Common Drug Review

Subsequent Entry Biologic Review Report

October 2016

Drug	Etanercept (Brenzys)
Indication	• Treatment of moderately to severely active rheumatoid arthritis (RA) in adults. • Reducing signs and symptoms of active ankylosing spondylitis (AS).
Listing request	[redacted]
Dosage form(s)	Prefilled syringe auto-injector for subcutaneous injection (50 mg/mL in 0.98 mL)
NOC date	August 31, 2016
Manufacturer	Samsung Bioepis Co., Ltd; distributed by Merck Canada Inc.

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

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ABBREVIATIONS

2-AB	2-aminobenzamide
ACR20	American College of Rheumatology 20% response
ACR50	American College of Rheumatology 50% response
ACR70	American College of Rheumatology 70%response
ACR-N	American College of Rheumatology N Index
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
AS	ankylosing spondylitis
Asn	asparagine
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to last quantifiable concentration
AUC_{τ}	AUC during the dosing interval
Brenzys	Samsung Bioepis 4 (etanercept SEB/biosimilar)
CD	circular dichroism
CDC	complement-dependent cytotoxicity
CDR	CADTH Common Drug Review
CE-SDS	capillary electrophoresis-sodium dodecyl sulphate
CEX	cation exchange chromatography
CI	confidence interval
C_{max}	maximum concentration
C_{min}	minimum concentration
CRP	C-reactive protein
CSR	Clinical Study Report
CTD	Common Technical Document
C_{trough}	serum concentration prior to dosing
DAS28	Disease Activity Score 28
DB	double-blind
DLS	dynamic light scattering
DMARD	disease-modifying antirheumatic drug
DP	drug product
DS	drug substance
DSC	differential scanning calorimeter
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ESI	electrospray ionization
ESR	erythrocyte sedimentation rate

ETN	Enbrel Etanercept
EU	European Union
EULAR	European League Against Rheumatism
Fc	fragment, crystallizable
FcγR	fragment, crystallizable-gamma receptor
FcRn	neonatal Fc receptor
FDA	United States Food and Drug Administration
FRET	fluorescence resonance energy transfer
FTIR	Fourier transform infrared
GGT	gamma-glutamyl transferase
HAQ-DI	Health Assessment Questionnaire–Disability Index
H/DX	hydrogen/deuterium exchange
HIC	hydrophobic interaction chromatography
HP-SEC	high pressure size-exclusion chromatography
HPLC	high-performance liquid chromatography
icIEF	imaged capillary isoelectric focusing
IP	investigational product
LC	liquid chromatography
MALLS	multi-angle laser light scattering
MFI	micro-flow imaging
MS	mass spectrometry
mTSS	modified total Sharp score
MTX	methotrexate
MW	molecular weight
NAb	neutralizing antibody
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NSAID	nonsteroidal anti-inflammatory drug
PFS	pre-filled syringe
PK	pharmacokinetic
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RCT	randomized controlled trial
SA	scientific advice
SAE	serious adverse event
SAWP	Scientific Advice Working Party
SDS	sodium dodecyl sulphate
SEB	subsequent entry biologic
SEC	size exclusion chromatography
	size exclusion–high-performance liquid chromatography
SPR	surface plasma resonance
SV-AUC	sedimentation velocity-analytical ultracentrifugation
$T_{1/2}$	Terminal elimination half-life

TB	tuberculosis
TEAE	treatment-emergent adverse event
T_{max}	time to C_{max}
TNF-α	tumour necrosis factor alpha
TNFR	tumour necrosis factor receptor
TSA	total sialic acid
UPLC	Ultra Performance Liquid Chromatography
UV	ultraviolet
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Approach to the Review

The CADTH Common Drug Review (CDR) approach to reviewing Brenzys (etanercept subsequent entry biologic [SEB]) followed the *Common Drug Review 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

Brenzys, which is based on the reference biologic etanercept (Enbrel), was granted a Notice of Compliance (NOC) 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).

The reference biologic product, Enbrel, is also indicated for psoriatic arthritis, juvenile rheumatoid arthritis, and plaque psoriasis; however, the manufacturer is requesting that Brenzys be reimbursed only for the RA and AS indications, which are the two indications for which Health Canada granted an NOC. [redacted] The exact wording of the manufacturer-requested reimbursement criteria is provided in section 3.1 Requested Listing Criteria.

Clinical Evidence

The manufacturer provided one phase 3 equivalence randomized controlled trial (RCT), along with an extension phase, that enrolled patients suffering from RA (SB4-G31-RA), and one phase 1 pharmacokinetic study that enrolled healthy volunteers (Study SB4-G11-NHV).

SB4-G31-RA was a randomized, double-blind, 52-week, parallel-group, multi-centre clinical study conducted in Europe, South Korea, and Latin America that was designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of Brenzys (etanercept SEB) compared with Enbrel (reference product) in patients with moderate-to-severe RA despite methotrexate therapy. The primary end point was the American College of Rheumatology 20% response criteria (ACR20) at week 24, through which therapeutic equivalence was concluded between Brenzys and Enbrel if the 95% confidence interval (CI) of the adjusted treatment difference was entirely contained within the equivalence margin of −15% to 15%. Additional efficacy, safety, pharmacokinetic, and immunogenicity outcomes were also assessed. Results of the primary end point of ACR20 response at week 24 were similar for both the per-protocol set 1 (PPS1) (78.1% versus 80.5%) and the full analysis set (FAS) (73.6% versus 71.1%) between Brenzys and Enbrel, respectively. The 95% CIs of the adjusted difference rates fell within the predefined equivalence margin of ± 15% for both PPS1 (–9.54% to 4.80%) and FAS (–5.50% to 8.82%). In addition, all other efficacy, safety, and pharmacokinetic end points were similar, with fewer injection-site reactions in the Brenzys-treated group, and statistically significantly less immunogenicity in terms of anti-drug antibodies in the Brenzys group compared with Enbrel (0.7% versus 13.1% at 24 weeks, *P* value < 0.001).

Study SB4-G11-NHV was a controlled, randomized, single-blind, three-part, two-period, two-sequence, single-dose, crossover study to compare the pharmacokinetics, safety, tolerability, and immunogenicity of three formulations of etanercept (Brenzys, European Union–sourced Enbrel [EU-Enbrel], and United States–sourced Enbrel [US-Enbrel]) in healthy male participants. The primary end points (pharmacokinetics) were area under the concentration-time curve (AUC) from time 0 to infinity (AUC_{inf}) and maximum concentration (C_{max}), through which pharmacokinetic similarity was concluded between Brenzys and Enbrel if the 90% CI of the ratios of the geometric means were entirely contained within the equivalence margin of 80% to 125%. Additional safety, pharmacokinetic, and immunogenicity outcomes were also assessed. The results of this study demonstrated that the pharmacokinetic outcomes were similar between Brenzys and EU-Enbrel in part A, Brenzys and US-Enbrel in part B, and EU-Enbrel and US-Enbrel in part C.

Long-term, single-group, extension studies of SB4-G31-RA were planned for an additional 48 weeks (total of 100 weeks). Patients were either maintained on Brenzys or switched from Enbrel to Brenzys. Efficacy, safety, and immunogenicity responses were sustained throughout in 245 patients (41.1%) of the original 596 patients in the study populations.

Both studies were generally well designed and executed with no major biases. The available data for SB4-G31-RA were consistent with the conclusion that Brenzys and Enbrel have similar efficacy and safety profiles in patients with RA. The available data for SB4-G11-NHV were consistent with the conclusion that Brenzys 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.

Brenzys was approved by the European Medical Agency and by the Therapeutic Goods Administration in Australia for RA, AS, psoriatic arthritis, and plaque arthritis, based on the similarity between Brenzys and Enbrel.

Extrapolation

The results of a phase 3 RCT suggest equivalence in clinical efficacy, immunogenicity, and pharmacokinetic and safety profiles between Brenzys and Enbrel. The findings from a phase 1 trial in healthy volunteers provide additional support for similarity in pharmacokinetic profiles between Brenzys and Enbrel. In addition, the consistency of treatment effect with Brenzys was demonstrated by an extension study. Furthermore, clinicians' experience with the use of etanercept for AS is extensive. Consideration is also given to the similarity in disease etiology and the role of tumour necrosis factor (TNF) in both RA and AS, which suggests that extrapolation of the RA results to the AS indication is appropriate.

Potential Place in Therapy[1]

The reference product, etanercept (Enbrel), has been widely used for patients with RA, psoriatic arthritis and AS for more than 10 years. According to the clinical expert consulted for this review, anti-TNF agents have been the first treatment option for a biologic drug in all three of these indications and etanercept has been one of the most frequently chosen. Typically, anti-TNF agents are used after an inadequate trial of two nonsteroidal anti-inflammatory drugs (NSAIDs) for patients with AS, and after an inadequate trial of a disease-modifying antirheumatic drug (DMARD), as either monotherapy or combination therapy) in patients with RA. 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.

According to the clinical expert consulted for this review, the etanercept SEB would be an appropriate choice for any biologic-naive or biologic-experienced patient who would receive the reference product, Enbrel, for treatment of both indications under review (RA and AS). At this time, there is limited evidence to support switching a patient from the reference product (Enbrel) to the etanercept SEB.

Cost Comparison

The manufacturer's submitted price for Brenzys ($305.00 per 50 mg pre-filled syringe/auto-injector) is 25% lower than the price for Enbrel ($405.99 per 50 mg pre-filled syringe/auto-injector), when using the Ontario Drug Benefit Formulary price for Enbrel.

Conclusion

Overall, the manufacturer provided sufficient data from one phase 3 clinical equivalence trial and one phase 1 pharmacokinetic trial to demonstrate similar efficacy across the primary and secondary outcomes, as well as safety outcomes, between the SEB Brenzys and the reference drug, Enbrel. The extrapolation of the evidence to support equivalence of these outcomes in RA patients to AS patients also appears to be reasonable. There is currently limited evidence available to support switching a patient from the reference product, Enbrel, to the etanercept SEB Brenzys.

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

Note: References in brackets () indicate the references cited by the manufacturer, while the references cited by the CADTH Common Drug Review (CDR) are indicated by superscripts.

1. PRODUCT INFORMATION

1.1 Overview of the Reference Product

TABLE 1: OVERVIEW OF THE SEB PRODUCT

Characteristics	Manufacturer-Provided Details			
	Brenzys	Canadian-Enbrel®	EU-Enbrel®	US-Enbrel®
Brand name:	Brenzys Trademark TBC	Enbrel®		
Non-proprietary name:	Etanercept; Brenzys	Etanercept		
Manufacturer:	Samsung Bioepis Co., Ltd. (distributed by Merck Canada Inc.)	Immunex Corp. (distributed by Amgen Canada Inc.)	Wyeth Pharmaceuticals (distributed by Pfizer Ltd.)	Immunex Corp. (distributed by Amgen Inc. and Pfizer Inc.)
Strength(s):	50 mg/mL in 0.98 mL	• 50 mg/mL in 0.98 mL PFS (02274728) • 50 mg/mL in 0.98 mL SureClick auto-injector (99100373) • 25 mg vial (02242903)	• 25 mg and 50 mg PFS • 50 mg pre-filled pen • 10 mg, 25 mg, and 50 mg vials (powder)	• 25 mg and 50 mg PFS • 50 mg SureClick® autoinjector • 25 mg vial
Dosage form:	Sterile solution for injection in: • Pre-filled syringe (PFS) • Pre-filled auto-injector • Both with 27-gauge, 1⁄2 inch needles	Sterile solution for injection in: • Single-use PFS (02274728) • Single-use SureClick® auto-injector (99100373) • Both with 27-gauge, 1⁄2 inch needles Kit: Liquid, Powder For Solution • Lyophilized powder for reconstitution in vial (02242903)	Solution for injection in: • PFS • Solution for injection in pre-filled pen Powder for solution for injection • Lyophilized powder for reconstitution in vial	Solution for injection in: • Single-use PFS • Single-use prefilled SureClick® autoinjector Powder for solution for injection • Lyophilized powder for reconstitution in multiple-use vial
Route of administration:	Subcutaneous	Subcutaneous		
Drug Identification Number(s):	Not available; pre-NOC submission	• 02274728 (50 mg/mL PFS) • 99100373 (50 mg/mL SureClick auto-injector) • 02242903 (25 mg/vial)	Not applicable	
Therapeutic classification:	Biological Response Modifier			

Characteristics	Manufacturer-Provided Details			
	Brenzys	Canadian-Enbrel®	EU-Enbrel®	US-Enbrel®
Excipients	Sterile solution for injection • Preservative free • pH 6.2±0.3 • 1% sucrose • 140 mM sodium chloride • 10 mM sodium phosphate	Sterile solution for injection • Preservative free • pH 6.3±0.2 • 1% sucrose • 100 mM sodium chloride • 25 mM sodium phosphate • 25 mM L-arginine hydrochloride Kit: Liquid, Powder For Solution Reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection (BWFI), USP (containing 0.9% benzyl alcohol) yields a multiple-use, clear, and colourless solution with a pH of 7.4±0.3 containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine	Sterile solution for injection • Sucrose • Sodium chloride • L-arginine hydrochloride • Sodium phosphate (monobasic dehydrate) • Sodium phosphate (dibasic dihydrate and water)	**Sterile solution for injection** • 1% sucrose • 100 mM sodium chloride • 25 mM sodium phosphate • 25 mM L-arginine hydrochloride
Impurities	[redacted]	[redacted]	[redacted]	[redacted]

ppm: parts per million; ppb: parts per billion; LOQ: limit of quantitation.
Source: CTD 2.3.P, section 5.1 (Table 10), section 5.4.5 (Table 13); CTD 2.3.R, sections 5.1.1 (Table 7), 5.2.9; CTD 3.2.R.5.

Please provide a brief summary of the **similarities and differences between the SEB and the reference product**, particularly with respect to the following:

- pharmaceutical form and composition
- the dosage form, strength, and route of administration
- purity and impurities.

Note: for the following comparison, the 50 mg/mL PFSs (and auto-injectors) for both Brenzys and Enbrel® are compared since the reference product used in these studies were PFSs.

1.1.1 Pharmaceutical Form

Etanercept is a recombinant human tumour necrosis factor receptor dimeric fusion protein. Etanercept is not a monoclonal antibody.

