physical examination, and electrocardiogram findings were similar for the GP2015 and Enbrel groups, and for the pooled continued and pooled switched groups; no patterns were evident that would suggest a relation to treatment or a potential safety concern.

4.3 Pharmacokinetics

The manufacturer provided the information in this section.

The pivotal pharmacokinetic study, GP15-104, was a single-centre, randomized, double-blind, two-way crossover study in 54 healthy adult (aged 18 to 49 years) male subjects following a single subcutaneous administration of 50 mg Erelzi (GP2015) or Enbrel. The maximum observed serum concentration, the area under the serum concentration time curve from zero (hours) to infinity ($AUC_{0\text{-inf}}$), and the area under the serum concentration time curve measured from the time of dosage to the last measurable concentration ($AUC_{0\text{-tlast}}$) were the primary pharmacokinetic parameters. The time to the maximum observed serum concentration, the apparent elimination rate constant, and the apparent terminal half-life of elimination phase of etanercept were the secondary pharmacokinetic parameters.[4, 5]

The mean maximum observed serum concentration, $AUC_{0\text{-tlast}}$, and $AUC_{0\text{-inf}}$ were similar between the treatments for nominal dose concentrations and were contained within the pre-specified limits of 0.8 to 1.25, therefore demonstrating bioequivalence (Table 21).[4, 5]

Table 21: Statistical Analyses of Primary Pharmacokinetic Parameters (Nominal Dose, PK set)[4,5]

Pharmacokinetics	Erelzi (GP2015) LS	Enbrel	Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-Individual CV (%)
C_{max} (ng/mL), LS mean	3,416.22	3,087.00	1.11	1.05 to 1.17	16.4
$AUC_{0\text{-tlast}}$ (h × ng/mL), LS mean	630,363.18	642,235.26	0.98	0.94 to 1.02	12.1
$AUC_{0\text{-inf}}$ (h × ng/mL), LS mean	678,786.96	705,159.10	0.96	0.93 to 1.00	12.3

$AUC_{0\text{-inf}}$ = area under the serum concentration time curve from 0 h to infinity; $AUC_{0\text{-tlast}}$ = area under the serum concentration time curve from 0 h to the last quantifiable concentration; C_{max} = maximal serum concentration; CV = coefficient of variability; LS = least squares; PK = pharmacoeconomic.

All secondary pharmacokinetic parameters were similar between treatments. The 90% CIs for the ratios of the geometric means for the secondary pharmacokinetic end points of apparent terminal half-life of elimination phase and apparent elimination rate constant were within 0.8 to 1.25, thereby meeting the bioequivalence criteria.[4] In addition, the time to the maximum observed serum concentration was similar between treatments (Table 21). Among the secondary end points, the mean values for the apparent terminal half-life of elimination phase for GP2015 and Enbrel were 104.7 hours and 110.7 hours, respectively, and the median values for time to the maximum observed serum concentration were 58.3 hours and 59.8 hours, respectively.[5]

In the EGALITY study, trough serum concentrations of etanercept were similar in a subset of 147 patients (GP2015: n = 72; Enbrel n = 75) at weeks 2, 4, 8, and 12, indicating similarity of sustained exposure to etanercept and comparable clearance of GP2015 and Enbrel.[6, 7]

4.4 Immunogenicity

The manufacturer provided the information in this section.

In the pharmacokinetic studies in healthy volunteers (GP15-104, GP15-101, GP15-102, and GP15-103), blood samples for the assessment of immunogenicity were collected at pre-dose in period I (injection of either GP2015 or Enbrel), in period II (injection of alternate treatment), and at the follow-up visit. Anti-drug antibodies (ADAs; i.e., anti-etanercept) were not detected in any of the pharmacokinetic studies in healthy volunteers, except for the GP15-104 study.

In GP15-104, all subjects had negative ADA results on day 1 of both treatment periods. A total of three participants had confirmed binding ADAs at the follow-up visit (day 65), with titres near the detection limit. All three subjects were in the treatment sequence of GP2015/Enbrel/EU (with Enbrel/EU in TP2), and none of the ADAs were neutralizing. The binding ADA-positive results were considered not clinically meaningful due to the very low titres, and no other safety issues were identified.

In the EGALITY study, binding ADAs were reported infrequently; all patients in the GP2015 treatment group had negative ADA results, and a total of five patients (1.9%) in the Enbrel group had at least one confirmed positive binding ADA result in TP1 up to week 18 (Table 22). All positive ADA results in TP1 were detected within the first four weeks of treatment, and all samples tested negative for neutralizing antibodies. No ADAs were detected during TP2. One ADA-positive sample was detected at one time point during the extension period, in a patient in the pooled switched group. This binding ADA-positive sample tested negative for neutralizing antibodies. In addition, this patient had no further confirmed ADA response before or after week 36 up to week 52.

Table 22: Summary of Patients with Confirmed Positive ADA Response in the EGALITY Study up to Week 18[6]

Patient Number Age/Sex/Race	Positive Sample	Concentration (ng/mL)	Titre	Neutralizing Antibody Assay	Comments
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

[redacted]

ADA = anti-drug antibody; [redacted]

5. Critical Appraisal of Clinical Studies

This review included two pivotal studies: (1) EGALITY (GP15-302) was an equivalence randomized controlled clinical trial that evaluated the efficacy, safety, and immunogenicity of Erelzi (etanercept biosimilar) versus Enbrel (the reference biologic). (2) Study GP15-104 was a single-centre, randomized, double-blind, two-way crossover study to compare the pharmacokinetics, safety, and immunogenicity of Erelzi and Enbrel following a single dose of 50 mg subcutaneous injection in healthy male patients. The information presented below is based on an appraisal of the manufacturer's submission.

5.1 Internal Validity

Study EGALITY (GP15-302)

TP1 (weeks 0 to 12) was an equivalence, parallel, multi-centre, double-blind, randomized controlled clinical trial that evaluated the efficacy of Erelzi (etanercept SEB) versus Enbrel (the reference biologic) in patients with moderate to severe chronic plaque-type psoriasis with respect to PASI 75. Patients who had achieved at least a PASI 50 response at week 12 were to proceed to TP2 and were re-randomized either to continue the same treatment or to alternate treatment with GP2015 or Enbrel for periods of six consecutive weeks, i.e., switching to the alternating treatment after week 12 and switching back to the original treatment after week 18 followed by a third switch of treatment regimen after week 24. After the end of TP2, patients continued to be treated for an additional 22 weeks during the extension period. They received the treatment they had last received during TP2.

Overall, the clinical trial was designed with a sufficient number of enrolled patients (N = 531) for a two-sided alpha level of 0.05, 90% power, in the primary outcome of PASI 75 rate at week 12, given a two-sided 18% equivalence margin and allowing for a 15% loss of patients.[1,2] This power calculation was applicable only to TP1.

The calculation of the equivalence margin was briefly described, and the FDA indicated that a similarity margin of 18% for the primary end point of PASI 75 at week 12 may be appropriate.[3] It was not clear if the equivalence margin was derived from a fully comprehensive systematic review of etanercept versus placebo or other non-biologic systemic therapies, or if it

was derived solely from etanercept's pivotal studies. The equivalence margin aimed to preserve 60% of the observed treatment effects of etanercept relative to placebo (45% to 46%) reported in Leonardi et al.[4] and Papp et al.[5], and it is not clear if this margin exceeds any clinically meaningful differences that might affect the decision-making process of clinicians. The clinical expert consulted in this review indicated that he would have preferred to have the study maintain more than 60% of treatment effect of Enbrel versus placebo.

The key secondary end point was the percentage change from baseline in PASI score up to week 12. This outcome was tested for therapeutic equivalence using a pre-specified margin range (−15 to 15%), however it was not clear how this margin was calculated.

Type I error rate control was applicable only to the primary and key secondary end points. The type I error was controlled by only one primary end point and by a power of at least 99% for the key secondary end points. Hence, type I error rate was not controlled for multiple testing for the testing of all other outcomes.

[redacted]

The randomization was stratified on prior systemic therapy (no prior systemic therapy, any prior systemic therapy but no prior treatment with a TNF antagonist, or prior treatment with a TNF antagonist) and body weight (< 90 kg versus ≥ 90 kg). However, after the week 12 database lock, it was found that the stratification had been incorrectly performed for many patients and that the stratification classification used for the randomization did not agree with the data collected for the study. A reclassification of patients based on the data recorded in the case report form was undertaken at week 12 and week 30.

The prior therapy classification is relevant to the analyses because, although the protocol stated that the PASI 75 end point would be evaluated with exact confidence intervals, the statistical analysis plan stated that the primary analysis was to be performed adjusting for stratification factors using logistic regression. The logistic regression model included the following terms: treatment group ("Erelzi" or "Enbrel"), body weight category ("< 90 kg" or "≥ 90 kg"), prior systemic therapy ("no prior systemic therapy," "any prior systemic therapy including biologic immunomodulating agents," or "prior treatment with a TNF antagonist") as factors in the model. Hence, the results depend upon which version of the prior therapy classification is used in the model (randomization classification, week 12 classification, or week 30 classification). Even though results from using all three versions of the prior therapy classification are similar, changing the prior therapy groupings twice, including making changes after the initial study report had been finalized raises concerns with post hoc changes to the database.

In the EGALITY study, the week 12 PASI 75 response rate for both Erelzi and Enbrel was approximately 70%, which is much higher than the week 12 PASI 75 response rate for etanercept 50 mg twice weekly of approximately 49% reported in Leonardi et al.[4] and Papp et al.[5] The reason for the higher response rate in the EGALITY study relative to the historical studies is unclear. Disease-related inclusion criteria were similar between the EGALITY study and the historical studies, with slight differences where the EGALITY study required patients to have IGA ≥ 3. Also, the EGALITY study permitted patients who had prior use of a TNF alpha inhibitor, which the previous studies did not; only seven patients in the EGALITY study reported using prior TNF alpha inhibitors. Study location was another major difference: the EGALITY study was conducted in Europe and South Africa, with most centres in Eastern Europe, while the historical etanercept studies were conducted in the US, Canada, and Western Europe. There may be differences in clinical practice or access to drugs in the study site countries compared with Canada. Of note, greater than two-thirds of patients enrolled in EGALITY had no prior systemic therapy. In Canada, most patients with plaque psoriasis would receive non-biologic systemic therapy before moving to a biologic such as etanercept. Patients enrolled in EGALITY may have been more responsive to therapy with a biologic based on having more moderate disease. In response to Health Canada Clarifaxes, the manufacturer indicated that there was no placebo control arm included in the EGALITY study, and having only active treatment arms might lead to a higher treatment effect size compared with placebo-controlled studies. The manufacturer also indicated that patients in the EGALITY study

had a mean body weight that was lower than the body weight published in other Enbrel studies, and in the EGALITY study, body weight had a statistically significant impact on the PASI 75 response, where the proportion of patients achieving PASI 75 at week 12 was numerically higher in the < 90 kg subgroup (81.2% and 84.2% in the Erelzi and Enbrel groups, respectively) than in the ≥ 90 kg subgroup (62.2% and 63.6% in the Erelzi and Enbrel groups, respectively). The clinical reviewer acknowledges that there may be differences in treatment effect size based on trial design (e.g., including different comparators) and patient characteristics (e.g., potential impact of larger body weight on clinical effect); however, the difference in response of more than 20% versus previous placebo-controlled trials on etanercept might not be explained just by having active-controlled trial versus placebo-controlled trial and having patients who are lighter in weight.