1.1.2 Pharmaceutical Composition

Both Brenzys and Enbrel® PFS/auto-injectors are preservative-free solutions containing 49 mg (50 mg/mL in 0.98 mL) etanercept and 1% sucrose. In addition, Brenzys contains 140 mM sodium chloride and 10 mM sodium phosphate, Enbrel® contains 100 mM sodium chloride, 25 mM sodium phosphate, and 25 mM L-arginine hydrochloride.

Although minor differences in excipients exist between the Brenzys and the Enbrel® PFSs/auto-injectors, results from both comparative analytical analyses (using drug products), clinical trials in healthy volunteers (pharmacokinetics) and RA patients suggested highly biosimilar fusion protein as well as a lack of meaningful differences between the two products in terms of overall pharmacokinetics, safety, and efficacy. Nevertheless, lack of L-arginine in Brenzys may have contributed to the lowered injection site reactions seen for Brenzys compared to Enbrel® (see section 4.2.2. SB4-G31-RA under sub-section *Injection Site Reactions*).

1.1.3 Dosage Form

Both Brenzys and Enbrel® are identical, namely formulated as sterile solution for injection.

1.1.4 Strength

Both Brenzys and Enbrel® are supplied as PFSs/auto-injectors containing 0.98 mL of 50 mg/mL etanercept.

1.1.5 Route of Administration

Both Brenzys and Enbrel® are administered subcutaneously.

1.1.6 Purity and Impurities

a) Product-Related Impurities

Drug product-related impurities were tested by capillary electrophoresis-sodium dodecyl sulphate (CE-SDS; reducing), size-exclusion chromatography (SEC), and hydrophobic interaction chromatography (HIC). [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]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.2 Overview of the Reference Product

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumour necrosis factor receptor (TNFR) linked to the Fc portion (containing CH2 and CH3, but not CH1 domains) of human immunoglobulin G1 (IgG1). Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

The reference product described in this submission is Enbrel® (etanercept; sterile solution for injection/ 50 mg/mL PFS [0.98 mL] and 50 mg/mL auto-injector [0.98 mL]; Lyophilized powder for reconstitution/ 25 mg/vial) (1). Enbrel® is currently authorized for sale and marketing in Canada with the following formats:

- 50 mg/mL in 0.98 mL PFS (DIN: 02274728)
- 50 mg/mL in 0.98 mL SureClick auto-injector (DIN: 99100373)
- 25 mg/vial (DIN: 02242903)

It should be noted that the batches of Enbrel® used in the SB4-G31-RA trial (rheumatoid arthritis; RA) were sourced from the EU and those used in the SB4-G11-NHV trial (health volunteers) were sourced from the EU and the US (CTD 2.3.R, section 5.1.1).

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

During development of Brenzys, EU-Enbrel® was used as the main reference biological drug and was used to demonstrate biosimilarity in the Phase III pivotal clinical study, whereas US-Enbrel® was used to generate supportive data in the quality comparability exercise, as well as in the non-clinical and Phase I PK studies:

	Reference Status	Physicochemical & Functional Studies	Phase I Study	Phase III Study
EU-Enbrel®	Accepted Non-Canadian Reference	Yes	Yes	Yes
US-Enbrel®	Supportive – used for bridging to Canadian Reference	Yes*	Yes	No

* Except for the hydrogen/deuterium exchange assay.

Linkage in corporate entities and formulation has been demonstrated between Canadian and US-Enbrel® (see section 1.1 Overview of the SEB Product above). Extensive characterization was performed using EU- and US-Enbrel®. Characterization results presented in CTD Module 3.2.R.5 (provided upon request) demonstrated that the similarity ranges set for EU- and US-Enbrel® overlap with one another. Moreover, characterization data presented in the CTD 2.3.R (summarized in section 4.1 Quality Information below) demonstrated comparability in the structural, physicochemical, and biological characteristics between US- and EU-Enbrel®.

Based on the above, EU-Enbrel® may be used as a reference biologic drug for the Brenzys (as accepted by Health Canada for a New Drug Submission), and no additional comparability studies using Canadian-sourced Enbrel® were deemed necessary (CTD 2.3.R, section 5.1.1).

1.2.2 Indications

In Canada, Enbrel® is indicated for the following:

- 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. 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 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). ENBREL® has not been studied in children less than 4 years of age.
- reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in adult patients with **psoriatic arthritis (PsA)**. ENBREL® can be used in combination with methotrexate in adult patients who do not respond adequately to methotrexate alone.
- reducing signs and symptoms of active **ankylosing spondylitis (AS)**.
- treatment of adult patients with chronic moderate to severe **plaque psoriasis** who are candidates for systemic therapy or phototherapy.

2. INDICATIONS

2.1 Health Canada-Approved Indications

Indication(s)	Extrapolation
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. Brenzys can be initiated in combination with methotrexate (MTX) in adult patients or used alone.	No
Reducing signs and symptoms of active ankylosing spondylitis (AS)	Yes

2.2 Proposed Indications Under Review by Health Canada

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

3. MANUFACTURER'S REQUESTED LISTING CRITERIA

3.1 Requested Listing Criteria

3.1.1 Requested Listing Criteria for Indications to be Reviewed by the CADTH Common Drug Review

[redacted]

3.2 Rationale for Requested Listing Criteria

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

First, a Notice of Compliance (NOC) for Brenzys was granted from Health Canada for both RA and AS indications:

- Brenzys has demonstrated **highly comparable safety and efficacy profile** to the reference product Enbrel® in RA patients in the pivotal efficacy study SB4-G31-RA (described in detail in section 4.2.1 below). Briefly, Brenzys was demonstrated to be therapeutically similar to Enbrel® (both groups received concurrent MTX), as determined by the similar American College of Rheumatology 20% (ACR20) response at week 24 (Brenzys vs. Enbrel®; per-protocol set 1: 78.1% vs. 80.5%, 95% CI: -9.54% to 4.80%; full-analysis set: 73.6% vs. 71.1%, 95% CI: -5.50% to 8.82%) which was within pre-

defined therapeutic equivalence margin of ±15%). In addition, all other efficacy and safety endpoints were highly similar between both products

- Brenzys elicited **lower level of immunogenicity** compared to Enbrel® in both RA subjects and healthy volunteers. As per the European Medicines Agency (EMA) (8), such finding would not preclude Brenzys from being classified as a biosimilar since clinical efficacy of Brenzys and Enbrel® were highly similar in patients with antidrug antibody (ADA)-negative results and no apparent correlation between ADA and clinical response or safety was observed.
- Brenzys has **demonstrated PK similarity** to Enbrel® in both RA subjects and healthy volunteers:
  - The 90% CIs of the ratios (Brenzys/Enbrel®) of the geometric means were all contained within the regulatory agency-accepted equivalence margin for all key PK outcomes (study SB4-G11-NHV).
- Brenzys has shown **highly similar physicochemical properties and biological activities** to Enbrel® as demonstrated by the results from an extensive series of analytical and *in vitro* assays.
- The pathophysiological mechanism underlying both RA and AS are reported to be highly similar (see details in section 6).

Second, the top line summary of results from the extension period of the Phase III trial (new data) demonstrated that Brenzys had comparable efficacy, safety and immunogenicity profiles at Week 100 in RA patients who switched from Enbrel® to Brenzys following the 52-week double-blind portion of the study versus patients who remained on Brenzys throughout the 100 weeks (described in detail in section 4.2.3 below).

Although not directly applicable to Brenzys, a recent British Society of Gastroenterology (BSG) guidance states that "*there is sufficient evidence to recommend that patients who are in a stable clinical response or remission on Remicade therapy can be switched to Remsima or Inflectra at the same dose and dose interval.*" This demonstrates that physicians are generally comfortable with switching patients to an SEB (9).

Third, the minor differences in formulation between Brenzys and Enbrel® did not have impact on the stability of Brenzys and had no apparent impact on the comparability between the two products in terms of analytical function, as well as clinical pharmacology, safety, and efficacy.

[redacted]

Fifth, the conclusive demonstration of Brenzys as a biosimilar of Enbrel® was recognized by the EMA as evident by the marketing authorization granted to Benepali™ (EU trade name) in January of 2016 for the following indications (10, 11):

- Rheumatoid arthritis
- Psoriatic arthritis
- Axial spondylitis
  - Ankylosing spondylitis
  - Non-radiographic axial spondylitis
- Plaque psoriasis

Although Brenzys was approved for multiple indications in the EU, Samsung Bioepis is currently seeking approval for two indications of RA and AS in Canada. [redacted]

[redacted]

Sixth, the requested indications of Brenzys (namely RA and AS) are identical to the RA and AS indications of the reference medicinal product, Enbrel®, for which the drug has been extensively characterized pharmacologically (12). There is also nearly 18 years of clinical experience from both an efficacy and safety standpoint, all of which are well reported in the literature (13, 14).

Based on the above, Brenzys is also expected to have similar efficacy as Enbrel® in all of the requested indications.

From the Canadian health technology assessment perspective, in July of 2010, CADTH Therapeutic Review Panel issued a Final Recommendations document titled: "*Biological Response Modifier Agents for Adults with Rheumatoid Arthritis*" (15). The purpose of the review was to evaluate the comparative safety and efficacy of available biologic agents in the treatment of adults with RA following the failure of disease-modifying antirheumatic drugs (DMARDs). Based on the evidence reviewed by CADTH, the following recommendation was made:

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

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

From the Canadian reimbursement perspective, etanercept (Enbrel®) is currently reimbursed by all CDR-participating drug plans across the country for the treatment of RA and AS (with very minor exceptions, see Appendix 2). Consequently, we anticipate that Brenzys will receive generally similar listing decisions as Enbrel® from these CDR-participating drug plans, assuming that the Canadian Drug Expert Committee issues a positive recommendation for Brenzys.

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

i) demonstrated biosimilarity in terms of physicochemical characteristics and in vitro activities between Brenzys and Enbrel®;
ii) highly comparable PK profile between Brenzys and Enbrel® in healthy volunteers and RA patients;
iii) highly comparable safety profile (in RA subjects and healthy volunteers) and therapeutic similarity (in RA subjects) between Brenzys and Enbrel®; and
iv) NOC issued by Health Canada as an SEB;
v) demonstrated safety and efficacy of Brenzys in patients who previously received Enbrel® based on a top line summary of the 100-week extension phase study results;
vi) marketing authorization by the EMA for all indications

the requested listing criteria for Brenzys are reasonable and justified.

4. BIOSIMILARITY

4.1 Quality Information

[redacted]. Brenzys was characterized using appropriate techniques as described in the ICH guideline Q6B. The study involved determination of the physicochemical properties, biological activity, potency, purity, impurities and quantity of Brenzys using state-of-the-art orthogonal analytical methods to confirm the similarity in quality to Enbrel®, to ensure that the safety and efficacy profiles of Brenzys would be highly similar to the reference product. Results presented below are based on comparability exercises conducted between Brenzys drug product and Enbrel®. Please refer to Common Technical Document (CTD) Module 2.3.S.for the results of the studies with Brenzys drug product (DP) and drug substance,

The primary structures of Brenzys and Enbrel® were determined and confirmed to be identical by a series of assays, including amino acid sequencing, N- and C-terminal sequencing as well as peptide mapping. Other structural characterizations included, but not limited to, disulphide bond and C-terminal lysine variant analyses. Lysine variant analyses indicated the variants existed for both Brenzys and Enbrel® but were considered to be clinically inconsequential since the terminal lysines are cleaved as it enters the blood stream (Table 2).

A series of other physiochemical studies (various chromatographic, electrophoretic, and glycan profile analytical assays) were also conducted. With regards to the glycosylation, Brenzys and Enbrel® are both N- and O-glycosylated at the identical positions. However, minor differences in glycosylation profile existed, nevertheless, these differences **did not translate into differences in various *in vitro* binding or functional activities** (Table 2, Table 3). An extensive series of analytical tests were also employed to characterize the higher order structure of Brenzys related to Enbrel®. Results from differential scanning calorimeter (μ-DSC), Fournier-transformed infrared (FTIR), UV circular dichroism (UV-CD), among many others, demonstrated that **Brenzys and Enbrel® have highly comparable higher-order structures** (Table 2). Results of the key assays are summarized below; detailed descriptions of these assays and all other relevant assays can be found in Table 30 in Appendix 1 and CTD Module 2.3.R.

TABLE 2: SUMMARY OF SELECT PHYSICOCHEMICAL AND BIOPHYSICAL TEST METHODS FOR COMPARABILITY OF BRENZYS (BRENZYS) DRUG PRODUCT AND ENBREL® (ETN)

Test Method(s)	Summary of Results	Reference(s)
Confirmation of Structure Characterization		CTD 2.3.R, section 5.2.1
• Full sequencing	• Amino acid sequence of Brenzys was identical to that of EU-ETN	
• Peptide Mapping	• Brenzys and EU-ETN were digested with different proteases. • Chromatograms patterns were identical between products, irrespective of protease used. • **Therefore, the peptide map for Brenzys was considered similar to that of the ETN.**	
• N-terminal sequence analysis	• Three forms of tryptic N-terminal peptide were found for Brenzys and EU-ETN, depending on source of origin. • It is understood that the heterogeneity could not be controlled during manufacturing. • Results from *in vitro* functional assays demonstrated these differences had no effect on the biological activity (substantiated between the FDA and a different manufacturer).	