The randomization procedure and allocation concealment were well conducted. All eligible patients were randomized via Interactive Response Technology in a 1:1 ratio to one of two treatment arms, Erelzi or Enbrel. After confirming that the patient fulfilled all inclusion/exclusion criteria, the Interactive Response Technology assigned a unique patient identification number which was associated in the system with the treatment arm to which the patient had been assigned. Randomization data were kept strictly confidential until the time of unblinding and were not accessible to anyone else involved in the study, and the identity of the treatments was concealed by the use of study drugs that were identical in packaging, labelling, schedule of administration, and appearance. Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomization until final database lock at the end of the study (week 52).

Both Erelzi and Enbrel were self-administered at a dose level of 50 mg twice weekly for the first 12 weeks and 50 mg once weekly thereafter. Treatment adherence was assessed by the appropriate site personnel and transcribed into the electronic case report form. The patient was to return the used syringes for appropriate disposal. Adherence with the study drug administration was to be further assessed by the contract research organization personnel at each visit using counts of the pre-filled syringes and the study drug accountability documentation. The majority of patients (86.6%) did not miss any doses of study drug. Only 3.6% of patients missed more than four doses of study drug during TP1: 2.7% and 4.5% in the Erelzi and Enbrel groups, respectively.

Demographic characteristics, body weight, time since initial diagnosis of plaque-type psoriasis, IGA modified 2011 score, PASI score, presence of psoriatic arthritis, prior systemic therapy, and percentage of body surface area affected were well balanced between groups.

The primary outcome in this study, PASI 75 response rate, was evaluated after the first 12 weeks of treatment. The choice of the outcome and analysis point aligns with those from the Enbrel pivotal studies, from which the equivalence margin was derived.

The proportions of patients who discontinued the study during TP1 were generally low (3.0% in the Erelzi treatment group and 4.5% in the Enbrel treatment group). Discontinuation rates and reasons for discontinuation were generally balanced between treatment arms.

The primary and the key secondary outcomes were assessed using a per-protocol population and were compared with the results of a sensitivity analysis with the results from the full analysis set (defined as all randomized patients to whom study treatment was assigned) as a sensitivity analysis. Missing data were not imputed for the per-protocol population. Missing response data in the full analysis set were to be imputed as nonresponse regardless of the reason for missing data. The results of the sensitivity analysis were similar to the results of the primary analysis.

Patients in TP2 who switched treatment groups were exposed to two drugs during the switch periods due to overlapping half-lives, allowing for characterization of the efficacy, safety, and immunogenicity profile when treated with both drugs. Further comparative data on the efficacy and safety of Erelzi and Enbrel were obtained from patients who received the initially assigned treatment continuously in TP2. Patients in the extension period (week 31 to week 52) received the treatment they had last received during TP2; further data on efficacy, safety, and on immunogenicity of both drugs were generated from extension period. The PASI 75 response rates were similar from weeks 18 to 52 across all four arms (Erelzi only, Enbrel only, Erelzi to Enbrel to Erelzi to Enbrel, and Enbrel to Erelzi to Enbrel to Erelzi). On the other hand, in TP2

there was no washout period before switching treatment; hence, it is not clear if the treatment effect or safety issues were due to the original treatment or the switched treatment.

Although the safety data in the initial phase and the extension period of the study were well reported, the sample size was too small to detect rare but serious adverse events associated with etanercept such as pancytopenia and possible malignancies.

Study GP15-104

GP15-104 was a phase I pharmacokinetic study comparing Erelzi and Enbrel in healthy male volunteers. The study provides evidence of similar pharmacokinetic profiles for Erelzi and Enbrel. This study was a single-centre, randomized, double-blind, two-way crossover study. The pharmacokinetics, safety, and immunogenicity of Erelzi and Enbrel/EU were assessed following a single dose of 50 mg subcutaneous injection. Overall, the study was well conducted and reported.

The study had sufficient participants (N = 54) in each study arm (n = 27) to meet the predetermined sample size of 48 that would provide at least 90% power to show bioequivalence within the predefined range of 0.80 to 1.25. Participants were randomized to receive a single 50 mg subcutaneous injection of Erelzi or Enbrel/EU. Participants had a washout period of 35 days before crossing over. After the washout period patients were crossed over and received a single 50 mg subcutaneous injection of the opposite treatment.

The primary outcome, pharmacokinetic profile, was sufficiently described and well conducted. A standard pharmacokinetic equivalence range of 0.80 to 1.25 was used to indicate pharmacokinetic bio-equivalency. Similarly, the immunogenicity testing was well conducted. A total of three participants had confirmed binding ADAs at the follow-up visit (day 65) with titres near the detection limit. All three participants were in the treatment sequence of GP2015 to Enbrel/EU (with Enbrel/EU in TP2), and none of the ADAs were neutralizing. The binding ADA-positive results were considered not clinically meaningful due to the very low titres, and no other safety issues were identified.

5.2 External Validity

Study EGALITY (GP15-302)

The trial recruited patients with active but clinically stable chronic plaque-type psoriasis diagnosed ≥ 6 months before baseline from 74 centres across 11 European countries and South Africa. However, the applicability of the results to the Canadian population has the following limitations:

- No North American sites were included in the trial; it is unclear how this may affect outcomes.
- More than 98% of the study population was white; generalizability of the results to other racial groups is unclear.
- Time since initial diagnosis of plaque-type psoriasis was more than 18 years, which is quite a long time to be biologic-naïve and which might not be seen in North America.
- The applicability of the results to populations with more concomitant medications and comorbidities is unknown.
- Around 70% of patients included in the study did not receive any prior systemic therapy before enrolling in the study, while in Canada most patients would have received a systemic therapy prior to receiving etanercept.

Study GP15-104

GP15-104 was a phase I pharmacokinetic study, and as such no clinical efficacy data can be generalized to the Canadian population. Safety data suggest little difference in the adverse events profile compared with Enbrel; however, sample sizes were small, and follow-up was relatively short to detect serious but uncommon adverse events.

6. Extrapolation of Indications

The manufacturer provided the information in this section.

6.1 Manufacturer's Rationale for Extrapolation

A detailed rationale for extrapolation is located in Module 2.7.3, Summary of Clinical Efficacy.

The extrapolation approach for a biosimilar is not to extrapolate from one indication to another, but rather from one product to another by demonstrating that Erelzi (GP2015) and Enbrel are highly similar and that there are no clinically meaningful differences between the two drugs. Analytical, nonclinical, and clinical similarities, once established, provide scientific justification for extrapolation and support the safe use of the biosimilar in all indications* for which the reference product is approved and share the same mechanism of action.

Based on the analytical, nonclinical, and clinical results described in the Erelzi dossier, all of which contribute to the totality of the evidence, Sandoz concludes that biosimilarity of Erelzi and the originator product Enbrel has been successfully demonstrated in accordance with Health Canada guidance documents (including both the Draft Revised Guidance Document — Information and Submission Requirements for Subsequent Entry Biologics, 2015-08-13, as well as the recently published Guidance Document - Information and Submission Requirements for Biosimilar Biologic Drugs, 2016-11-14).

Thus, since a molecule that is shown to be structurally and functionally highly similar to a reference product is anticipated also to behave like the reference product, Sandoz considers extrapolation from Enbrel to the biosimilar product Erelzi scientifically justified. As a result, a label for Erelzi consistent with that of Enbrel, including all indications* for which Enbrel is currently approved in Canada and which share the same mechanism of action, is considered justified.

All conditions for which Enbrel/EU is approved are characterized by increased levels of TNF alpha as a prominent inflammatory mediator forming the necessary elements in the chain of pathophysiological events.[8] TNF alpha is a dominant cytokine in the inflammatory process of RA.[9, 10] Elevated levels of TNF alpha are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis* and in the serum and synovial tissue of patients with AS.[2] In plaque-type psoriasis*, infiltration by inflammatory cells, including T cells, leads to increased TNF alpha levels in psoriatic lesions compared with levels in uninvolved skin.[11] Etanercept is a competitive inhibitor of TNF alpha's binding to cell-surface receptors and thereby inhibits the biological activity of TNF alpha.

Role of TNF Signalling in Immune-Mediated Inflammatory Diseases

TNF alpha is a naturally occurring, highly pleiotropic cytokine with both pro-inflammatory and immune-regulatory functions. The biological activity of TNF alpha depends on its binding to two distinct cell-surface receptors: 55-kDa (p55; TNF receptor 1) and 75-kDa (p75, TNF receptor 2). Both TNF receptors exist in membrane-bound and soluble forms, whereby the soluble TNF receptors are thought to regulate biological activity of TNF alpha. TNF alpha is primarily expressed by activated monocytes, macrophages and T cells as a transmembrane protein arranged in stable homotrimers that is cleaved by proteases to yield trimeric soluble, circulating TNF alpha molecules. TNF alpha is involved in lymphoid tissue development and is crucial in the homeostasis of host defence.