Test Method(s)	Summary of Results	Reference(s)
• C-terminal sequence analysis	• Two forms of C-terminal peptides were found in both Brenzys and EU-ETN and both were identical to the expected sequence.	
• C-terminal Lys variant analysis	• The relative level of the lysine variant in Brenzys was lower than that in EU-ETN indicating that most of the lysine on the C-terminus of Brenzys was found cleaved. • The heterogeneity of C-terminal residues is a characteristic of therapeutic monoclonal antibodies and C-terminal lysine variation that is known not to impact pharmacokinetic profiles and the biological activity of the Fc fusion protein. • In addition, the C-terminal lysine does not possess any physiological effect as it is cleaved by carboxypeptidase as it enters the blood. • Results from the TNF-α binding functional assay demonstrated that C-terminal Lys content did not impact TNF-α binding activity. **Therefore, the difference in C-terminal Lys content is not considered significant.**	
• Disulphide bond	• Disulphide linkage patterns are similar for Brenzys and EU-ETN.	
Physicochemical: Electrophoresis		CTD 2.3.R, section 5.2.3
• Charge Heterogeneities by Imaged Capillary Isoelectric Focusing (icIEF)	• Brenzys was found to possess a higher content of acidic isoform and lower content of basic isoform when compared with ETN. The content of the main peak were comparable for Brenzys and ETN and the Brenzys results were within the similarity range. • **Structural activity relationship (SAR) studies found that the charge variant content did not affect TNF-α binding activity and therefore did not translate to differences in the biological activity of Brenzys.**	
Physicochemical: Glycan Profile		CTD 2.3.R, section 5.2.4
• N-linked Glycosylation Site	• N-linked glycosylation sites of Brenzys were identified as Asn149, Asn171, and Asn317, which were identical to those of EU-ETN.	
• N-glycan Profile	• N-glycan profiles differed between Brenzys batches and EU-ETN. • The afucosylated glycan content in Brenzys was higher than EU-ETN. • Afucosylated glycan level in therapeutic proteins is associated with FcγRIIIa binding activity and antigen-dependent cell-mediated cytotoxicity (ADCC), which is not considered to be a mechanism of action of etanercept and so differences would not be clinically meaningful. • ADCC analysis demonstrated absence of ADCC activity in both Brenzys and ETN. • [redacted] • Compared to EU-ETN, Brenzys had more neutral galactosylated glycan content, which is generally associated with complement-dependent cytotoxicity (CDC) activity for monoclonal antibodies, for which is not known to be a mechanism of action of etanercept. • Thus, the differences in N-glycan profiles of Brenzys and EU-ETN are not considered significant.	
• O-glycan Site	• All O-linked glycosylated sites identified in Brenzys were identical to those found in EU-ETN	
• O-glycan Profile	[redacted]	
• Total Sialic Acid	• The TSA, N-acetylneuraminic acid (NGNA), and N-glycolylneuraminic acid (NANA) contents of Brenzys were considered similar to those of EU-Enbrel®.	

Test Method(s)	Summary of Results	Reference(s)
Biophysical: Higher-Order Structure		CTD 2.3.R, section 5.2.5
• **DSC**	• The shapes of the thermal scans for Brenzys and EU-ETN were comparable and the melting temperature (T_m1, T_m2 and T_m3) values are considered similar for Brenzys and EU-ETN.	
• **FTIR**	[redacted]	
• **Far-UV CD Spectroscopy**	[redacted]	
Purity		
	• See Process-Related Impurities in section 1.1 Overview of the SEB Product above	CTD 2.3.R, section 5.2.9

A comprehensive number of comparative *in vitro* studies were also conducted to evaluate the functional similarity between Brenzys and Enbrel®. The relevant assays were qualified and closely associated with the mode of action of etanercept (TNF-α, LT-α3 binding assay and NF-κB reporter gene assay). Fc-related binding and functional activities were assessed as well, although the main function of the Fc region in etanercept is to prolong half-life rather than to impart on Fc-mediated effector activity. An overview of the *in vitro* studies conducted comparing Brenzys to Enbrel® is given in Table 3.

All *in vitro* studies results were within the similarity range, with the exception of FcγRIa. However, the difference was minor [redacted], and was considered to be within assay variability. Overall, the binding activity to FcγRIa is known to be associated with ADCC activity. As ADCC is not a mode of action of etanercept, the differences in FcγRIIIa were not considered to be significant. Subsequent studies evaluating the ADCC activity of Brenzys and Enbrel® confirmed the absence of ADCC activity. **In summary, the overall results of the *in vitro* assays associated with the mechanism of action of etanercept and Fc-related binding assays demonstrated similarity between Brenzys and Enbrel®.**

Detailed descriptions of these assays and all other relevant assays can be found in Table 31 in Appendix 1, as well as CTD Module 2.3.R.

TABLE 3: SUMMARY OF SELECT STUDIES COMPARING BIOLOGICAL ACTIVITIES BETWEEN BRENZYS (BRENZYS) DRUG PRODUCT AND ENBREL® (ETN)

Test Method(s)	Summary of Results	Reference(s)
Mechanism of Action (Fab')-related Biological Assays		
• TNF-α Binding Assay	The binding activities of Brenzys and EU-ETN relative to the bioassay standard were similar, and were all within the similarity range (91-112%).	CTD 2.3.R, section 5.2.6
• LT-α3 Binding Assay	The ranges for the LT-α3 binding activity of Brenzys and EU-ETN relative to the bioassay reference standard were within the similarity range (87-116%).	
[redacted]	[redacted]	

Test Method(s)	Summary of Results	Reference(s)
Fc-Related Biological Activities		CTD 2.3.R, section 5.2.7
• FcγRIa Binding Assay	[redacted]	
• FcγRIIb Binding Assay	[redacted]	
• FcγRIIIa Binding Assay (V158 allotype)	[redacted]	
Additional Biological Assays		
• CDC Assay	[redacted]	CTD 2.3.R, section 5.2.8
• ADCC Assay	[redacted]	

[redacted]

4.2 Pivotal Clinical Studies

4.2.1 Introduction

The drug development process for Brenzys has been designed to replicate Enbrel®. As such, an extensive biosimilarity and comparability exercise has been performed to demonstrate that Brenzys and the reference medicinal product Enbrel® correspond in terms of quality, safety and efficacy, which has been aligned to respective EU and Health Canada guidance. In addition to multiple jurisdiction-specific guidelines, the applicant requested scientific advice (SA) from the EMA/Scientific Advice Working Party (SAWP) on three occasions (EMA/CHMP/SAWP/9771/2012; EMA/CHMP/SAWP/451465/2012; EMA/CHMP/SAWP/749463/2013).

Furthermore, the applicant consulted with the US Food and Drug Administration (FDA) on the overall product development requirements in a pre-Investigational New Drug meeting (US FDA Meeting Minutes PIND 113462, 2012).

Finally, the applicant consulted with the Health Canada on specific requirements for biosimilar development in Canada during a pre-submission meeting in Oct 2014.

The SA received by EMA was generally taken into consideration and the development programme aligned accordingly. See CTD 2.5, section 1.1 for details.

a) Overview of Studies (CTD 2.5, Section 1.1)

As outlined in EU guidance (EMEA/CHMP/BMWP/42832/2005; EMA/CHMP/BMWP/403543/2010) (8, 17) and Health Canada guidance (Guidance for Sponsors: Information and Submission Requirements) (18), clinical evidence on comparability/similarity needs to be provided in respect to the efficacy of the biosimilar product as well as to safety and PK.

Based on the supportive quality similarity exercises and the *in vitro* and *in vivo* non-clinical study results, a clinical Phase I study was conducted to compare the PK, safety/tolerability, and immunogenicity in order to demonstrate similarity between Brenzys and Enbrel® (Study Brenzys-G11- NHV), subsequently followed by a clinical Phase III study in RA patients to demonstrate similarity in efficacy, safety/tolerability, immunogenicity, and patient PK profiles between Brenzys and Enbrel® (Study SB4-G31-RA)

Study SB4-G11-NHV was a pivotal, Phase I, crossover, single-blind, randomized controlled study designed to assess PK similarity between Brenzys as well as the EU- and US-sourced Enbrel® in healthy male subjects. Study methodology, in particular dosing and sample size, was subject of EMA SA and the study was conducted in accordance with EMA recommendations (EMA/CHMP/SAWP/9771/2012). Furthermore, in accordance with Health Canada guidance (Conduct and Analysis of Comparative Bioavailability Studies) (19), equivalence analysis results of Brenzys and the reference products in regards to AUC_{last} were additionally reported. For the acceptability of use of healthy volunteers in this study, please refer to section *Acceptability of Healthy Volunteers as a Sensitive PK Population* below.

Study SB4-G31-RA was a pivotal Phase III, parallel-group, multi-centre study. The randomized, double-blind period was designed to assess therapeutic (efficacy, safety/tolerability, and immunogenicity) similarity as well as steady-state PK between Brenzys and EU-Enbrel® in RA patients with moderate to severe RA despite MTX therapy. As of this submission, the randomized, double-blind period (up to Week 52) has been completed with full data available in the CTDs as well as CSRs; this was followed by an open-label extension period (in Czech Republic and Poland). The extension period consists of 48 weeks of active treatment and 4 weeks of safety follow-up to evaluate the long-term safety, tolerability, immunogenicity and efficacy of Brenzys in patients with RA treated previously with Brenzys or EU-Enbrel®. Subjects from the Poland and Czech Republic sites were selected [redacted] to enter the extension period of this study. For the acceptability of use of RA patients in this study, please refer to section *Acceptability of RA Subjects as a Sensitive Disease Population* below.

b) Acceptability of Healthy Volunteers as a Sensitive PK Population

In accordance with guideline EMA/CHMP/BMWP/403543/2010, healthy subjects were selected as the appropriate population for demonstrating equivalence in a comparative single-dose study as this population showed well tolerability and is considered more homogeneous and hence more sensitive as compared to patient populations. This was endorsed by EMA SA (EMA/CHMP/SAWP/9771/2012).

c) Acceptability of RA Subjects as a Sensitive Disease Population

In addition to being an indication (i.e. RA) for which CDR evaluation is being requested for, in order to demonstrate similarity in efficacy between Brenzys and Enbrel®, and following EU guidance (in particular EMEA/CHMP/BMWP/42832/2005; EMA/CHMP/BMWP/403543/2010 (8, 17)), the clinical Phase III study SB4-G31-RA was conducted in a study population appropriate for demonstrating biosimilarity and was designed sensitive enough for detecting potential differences between Brenzys and Enbrel®. Study SB4-G31-RA was not aimed at demonstrating efficacy *per se*, since efficacy in the respective therapeutic

indications has already been established with Enbrel®. The purpose was to investigate similarity between Brenzys and Enbrel®, assessed according to an equivalence approach.

Among the therapeutic indications, RA has been studied most thoroughly, with validated and reasonably sensitive methods to study the disease activity of RA available. The selected dose reflects the clinically effective and approved dose of EU-Enbrel®. The study methodology was aligned to EMA SA in terms of treatment regimen, patient population, study endpoints, and proposed equivalence margins (EMA/CHMP/SAWP/9771/2012; EMA/CHMP/SAWP/451465/2012). This approach has been endorsed by EMA (EMA/CHMP/SAWP/9771/2012) and the US FDA (US FDA Meeting Minutes PIND 113462, 2012). See CTD 2.5, section 4.1 for information.

In addition to the above, as detailed in the *Rationale for the Equivalence Margins Used* below, the pivotal trials conducted in Enbrel® demonstrated a large ACR20 response with Enbrel® over placebo (32-44%). This suggests that with an appropriate endpoint, RA subjects possess the sensitivity to detect differences between treatments.

Finally, the selection of RA subjects (with concomitant MTX treatment) as a sensitive population has been previously utilized and accepted for another SEB submission at the CDR (see Inflectra's CADTH Common Drug Review Report), for which extrapolation to other indications including psoriatic arthritis and psoriasis was partly based upon (2).

Study Name	Design	Objectives	Population
SB4-G31-RA	<u>Pivotal, Randomized, Double-blind</u> Phase III, pivotal safety/ efficacy, double blind, active-controlled, parallel assignment, multicentre RCT <u>Open-label, Extension Period</u> Open-label, single-arm, multicentre study	<u>Randomized, Double-blind</u> To compare the efficacy, safety, immunogenicity, and steady-state pharmacokinetics of Brenzys with reference product etanercept (ETN; Enbrel®) in patients with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) therapy. <u>Open-label, Extension Period (preliminary results available)</u> To investigate the long-term safety and immunogenicity, efficacy of Brenzys in those subjects completing the randomized, double-blind period.	The therapeutic area is rheumatology. Patients with moderate to severe rheumatoid arthritis (RA) despite MTX therapy; Diagnosed according to revised 1987 ACR criteria, on stable MTX therapy <u>Randomized, Double-blind</u> Key characteristics: The average age was 51.8 years and the proportion of patients aged over 65 was 15.4% in the Brenzys and 11.8% in the EU-Enbrel® treatment group. The majority of patients were female (84.2%) and white (92.6%). <u>Open-label, Extension</u> Demographic data is currently not yet available. However, subjects enrolled in the Poland and Czech Republic sites were entered into extension period.

Study Name	Design	Objectives	Population
SB4-G11-NHV	Pivotal, Phase I, pharmacokinetic (PK), single blind, three-part, two-period, two-sequence, single-dose, cross-over, randomized study	To demonstrate PK equivalence between Brenzys and EU sourced Enbrel® (Part A), between Brenzys and US sourced Enbrel® (Part B), and between EU-Enbrel® and US-Enbrel® (Part C). Safety, tolerability, and immunogenicity were investigated as secondary objectives.	Study was conducted in healthy subjects but the intended therapeutic area is rheumatology. Key characteristics: all were healthy male subjects between the age of 18-55 years old, inclusive (average age in each part ranged between 39-41 years old)

4.2.2 SB4-G31-RA (Randomized, Double-Blind Period)

a) Study Characteristics

Brief Description of the Study (One Paragraph)

The randomized, double-blind period of Study SB4-G31-RA was a 52-week, parallel group, multicentre clinical study designed to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of Brenzys (etanercept SEB) compared to Enbrel® (innovator) in subjects with moderate to severe RA despite MTX therapy. The primary endpoint was American College of Rheumatology 20% response criteria (ACR20) at Week 24, through which therapeutic similarity was concluded between Brenzys and Enbrel® if the 95% CI of the adjusted treatment difference was entirely contained within the equivalence margin of −15% to 15%. Additional efficacy, safety, PK, and immunogenicity outcomes were also assessed.