However, at high plasma levels, TNF alpha is a mediator of excess inflammation and subsequently may lead to organ damage and matrix destruction.[12, 13] Elevated levels of TNF alpha are found at sites of inflammation with various diseases, such as in the synovial fluid of patients with RA, JIA, psoriatic arthritis, and AS, and in the synovium and psoriatic plaques of patients with psoriatic arthritis and plaque-type psoriasis.* In plaque-type psoriasis*, infiltration by inflammatory cells, including T cells, leads to increased TNF alpha levels in psoriatic lesions compared with levels in unaffected skin.[11, 14] Furthermore, TNF alpha plays an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases.[8-10, 12, 13, 15, 16] In conclusion, TNF alpha is a prominent inflammatory mediator in the chain of pathophysiological events of the above mentioned immune-mediated inflammatory diseases.[8, 13, 15, 16]

* Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

Mechanism of Action

Enbrel is a dimeric soluble form of the TNF receptor 2 that binds to TNF, thus inhibiting its downstream pro-inflammatory effects on TNF receptor–expressing cells. These downstream physiological effects of TNF activation that have been implicated in causing disease include, among others, expression of adhesion molecules responsible for leukocyte migration (e.g., E-selectin) and, to a lesser extent, intercellular adhesion molecule–1, serum levels of cytokines (e.g., interleukin-6), and matrix metalloproteinase–3.[13, 17] Enbrel can also bind to the membrane form of TNF on the TNF-expressing cells, but in contrast to anti-TNF monoclonal antibodies such as infliximab and adalimumab, it is not able to cross-link multiple membrane TNF molecules to induce reverse signalling, an observation that has been associated with its lack of efficacy in the inflammatory bowel disease indications.[13, 16]

RA is a symmetric chronic inflammatory disease that affects multiple joints. It is considered a mainly T helper type 1–related disease. In addition, development of auto-antibodies drives immune activation, and B cells are important in disease pathogenesis.[18] Chronic synovial inflammation leads to the formation of auto-aggressive tissue, which is comprised mainly of infiltrating immune cells that progressively destroy joint cartilage and adjacent bones.[19] Enbrel has been shown to reduce levels of several inflammatory cytokines in the serum of RA patients, which correlates with a reduction in severity parameters for RA.[20] Furthermore, Enbrel has also been shown to reduce monocyte/macrophage numbers and not lymphocyte count in RA synovia via its downstream effects. The decrease in synovial cellularity under treatment with Enbrel was shown to be greater in therapy responders, according to American College of Rheumatology 20% improvement criteria.[21]

In JIA, multiple joints are affected by inflammatory synovial expansion or pannus, similar to what happens in RA. Inflammatory synovial expansion causes joint damage, cartilage degradation, and destruction of adjacent bones. Given the abundance of TNF alpha in JIA synovial tissues, it is likely that TNF alpha plays a pivotal role in the enhancement of inflammatory cell trafficking into inflamed synovia in this condition.[22]

AS is a member of the spondyloarthropathic group of disorders. It is a chronic inflammatory disease in which the major sites of pathology are at the articulations of the axial skeleton. Some factors that play a role in the disease initiation are different from RA, including genetic predisposition (particularly human leukocyte antigen B27, human leukocyte antigen B27 subtypes, and involvement of the interleukin-23 and interleukin-17 cytokine axis). The inflammatory synovitis with proliferation of synovial cells, lymphocytic infiltration, and hypervascularity are major histological findings in the affected joints.[23]

Plaque-type psoriasis* is an immune-mediated inflammatory disease of the skin, and recent research established that psoriasis* is also a systemic auto-inflammatory disease. The pathogenesis of plaque-type psoriasis (and also psoriatic arthritis)* is driven by T cells, mainly the T helper 1 and T helper 17 cell subsets. TNF alpha is one of the major cytokines involved in the T helper type 1 response. It stimulates various cell types (e.g., infiltrating T cells, dendritic cells, endothelial cells, and keratinocytes) to produce further cytokines and adhesion molecules involved in maintenance and progression of chronic epidermal/dermal inflammation in this disease.[24] However, the other cytokines and immune regulators (in particular interleukin-17 and interleukin-23) play an important role in psoriasis*.[14, 25]

Similar to the mode of action of anti-TNF biologics in chronic inflammatory arthropathies, including RA and spondyloarthropathy, it has been shown that Enbrel decreases both epidermal and dermal dendritic cells and T cell counts as well as expression of intercellular adhesion molecule–1. It also decreases gene expression of several other inflammatory cytokines, including interleukin-12 and interleukin-23. These findings correlated with an improvement in integrative histological disease severity scores.[26] Similar to the findings of an Enbrel-induced decrease in synovial cellularity predominantly by reducing macrophage/monocyte numbers in RA, as mentioned above, Enbrel was shown to reduce the numbers of infiltrating dermal cells (predominantly myeloid dermal cells) in psoriatic plaques*.[27]

In summary, the mechanism of action of Enbrel in chronic inflammatory arthropathies and in plaque-type psoriasis* is based on the inhibition of TNF alpha–induced and maintained inflammation of joints and skin, where TNF alpha represents a shared functionally vulnerable node in communication networks of cytokines. This anti-inflammatory mechanism of action is identical across all approved indications* of Enbrel/EU,[28, 29] thereby justifying the proposed extrapolation across indications* for Erelzi.

* Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

Further details concerning the rationale for extrapolation are located in Module 2.7.3, Summary of Clinical Efficacy.

6.2 Health Canada's Conclusion on Extrapolation

Health Canada considered extrapolation of clinical effects and adverse events to the RA, JIA, and AS populations, as appropriate.

6.3 International Regulatory Conclusions on Extrapolation

Regarding the extrapolation of indications for Erelzi, the FDA concluded that, in aggregate, the evidence supports the extrapolation of biosimilarity to RA, JIA, AS, and psoriatic arthritis as scientifically justified.* This conclusion was based on evidence provided by Sandoz that demonstrated the following points, as stated in the FDA briefing document:[30]

- "GP2015 is highly similar to US-licensed Enbrel based on extensive analytical characterization data, similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in an approved indication, as demonstrated in study GP15-302 in patients with plaque psoriasis."*
- "The primary mode of action of etanercept is through inhibiting binding of soluble TNF [alpha] to cell-surface receptors and through binding transmembrane TNF [alpha], inhibiting subsequent signal transduction and adhesion molecule expression. The scientific literature indicates that this [mode of action] is the primary [mode of action] in RA, JIA, AS, [psoriatic arthritis], and psoriasis.* In contrast to monoclonal antibodies to TNF [alpha], complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity have not been considered to be clinically relevant mechanisms of etanercept. The data provided by Sandoz showed similar TNF [alpha] binding and potency to neutralize TNF [alpha], supporting the demonstration of analytical similarity pertinent to this [mode of action]."
- "The pharmacokinetic parameters of US-licensed Enbrel in patients with psoriasis* were similar to those seen in patients with RA.[31] The estimated half-life of etanercept was about 100 hours and comparable in healthy subjects, JIA and RA patients. As a fusion glycoprotein and consisting entirely of human protein components, etanercept is expected to undergo proteolysis in patients across different diseases. There are no product-related attributes that would increase the uncertainty that the pharmacokinetic/biodistribution may differ between GP2015 and US-licensed Enbrel in the indications sought for licensure. Since similar pharmacokinetics were demonstrated between GP2015 and US-licensed Enbrel in healthy subjects and psoriasis*, a similar pharmacokinetic profile would be expected between GP2015 and US-licensed Enbrel in patients with RA, JIA, AS, and [psoriatic arthritis]*."
- "The immunogenicity of the US-licensed Enbrel was generally low (<10%).[31] In GP2015 clinical program, the ADA formation was also low and there were no notable differences between GP2015 and comparator Enbrel, both in patients with plaque psoriasis*, following repeat dosing without background immunosuppression, which is a reasonably sensitive setting, and in healthy subjects after single doses. Accordingly, similar immunogenicity would be expected between GP2015 and US-licensed Enbrel in patients with RA, JIA, [psoriatic arthritis], and AS*."
- "Similar clinical safety profile with chronic dosing was demonstrated between GP2015 and EU-approved Enbrel in patients with plaque psoriasis,* and following single doses in healthy subjects. As analytical and pharmacokinetic similarity was demonstrated between GP2015 and US-licensed Enbrel, a similar safety profile would be expected between GP2015 and US-licensed Enbrel in RA, JIA, [psoriatic arthritis], and AS.*"

While extrapolation to all Enbrel indications is scientifically justified, Sandoz Canada is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis for patent reasons.

* Sandoz is not currently seeking a marketing authorization for plaque psoriasis or psoriatic arthritis in Canada.

6.4 CADTH Common Drug Review (CDR) Comments on Extrapolation

Of the six indications approved in Canada for the use of Enbrel (RA, polyarticular JIA, AS, plaque psoriasis, and psoriatic arthritis), Health Canada has granted approval to Erelzi for the following three indications: RA, AS, and polyarticular JIA. Clinical trial data are available only for plaque psoriasis; therefore the approval for RA, AS, and polyarticular JIA was based on extrapolation.

The rationale supporting the extrapolation to patients with RA, polyarticular JIA, and AS is based on biosimilarity demonstrated between Erelzi and Enbrel in the following studies:

1. The results of a phase III randomized controlled trial suggest equivalence in clinical efficacy, pharmacokinetic profile, immunogenicity, and safety profile of Erelzi and Enbrel; the consistency of Erelzi is further supported by results of an extension period of the study;
2. A phase I trial in healthy volunteers further supports similarity in pharmacokinetic profile;
3. The identical mode of action for all indications of Enbrel.

Other factors that should be taken into consideration when determining the appropriateness of the extrapolation which is based on the totality of the data generated throughout the biosimilar development to RA, polyarticular JIA, and AS include:

1. Immunogenicity: the immunogenicity of the US-licensed Enbrel was generally low (<10%). In GP2015 clinical program, the ADA formation was also low and there were no notable differences between GP2015 and comparator Enbrel, both in patients with plaque psoriasis, following repeat dosing without background immunosuppression, which is a reasonably sensitive setting, and in healthy subjects after single doses. Accordingly, similar immunogenicity would be expected between GP2015 and US-licensed Enbrel in patients with RA, polyarticular JIA, and AS.
2. Safety: similar clinical safety profile with chronic dosing was demonstrated between GP2015 and EU-approved Enbrel in patients with plaque psoriasis, and following single doses in healthy subjects. As analytical and pharmacokinetic similarity was demonstrated between GP2015 and US-licensed Enbrel, a similar safety profile would be expected between GP2015 and US-licensed Enbrel in RA, polyarticular JIA, and AS.
3. Calculation of equivalence margin: The manufacturer did not provide a clinical opinion or justification for the basis of choosing a 60% preservation of the PASI 75 treatment effect of etanercept versus placebo as the basis of calculating the equivalence margin. It is unclear if the equivalence margin calculated for the PASI 75 indication can also be applied to the RA, polyarticular JIA, and AS indications.

The evidence presented in this submission suggests similarity between Erelzi and the reference etanercept (Enbrel) according to the primary outcome, PASI 75 in plaque psoriasis. In the absence of clinical evidence for patients with RA, polyarticular JIA, and AS, the above points suggest that extrapolation of the safety and efficacy results from the plaque psoriasis studies may be reasonable. Besides the Health Canada Notice of Compliance, Erelzi was also approved by the European Medicines Agency and the FDA for RA, polyarticular JIA, and AS indications, in addition to psoriatic arthritis and plaque arthritis, as well as pediatric plaque psoriasis by the European Medicines Agency.