	Characteristics	Details for SB4-G31-RA (Randomized, Double-blind)
Study Design	**Objective**	Pivotal efficacy and safety study
	Blinding	Double-blind (subject, caregiver, investigator, outcomes assessor)
	Study Period	2013-06 to 2014-11 (final completion date)
	Study Centres	73 centres across 10 countries in Europe, Latin America, and Asia
	Design	Equivalence
Study Population	**Randomized (N)**	596

	Inclusion Criteria	• Male or female aged 18–75 years at the time of signing the consent form;
		• Diagnosed as having RA according to the revised 1987 ACR criteria for at least 6 months but not exceeding 15 years prior to screening;
		• Showing moderate to severe active disease despite MTX therapy defined as:
		  • More than or equal to six swollen joints and more than or equal to six tender joints (from the 66/68 joint count system) at screening and randomization;
		  • Either erythrocyte sedimentation rate (Westergren) ≥ 28 mm/h or serum C-reactive protein (CRP) ≥ 1.0 mg/dL at screening;
		• Treated with MTX for at least 6 months prior to randomization and on a stable dose of MTX 10–25 mg/week given orally or parenterally for at least 4 weeks prior to screening;
		• If using non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics for RA, being on a stable dose for at least 4 weeks prior to randomization. If taking oral glucocorticoids, being on a stable dose equivalent to ≤ 10 mg prednisolone for at least 4 weeks prior to randomization;
		• Female patients who were not pregnant or nursing at screening and who were not planning to become pregnant from screening until 2 months after the last dose of study drug.

	Exclusion Criteria	• Have been treated previously with any biological agents including any tumour necrosis factor inhibitor • Have a known hypersensitivity to human immunoglobulin proteins or other

	Characteristics	Details for SB4-G31-RA (Randomized, Double-blind)

		components of Enbrel® or Brenzys
		• Had abnormal renal or hepatic function at Screening defined as the following:
		  • Serum creatinine ≥ 2 × the upper limit of normal (ULN).
		  • Serum alanine aminotransferase (ALT) or aspartate aminotransferase ≥ 2 × ULN.
		• Have a positive serological test for hepatitis B or hepatitis C or have a known history of infection with human immunodeficiency virus
		• Have a current diagnosis of active tuberculosis
		• Have been recently exposed to a person with active tuberculosis, or are considered to have latent TB from the screening tests (QuantiFERON® Gold test and chest X-ray). If such subjects complete at least 30 days of isoniazid prophylaxis or other anti-TB therapy according to country-specific guidelines and are willing to complete the entire course of recommended anti-TB therapy they may be enrolled into the study following re-screening.
		• Have had a serious infection or have been treated with intravenous antibiotics for an infection within 8 weeks or oral antibiotics within 2 weeks prior to Randomization.
		• Had a history of an infected joint prosthesis which had not been removed or replaced.
		• Have any of the following conditions
		  • Other inflammatory or rheumatic diseases.
		  • History of any malignancy within the previous 5 years prior to Screening
		  • History of lymphoproliferative disease including lymphoma.
		  • History of congestive heart failure
		  • Physical incapacitation (ACR functional Class IV or wheelchair-/bed-bound).
		  • History of demyelinating disorders.

Drugs	**Intervention**	• Brenzys (Brenzys; etanercept biosimilar), 50 mg, s.c., administered once weekly for up to 52 weeks. • All patients had to take methotrexate (10–25 mg/week) and folic acid (5–10 mg/week) during the study.
	Comparator(s)	• EU-sourced Enbrel® (etanercept), 50 mg, s.c., administered once weekly for up to 52 weeks. • All patients had to take methotrexate (10–25 mg/week) and folic acid (5–10 mg/week) during the study.
Duration	**Run-in**	6-week screening
	Treatment	52 weeks
	Follow-up	4 weeks (for those that did not enter the extension period)
Outcomes	**Primary End Point(s)**	• ACR20 response at Week 24.

	Other End Points	• ACR20 response at Week 52
		• ACR50 response at Week 24 and Week 52
		• ACR70 response at Week 24 and Week 52
		• Disease activity score based on a 28 joint count (DAS28) at Week 24 and Week 52
		• EULAR response at Week 24 and Week 52
		• Modified total Sharp score (change from baseline to Week 52)
		• Patients with adverse events/serious adverse events up to Week 56
		• Major PK Endpoints:
		  • Ctrough (serum concentration prior to dosing) up to Week 24
		  • Week 8
		  • AUC_{τ} (area under the concentration-time curve during the dosing interval)

	Characteristics	Details for SB4-G31-RA (Randomized, Double-blind)
		• C_{max} • C_{min} (minimum concentration) • peak-trough concentration ratio • C_{av} (average serum concentration during the dosing interval) • T_{max} • $T_{1/2}$
Notes	**Publications**	• Emery P, Vencovsky J, Sylwestrzak A, Leszczynski P, Porawska W, Baranauskaite A, et al. A phase III randomised, double-blind, parallel-group study comparing Brenzys with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2015 (20). (Please note that this publication is based on the 24-week CSR, and not the 52-week CSR provided in this submission. The 24-week CSR can be provided upon request). • Vencovsky J, Sylwestrzak A, Leszczynski P, Porawska W, Baranauskaite A, Tseluyko V, et al. A Phase III randomised, double-blind clinical study comparing Brenzys, an etanercept biosimilar, with etanercept reference product (Enbrel®) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy (24-week results). Ann Rheum Dis. 2015;74(Suppl2):467-8. (EULAR 2015 Poster) (21) • Vencovsky J, Sylwestrzak A, Leszczynski P, Porawska W, Baranauskaite A, Tseluyko V, et al. A Phase III randomised, double-blind clinical study comparing Brenzys, an etanercept biosimilar, with etanercept reference product (Enbrel®) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy (52-week results). ACR 2015; November 6-11, 2015; San Francisco, CA. (22) • NCT01895309 • EudraCT 2012-005026-30

Intervention and Comparators

Interventions Employed (e.g., Dose, Route and Frequency of Administration, Duration, Etc.)

At Week 0, eligible patients were randomized in a 1:1 ratio to receive 50 mg PFS of either Brenzys or EU-Enbrel®. Each patient self-administered etanercept 50 mg s.c. once weekly up to Week 51 (corresponding with up to 52 administrations of etanercept).

Reference Products Used

All batches of the reference product, Enbrel®, used in the trial, were sourced from the EU.

Placebos and Controls (If Applicable)

An active comparator (Enbrel®) was used in this trial; therefore, no placebo was used.

Concomitant Medications

All patients had to take oral or parenteral MTX (10–25 mg/week) and folic acid (5–10 mg/week) during the study.

Outcomes (Key Efficacy and Safety Outcomes)

ACR20: The primary endpoint was the ACR20 response at Week 24, through which therapeutic equivalence (as per study protocol definition) was to be established if the 95% CI of the adjusted treatment difference between Brenzys and Enbrel® was entirely contained within the equivalence margin of −15% to 15%.

The ACR20 response indicated:

- At least a 20% improvement from baseline in swollen joint count (66 joint count)
- At least a 20% improvement from baseline in tender joint count (68 joint count).
- At least a 20% improvement from baseline in at least three of the following five criteria:
  - Subject pain assessment using a 100 mm visual analogue scale (VAS)
  - Subject global assessment using a 100 mm VAS
  - Physician global assessment using a 100 mm VAS
  - Subjects assessment of disability using the Health Assessment Questionnaire - Disability Index (HAQ-DI)
  - Acute-phase reactant level (CRP) (23).

ACR20 time-response model up to 24 weeks: estimated separate time-response curves for each treatment group over the time course of the study.

ACR20, ACR50, ACR70: ACR20 at Week 52, ACR50 at Weeks 24 and 52; and ACR70 at Weeks 24 and 52

ACR-N at Week 52**:** The ACR-N provides a single number that characterizes the percentage of improvement from baseline that a patient has experienced in analogy to ACR20, ACR50, and ACR70 responses. Thus, patients with an ACR-N of 20 just meet but do not exceed criteria for an ACR20 response, patients with an ACR-N of 50 just meet criteria for an ACR50 response, and patients with an ACR-N of 70 meet but do not exceed criteria for an ACR70 response. To generalize, a patient with an ACR-N of X (e.g., 38) means that the patient has achieved an improvement of at least X% (e.g., 38%) in tender and swollen joints and an improvement of at least X% (e.g., 38%) in 3 of the 5 other parameters (24).

Disease activity score based on a 28-joint count (DAS28) at Weeks 24 and 52: The DAS28 score was calculated using the following equation (four-variable equation):

DAS28 = 0.56 × √(tender 28 joint count) + 0.28 × √(swollen 28 joint count) + 0.70 × ln(ESR) + 0.014 × general health.

General health was subject global assessment using a 100 mm VAS (25-27).

Change from baseline in DAS28 was considered to be equivalent between Brenzys and Enbrel® if the 2-sided 95% CI of the difference in DAS28 score between Brenzys and Enbrel® was entirely contained within the equivalence margin of [-0.6, 0.6].

AUC of Changes in DAS28 at Week 24, which was Base - Value

European League Against Rheumatism (EULAR) response criteria at Weeks 24 and 54:
The EULAR response was based upon the DAS28 score. Subjects were classified as having either a good, moderate or no response based on the following (28):

DAS28 at Endpoint	Improvement in DAS28 From Baseline		
	> 1.2	≤ 1.2 and > 0.6	≤ 0.6
≤ 3.2	Good response	Moderate response	No response
> 3.2 and ≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

Health Assessment Questionnaire-Disability Index (HAQ-DI) at baseline, Weeks 24 and 52**:** The HAQ-DI assesses physical function of the subject. Specifically, it assesses the degree of difficulty a person has had in accomplishing tasks in eight functional areas (1. dressing and grooming; 2. arising; 3. eating; 4. walking; 5. hygiene; 6. reach; 7. grip; and 8. common daily activities) over the previous 7 days, taking into account any aids or help required. Each question asks on a scale ranging from 0 to 3 if the categories can be performed without any difficulty (scale 0) up to cannot be done at all (scale 3) (29, 30).

Modified total Sharp score (mTSS) change from baseline to Week 52: mTSS is calculated from joint erosion score plus joint space narrowing score (31). The joint erosion score is a summary of erosion severity in 32 joints of the hands and 12 joints of the feet. Each joint is scored, according to the surface area involved, from 0 to 5, with 0 indicating no erosion, 1 indicating discrete erosions, 2 to 3 indicating larger erosions according to surface area involved, 4 indicating erosions extending over middle of the bone and 5 indicating extensive loss of bone from more than one half of the articulating bone. Because each side of a foot joint is graded on this scale, the maximum joint erosion score for a foot joint is 10. Thus, the maximal joint erosion score is 280. The JSN score summarizes the severity of JSN in 30 joints of the hands and 12 joints of the feet. Assessment of JSN, including subluxation, is scored from 0 to 4, with 0 indicating normal, 1 indicating focal or doubtful, 2 indicating generalized, less than 50% of the original joint space, 3 indicating generalized, more than 50% of the original joint space or subluxation and 4 indicating bony ankylosis or complete luxation. The score for JSN ranges from 0 to 120 in the hands and from 0 to 48 in the feet. Thus, the maximal JSN score is 168 and the worst possible mTSS is 448.

Immunogenicity: Blood samples for determination of immunogenicity were collected at baseline and Weeks 2, 4, 8, 12, 16, 24, and 52. MSD electrochemiluminescence (ECL) bridging assay (Meso Scale Discovery, Rockville, MD, USA) with acid dissociation was used to establish the cut points and to determine ADA in human RA serum.

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

The tiered approach for ADA determination was used. After the screening assay, the confirmatory assay was performed for ADA determination. The cut point for a screened positive signal was set with 5% false-positive rate and for a confirmed positive it was set with 0.01% false-positive rate.

Safety: All reported terms for AEs were coded using the Medical Dictionary for Regulatory Activities (MedRA). A treatment-emergent AE (TEAE) was defined as any AE with an onset date on or after the date of first dose of IP until the Follow-up Visit. AEs, which were already present during the pre-treatment period but increased in severity during the treatment period were considered as TEAEs. Pre-existing AEs before the treatment period with no increase in severity during the treatment period were not considered as TEAEs. Laboratory data, data from other tests (e.g., vital signs, twelve-lead ECG, etc.) were also recorded.

Statistical Analyses

Statistics Protocol for Equivalence Testing

Primary Endpoint (ACR20 at Week 24): Equivalence between the two treatment groups was declared if the 95% confidence interval (CI) of the difference of the two proportions was entirely contained within the equivalence margin of [–15%, 15%]. The 95% CI of the difference between the two treatment groups

in relation to the percentage of patients achieving an ACR20 response was estimated for the per-protocol set 1 (PPS1; see *Analysis Sets* below for definition), stratified by pooled study centres (or region) using the Mantel-Haenszel weights for the strata while adjusting for the baseline CRP non-parametrically. As sensitivity analysis, the same analysis was repeated for the full analysis set (FAS) to explore the robustness of the results. Patients who dropped out of the study prematurely were treated as non-responders in the analysis.

Supportive Analysis of Primary Efficacy Analysis — Time-Response Model: The time-response model estimated separate time-response curves for each treatment group over the time course of the study; and was used as a supportive analysis to the primary assessment of equivalence. The equivalence between the 2 treatments was declared if the 95% CI for the 2-norm of the difference in time-response functions was less than the pre-specified equivalence margin of 83.28.

Change from Baseline in DAS28: An ANCOVA model of change from baseline in DAS28 at Week 24 with treatment group and region as factors and the baseline DAS28 value as a covariate was used to test the treatment difference of Brenzys versus Enbrel®. The difference in the LSMeans, standard error and 2-sided 95% CI for the treatment difference were reported for FAS. The equivalence in the change of DAS28 was determined if the 2-sided 95% CI of the difference in DAS28 score between Brenzys and Enbrel® was entirely contained within the equivalence margin of [-0.6, 0.6].

Rationale for the Equivalence Margins Used

ACR20 at Week 24: The ACR20 responses from selected studies with regards to study population and treatment regimen were used for the equivalence margin and sample size calculation (Table 4).

TABLE 4: ACR20 RESPONSES IN PIVOTAL STUDIES IN ENBREL®

	ACR20 Response Events/Total (%)		Absolute Difference EU-Enbrel® – Placebo (%)	Time Measurement	DMARD
	EU-Enbrel®	Placebo			
Weinblatt et al. (32)	42/59 (71%)	8/30 (27%)	44%	24 weeks	MTX
Combe et al. (33)	74/100 (74%)	14/50 (28%)	46%	24 weeks	Sulfasalazine
Keystone et al.* (34)	95/192 (49%)	5/29 (17%)	32%	8 weeks	MTX
Overall	211/351 (60%)	27/109 (25%)	35%		

ACR20: American College of Rheumatology 20% response criteria; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate.

* Data only represent results from subjects continuing MTX treatment. For Enbrel® the subjects groups receiving 25 mg twice weekly and 50 mg once per week have been combined.

Source: CTD 2.7.3, Table 2.

A random-effects meta-analysis estimates a risk difference of 0.4049 with a 95% CI (0.3103, 0.4996). To preserve at least 50% of the effect of EU-Enbrel® over and above placebo, an equivalence limit of 15% was used for the primary analysis.

The equivalence margin of −15% to 15% at week 24 for ACR20 response rate was also in line with the US FDA Guidance for Industry Non-Inferiority Clinical Trials and the CHMP Guideline on the Choice of the Non-inferiority Margin and was also agreed with the regulatory agencies (35, 36).

Times Response Model: Using the time-response modelling on the historical data, the 95% CI for the 2-norm of the treatment difference was calculated as (166.56, 279.90). The equivalence margin was defined as 83.28, which was half of the lower bound of the 95% CI for the treatment effect. Therefore, the equivalence was concluded if the upper limit of 95% CI for the 2-norm of the difference between Brenzys and Enbrel® was less than 83.28.

Change from Baseline in DAS28: The equivalence limit of the change in DAS28 was chosen as 0.6, which is half of the minimum score of clinically significant improvement (1.2) in DAS28. Therefore, the equivalence in the change of DAS28 was determined if the 2-sided 95% CI of the difference in DAS28 score between Brenzys and Enbrel® was entirely contained within the equivalence margin of [-0.6, 0.6]. With the planned 438 subjects, over 90% of power was estimated to give the equivalence margin.

Analysis Sets (e.g., Intention to Treat or Per-protocol)

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

It should be noted here that all summaries of secondary efficacy variables except ACR50 response and ACR70 response were based on the available data analysis for FAS.

Per-protocol Set 1 (PPS1) consisted of all FAS who completed the Week 24 visit and had an adherence (from baseline to Week 24) within the range 80-120% of both the expected number of study drug injections and the expected sum of MTX doses without any major protocol deviations that affected the efficacy assessment. The PPS1 was the primary analysis set. Major protocol deviations that led to exclusion from this set were pre-specified prior to unblinding the treatment codes for analyses.

Per-protocol Set 2 (PPS2) consisted of all FAS subjects who completed the Week 52 visit and had an adherence (from baseline to Week 52) within the range 80-120% of both the expected number of IP injections and the expected sum of MTX doses without any major PDs that affected the efficacy assessment.

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

Pharmacokinetic Population (PK population): PK sub-population consisted of all subjects in the SAF who had at least one post-dose PK sample collected. PK sub-population was selected during site selection stage based on sites interested in taking part in the PK sub-study and were also fully equipped as per study requirements.

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

- For the description of the statistics protocol for therapeutic equivalence testing, please refer to CTD Modules 2.5 (p.31-32) and 2.7.3 (p.12-13); CSR SB4-G31-RA, sections 9.7.1.6.1, 9.7.1.6.2.
- For the description of the rationale for the therapeutic equivalence margins used, please refer to CTD Module 2.7.5 (p.31-32) ; CSR SB4-G31-RA, sections 9.7.1.6.1, 9.7.1.6.2.

- For description of the analysis set, please refer to CTD Modules 2.7.2 (p.6-7), 2.7.3 (p.12), 2.7.4 (p.10); CSR SB4-G31-RA, section 9.7.1.1.
- The selection process of the PK sub-population was from an internal correspondence.

b) Results

Baseline Characteristics

TABLE 5: MAJOR DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR STUDY SB4-G31-RA

	Brenzys 50 mg N=299		EU-Enbrel® 50 mg N=297		Total N=596	
Age (years)	52.1	(11.72)	51.6	(11.63)	51.8	(11.67)
Gender n (%)						
Male	50	(16.7)	44	(14.8)	94	(15.8)
Female	249	(83.3)	253	(85.2)	502	(84.2)
Race, n (%)						
White	279	(93.3)	273	(91.9)	552	(92.6)
American Indian or Alaskan Native	5	(1.7)	7	(2.4)	12	(2.0)
Asian	11	(3.7)	13	(4.4)	24	(4.0)
Other	4	(1.3)	4	(1.3)	8	(1.3)
Ethnicity n (%)						
Hispanic or Latino	18	(6.0)	19	(6.4)	37	(6.2)
Other	281	(94.0)	278	(93.6)	559	(93.8)
Weight (kg)	72.51	(15.926)	70.98	(14.631)	71.75	(15.300)
Height (cm)	164.39	(8.781)	164.37	(8.551)	164.38	(8.660)
BMI (kg/m^2)	26.81	(5.511)	26.32	(5.296)	26.57	(5.406)
Disease duration (years)	6.03	(4.201)	6.16	(4.405)	6.09	(4.301)
Duration of MTX use (months)	48.19	(39.887)	47.10	(40.727)	47.65	(40.277)
Weekly dose of MTX at baseline (mg)	15.59	(4.520)	15.46	(4.597)	15.53	(4.555)
Swollen joint count (0-66)	15.4	(7.48)	15.0	(7.30)	15.2	(7.39)
Tender joint count (0-68)	23.5	(11.90)	23.6	(12.64)	23.5	(12.26)
Physician global assessment VAS (0-100)	62.2[a]	(15.09)	63.2[b]	(14.76)	62.7[c]	(14.92)
Patient global assessment VAS (0-100)	61.7[d]	(18.97)	63.0	(17.70)	62.4[e]	(18.35)
Patient pain assessment VAS (0-100)	61.8[d]	(20.22)	62.3	(19.22)	62.1[e]	(19.71)
HAQ-DI (0-3)	1.4904[d]	(0.55292)	1.5097	(0.55983)	1.5000[e]	(0.55600)
C-reactive protein (mg/L)	14.6	(20.01)	12.7	(15.97)	13.7	(18.12)
C-reactive protein n (%)*						
≥ 10 mg/L	121	(40.5)	114	(38.4)	235	(39.4)
< 10 mg/L	178	(59.5)	183	(61.6)	361	(60.6)
Erythrocyte sedimentation rate (mm/h)	46.5	(22.10)	46.4	(22.62)	46.5	(22.34)
Rheumatoid factor n (%)*						
Positive	237	(79.3)	231	(77.8)	468	(78.5)
Negative	62	(20.7)	66	(22.2)	128	(21.5)

[a] n=296; [b] n=291; [c] n=587; [d] n=298; [e] n=595.

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

Source: CTD 2.7.3, Tables 4–6.

Similarity/Differences

The demographic characteristics, baseline characteristics, and baseline disease characteristics were comparable and well balanced between the treatment groups with no significant differences between groups. The majority of patients were females and white.

Concomitant Conditions/Medications

[redacted]

A similar proportion of patients in the Brenzys and EU-Enbrel® treatment groups (46.2% vs. 46.8%) had taken medication, which started and stopped prior to the study (i.e., prior medication), and the majority of patients received concomitant medication during the study (95.0% vs. 97.0%). Reflective of the study population, the most commonly used prior medications were glucocorticoids (23.1% vs. 22.6% of patients), also used by more than half of patients during the study (56.5% vs. 56.9%).

The use of prohibited prior or concomitant medications was reported in 5.5% of patients: 5.0% in the Brenzys treatment group used 21 prohibited medications and 6.1% in the EU-Enbrel® treatment group used 34 prohibited medications. The most commonly used prohibited medications were glucocorticoids (7 events in 4 subjects in the Brenzys treatment group and 7 events in 5 subjects in the EU-Enbrel® treatment groups), acetic acid derivatives and related substances (2 events in 2 patients vs. 11 events in 6 patients) and other opioids (5 events in 5 patients vs. 8 events in 4 patients).

Patient Disposition

A total of 596 patients with moderate to severe RA despite MTX therapy were randomized. A total of 551 (92.4%) patients completed 24 weeks and 505 (84.7%) patients completed 52 weeks of the study. All randomized patients were included in the FAS, of which 483 (81.0%) patients were included in PPS1. 440 (73.8%) patients were included and analysed in the PPS2.

Prior to Week 24, 45 (7.6%) patients withdrew, with 16 patients (5.4%) from the Brenzys and 29 (9.8%) from the EU-Enbrel® treatment group. In both treatment groups, the most common reasons for withdrawal were adverse events (AEs) (3.7%) and withdrawal of consent (2.7%).

Prior to Week 52, 91 (15.3%) patients withdrew (40 [13.4%] patients from Brenzys vs. 51 [17.2%] patients from the EU-Enbrel® treatment group; counting those withdrew prior to Week 24). In both treatment groups, the most common reasons for withdrawal were again AEs (5.0%) and withdrawal of consent (4.5%) (Table 6).

TABLE 6: SUMMARY OF PATIENT DISPOSITION FOR STUDY SB4-G31-RA (RANDOMIZED, DOUBLE-BLIND)

Disposition	SB4-G31-RA (Randomized, Double-Blind)		
	Brenzys (50 mg)	Enbrel® (50 mg)	Total
Screened, N	777		
Randomized, N	299	297	596
Completed Week 24 of treatment, N (%)	283 (94.6%)	268 (90.2%)	551 (92.4%)
Discontinued (prior to Week 24), N (%)	16 (5.4%)	29 (9.8%)	45 (7.6%)
WDAEs, N (%)	8 (2.7%)	14 (4.7%)	22 (3.7%)
Protocol deviation, N (%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
Lack of efficacy, N (%)	0 (0.0%)	3 (1.0%)	3 (0.5%)

Disposition	SB4-G31-RA (Randomized, Double-Blind)		
	Brenzys (50 mg)	Enbrel® (50 mg)	Total
Investigator discretion, N (%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Withdrew consent, N (%)	5 (1.7%)	11 (3.7%)	2.7 (2.7%)
Completed Week 52 of treatment, N (%)	259 (86.6%)	246 (82.8%)	505 (84.7%)
Discontinued (prior to Week 52), N (%)*	40 (13.4%)	51 (17.2%)	91 (15.3%)
WDAEs, N (%)	13 (4.3%)	17 (5.7%)	30 (5.0%)
Protocol deviation, N (%)	1 (0.3%)	0 (0%)	1 (0.2%)
Lack of efficacy, N (%)	1 (0.3%)	3 (1.0%)	4 (0.7%)
Subject lost to follow-up, N (%)	1 (0.3%)	3 (1.0%)	4 (0.7%)
Investigator discretion, N (%)	15 (5.0%)	10 (3.4%)	25 (4.2%)
Withdrew consent, N (%)	9 (3.0%)	18 (6.1%)	27 (4.5%)
Full Analysis Set, N	299	297	596
Per-Protocol Set 1, N	247	236	483
Per-Protocol Set 2, N	224	216	440
Pharmacokinetic Set, N	41	38	79
Safety, N	299	297	596

* Includes those discontinued prior to Week 24.
SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: CTD 2.7.2; CTD 2.7.3, Table 3; CTD 2.7.4, Table 2.

Efficacy Results

ACR20 at Week 24

The primary endpoint of study SB4-G31-RA was the ACR20 response at Week 24, through which therapeutic equivalence (as per study protocol definition) was to be established if the 95% CI for the treatment difference between Brenzys and Enbrel® was within ±15%. Results from both the PPS1 and FAS showed highly comparable response ACR20 response rates at Week 24 between Brenzys and Enbrel® (PPS1: 78.1% vs. 80.5%, respectively; FAS: 73.6% vs. 71.7%, respectively). The 95% CIs of the adjusted difference rates falling within the predefined equivalence margin of ±15% for both PPS1 and FAS (-9.54%, 4.80% and -5.50%, 8.82%, respectively) (Table 7). Additional analyses of ACR20 at Week 24 by Table 32 in Appendix 1. No significant interactions in response rates between ADA status as well as baseline CRP levels with treatment were observed. As the sensitivity analysis to the non-parametric method for the primary endpoint, the analysis of covariance (ANCOVA) with treatment group and region as factors and the baseline CRP value as a covariate showed similar results with the primary analysis.

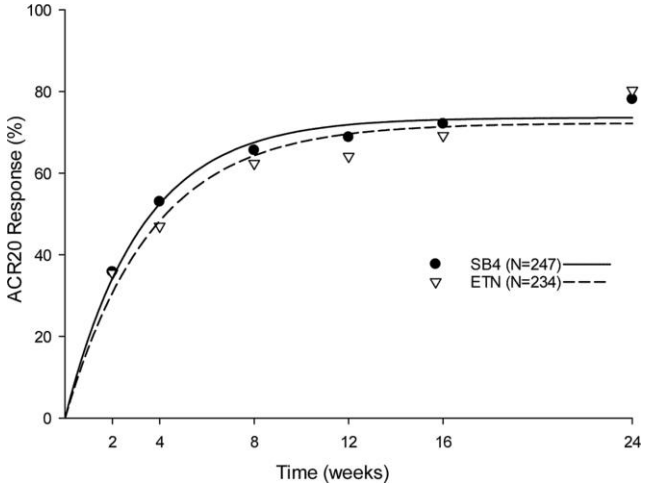
TABLE 7: ACR20 RESPONSE RATE AT WEEK 24 FOR STUDY BRENZYS-R31-RA (PPS1 AND FAS)

Population	n/N (%)		Adjusted Difference Rate	95% CI
	Brenzys 50 mg	Enbrel® 50 mg		
PPS1	193/247 (78.1)	190/236 (80.5)	-2.37%	-9.54%, 4.80%
FAS[a]	220/299 (73.6)	213/297 (71.7)	1.66%	-5.50%, 8.82%

N: number of patients in either the PPS1 or FAS; n: number of responders.
[a] For the FAS, patients with missing ACR20 at Week 24 were considered as non-responders at Week 24.
Source: CTD 2.7.3, Tables 7, 8.

To further demonstrate the robustness of the primary efficacy analysis, time-response curves for ACR20 response (PPS1) for Brenzys and Enbrel® were constructed (37). Results showed that over the course of the first 24 weeks of treatment, the ACR20 response between Brenzys and Enbrel® can be considered as highly comparable (Figure 1). The 2-norm (which can be viewed as the response difference between the two treatments over time course) of the treatment difference was 10.8 and the 95% CI of the treatment difference was (–6.2, 27.9), where the upper limit 27.9 was less than the pre-specified equivalence margin of 83.28.