7. Cost Comparison

An Erelzi 50 mg pre-filled syringe will carry a 25.00% lower price ($304.4888) relative to an Enbrel 50 mg pre-filled syringe, which is $405.9850 (Ontario Exceptional Access Program Formulary). The 25.00% cost differential equates to $101.4962 per 50 mg pre-filled syringe. Expected savings may vary among public drug plans, reaching as high as 30.88% in Newfoundland and Labrador (Newfoundland and Labrador Prescription Drug Program Enbrel list price: $440.4937). Erelzi is also available in a 25 mg pre-filled syringe and 50 mg autoinjector formats and will be priced equally on a per mg basis.

Table 23: Cost Comparison of SEB and the Reference Product for Rheumatoid Arthritis

Drug / Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost ($)/Year
Erelzi	50 mg	Pre-filled syringe	$304.4888	50 mg/week	$15,833.42
Enbrel	50 mg	Pre-filled syringe	$405.9850	50 mg/week	$21,111.22

SEB = subsequent entry biologic.

[a] Ontario Exceptional Access Program Formulary.

[b] Erelzi and Enbrel Health Canada product monographs.

Table 24: Cost Comparison of SEB and the Reference Product for Ankylosing Spondylitis

Drug / Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost ($)/Year
Erelzi	50 mg	Pre-filled syringe	$304.4888	50 mg/week	$15,833.42
Enbrel	50 mg	Pre-filled syringe	$405.9850	50 mg/week	$21,111.22

SEB = subsequent entry biologic.

[a] Ontario Exceptional Access Program Formulary.

[b] Erelzi and Enbrel Health Canada product monographs.

Table 25: Cost Comparison of SEB and the Reference Product for Juvenile Idiopathic Arthritis

Drug / Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost ($)/Year[c]
Erelzi	50 mg	Pre-filled syringe	$304.4888	0.8 mg/kg/week	$4,965.36
Enbrel	50 mg	Pre-filled syringe	$405.9850	0.8 mg/kg/week	$6,620.48

JIA = juvenile idiopathic arthritis; SEB = subsequent entry biologic.

[a] Ontario Exceptional Access Program Formulary.

[b] Erelzi and Enbrel Health Canada product monographs.

[c] JIA patients are assumed to weigh 35 kg.

CDR Reviewers' Comments Regarding Cost Information

Summary of the Manufacturer's Analysis

Subsequent entry etanercept (Erelzi) is available as a 50 mg/mL pre-filled syringe (25 mg/0.5 mL and 50 mg/1.0 mL) and a 50 mg/1.0 mL pre-filled autoinjector for subcutaneous injection at a manufacturer-submitted price of $304.4888 per 50 mg/mL injection. The manufacturer conducted a cost-comparison analysis of Erelzi compared with its reference biologic product (Enbrel) for three indications: (1) moderately to severely active RA, (2) moderately to severely active polyarticular JIA, and (3) active AS. As part of the submitted cost comparison, the manufacturer considered a recommended maximum dose of 50 mg per week for all available dosage forms and in accordance with all Health Canada–approved indications as outlined within the product monograph. Under the assumption of similar clinical effects and dosage, the manufacturer reported that Erelzi is 25% less costly ($101.4962 less per 50 mg/mL pre-filled syringe) than Enbrel based on the manufacturer-submitted price of Erelzi ($304.49) and the Ontario Drug Benefit formulary price (ODB, May 2017) of Enbrel ($405.9850).[6]

CDR Assessments and the Manufacturer's Cost Comparison

- The methods used by the manufacturer for the cost comparison were found to be appropriate by CDR and the clinical expert involved in this review. However, CDR noted that the manufacturer's cost comparison for polyarticular JIA (Table 25) did not account for the wastage that would result from the single-use pre-filled syringe or single-use autoinjector formats.
- CDR noted that another etanercept biosimilar product (Brenzys) received a positive recommendation from CADTH (October 2016) for use in patients with RA and AS; however, this product was not considered as a comparator in the analysis submitted by the manufacturer.
- Using the price submitted to CADTH for Brenzys ($305 per 50 mg/mL pre-filled syringe/autoinjector) as a reference,[7] the annual cost of Erelzi is < 1% lower ($0.5112 less per 50 mg/mL pre-filled syringe) than that of Brenzys (Table 26).

Table 26: CDR Cost Comparison Table for Etanercept Biosimilar and Reference Biologic Products

Treatment/ Indications	Recommended Dose[a]	Number of Treatments Per Year[a]	Price Per 50 mg Pre-Filled Syringe ($)[b]	Annual Cost($)[c]	% Increase in Cost vs. Erelzi
Erelzi/RA, polyarticular JIA, AS	50 mg/week	52	304.4888	15,833	
Brenzys/RA, AS	50 mg/week	52	305.0000	15,860	0.17%
Enbrel/RA, polyarticular JIA, AS	50 mg/week	52	405.9850	21,111	33.33%

AS = ankylosing spondylitis; JIA = juvenile idiopathic arthritis; ODB = Ontario Drug Benefit; RA = rheumatoid arthritis; vs. = versus.

[a] Erelzi,[8] Brenzys,[9] and Enbrel[10] product monographs.

[b] Manufacturer-submitted price for Erelzi and Brenzys;[7] ODB price for Enbrel.[6]

[c] Annual costs account for expected product wastage from single-use syringes/autoinjectors in polyarticular JIA patients who require weight-based dosing.

Issues for Consideration

- The clinical expert consulted by CADTH for this review expressed no concerns relating to starting patients on Erelzi, but noted that additional clinical evidence would be helpful to support switching from the reference biologic product to SEB etanercept.

- Enbrel is also available for the following Health Canada–approved indications: treatment of adult patients with psoriatic arthritis and treatment of adult patients with chronic moderate-to-severe plaque psoriasis. While these are not covered under the Notice of Compliance application for Erelzi, there is potential for the off-label use of Erelzi for these indications.
- Enbrel is additionally available as a 25 mg/vial lyophilized powder for reconstitution, while Erelzi is available as a 50 mg/mL pre-filled syringe (25 mg/0.5 mL and 50 mg/1.0 mL) and a 50 mg/1.0 mL autoinjector. The clinical expert consulted by CADTH for this review indicated that the 25 mg vial of lyophilized power for reconstitution is seldom used in clinical practice (i.e., less than 10% of patients); therefore, there would not be a preference to have Erelzi available in this dosage form.
- The reimbursement criteria for Enbrel differ across CDR-participating drug plans in Canada, whereby Enbrel is available as a restricted benefit with specific reimbursement criteria (Appendix 2). The expected savings from Erelzi compared with Enbrel are based on the assumption that the reimbursement criteria for Erelzi would be applied to Enbrel.

Conclusion

At the submitted price of $304.49 per week, Erelzi is 25% less costly ($101.50 less per 50 mg/mL pre-filled syringe) than the reference biologic etanercept (Enbrel) based on the Ontario Drug Benefit price ($405.99 per 50 mg/mL pre-filled syringe) but similar in cost to the other SEB etanercept (Brenzys).

8. Discussion

The manufacturer has provided one phase III, equivalence randomized controlled trial along with a treatment period in which some patients had a sequence of three treatment switches between Erelzi and Enbrel and an extension period after that, enrolling patients with moderate to severe chronic plaque-type psoriasis (EGALITY study), and a phase I pharmacokinetic study enrolling healthy male volunteers (study GP15-104). The EGALITY study demonstrated that Erelzi falls within the equivalence margin to the reference product etanercept for the primary outcome of PASI 75 response rate after the first 12 weeks of treatment (TP1) and the key secondary outcome of percentage change from baseline in PASI score up to week 12. PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment with a score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease and a score greater than 10 is considered severe. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and the criterion for efficacy of new psoriasis treatments approved by the FDA.[11]

In TP2 of the EGALITY study, patients randomized to the switching arms used the other treatment between weeks 12 and 18, the original treatment between weeks 18 and 24, and the other treatment between weeks 24 and 52. The PASI 75 response rates were similar from weeks 18 to 52 across all four arms (Erelzi only, Enbrel only, Erelzi to Enbrel to Erelzi to Enbrel, and Enbrel to Erelzi to Enbrel to Erelzi); however, there was no statistical comparison between the treatment groups. Also, comparable safety and immunogenicity were demonstrated when the switching effect was evaluated in the EGALITY study. GP15-104 provided evidence of equivalency in the pharmacokinetic profile of Erelzi compared with the reference etanercept.

[redacted]

In the EGALITY study, similar rates of adverse events, serious adverse events, and study discontinuations due to adverse events occurred in the Erelzi and Enbrel treatment arms in TP1.

The evidence provided in this submission had several limitations regarding generalizability to the Canadian population. These limitations included the lack of North American sites, a limited representation of many racial and ethnic minorities, and time since initial diagnosis of plaque-type psoriasis being more than 18 years, which is quite long time to be biologic naïve and which might not be seen in North America.

Given the important role of TNF in RA, polyarticular JIA, and AS diseases and the provided evidence of clinical and pharmacokinetic equivalence, the extrapolation of evidence for equivalency between Erelzi and the reference product from studies conducted in patients with plaque psoriasis to patients with RA, polyarticular JIA, and AS is likely reasonable.

For patients who are on the reference product, Enbrel, a concern from patient groups is that they will be switched to the biosimilar, even if they are doing well on the reference drug, and without their consent. The clinical expert consulted for this review also indicated some resistance to switching patients from the reference product to the biosimilar given the lack of longer term data on safety and sustainability. In TP2 of the EGALITY study, some patients were randomized to the switching arm to use the other treatment between weeks 12 and 18, the original treatment between weeks 18 and 24, and the other treatment between weeks 24 and 52, and results suggested that these patients continued to improve. However, these results were not compared statistically and, as such, any results obtained are considered descriptive and exploratory in nature and offer limited evidence to draw conclusions about the appropriateness of switching patients from the reference product to the biosimilar. In addition, there was no washout period before switching treatment, and hence it is not clear if the treatment effect was due to the original treatment or the switched treatment.