FIGURE 1: TIME-RESPONSE MODEL FOR ACR20 RESPONSE UP TO WEEK 24 (PPS1) FOR STUDY SB4-G31-RA



Source: CTD 2.7.3, Fig. 3.

Subgroup analyses in PPS1 showed similar proportion of ADA-negative patients achieving ACR20 response at Week 24 (adjusted treatment difference [95% CI]: −3.74% [–11.27%, 3.79%], which was within the equivalence margin of [–15%, 15%]). In the ADA-positive group, the adjusted treatment difference and its 95% CI in ACR20 response rate at Week 24 was 22.14% (–54.79%, 99.07%), although only 2 subjects in the Brenzys group was ADA positive vs. 21 in the EU-Enbrel® group. Overall, there was no significant interaction in ACR20 response rate at Week 24 between treatment and overall post-dose ADA status at Week 24 (p = 0.293).

There was also no significant interaction in ACR20 response rate at Week 24 between treatment and baseline CRP level (≥ 10 mg/L and < 10 mg/L; p = 0.708)

Therefore, based on the primary outcome, it can be concluded that Brenzys is therapeutically similar to Enbrel®.

Other ACR Responses

In this study, several other ACR response endpoints were also evaluated, which included ACR20 at Week 52, ACR50 at Weeks 24 and 52, ACR70 at Weeks 24 and 52, as well as ACR-N at Weeks 24 and 52. The results for these ACR response rates are presented for both the PPS1/2 (Table 8) and the FAS (Table 9). All ACR response rates for both the PPS1/2 and the FAS at different time points were highly comparable, with the 95% CI of the adjusted difference rates within the equivalence margin of ±15% defined for the primary endpoint (with the exception of ACR50 at Week 52 for the PPS2). These results further supported the therapeutic similarity between Brenzys and Enbrel®.

TABLE 8: ACR RESPONSE RATES FOR STUDY SB4-G31-RA (PPS)

ACR Response	Time Point	Treatment (Brenzys 50 mg) (Enbrel® 50 mg)	n/n'	(%)	Adjusted Difference Rate	95% CI
ACR20[a]	Week 52[b]	Brenzys (N=224)	181/224	(80.8)	[redacted]	[redacted]
		Enbrel® (N=216)	176/216	(81.5)		
ACR50[c]	Week 24[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52[b]				[redacted]	[redacted]
ACR70[e]	Week 24[d]				[redacted]	[redacted]
	Week 52[b]				[redacted]	[redacted]

[a] ACR20: American College of Rheumatology 20% response criteria; [b] PPS2;
[c] ACR50: American College of Rheumatology 50% response criteria; [d] PPS1.
[e] ACR70: American College of Rheumatology 70% response criteria.
CI: confidence interval; N: number of patients in the per-protocol set 1 or 2; n': number of patients with an assessment; n: number of responders.
Source: CTD 2.7.3, Tables 9-11, Section 3.2.2.

TABLE 9: ACR RESPONSE RATES FOR STUDY SB4-G31-RA (FAS)

ACR Response	Time Point	Treatment (Brenzys 50 mg, N=299) (Enbrel® 50 mg, N=297)	n/N	(%)	Adjusted Difference Rate	95% CI
ACR20[a]	Week 52[b]	Brenzys	210/299	70.2	4.48%	-2.90%, 11.87%
		Enbrel®	195/297	65.7		
ACR50[c]	Week 24[b]	Brenzys	128/299	42.8	3.84%	-3.91%, 11.60%
		Enbrel®	116/297	39.1		
	Week 52[b]	Brenzys	143/299	47.8	5.48%	-2.32%, 13.29%
		Enbrel®	125/297	42.1		
ACR70[d]	Week 24[b]	Brenzys	69/299	23.1	3.25%	-3.20%, 9.70%
		Enbrel®	59/297	19.9		
	Week 52[b]	Brenzys	91/299	30.4	5.90%	-1.12%, 12.93%
		Enbrel®	73/297	24.6		
ACR-N[e]	Week 24[b]	Brenzys	287[f]/299	45.03	1.8%[g]	-2.8%, 6.4%
		Enbrel®	272[f]/297	43.72		
	Week 52[b]	Brenzys	259[f]/299	52.08	3.2%[g]	-2.0%, 8.4%
		Enbrel®	246[f]/297	49.17		

[a] ACR20: American College of Rheumatology 20% response criteria; [b] patients with missing ACR20 at Week 52 were considered as non-responders at Week 52.
[c] ACR50: American College of Rheumatology 50% response criteria.
[d] ACR70: American College of Rheumatology 70% response criteria.
[e] ACR-N: Numeric index of the ACR response; [f] number of patients with an assessment; [g] treatment difference in the Least Square Means (LSMeans).
Patients with missing ACR20, ACR50 or ACR70 responses at Week 24 or Week 52 were considered as non-responders at the corresponding week.
CI: confidence interval; N: number of patients in the FAS; n: number of responders.
Source: CTD 2.7.3, Section 3.2.2.

ACR-N AUC

The mean AUC of ACR-N up to Week 24 was 5822.252 in the Brenzys treatment group vs. 5525.212 in the EU-Enbrel® treatment group (FAS) [redacted]

Major Clinical Response

Finally, the major clinical response rate (maintenance of an ACR70 response over a 6-consecutive month period) at Week 52 for the FAS was [redacted] in the Brenzys patients and [redacted] in Enbrel® patients. These results demonstrated that the proportion of patients achieving major clinical response at Week 52 was comparable between the two treatment groups.

DAS28

Similar to ACR responses, the DAS28 (FAS) results were also highly comparable between the Brenzys and EU-Enbrel® group (Table 10). The 95% CI of treatment difference in the LSMeans at both Weeks 24 and 52 were contained within the equivalence margin of ±0.6. Therefore, DAS28 results further supported the therapeutic similarity between Brenzys and Enbrel®.

TABLE 10: MEAN CHANGE IN DAS28 SCORES FROM BASELINE IN STUDY SB4-G31-RA (FAS)

	Time Point	Treatment (Brenzys 50 mg, N=299) (Enbrel® 50 mg, N=297)	n/N	Mean Change	LSMeans Difference	95% CI
FAS	Week 24	Brenzys	287/299	2.5697	0.072	-0.135, 0.279
		Enbrel®	272/297	2.5037		
	Week 52	Brenzys	259/299	2.9108	0.118	-0.092, 0.328
		Enbrel®	246/297	2.7990		

LSMeans: Least Square Means; N: number of subjects in the FAS; n: number of subjects with assessment.
Source: CTD 2.7.3, Section 3.2.2.

AUC of the Change in DAS28 From Baseline Up to Week 24

The mean AUC of the change in DAS28 score from Baseline up to Week 24 was 358.2569 in the Brenzys treatment group and 343.5417 in the EU-Enbrel® treatment group (FAS). The adjusted treatment difference in LSMeans and its 95% CI was [redacted] which showed that the AUC of DAS28 up to Week 24 was comparable between the Brenzys and EU-Enbrel® treatment groups.

EULAR

The proportion of subjects who had good, moderate and no response was generally comparable between the Brenzys and EU-Enbrel® treatment groups at Week 24 and Week 52 (Table 11).

TABLE 11: EULAR RESPONSE RATE IN STUDY SB4-G31-RA (FAS)

	Time Point	Treatment (Brenzys 50 mg, N=299) (Enbrel® 50 mg, N=297)	Response (%)		
			Good	Moderate	No
FAS	Week 24	Brenzys	[redacted]	[redacted]	[redacted]
		Enbrel®	[redacted]	[redacted]	[redacted]
	Week 52	Brenzys	[redacted]	[redacted]	[redacted]
		Enbrel®	[redacted]	[redacted]	[redacted]

LSMeans: Least Square Means; N: number of patients in the FAS.
Source: CTD 2.7.3, Section 3.2.2.

HAQ-DI

Results for the physical function test as assessed by HAQ-DI are provided in Table 12. Overall, results showed highly comparable degree of physical function between treatment groups at different assessment time points.

TABLE 12: SUMMARY OF PHYSICAL FUNCTION TEST RESULTS AT BASELINE, WEEKS 24 AND 52 FOR STUDY SB4-G31-RA (FAS)

HAQ-DI (0-3)		Brenzys 50mg (N=299)	Enbrel® 50mg (N=297)
Baseline	n	298	297
	Mean (SD)	1.4904 (0.55292)	1.5097 (0.55983)
	Min, Max	0.000, 3.000	0.000, 2.875
Week 24	n	287	272
	Mean (SD)	0.8541 (0.60771)	0.8616 (0.60612)
	Min, Max	0.000, 2.875	0.000, 2.750
Week 52	n	259	246
	Mean (SD)	0.7674 (0.59791)	0.7973 (0.65357)
	Min, Max	0.000, 2.750	0.000, 2.625

HAQ-DI: Health Assessment Questionnaire-Disability Index; SD: standard deviation; Min: minimum; Max: maximum
Source: Brenzys Product Monograph, Table 18

Joint Damage

The change from baseline in mean modified total Sharp score (mTSS) was comparable between the Brenzys and Enbrel® treatment groups (0.45 and 0.74, respectively) at Week 52 (Table 13). The mean change in mTSS at Week 52 and 95% CI was –0.27 and (–0.80, 0.26), demonstrating prevention of radiographic progression to a comparable extent between Brenzys and Enbrel® treatment groups.

TABLE 13: SUMMARY OF STRUCTURAL JOINT DAMAGE AT WEEK 52 FOR STUDY SB4-G31-RA (FAS)

	Brenzys 50 mg (N=299)	Enbrel® 50 mg (N=297)
Modified total Sharp score, mean (SD)		
n	250	228
Week 0	43.26 (67.083)	38.88 (53.256)
Week 52	43.70 (67.081)	39.62 (53.414)
Change	0.45 (2.497)	0.74 (3.356)
Joint erosion score, mean (SD)		
n	250	228
Week 0	24.01 (39.625)	20.52 (28.324)
Week 52	24.28 (39.547)	20.84 (28.391)
Change	0.26 (1.608)	0.31 (1.677)
Joint space narrowing score, mean (SD)		
n	250	228
Week 0	19.24 (28.834)	18.35 (26.479)
Week 52	19.43 (28.936)	18.78 (26.550)
Change	0.18 (1.142)	0.43 (2.096)

n: number of completers with available radiographic assessment results at Week 0 and Week 52.
Source: CTD 2.7.3, Table 12.

Safety Results

Adverse Events

1179 TEAEs were reported by total of 354 (59.4%) patients any time after the first dose of the study drugs (Table 14). The number (%) of patients with TEAEs and number of TEAEs that occurred in ≥ 2% of patients are in Table 33 in Appendix 1.

The proportion of subjects that experienced drug-related TEAEs were comparable between the Brenzys and the EU-Enbrel® groups.

In both treatment groups, relatively few subjects experienced SAEs and those SAEs were generally considered unrelated to the study drugs. In the Brenzys group, there were 3 SAEs (in 2 subjects) that were considered related to the study drug (breast cancer in 1 subject, 2 cases of Still's disease in 1 subject). In the EU-Enbrel® group, there were 7 SAEs (in 7 subjects) considered related to the study drug (1 case in 1 subject each: pneumonia, neutropenia, chorioretinopathy, invasive ductal breast carcinoma, erysipelas; 2 cases in 2 subjects: cellulitis).

Overall, the incidence of TEAEs leading to study drug discontinuation was comparable between the Brenzys and EU-Enbrel® treatment groups. The TEAEs leading to discontinuation reported in at least 2 patients were RA (Brenzys: 2 events in 2 [0.7%] patients; EU-Enbrel®: 5 events in 5 [1.7%] patients; 2 [1 in each treatment group] of which were considered to be related to the investigational product) and injection site erythema (Brenzys: 1 event in 1 [0.3%] patient; EU-Enbrel®: 4 events in 4 [1.3%] patients; all of which were considered to be related to investigational product).

Two deaths were reported in the Brenzys group – they were not considered related to the study drug.

TABLE 14: SUMMARY OF TEAES IN STUDY SB4-G31-RA (SAFETY SET)

	Brenzys (N=299)	EU-Enbrel® (N=297)	Total (N=596)
Total number of TEAEs	533	646	1179
[redacted]			
Number (%) of patients with at least 1 TEAE	175 (58.5%)	179 (60.3%)	354 (59.4%)
[redacted]			
Total number of SAEs	23	15	38
Related	3	7	10
Unrelated	20	8	28
Number (%) of patients with at least 1 SAE	18 (6.0%)	15 (5.1%)	33 (5.5%)
Related	2 (0.7%)	7 (2.4%)	9 (1.5%)
Unrelated	16 (5.4%)	8 (2.7%)	24 (4.0%)
[redacted]			
Number (%) of patients with at least 1 AE leading to permanent study treatment discontinuation	16 (5.4%)	20 (6.7%)	36 (6.0%)
Deaths	2 (0.7%)	0 (0.0%)	2 (0.3%)

Source: CTD 2.7.4, Tables 8-12.

Although not presented here, the subgroup analysis of TEAEs by ADA status (positive vs. negative), age (< 65 and ≥ 65 years old), and race/ethnicity revealed that ADA status and race/ethnicity did not impact safety profile between treatments. Furthermore, the proportion of patients who experienced any TEAEs was comparable between the Brenzys and EU-Enbrel® treatment groups within patients aged < 65 years and within patients aged ≥ 65 years. In both treatment groups, the incidence of TEAEs including infections was not higher in patients ≥ 65 years compared to patients < 65 years.

The TEAEs considered causally related to the study drug occurring in ≥ 2% of patients in any treatment group are presented in Table 15. The proportion of patients experiencing each preferred term TEAEs was similar between the Brenzys and the EU-Enbrel® groups. The only notable exception was *Injection Site Erythema*, in which was experienced by 2.0% of subjects in the Brenzys group compared to 11.1% of subjects in the Enbrel® group.