The clinical expert consulted for this review indicated that the reference product, etanercept (Enbrel), has been widely used for patients with RA, polyarticular JIA, AS, psoriatic arthritis, and plaque psoriasis for more than 10 years. Etanercept has been one of the most frequently chosen biologics to treat these diseases. Typically, anti-TNF agents are used after an inadequate trial of two NSAIDs (nonsteroidal anti-inflammatory drugs) for patients with AS and after an inadequate trial of DMARD monotherapy or combination therapy in patients with RA or juvenile arthritis. Etanercept has the advantage of having the longest observation period for safety and efficacy for a subcutaneous anti-TNF. It may be used with or without methotrexate, which is often poorly tolerated. The etanercept biosimilar would be an appropriate choice for any biologic-naive or biologic-experienced patient who would be eligible to receive the reference product, Enbrel, for treatment of indications under review (RA, polyarticular JIA, and AS). At this time, there is limited evidence regarding switching a patient from the reference product, Enbrel, to the etanercept biosimilar.

Appendix 1: Additional Data

Table 27: Treatment-Related TEAEs by Treatment Groups up to Week 52 (Overall Safety Set)[7]

Preferred Term	Continued GP2015 N = 164 n (%)	Continued Enbrel N = 171 n (%)	Switched GP2015[a] N = 100 n (%)	Switched Enbrel[b] N = 96 n (%)
Any treatment-related TEAE	34 (20.7)	33 (19.3)	22 (22.0)	20 (20.8)
Nasopharyngitis	4 (2.4)	2 (1.2)	1 (1.0)	6 (6.3)
Viral upper respiratory tract infection	2 (1.2)	4 (2.3)	2 (2.0)	4 (4.2)
Upper respiratory tract infection	2 (1.2)	3 (1.8)	1 (1.0)	2 (2.1)
Weight increased	2 (1.2)	3 (1.8)	2 (2.0)	0
Gamma-glutamyltransferase increased	2 (1.2)	0	2 (2.0)	0
Alanine aminotransferase increased	1 (0.6)	1 (0.6)	1 (1.0)	2 (2.1)
Headache	0	2 (1.2)	2 (2.0)	0
Folliculitis	0	1 (0.6)	2 (2.0)	0
Somnolence	0	0	2 (2.0)	0
Aspartate aminotransferase increased	0	0	1 (1.0)	2 (2.1)

AE = adverse event; ETN = etanercept originator product (Enbrel); MedDRA = medical dictionary for regulatory activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event; TP2 = treatment period 2.

Note: PTs with events occurring with an incidence ≥ 2% in any of the treatment groups in the overall analysis safety set are presented and sorted by descending order of frequency in the continued GP2015 column. Patients experiencing multiple events within the same SOC or PT are counted only once under those categories and total row. A related TEAE is defined as a TEAE suspected to be related to the study drug. TEAEs with a missing relationship to the study drug are considered as related to study drug. AE terms are coded using MedDRA version 17.0.

[a] Switched GP2015: Switched to treatment sequence ETN to GP2015 to ETN in TP2 and continued with ETN in extension period.

[b] Switched ETN: Switched to treatment sequence GP2015 to ETN to GP2015 in TP2 and continued with GP2015 in extension period.

Table 28: TEAEs With a ≥ 2% Incidence From the EGALITY Study[7]

Preferred Term	Continued GP2015 N = 164 n (%)	Continued Enbrel N = 171 n (%)	Switched GP2015[a] N = 100 n (%)	Switched Enbrel[b] N = 96 n (%)
Nasopharyngitis	20 (12.2)	17 (9.9)	14 (14.0)	10 (10.4)
Pharyngitis	7 (4.3)	10 (5.8)	5 (5.0)	3 (3.1)
Back pain	7 (4.3)	3 (1.8)	2 (2.0)	4 (4.2)
Alanine aminotransferase increased	6 (3.7)	2 (1.2)	1 (1.0)	2 (2.1)
Gamma-glutamyltransferase increased	6 (3.7)	0	3 (3.0)	0
Tonsillitis	5 (3.0)	1 (0.6)	1 (1.0)	2 (2.1)
Viral upper respiratory tract infection	5 (3.0)	6 (3.5)	4 (4.0)	8 (8.3)
Aspartate aminotransferase increased	5 (3.0)	1 (0.6)	1 (1.0)	2 (2.1)
Arthralgia	5 (3.0)	7 (4.1)	3 (3.0)	5 (5.2)
Hypertension	5 (3.0)	7 (4.1)	3 (3.0)	2 (2.1)
Upper respiratory tract infection	4 (2.4)	5 (2.9)	1 (1.0)	3 (3.1)
Bronchitis	4 (2.4)	3 (1.8)	0	1 (1.0)
Respiratory tract infection viral	4 (2.4)	2 (1.2)	4 (4.0)	1 (1.0)

Preferred Term	Continued GP2015 N = 164 n (%)	Continued Enbrel N = 171 n (%)	Switched GP2015[a] N = 100 n (%)	Switched Enbrel[b] N = 96 n (%)
Diarrhea	4 (2.4)	2 (1.2)	1 (1.0)	3 (3.1)
Lymphadenopathy	4 (2.4)	0	1 (1.0)	1 (1.0)
Headache	3 (1.8)	8 (4.7)	4 (4.0)	3 (3.1)
Cough	3 (1.8)	2 (1.2)	3 (3.0)	0
Oropharyngeal pain	3 (1.8)	2 (1.2)	3 (3.0)	1 (1.0)
Herpes simplex	2 (1.2)	1 (0.6)	2 (2.0)	0
Urinary tract infection	2 (1.2)	3 (1.8)	2 (2.0)	1 (1.0)
Rhinitis	2 (1.2)	4 (2.3)	1 (1.0)	3 (3.1)
Weight increased	2 (1.2)	4 (2.3)	3 (3.0)	0
Blood pressure increased	2 (1.2)	2 (1.2)	4 (4.0)	0
Pruritus	2 (1.2)	4 (2.3)	0	1 (1.0)
Toothache	2 (1.2)	1 (0.6)	0	3 (3.1)
Acute tonsillitis	1 (0.6)	1 (0.6)	0	3 (3.1)
Folliculitis	1 (0.6)	2 (1.2)	2 (2.0)	0
Nausea	1 (0.6)	2 (1.2)	1 (1.0)	2 (2.1)
Sciatica	1 (0.6)	0	0	2 (2.1)
Somnolence	1 (0.6)	0	2 (2.0)	0
Fatigue	1 (0.6)	3 (1.8)	2 (2.0)	0
Pain in extremity	0	3 (1.8)	2 (2.0)	1 (1.0)
Psoriasis	0	5 (2.9)	3 (3.0)	1 (1.0)
Gastritis	0	4 (2.3)	2 (2.0)	2 (2.1)
Oral herpes	0	1 (0.6)	2 (2.0)	1 (1.0)
Dental caries	0	1 (0.6)	0	2 (2.1)
Hyperuricaemia	0	1 (0.6)	2 (2.0)	0
Pyrexia	0	1 (0.6)	2 (2.0)	2 (2.1)
Diabetes mellitus	0	0	1 (1.0)	2 (2.1)
Pyelonephritis	0	0	2 (2.0)	0
Hepatitis alcoholic	0	0	0	2 (2.1)

AE = adverse event; ETN = etanercept originator product (Enbrel); MedDRA = medical dictionary for regulatory activities; PT = preferred term; TEAE = treatment-emergent adverse event; TP2 = treatment period 2.

Note: Patients experiencing multiple events were counted only once within each treatment group. PTs with events occurring with an incidence ≥ 2% in any of the treatment groups in the overall analysis safety set are presented and sorted by descending order of frequency within the continued GP2015 column. AE terms are coded using MedDRA version 17.0.

[a] Switched GP2015: Switched to treatment sequence ETN to GP2015 to ETN in TP2 and continued with ETN in extension period.

[b] Switched Enbrel: Switched to treatment sequence GP2015 to ETN to GP2015 in TP2 and continued with GP2015 in extension period.

Table 29: TEAEs of Special Interest by Treatment Groups From Baseline to Week 52 (Overall Safety Set)[6, 7]

Preferred Term	Continued GP2015 N = 164 n (%)	Continued Enbrel N = 171 n (%)	Switched GP2015[a] N = 100 n (%)	Switched Enbrel[b] N = 96 n (%)
Any TEAE of special interest	18 (11.0)	8 (4.7)	11 (11.0)	5 (5.2)
Herpes simplex	2 (1.2)	1 (0.6)	2 (2.0)	0
Tinea infection	2 (1.2)	0	0	0
Neutropenia	2 (1.2)	0	1 (1.0)	0
Onychomycosis	1 (0.6)	0	1 (1.0)	0
Hypersensitivity	1 (0.6)	1 (0.6)	0	1 (1.0)
Melanocytic naevus	1 (0.6)	0	1 (1.0)	0
Skin papilloma	1 (0.6)	0	0	1 (1.0)
Herpes zoster	0	1 (0.6)	0	1 (1.0)
Oral herpes	0	1 (0.6)	2 (2.0)	1 (1.0)
Skin candida	0	0	1 (1.0)	0
Tinea versicolour	0	0	0	1 (1.0)
Squamous cell carcinoma of the cervix	0	0	1 (1.0)	0
Anemia	0	0	1 (1.0)	0
Rash	0	1 (0.6)	1 (1.0)	0
Urticaria	0	1 (0.6)	1 (1.0)	0
Multiple sclerosis	0	0	1 (1.0)	0

AE = adverse event; ETN = etanercept originator product (Enbrel); MedDRA = medical dictionary for regulatory activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event; TP2 = treatment period 2.

Note: PTs with events occurring with an incidence ≥1% in any of the treatment groups in the overall analysis safety set are presented and sorted by descending order of frequency in the continued GP2015 column. Patients experiencing multiple events within the same SOC or PT are counted only once under those categories and total row. AE terms are coded using MedDRA version 17.0

[a] Switched GP2015: Switched to treatment sequence ETN to GP2015 to ETN in TP2 and continued with ETN in extension period.

[b] Switched ETN: Switched to treatment sequence GP2015 to ETN to GP2015 in TP2 and continued with GP2015 in extension period.

Appendix 2: Drug Plan Reimbursement Status for Reference Product

For each indication that is approved by Health Canada for the subsequent entry biologic (or likely to be approved, in the case of a submission filed on a pre–Notice of Compliance basis), please provide the publicly available reimbursement status and criteria for the reference product. CADTH may update the information provided by the manufacturer with new information provided by the CADTH Common Drug Review (CDR)–participating drug plans, as required.

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

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

Table 30: Reimbursement Status for Enbrel

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	NaB	RES	RES	RES	NaB	RES	RES	RES	RES	RES
Ankylosing Spondylitis	RES	RES	NaB	NaB	NaB	RES	RES	RES	NaB	RES	RES	RES	RES	RES
Polyarticular Juvenile Idiopathic Arthritis	NaB	RES	RES	RES	NaB	RES	NaB	NaB	NaB	NaB	RES	RES	NaB	RES

AB = Alberta, BC = British Columbia, CDR = CADTH Common Drug Review; DND = Department of National Defence; MN = Manitoba; NaB = Not a benefit; NB = New Brunswick; 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; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

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

Table 31: Restricted Benefit Criteria for Enbrel for the Treatment of Rheumatoid Arthritis

Drug Plan	Rheumatoid Arthritis
British Columbia	Treatment of RA according to established criteria when prescribed by a rheumatologist
Alberta	• Special authorization coverage may be provided for use in combination with MTX for the reduction in signs and symptoms of severely active RA in adult patients (18 years of age or older) who are refractory or intolerant to (i) MTX at 20 mg (oral, subcutaneous, or intramuscular) or greater total weekly dosage (15 mg or greater if the patient is 65 years of age or older) for more than 12 weeks (patients who do not exhibit a clinical response to oral MTX or experience gastrointestinal intolerance to oral MTX must have a trial of parenteral MTX before being accepted as refractory); (ii) MTX with other DMARDs (minimum 4-month trial; e.g., MTX with hydroxychloroquine or methotrexate with sulfasalazine); and (iii) leflunomide (minimum 10-week trial at 20 mg daily). • Special authorization coverage of this agent may be provided for use as monotherapy in adult patients for whom MTX is contraindicated and/or for those patients who have experienced serious adverse effects. • "Refractory" is defined as a lack of effect at the recommended doses and for the 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 50 mg per week for 8 weeks. • Patients will be limited to receiving a 1-month supply of etanercept per prescription at their pharmacy. • Patients will be permitted to switch from 1 biologic agent to another (with the exception of anakinra) 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 dosage (e.g., initial coverage period). • Patients will not be permitted to switch back to a previously trialled biologic agent if they were deemed unresponsive to therapy. • Patients will not be permitted to switch from anakinra to other biologic agents except under exceptional circumstances. • Patients are limited to receiving 1 biologic agent at a time regardless of the condition for which it is being prescribed. • For continued coverage beyond 8 weeks, the patient must meet the following criteria: (i) The patient must be assessed by an RA specialist after 8 weeks but no longer than 12 weeks after treatment to determine response. The RA specialist must confirm in writing that the patient is a responder who meets the following criteria: ACR20 or an improvement of 1.2 units in the DAS28 score (reported to 1 decimal place) and an improvement of 0.22 in HAQ score (reported to 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.

Drug Plan	Rheumatoid Arthritis
	• Following this assessment, continued coverage may be approved for 50 mg per week for a period of 12 months. Ongoing coverage may be considered only if the following criteria are met at the end of each 12-month period: (i) The patient has been assessed by an RA specialist to determine response; (ii) the RA specialist confirms in writing that the patient has maintained a response to therapy, as indicated by confirmation of maintenance of ACR20 or maintenance of a minimum improvement of 1.2 units in DAS28 score (reported to 1 decimal place) from baseline; and (iii) a current HAQ score (reported to 2 decimal places) is 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 etanercept for RA must be completed using the Abatacept/Adalimumab/Anakinra/Certolizumab/Etanercept/Golimumab/Infliximab/Tocilizumab for Rheumatoid Arthritis Special Authorization Request Form (ABC 60027).
Saskatchewan	Active RA in patients who have failed or are intolerant to MTX and leflunomide.
Manitoba	1. 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 three DMARD therapies, 1 of which is MTX and/or leflunomide, unless intolerance or contraindications to these agents is documented. One combination therapy of DMARDs must also be tried. Initial application information should include details on disease activity such as the number of tender joints and swollen joints, the ESR, and the CRP value. 2. Request for coverage must be made by a specialist in rheumatology.
New Brunswick	1. For the treatment of severely active RA, in combination with MTX or other DMARDs in adult patients who are refractory or intolerant to (i) MTX (oral or parenteral), alone or in combination with another DMARD, at a dose of ≥ 20 mg weekly (≥ 15 mg if patient is ≥ 65 years of age) for a minimum of 12 weeks and (ii) MTX in combination with at least 2 other DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 12 weeks. 2. Clinical notes: (i) For patients who do not demonstrate a clinical response to oral MTX, or who experience gastrointestinal intolerance, a trial of parenteral MTX must be considered. (ii) Optimal treatment response to DMARDs may take up to 24 weeks; however, coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. (iii) For patients who have intolerances preventing the use of triple DMARD therapy, these must be described, and dual therapy with DMARDs must be tried. (iv) “Refractory” is defined as lack of effect at the recommended doses and for the durations of treatments specified above. (v) “Intolerant” is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of the intolerance(s) must be clearly documented. 3. Claim notes: (i) Must be prescribed by a rheumatologist. (ii) Combined use of more than 1 biologic DMARD will not be reimbursed. (iii) All requests for coverage of infliximab for infliximab-naive patients (including those on induction therapy) will be approved for Inflectra brand only. (iv) Initial approval: 6 months. (v) Renewal approval: 1 year. Confirmation of continued response is required. (vi) Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions. 4. Maximum quantity reimbursed: 25 mg twice a week or 50 mg per week.
Nova Scotia	1. For the treatment of severely active RA, in combination with MTX or other DMARDs, in adult patients who are refractory or intolerant to (i) MTX (oral or parenteral) at a dose of ≥ 20 mg weekly (≥ 15 mg if the patient is ≥ 65 years of age), alone or in combination with another DMARD, for a minimum of 12 weeks and (ii) MTX in combination with at least 2 other DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 12 weeks.

Drug Plan	Rheumatoid Arthritis
	2. Clinical notes: (i) For patients who do not demonstrate a clinical response to oral MTX, or who experience gastrointestinal intolerance, a trial of parenteral MTX must be considered. (ii) Optimal treatment response to DMARDs may take up to 24 weeks; however, coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. (iii) If patient factors (e.g., intolerance) prevent the use of triple DMARD therapy, these must be described, and dual therapy with DMARDs must be tried. (iv) "Refractory" is defined as a lack of effect at the recommended doses and for the durations of treatments specified above. (v) "Intolerant" is defined as demonstrating serious adverse effects or contraindications to treatments, as defined in product monographs. The nature of the intolerance(s) must be clearly documented. 3. Claim notes: (i) Must be prescribed by a rheumatologist. (ii) Combined use of more than 1 biologic DMARD will not be reimbursed. (iii) Initial approval: 6 months. (iv) Renewal approval: 1 year. Confirmation of continued response is required. (v) Maximum dosage approved: 25 mg twice a week or 50 mg once a week with no dose escalation permitted.
Prince Edward Island	1. For the treatment of severely active RA, in combination with MTX or other DMARDs, in adult patients who are refractory or intolerant to (i) MTX (oral or parenteral) at a dose of ≥ 20 mg weekly (≥ 15 mg if the patient is ≥ 65 years of age), alone or in combination with another DMARD, for a minimum of 12 weeks and (ii) MTX in combination with at least 2 other DMARDs, such as hydroxychloroquine and sulfasalazine, for a minimum of 12 weeks. 2. Clinical notes: (i) For patients who do not demonstrate a clinical response to oral MTX, or who experience gastrointestinal intolerance, a trial of parenteral MTX must be considered. (ii) Optimal treatment response to DMARDs may take up to 24 weeks; however, coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. (iii) If patient factors (e.g., intolerance) prevent the use of triple DMARD therapy, these must be described, and dual therapy with DMARDs must be tried. (iv) "Refractory" is defined as a lack of effect at the recommended doses and for the durations of treatments specified above. (v) "Intolerant" is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. The nature of the intolerance(s) must be clearly documented. 3. Claim notes: (i) Must be prescribed by a rheumatologist. (ii) Combined use of more than 1 biologic DMARD will not be reimbursed. (iii) Initial approval: 6 months. (iv) Renewal approval: 1 year. Confirmation of continued response is required 4. The request for coverage must be made by a rheumatologist or prescriber with a specialty in rheumatology using the Rheumatoid Arthritis Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms. 5. 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. 6. Etanercept, pre-filled syringe, 50 mg/mL; injection powder, 25 mg/kit (Enbrel-AMG): Maximum adult dose is 50 mg weekly or 25 mg twice weekly. For pediatric patients 4 to 17 years of age, coverage is for 0.8 mg/kg weekly to a maximum of 50 mg weekly.
Yukon	For severely active RA on recommendation of an RA specialist. The specialist's consult is to be provided. For patients who are refractory or intolerant to parenteral MTX after at least a 12-week trial; and a 3-month trial of at least 2 of leflunomide, sulfasalazine, and azathioprine; and a 3-month trial of at least 1 DMARD combination such as (a) MTX and cyclosporine; (b) MTX with hydroxychloroquine and sulfasalazine; or (c) MTX with leflunomide.
Non-Insured Health Benefits	Criteria for initial 1 year: Prescribed by a rheumatologist. Coverage is provided for use, in combination with MTX or other DMARDs, for the reduction in signs and symptoms of severely active RA in adult patients ≥ 18 years who have failed (i) MTX (oral or parenteral a dose ≥ 20 mg weekly, or ≥ 15 mg weekly if patient is ≥ 65 years) for a minimum of 12 weeks of

Drug Plan	Rheumatoid Arthritis
	continuous treatment (Note: Patients who do not exhibit a clinical response to oral MTX or who experience gastrointestinal intolerance may consider a trial of parenteral MTX) and (ii) MTX in combination with at least 2 other DMARDs, such as sulfasalazine and hydroxychloroquine, for a minimum of 12 weeks of continuous treatment. Coverage is also provided for use if the patient has a contraindication or intolerance to MTX and has failed a combination of at least 2 DMARDs, such as sulfasalazine, hydroxychloroquine, azathioprine, leflunomide, cyclosporine, or gold, for a minimum of 12 weeks of continuous treatment, or is refractory to a combination of at least 2 DMARDs.
Department of National Defence	When prescribed by a rheumatologist or a prescriber with a specialty in rheumatology for patients with moderate to severe active RA despite treatment with at least 2 DMARDs (including MTX, unless contraindicated) in mono or combination therapy after 3 months at the target dose. Note: MTX at a 20 mg (oral, subcutaneous, or intramuscular) or greater total weekly dosage for more than 12 weeks. Patients who do not exhibit a clinical response to oral MTX or experience gastrointestinal intolerance to oral MTX must have a trial of parenteral MTX and 1 or more of the following before being accepted as refractory: • 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 3mg/kg/day for 3 months.
Veterans Affairs Canada	**Special Authorization:** Access to VAC drug benefits will vary depending upon an individual's eligibility and specific health needs.