TABLE 15: NUMBER (%) OF PATIENTS WITH TEAES CONSIDERED CAUSALLY RELATED AND NUMBER OF EVENTS BY PREFERRED TERM IN ≥ 2% OF PATIENTS IN STUDY SB4-G31-RA (SAFETY SET)

	Brenzys (N=299)			EU-Enbrel® (N=297)		
Preferred Term	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Any TEAE	175	(58.5)	533	179	(60.3)	646
ALT increased	12	(4.0)	14	11	(3.7)	15
Injection site erythema	6	(2.0)	16	33	(11.1)	84
Upper respiratory tract infection	6	(2.0)	6	4	(1.3)	4
Rheumatoid arthritis	6	(2.0)	7	1	(0.3)	1
AST increased	4	(1.3)	5	6	(2.0)	6
Erythema	2	(0.7)	4	6	(2.0)	6
Injection site rash	2	(0.7)	2	6	(2.0)	11
Injection site reaction	1	(0.3)	1	8	(2.7)	13

ALT: alanine aminotransferase; AST: aspartate aminotransferase; E: frequency of adverse events; TEAE: treatment-emergent adverse event. Percentages were based on the number of patients in the safety set.
Source: CTD 2.7.4, Table 11.

The summary of TEAEs by severity is presented in Table 16. Majority of the TEAEs experienced in both groups were considered to be mild in nature. Comparable proportion of subjects experienced mild and moderate TEAEs across both Brenzys and EU-Enbrel® treatment groups.

[redacted]

TABLE 16: SUMMARY OF TEAES BY SEVERITY IN STUDY SB4-G31-RA (SAFETY SET)

	Brenzys (N=299)			EU-Enbrel® (N=297)		
	n	(%)	E	n	(%)	E
Any TEAE	175	(58.5)	553	179	(60.3)	646
Mild	78	(26.1)	307	91	(30.6)	445
Moderate	83	(27.8)	199	77	(25.9)	189
Severe	14	(4.7)	27	11	(3.7)	12

E: frequency of adverse events; TEAE: treatment-emergent adverse event. Percentages were based on the number of patients in the safety set. When a patient experienced the same event multiple times with different severity, then the patient was counted only once at the maximum severity.
Source: CTD 2.7.4, Table 9.

Injection Site Reactions

There were 179 injection site reactions reported in 63 (10.6%) patients (Brenzys: 22 events in 11 [3.7%] patients; EU-Enbrel®: 157 events in 52 [17.5%] patients) when the high-level group term (HLGT) of *administration site reaction* was regarded as injection site reaction (Table 34 in Appendix 1). Most of the injection site reactions were mild and patients recovered. The most commonly reported injection site reactions at the PT level were injection site erythema (Brenzys: 16 events in 6 [2.0%] patients; EU-Enbrel®: 85 events in 33 [11.1%] patients). Although it is unclear why the incidence of injection site reactions was lower in Brenzys compared with Enbrel®, the difference in drug product formulation and container closure system may have contributed to the lower incidence. The only difference in drug composition between Brenzys and Enbrel® is the absence of L-arginine in Brenzys. It has not been shown that L-arginine is associated with increased risk of injection site reaction; however, we cannot preclude the sole difference in formulation (absence of L-arginine) as the cause of incidence site reaction. In addition, natural rubber latex known to cause hypersensitivity reactions has not been used in the needle shield of Enbrel®. No obvious trend could be discerned when injection site reactions were stratified by ADA status (see CTD 2.7.4, Table 14), which is consistent with previously conducted studies (20, 38).

The same pattern (lower incidence of injection site reactions in Brenzys and no correlation between injection site reaction and ADA development) was observed when injection site reaction was separately assessed for the clinically significant abnormality or abnormality worsening from previous visits. No obvious trend could be discerned when these clinically significant abnormality results were stratified by ADA status (see CTD 2.7.4, Table 15).

Overall, lower incidence of injection site reactions was observed in the Brenzys treatment group compared to the EU-Enbrel® treatment group, whether counted by clinically significant abnormality / abnormality worsening or by HLGT of administration site reaction. Therefore, with limited number of post-dose ADA-positive patients in the Brenzys treatment group, it is difficult to conclude on the relationship between the ADA status and the incidence of injection site reactions. In general, however, no correlation between injection site reaction and ADA development was observed.

Safety of Special Interest – Serious Infections, Tuberculosis

For all anti-TNF agents, infections are of general concern, particularly reactivation of latent tuberculosis (TB) (39). Although study SB4-G31-RA excluded patients exposed to individuals with active tuberculosis, or were considered to have latent TB from the screening tests (see *Exclusion Criteria*) and thus could not be evaluated here, the rate of TB has been reported to be three to four-fold lower in patients receiving etanercept than other anti-TNF agents (39).

In this study, there were 8 TEAEs considered to be of special interest (i.e., classified as serious infection, TB), all were infections. No cases of active tuberculosis were reported. In the Brenzys treatment group, 3 TEAEs of special interest were reported in 1 (0.3%) patient. All were moderate in intensity, not considered to be causally related to the study drug and required hospitalization and discontinuation of study drug.

In the EU-Enbrel® treatment group, 5 (1.7%) patients were each reported 1 TEAE of special interest. Three of these TEAEs were considered to be related to study drug and 1 considered related to investigational product. All ranged between mild to severe in intensity and required hospitalization and were eventually resolved.

Overall, the incidence of TEAEs of special interest was comparable between the Brenzys and EU-Enbrel® treatment groups.

Malignancies

[redacted]

Laboratory Parameters

Hematology

There were no notable differences in mean and median values of hematology parameters observed between the Brenzys and EU-Enbrel® groups. The number of patients reported with at least one post-dose significant abnormality in any hematology parameters up to Week 52 is summarized in Table 38 in Appendix 1. The most commonly reported significant abnormality in haematology was high neutrophil (Brenzys: 5 [1.7%] patients vs. EU-Enbrel®: 2 [0.7%] patients) and low neutrophil and lymphocyte (Brenzys: 3 [1.0%] patients vs. EU-Enbrel®: 4 [1.4%] patients for each abnormality).

[redacted]

Blood Chemistry

There were small increases and decreases in mean and median values for biochemistry parameters (albumin, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, calcium, creatinine, gamma-glutamyl transferase [GGT], lactate dehydrogenase, phosphorus, potassium, sodium and glucose) over time, with no notable difference between the Brenzys and EU-Enbrel® groups. The number of patients reported with at least one post-dose significant abnormality in any biochemistry parameters up to Week 52 is summarized in Table 39 in Appendix 1. The most commonly reported significant abnormality was high ALT (Brenzys: 16 [5.4%] patients; EU-Enbrel®: 10 [3.4%] patients). High AST was reported in 8 (2.7%) vs. 4 (1.4%) patients, respectively, and high GGT was reported in 7 (2.3%) vs. 2 (0.7%) patients, respectively.

[redacted]

[redacted]

Auto-Antibodies

[redacted]

Urinalysis

In both treatment groups, there were no notable changes over time in urinalysis parameters.

[redacted]

Vitals, Physicals, and ECGs

[redacted]

There were no notable differences in incidence of clinically significant abnormal physical examination findings between the Brenzys and EU-Enbrel® treatment groups [redacted]

4.2.3 SB4-G31-RA (Open-label, Extension Period; Top-line Results)

a) Study Characteristics

Brief Description of the Study

The extension period of study SB4-G31-RA was 48-week (followed by a 4-week safety-follow-up), open-labeled, single-armed designed to investigate the long-term safety and immunogenicity, efficacy of Brenzys in those subjects completing the randomized, double-blind period. The extension period is an open-label, single-arm (all subjects to receive Brenzys therapy, including those that received Enbrel® during the 52 weeks in the randomized, double-blind period), subjects enrolled in Poland and the Czech Republic centres [redacted] and completed the 52 week randomized, double-blind portion of the study (and consented to) were invited to enter immediately into the extension

period without a washout period. No etanercept-naïve subjects entered the extension period [redacted]

Characteristics		Details for SB4-G31-RA (Open-label, Extension)
Study Design	**Objective**	Long-term safety and efficacy
	Blinding	Open-label
	Study period	[redacted]
	Study centres	[redacted]
	Design	Extension period of the equivalence study
Study Population	**Randomized (N)**	245 patients from Poland and Czech Republic were enrolled in the open-label phase.
	Inclusion criteria	Subjects from Poland and Czech Republic who met the initial inclusion criteria in the randomized, double-blind period and completed 52-weeks
	Exclusion criteria	Subjects from Poland and Czech Republic who did not met the initial exclusion criteria in the randomized, double-blind period and completed 52-weeks
Drugs	**Intervention**	• Brenzys (Brenzys; etanercept biosimilar), 50 mg, s.c., administered once weekly for up to 52 weeks. • All patients had to take methotrexate (10–25 mg/week) and folic acid (5–10 mg/week) during the study.
	Comparator(s)	None
Duration	**Run-in**	None
	Treatment	48 weeks
	Follow-up	4 weeks
Outcomes	**Primary End Point(s)**	NA
	Other End Points	• To evaluate long-term safety and tolerability of Brenzys in subjects with RA treated previously with Brenzys or Enbrel®. • To evaluate long-term immunogenicity of Brenzys in subjects with RA treated previously with Brenzys or Enbrel®. • To evaluate long-term efficacy of Brenzys in subjects with RA treated previously with Brenzys or Enbrel®
Notes	**Publications**	• Study SB4-G31-RA: 100-week Top Line Summary. 2016. Feb 29, 2016 – Data on file (40) • Emery P, Vencovsky J, Sylwestrzak A, Leszczynski P, Porawska W, Stasiuk B, et al. Long-term safety and efficacy of Brenzys (etanercept biosimilar) in patients with rheumatoid arthritis: comparison between continuing Brenzys and switching from etanercept reference product to Brenzys. EULAR 2016; June 8-11, 2016; London, UK (41). • NCT01895309 • EudraCT 2012-005026-30

Intervention and Comparators

Interventions Employed (e.g., Dose, Route and Frequency of Administration, Duration, Etc.)

All subjects entering the extension period (after completing Week 52) were to receive 50 mg PFS of Brenzys. Each patient self-administered etanercept 50 mg s.c. once weekly up to Week 100 (corresponding with up to 52 administrations of etanercept).

Reference Products Used

All batches of the reference product, Enbrel®, used in the trial, were sourced from the EU.

Placebos and Controls (If Applicable)

No comparators were used in the extension period of the study.

Concomitant Medications

All patients had to take oral or parenteral MTX (10–25 mg/week) and folic acid (5–10 mg/week) during the study.

Outcomes (Key Efficacy and Safety Outcomes)

- **ACR20, ACR50, ACR70 response rates** up to Week 100.
- **DAS28** up to Week 100 and changes from baseline.
- **Immunogenicity** results up to Week 100.
- **Safety:** as in the section 4.2.2 above.

Statistical Analyses

[redacted]

Extended Population consisted of all subjects enrolled into the open-label, extension period.

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

For description of the analysis set, please refer to 100-week Top Line Summary for Study SB4-G31-RA (p.2).

b) Results

Baseline Characteristics

Results currently not available.

Patient Disposition

Out of 596 randomised patients in Study SB4-G31-RA, 505 patients completed 52 weeks of treatment. 245 patients from Poland and Czech Republic were enrolled in the open-label phase. After unblinding, 126 patients were maintained on Brenzys treatment (i.e. Brenzys/Brenzys treatment), and 119 patients who had been treated with Enbrel® were switched to Brenzys treatment (i.e. Enbrel®/Brenzys treatment). No patients were switched from Brenzys to Enbrel® treatment. During the open-label extension period, the rate of withdrawal before Week 100 was similar between the two groups.

TABLE 17: SUMMARY OF PATIENT DISPOSITION FOR STUDY SB4-G31-RA (EXTENSION)

Disposition	SB4-G31-RA (Extension)	
	Brenzys/Brenzys	Enbrel®/Brenzys
Screened, N	N/A	N/A
Enrolled, N	126	119
Discontinued, N (%)	7 (5.6)	6 (5)
WDAEs, N (%)	4 (3.2)	1 (0.8)
Lost to follow-up, N (%)	0 (0)	1 (0.8)
Withdrew consent	3 (2.4)	4 (3.4)
Extended Population, N	126	119

N/A = not applicable SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Please rename these column headings with brand names of the SEB and the reference product.
Source: 100-week Top Lines Summary SB4-G31-RA, Table 1.

Efficacy Results

ACR20, ACR50, and ACR70

The ACR20 response rates at Week 100 for the extended population was 77.9% (95/122) in the Brenzys/Brenzys treatment group and 79.1% (91/115) in the Enbrel®/Brenzys treatment group (Table 18).

TABLE 18: SUMMARY OF ACR20 RESPONSE UP TO WEEK 100 (EXTENDED POPULATION)

Timepoint	Brenzys/Brenzys N=126 n/n' (%)	Enbrel®/Brenzys N=119 n/n' (%)	Total N=245 n/n' (%)
[redacted]	[redacted]	[redacted]	[redacted]
Week 52	99/125 (79.2)	98/119 (82.4)	197/244 (80.7)
Week 76	102/125 (81.6)	90/117 (76.9)	192/242 (79.3)
Week 100	95/122 (77.9)	91/115 (79.1)	186/237 (78.5)

n': number of subjects with available assessment results at each timepoint; percentages were based on n'. Week 2 to Week 40 were visits during the randomised, double-blind period; Week 52 was a visit that connects the two study periods; Week 76 to Week 100 were visits during the open-label, extension period.
Source: 100-week Top Lines Summary SB4-G31-RA, Table 3.

The ACR50 response rates at Week 100 for the extended population was 59.8% (73/122) in the Brenzys/Brenzys treatment group and 60.9% (70/115) in the Enbrel®/Brenzys treatment group (Table 19).

TABLE 19: SUMMARY OF ACR50 RESPONSE UP TO WEEK 100 (EXTENDED POPULATION)

Timepoint	Brenzys/Brenzys N=126 n/n' (%)	Enbrel®/Brenzys N=119 n/n' (%)	Total N=245 n/n' (%)
[redacted]			
Week 52	65/125 (52.0)	64/119 (53.8)	129/244 (52.9)
Week 76	74/125 (59.2)	62/117 (53.0)	136/242 (56.2)
Week 100	73/122 (59.8)	70/115 (60.9)	143/237 (60.3)

n': number of subjects with available assessment results at each timepoint; percentages were based on n'.Week 2 to Week 40 were visits during the randomised, double-blind period; Week 52 was a visit that connects the two study periods; Week 76 to Week 100 were visits during the open-label, extension period.
Source: 100-week Top Lines Summary SB4-G31-RA, Table 4.