ACR20 = American College of Rheumatology 20% improvement criteria; CRP = C-reactive protein; DAS = disease activity score; DMARD = disease-modifying antirheumatic drug; ESR = erythroctye sedimentation rate; HAQ = Health Assessment Questionnaire; MTX = methotrexate; RA = rheumatoid arthritis; VAC = Veterans Affairs Canada.

Table 32: Restricted Benefit Criteria for Enbrel for the Treatment of Ankylosing Spondylitis

Drug Plan	Ankylosing Spondylitis
British Columbia	Treatment of AS according to established criteria when prescribed by a rheumatologist
Alberta	• Special authorization coverage may be provided for the reduction in the signs and symptoms of severely active AS, as defined by the Modified New York criteria for AS, in adult patients (18 years of age or older) who have active disease as demonstrated by (i) a BASDAI ≥ 4 units, demonstrated on 2 occasions at least 8 weeks apart; and (ii) a spinal pain VAS of greater than or equal to 4 cm (on a 0 cm to 10 cm scale), demonstrated on 2 occasions at least 8 weeks apart; and (iii) refractory or intolerant to treatment with 2 or more NSAIDS each taken for a minimum of 4 weeks at the maximum tolerated or recommended doses. • "Refractory" is defined as lack of effect at the recommended doses and for the durations 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 50 mg per week for 12 weeks. • Patients will be limited to receiving a 1-month supply of etanercept per prescription at their pharmacy. • Patients will be permitted to switch from 1 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 dosage (e.g., initial coverage period). • Patients will not be permitted to switch back to a previously trialled biologic agent if they were deemed unresponsive to therapy. • Patients are limited to receiving 1 biologic agent at a time regardless of the condition for which it is being prescribed. • For continued coverage beyond 12 weeks, the patient must meet the following criteria: (i) The patient must be assessed at week 12 by an RA specialist after the initial 12 weeks of therapy to determine response. (ii) 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 or more. • Following this assessment, continued coverage may be approved for 50 mg per week for a period of 12 months. Ongoing coverage may be considered if the patient is re-assessed by an RA specialist every 12 months and is confirmed to be continuing to respond to therapy by meeting criteria as outlined in (ii) above. • All requests (including renewal requests) for etanercept for AS must be completed using the Adalimumab/Certolizumab/Etanercept/Golimumab/Infliximab for Ankylosing Spondylitis Special Authorization Request Form (ABC 60028).
Saskatchewan	1. For treatment of AS according to the following criteria: (i) For patients who have already been treated conventionally with 2 or more NSAIDs taken sequentially at the maximum tolerated or recommended doses for 4 weeks without symptom control and who (ii) satisfy New York diagnostic criteria with a score ≥ 4 on the BASDAI and a score of ≥ 4 cm on the 0 cm to 10 cm spinal pain VAS on 2 occasions at least 12 weeks apart without any

Drug Plan	Ankylosing Spondylitis
	change of treatment and (iii) who are assessed to have adequate response to treatment at 12 weeks, which is defined as at least a 50% reduction in the pre-treatment baseline BASDAI score or a decrease ≥ 2 units and a reduction of ≥ 2 cm in the spinal pain VAS. 2. 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. 3. 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. 4. Subsequent annual renewal requests (beyond 15 months) will be considered for patients whose BASDAI scores do not worsen (i.e., remains within 2 points of the second assessment).
Manitoba	1. For the treatment of patients with active AS who have failed to respond to an adequate trial of at least 3 different NSAIDs and, in patients with peripheral joint involvement, who have failed to respond to MTX or sulfasalazine. 2. Request for coverage must be made by a specialist in rheumatology.
New Brunswick	1. 1. For the treatment of patients with moderate to severe AS (e.g., who have a BASDAI score ≥ 4 on 10-point scale) who: (i) have axial symptoms and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months or in whom NSAIDs are contraindicated, or (ii) have peripheral symptoms and who have failed to respond, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months and have had an inadequate response to an optimal dose or the maximal tolerated dose of a DMARD. 2. 2. Requests for renewal must include information demonstrating the beneficial effects of the treatment, specifically (i) a decrease of at least 2 points on the BASDAI scale, compared with the pre-treatment score, or (ii) 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"). 3. 3. Claim notes: (i) Must be prescribed by a rheumatologist or internist. (ii) Combined use of more than 1 biologic DMARD will not be reimbursed. (iii) All requests for coverage of infliximab for infliximab-naive patients (including those on induction therapy) will be approved for Inflectra brand only. (iv) Initial approval: 6 months. (v) Renewal approval: 1 year. (vi) Claims that exceed the maximum claim amount of $9,999.99 must be divided and submitted as separate transactions. 4. 4. Maximum quantity reimbursed: 50mg per week.
Nova Scotia	1. For the treatment of patients with moderate to severe AS (with a BASDAI score ≥ 4 on 10-point scale) who (i) 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 of observation, or in whom NSAIDs are contraindicated, or (ii) have peripheral symptoms, and 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 of observation, and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD. 2. Must be prescribed by a rheumatologist or prescriber with a specialty in rheumatology. 3. Requests for renewal must include information demonstrating the beneficial effects of the treatment, specifically (i) a decrease of at least 2 points on

Drug Plan	Ankylosing Spondylitis
	the BASDAI scale, compared with the pre-treatment score, or (ii) 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"). 4. Initial coverage period: initial period of 6 months with a maximum dose of 50 mg per week, not in combination with other anti-TNF agents.
Prince Edward Island	1. For the treatment of patients with moderate to severe AS (BASDAI score of 4 on 10-point scale who (i) 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 of observation or in whom NSAIDs are contraindicated or (ii) 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 of observation and have had an inadequate response to an optimal dose or the maximal tolerated dose of a DMARD. 2. 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. 3. Etanercept, pre-filled syringe, 50 mg/mL; injection powder, 25 mg/kit (Enbrel-AMG): Approvals will be for a maximum adult dose of 50 mg per week or 25 mg twice weekly. 4. Requests for renewal must include information showing the beneficial effects of the treatment, specifically (i) a decrease of at least 2 points on the BASDAI scale, compared with pre-treatment score or (ii) patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as HAQ or patient's ability to return to work). 5. The request for coverage must be made by a rheumatologist or prescriber with a specialty in rheumatology using the Ankylosing Spondylitis Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms. 6. 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.
Yukon	1. For AS patients with a BASDAI score greater than or equal to 4. For patients with predominantly axial disease who are refractory or intolerant to a minimum 4-week trial of 2 NSAIDs at the maximal dosage. 2. For predominantly peripheral disease, patients refractory to a 3-month trial of parenteral MTX and a 3-month trial of sulfasalazine. Rheumatologist consult to be provided. 3. For psoriatic arthritis patients with moderate to severe disease who are refractory or intolerant to a 12-week trial of parenteral MTX and an adequate trial (at least 4 months) of at least 1 other DMARD. 4. Initial approval for 12 months, then for 24 months after first year.
Non-Insured Health Benefits	Criteria for initial 1 year: Prescribed by rheumatologist For patients who meet all of the following criteria: (i) BASDAI > 4; (ii) patient is refractory to a 3-month trial of at least 3 NSAIDs at the maximum tolerated dose; (iii) for peripheral joint involvement, patient is refractory to weekly parenteral (subcutaneous or intramuscular) at 20 mg or greater (15 mg or greater if patient is > 65 years of age) for more than 8 weeks; and (iv) sulfasalazine 2 g/day for 4 months. Note: For axial involvement, patient does not need to be tried on MTX or sulfasalazine.

Drug Plan	Ankylosing Spondylitis
Department of National Defence	• 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 greater than or equal to 4 units. • Treatment failure or intolerance to three NSAIDs, each taken for a minimum of 4 weeks sequentially and at maximum tolerated or recommended dosage, and, if there is peripheral involvement, patient is refractory to a minimum 3-month trial of an optimal dose or a maximum tolerated dose of MTX or sulfasalazine.
Veterans Affairs Canada	**Special Authorization:** Access to VAC drug benefits will vary depending upon an individual's eligibility and specific health needs.

AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; TNF = tumour necrosis factor; VAC = Veterans Affairs Canada; VAS = visual analogue scale.

Table 33: Restricted Benefit Criteria for Enbrel for the Treatment of Polyarticular Juvenile Idiopathic Arthritis

Drug Plan	Polyarticular Juvenile Idiopathic Arthritis
Alberta	• Special authorization coverage may be provided for the reduction in signs and symptoms of severely active polyarticular JIA in patients 4 years of age and older who (i) have 5 or more active joints (defined by either swelling or limitation of motion plus pain and/or tenderness), and (ii) are refractory to 1 or more DMARDs conventionally used in children (minimum 3-month trial). • "Refractory" is defined as 1 or more of the following: lack of effect, serious adverse effects (e.g., leukopenia, hepatitis), or contraindications to treatments as defined in the product monographs. • For coverage, this drug must be prescribed by a prescriber affiliated with a Pediatric Rheumatology Clinic in Edmonton or Calgary (i.e., a pediatric rheumatology specialist). • Coverage may be approved for 0.8 mg/kg/dose (maximum dose of 50 mg) weekly for 12 weeks. • Patients will be limited to receiving a 1-month supply of etanercept per prescription at their pharmacy. • Patients will be permitted to switch from 1 biologic agent to another (with the exception of abatacept) following an adequate trial of the first biologic agent if they are unresponsive to therapy, or due to serious adverse effects or contraindications. An adequate trial is defined as, at a minimum, the completion of the induction dosage (e.g., the initial coverage period). • Patients will not be permitted to switch back to a previously trialled biologic agent if they were deemed unresponsive to therapy. • Patients will not be permitted to switch from abatacept to other biologic agents except under exceptional circumstances. • Patients are limited to receiving 1 biologic agent at a time regardless of the condition for which it is being prescribed. • For continued coverage of this agent beyond 12 weeks, the patient must meet the following criteria: (i) The patient must be assessed by a pediatric rheumatology specialist after 12 weeks (but no later than 16 weeks) of treatment with this biologic agent, to determine response. (ii) The pediatric

Drug Plan	Polyarticular Juvenile Idiopathic Arthritis
	rheumatology specialist must confirm in writing that the patient is a responder that meets the following criteria (ACR Pedi 30): 30% improvement from baseline in at least 3 of the following 6 response variables, with worsening of 30% or more in no more than 1 of the 6 variables. The variables include global assessment of the severity of the disease by the pediatric rheumatology specialist, global assessment of overall wellbeing by the patient or parent, number of active joints (joints with swelling not due to deformity or joints with limitation of motion with pain tenderness or both), number of joints with limitation of motion, functional ability based on CHAQ scores and ESR or CRP. (iii) Data from all of the six variables comprising the ACR Pedi 30 and the CHAQ scores must be reported in each request. • Following this assessment, continued coverage may be approved for 0.8 mg/kg/dose (maximum dose 50 mg) weekly, for a maximum of 12 months. After 12 months, in order to be considered for continued coverage, the patient must be re-assessed every 12 months by a pediatric rheumatology specialist and must meet the following criteria: (i) The patient has been assessed by a pediatric rheumatology specialist to determine response. (ii) The pediatric RA specialist must confirm in writing that the patient has maintained a response to therapy as indicated by maintenance of the ACR Pedi 30. (iii) Data from all of the 6 variables comprising the ACR Pedi 30 and the CHAQ scores must be reported in each request. • Once a child with polyarticular JIA has had 2 disease-free years, it is common clinical practice for drug treatment to be stopped. • All requests (including renewal requests) for etanercept for polyarticular JIA must be completed using the Adalimumab/Etanercept/Tocilizumab for Polyarticular Juvenile Idiopathic Arthritis Special Authorization Request Form (ABC 60011).
New Brunswick	1. For the treatment of children (ages 4 to 17) with moderately to severely active polyarticular JIA who have had inadequate response to 1 or more DMARDs. 2. Note: Must be prescribed by, or in consultation with, a rheumatologist who is familiar with the use of biologic DMARDs in children. 3. Maximum quantity reimbursed: 0.8mg/kg up to 50 mg per week.
Non-Insured Health Benefits	Patients must meet all the following criteria: (i) ≥ 5 swollen joints; (ii) ≥ 3 joints with limited range of motion and/or pain/tenderness; (iii) condition is refractory to an adequate trial of a therapeutic dose of MTX.
Veterans Affairs Canada	**Special Authorization:** Access to VAC drug benefits will vary depending upon an individual's eligibility and specific health needs.

ACR Pedi 30 = American College of Rheumatology Pediatric 30% improvement criteria; CHAQ = Childhood Health Assessment Questionnaire; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; ESR = erythroctye sedimentation rate; JIA = juvenile idiopathic arthritis; MTX = methotrexate; VAC = Veterans Affairs Canada.

Appendix 3: Summary of Patient Input

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

1. Brief Description of Patient Groups Supplying Input

Four patient groups provided input for this submission: Arthritis Consumer Experts, Canadian Arthritis Patient Alliance, The Arthritis Society, and The Canadian Spondylitis Association.

Arthritis Consumer Experts is a national organization that provides science-based information, education, and support programs to people with arthritis. Canadian Arthritis Patient Alliance is a national education and advocacy organization that creates links between Canadians with arthritis to assist them in becoming more effective advocates and to improve their quality of life. The Arthritis Society is a health charity providing education, research funding, programs, and patient support. The Canadian Spondylitis Association is a volunteer-run patient organization aiming to raise awareness of spondyloarthitis and to support, educate, and advocate for those living with the condition.

None of the four organizations declared any conflict of interest with respect to those playing a significant role in compiling their submission. Arthritis Consumer Experts declared receiving funding in the form of unrestricted grants-in-aid from the following private and public sector organizations: Amgen Canada, Arthritis Research Canada, AstraZeneca Canada, Canadian Institutes of Health Research, Celgene, Hoffman-La Roche Canada Ltd., Eli Lilly Canada, Merck Canada, Novartis, Pfizer Canada, Sanofi Canada, St. Paul's Hospital (Vancouver), UCB Canada Inc., and the University of British Columbia. Canadian Arthritis Patient Alliance declared receiving funding within the last year from AbbVie, Amgen Canada, Eli Lilly, Hoffman-La Roche, Janssen, Purdue, Novartis, and UCB Pharma. The Arthritis Society has accepted funding from the following members of the pharmaceutical industry: AbbVie, Amgen, AstraZeneca, Bayer, Celgene, Eli Lilly, GSK, Hospira, Janssen, Merck, Novartis, Pfizer, Purdue, Roche, Takeda, and UCB. The Canadian Spondylitis Association has received restricted educational and developmental grants from AbbVie, Amgen, and Janssen and restricted travel grants from UCB Canada.

2. Condition-Related Information

Patient groups gathered their information from a variety of sources: personal experience of board members living with ankylosing spondylitis (AS), rheumatoid arthritis (RA), or polyarticular juvenile idiopathic arthritis (JIA); personal experience from years of interfacing with members; requests for lived experiences through different social media outlets; close work with clinical researchers; and one-on-one e-conversations. Information was also gathered from contact with 25 families caring for a child living with polyarticular JIA who responded to requests for feedback for CADTH, and 46 people participated in focus groups on biologics and biosimilars.

Ankylosing Spondylitis

The onset of AS typically occurs between the ages of 15 and 45. The disease affects joints in the spine, causing pain in the back, hips, and neck as well as morning stiffness that may cause immobility, often taking hours to resolve. These symptoms often lead to fatigue, anxiety, and depression. This form of inflammatory arthritis affects every aspect of a patient's life during what is typically considered a person's most productive period of life. The wide range of symptoms affects work, recreational activity, and social activity, causes hardships on the patient's family, and places strain on relationships.

Patients consider pain, fatigue, and stiffness to be the most important symptoms to control, since they can have debilitating effects on a patient's life. One patient is quoted as saying, "These affect my everyday life in many ways — sitting at work, concentrating at work, and making it through the day. Bending down to play with my kids or helping them do things."

Rheumatoid Arthritis

Similar to AS, RA is usually diagnosed during the most productive period of a person's life: between the ages of 25 and 50. Rheumatoid arthritis can affect all joints in the body, resulting in significant inflammation, pain, and disability, with many other systemic effects that flare and wane and cause stiffness. For those whose RA is not well controlled, day-to-day activities, such as participating in post-secondary education, becoming and staying employed, taking care of oneself, walking, cooking, grocery shopping, housework, being in a relationship, getting married, having and caring for children, and physical and social activities can be extremely difficult and, in some cases, impossible to undertake. Such limitations take a toll on a patient's psychological and emotional well-being, leading to depression and further social isolation.

Patients often hope to be able to maintain their mobility and lead a normal, well-rounded lifestyle. Therefore, many patients consider joint swelling, fatigue, and flare-ups as the most important symptoms to control.

In both AS and RA, families and caregivers are affected through the need to compensate for loss of income, ever-increasing efforts to help patients in their day-to-day activities, and dealing with many of the psychological manifestations resulting from the pain and reduced quality of life caused by these two conditions.

Polyarticular juvenile idiopathic arthritis (JIA)

Polyarticular JIA is a serious, disabling autoimmune disease affecting five or more joints. Children diagnosed with JIA can expect to live with the disease for the rest of their lives. Girls are more likely to have this disease than boys, and it can affect children of all ages. Often, the small joints of the hands, as well as other joints, are affected symmetrically. One of the unique complications associated with polyarticular JIA is uveitis, which can cause vision impairment and blindness. Patients endure severe inflammation, chronic pain, and fatigue, which affect every aspect of their day-to-day life (physical, social, and emotional), including concentration and cognitive abilities in class and reduced ability to perform tasks such as tying up shoelaces, pulling zippers, or completing basic household chores. Children with JIA are unable to participate in sports, which affects their ability to socialize with other children. Children may sometimes need to be absent from school, causing them to fall behind in schoolwork.

Polyarticular JIA is a seriously debilitating chronic illness that affects all aspects of a child's life and requires extensive parental support and assistance. Parents need to pay greater attention to their child with polyarticular JIA, thereby meaning less time and energy devoted to the child's siblings and each other; hence, there may be added stress on sibling relationships, as children without arthritis often feel that the child with arthritis is getting special attention from their parents. The disease can become a serious physical and psychological burden for children. Furthermore, parents report increased stress as a result of employment absences and reduced production due to medical appointments. Some have to make long drives for the physician appointments.

3. Current Therapy-Related Information

The current objectives of treatment for RA, AS, and polyarticular JIA are symptom control and slowing the progression of the disease. Patients usually have to try several treatments before reaching an effective regimen. Many patients end up receiving several drugs at once, each with their own profile of potential side effects. Patients taking NSAIDs (nonsteroidal anti-inflammatory drugs) frequently complain about stomach pain, heartburn, and gastroesophageal reflux. Patients taking methotrexate feel nauseated and fatigued most of the time.

Many patients taking biologics such as Enbrel (the original etanercept) and Humira have reported them to be "life-changers" that allowed them to largely resume a normal lifestyle. While many patients have seen improvements using biologics, there are some who see no improvements at all, others who develop serious adverse effects that require the withdrawal of the medication, and some who report that the efficacy lasted only a few years. The most common adverse effects cited include infections, allergic reactions, and injection site reactions. There was a commonly voiced concern that Enbrel may cause cancer. Due to the nature of subcutaneous administration, treatment may leave scars or cause skin infections; however, patients seem to be willing to tolerate injection site reactions as part of the risk–reward calculation of being on a biologic.

A common theme across the four patient group submissions indicated that access to Enbrel was hindered by the high cost of the drug and the amount of paperwork required for receiving funding assistance; even patients with private insurance see a significant financial burden from 10% co-pay.

4. Expectations About the Drug Being Reviewed

Among patients who are familiar with the concept of a subsequent entry biologic (SEB), many expect it to have similar efficacy and side effects to the reference biologic but at a much lower cost. Patients see this as a great advantage in improving access to the medication and reducing the burden to public plans.

Nonetheless, patient groups have highlighted the importance of the support programs that are currently offered to patients by the manufacturer of Enbrel. Also, a common concern was that patients may be forced to switch to the SEB, or that switching would occur without proper consultation between the patient and the physician.

Many patients surveyed in one of the patient input submissions were not aware that an SEB is a medication that has similar but not identical structure to the reference drug and that would have a similar efficacy and safety profile. Frequently, these patients were expecting the SEB to have a better efficacy and safety profile than the reference biologic.

5. Key Messages

- Patients show concern about switching to the SEB from the reference drug without their consent.
- SEBs have a role to play in the care and management of people living with inflammatory arthritis.
- Although patients have pointed out the high price associated with the reference drug Enbrel, they also greatly value the patient support program the manufacturer provides. Patient groups would expect to see quality patient programs for the new SEBs entering the market.
- Patient groups exhibit their support for the availability of several choices to best address the individual patient's response.
- Patients see an advantage to SEBs in improving access to the medication and reducing the burden to public plans.
- A process for post-market surveillance must be put in place to track the long-term safety and efficacy of SEBs.
- One patient group indicated that while some patients are concerned about the efficacy of biosimilar (SEB) etanercept for different patients and that it may not be as effective in treating disease progression and pain, an abundant amount of evidence exists showing both efficacy and safety.

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