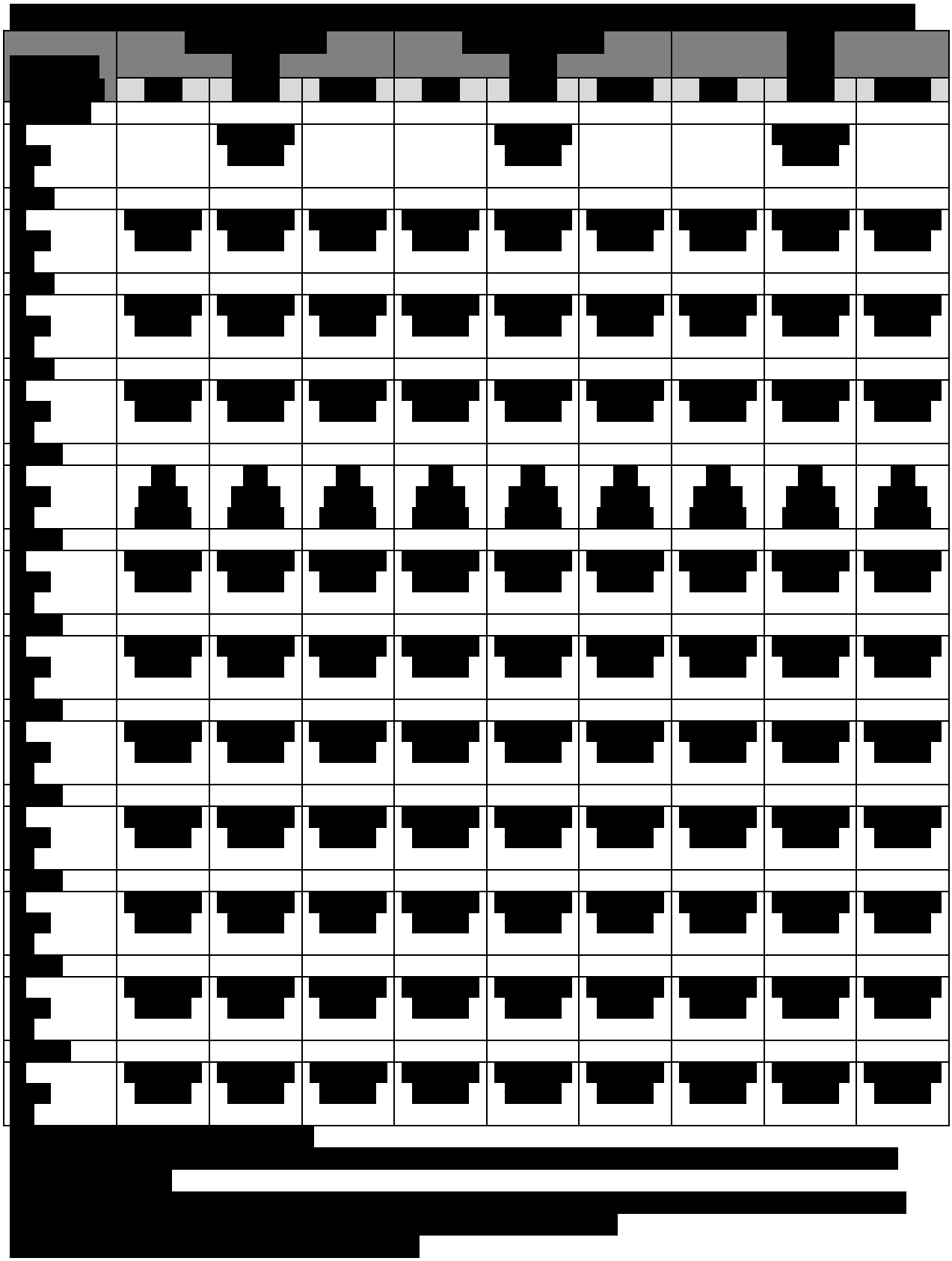
The ACR70 response rates at Week 100 for the extended population was 42.6% (52/122) in the Brenzys/Brenzys treatment group and 41.7% (48/115) in the Enbrel®/Brenzys treatment group (Table 20).

TABLE 20: SUMMARY OF ACR70 RESPONSE UP TO WEEK 100 (EXTENDED POPULATION)

Timepoint	Brenzys/Brenzys N=126 n/n' (%)	Enbrel®/Brenzys N=119 n/n' (%)	Total N=245 n/n' (%)
[redacted]			
Week 52	48/125 (38.4)	39/119 (32.8)	87/244 (35.7)
Week 76	49/125 (39.2)	44/117 (37.6)	93/242 (38.4)
Week 100	52/122 (42.6)	48/115 (41.7)	100/237 (42.2)

n': number of subjects with available assessment results at each timepoint; percentages were based on n'. Week 2 to Week 40 were visits during the randomised, double-blind period; Week 52 was a visit that connects the two study periods; Week 76 to Week 100 were visits during the open-label, extension period.
Source: 100-week Top Lines Summary SB4-G31-RA, Table 5

[redacted]



Safety Results

In the extension period of the study, highly similar proportion of patients in the Brenzys/Brenzys group and Enbrel®/Brenzys group experienced any TEAEs [redacted], respectively; Table 21).

The incidences of TEAEs and serious TEAEs were similar between groups. Majority of the TEAEs were unrelated to the study drugs (Table 21) and were mild in nature (Table 22).

The most commonly experienced TEAEs in the extension period were upper respiratory tract infection (10 [7.9%] subjects experienced 11 events vs. 9 [7.6%] subjects experienced 11 events), pharyngitis (9 [7.1%] subjects experienced 11 events vs. 5 [4.2%] subjects experienced 6 events), bronchitis (6 [4.8%] subjects experienced 6 events vs. 7 [5.9%] subjects experienced 7 events), and nasopharyngitis (6 [4.8%] subjects experienced 7 events vs. 5 [4.2%] subjects experienced 5 events) in the Brenzys/Brenzys and Enbrel®/Brenzys groups, respectively.

One death occurred in the extension period, which was in the Brenzys/Brenzys group. The mortality was due to hepatic cancer [redacted]

TABLE 21: SUMMARY OF TEAES IN THE EXTENSION PERIOD OF STUDY SB4-G31-RA (EXTENDED POPULATION)

	Brenzys/Brenzys (N=126)	Enbrel®/Brenzys (N=119)	Total (N=245)
Total number of TEAEs	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of patients with at least 1 TEAE	60 (47.6%)	58 (48.7%)	118 (48.2%)
Related	[redacted]	[redacted]	[redacted]
Unrelated	[redacted]	[redacted]	[redacted]
Total number of SAEs	6	2	8
Related	[redacted]	[redacted]	[redacted]
Unrelated	[redacted]	[redacted]	[redacted]
Number (%) of patients with at least 1 SAE	6 (4.8%)	2 (1.7%)	8 (3.3%)
Related	[redacted]	[redacted]	[redacted]
Unrelated	[redacted]	[redacted]	[redacted]
Total number of AEs leading to permanent investigational product discontinuation	[redacted]	[redacted]	[redacted]
Number (%) of patients with at least 1 AE leading to permanent investigational product discontinuation	4 (3.2%)	2 (1.7%)	6 (2.4%)
Deaths	1 (0.8%)	0 (0.0%)	1 (0.4%)

TEAE was defined as any AE with an onset date on or after the first study drug date of the randomized, double-blind period.
Percentages were based on the number of subjects in the Extended Population.
If a subject had multiple events of the same severity or causality, then the subject was counted only once in that severity or causality.
If a subject had multiple events with different severity or causality, then the subject was counted only once for more severe adverse event or related adverse event.
Source: SB4-G31-RA Extension Top Line Summary, Table 8.

TABLE 22: SUMMARY OF TEAES BY SEVERITY IN THE EXTENSION PERIOD OF STUDY SB4-G31-RA (EXTENDED POPULATION)

	Brenzys/Brenzys (N=126)			Enbrel®/Brenzys (N=119)		
	n	(%)	E	n	(%)	E
Any TEAE	60	47.6%	173	58	48.7%	123
[redacted]						

E: frequency of adverse events; TEAE: treatment-emergent adverse event. Percentages were based on the number of patients in the safety set. When a patient experienced the same event multiple times with different severity, then the patient was counted only once at the maximum severity.
Source: SB4-G31-RA Extension Top Line Summary, Table 9.

Discontinuation

Overall, the incidence of TEAEs leading to investigational product discontinuation was comparable between the Brenzys/Brenzys and Enbrel®/Brenzys groups (Table 21).

Injection Site Reactions

There were no injection site reactions reported in the extension period of the study.

Safety of Special Interest — Serious Infections, Tuberculosis

In the extension period of the study, TEAEs of special interest (all non-tuberculosis infections) occurred once in 1 subject (0.8%; unrelated to IP) in the Brenzys/Brenzys group and twice in 1 subject (0.8%; related and unrelated to IP) in the Enbrel®/Brenzys group.

Malignancies

One patient in the Brenzys/Brenzys group reported malignancy (hepatic cancer) [redacted]

In summary, the preliminary results from the extension period of study SB4-G31-RA suggested that Brenzys is safe and effective and administered long-term with no unexpected results. Similarly, subjects previously treated with Enbrel® can safely switch to Brenzys and achieve similar clinical profile.

4.2.4 SB4-G11-NHV

a) Study Characteristics

Brief Description of the Study

Study SB4-G11-NHV is a controlled, randomized, single-blind, 3-part, 2-period, 2-sequence, single-dose, cross-over study to compare the PK, safety / tolerability, and immunogenicity of three formulations of etanercept (Brenzys, EU-Enbrel®, US-Enbrel®), in healthy male subjects. The primary endpoints (PK) were AUC_{inf} and C_{max}, through which pharmacokinetic similarity was conclude between Brenzys and Enbrel® if the 90% CI of the ratios of the geometric means were entirely contained within the equivalence margin of 80-125%. Additional safety, PK, and immunogenicity outcomes were also assessed.

Characteristics		Details for SB4-G11-NHV
Study Design	**Objective**	Pivotal pharmacokinetic, safety, and immunogenicity study
	Blinding	Single-blind (subject)
	Study period	2013-05 to 2013-07
	Study centres	1
	Design	Equivalence (pharmacokinetic)
Study Population	**Randomized (N)**	138
	Inclusion criteria	• Healthy male subjects • 18-55 years old • Have a body weight between 60 and 94.9 kg and a body mass index between 20.0 and 29.9 kg/m², inclusive
	Exclusion criteria	• History and/or current presence of clinical significant atopic allergy, hypersensitivity or allergic reactions, also including known or suspected clinically relevant drug hypersensitivity to any components of the test and reference IP formulation or comparable drugs. • Active or latent Tuberculosis or who have a history of TB. • History of invasive systemic fungal infections or other opportunistic infections • Systemic or local infection, a known risk for developing sepsis and/or known active inflammatory process • Serious infection associated with hospitalisation and/or which required intravenous antibiotics • History of and/or current cardiac disease • Subjects with a history of and/or current gastrointestinal, renal, hepatic, cardiovascular, haematological (including pancytopenia, aplastic anaemia or blood dyscrasia), metabolic (including known diabetes mellitus) or pulmonary disease classed as significant by the Investigator. • Subjects with a history of cancer including lymphoma, leukaemia and skin cancer. • Subjects with a history of immunodeficiency including those subjects with a positive test for human immunodeficiency virus. • Have received live vaccine(s) within 30 days prior to Screening or who will require live vaccine(s) between Screening and the final study visit. • Intake medication with a half-life > 24 h within 1 month or 10 half-lives of the medication prior to the first administration of IP.
Drugs	**Intervention**	• Brenzys (Brenzys; etanercept biosimilar), 50 mg, s.c., administered as a single-dose
	Comparator(s)	• EU-sourced Enbrel® (etanercept), 50 mg, s.c., administered as a single-dose • US-sourced Enbrel® (etanercept), 50 mg, s.c., administered as a single-dose
Duration	**Run-in**	Not applicable
	Treatment	Each treatment period was 21 days (drug was administered on day 1 of each period) separated by 7 days, resulting in a 28-day washout between study drug administrations
	Follow-up	Not applicable
Outcomes	**Primary (PK) End Point(s)**	• Area under the concentration-time curve from time zero to infinity (AUCinf) of etanercept • Maximum serum concentration (Cmax) of etanercept
	Other (PK) End Points	• AUC from time zero to last quantifiable concentration (AUClast) of etanercept • Time to Cmax (Tmax) of etanercept • Terminal half-life (T1/2)

Characteristics		Details for SB4-G11-NHV
Notes	**Publications**	• Lee YJ, Shin D, Kim Y, Kang JW, Gauliard A, Fuhr R. A randomised Phase I pharmacokinetic study comparing Brenzys and etanercept reference product (Enbrel®(R)) in healthy subjects. Br J Clin Pharmacol. 2016 (42) • Lee YJ, Shin D, Kim Y, Kang JW, Fuhr R, Gauliard A. A Phase I pharmacokinetic study comparing Brenzys, an etanercept biosimilar, and etanercept reference product (Enbrel®) in healthy male subjects. Ann Rheum Dis. 2015;74(Suppl2):718. (43) • NCT01865552 • EudraCT 2012-004371-39

Intervention and Comparators

Interventions Employed (e.g., Dose, Route and Frequency of Administration, Duration, Etc.)

This was a three-part (Part A, Part B and Part C), 2-treatment, 2-period cross-over study:

- Part A: Brenzys or EU-Enbrel® (both 50 mg PFSs)
- Part B: Brenzys or US-Enbrel® (both 50 mg PFSs)
- Part C: EU-Enbrel® or US-Enbrel® (both 50 mg PFSs)

In each period subjects received a single dose of the respective etanercept product and were followed for 21 days during which PK, safety / tolerability, and immunogenicity measurements were conducted. Treatment periods were separated by 7 days, resulting in a 28-day washout between study drug administrations.

Reference Products Used

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

Placebos and Controls (If Applicable)

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

Concomitant Medications

None.

Outcomes (Key Efficacy and Safety Outcomes)

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

Safety: All reported terms for AEs were coded using the Medical Dictionary for Regulatory Activities (MedRA). Laboratory data, data from other tests (e.g., vital signs, 12-lead ECG, etc.), and immunogenicity were also recorded. A local injection site reaction with a score of ≥ 2 according to the rating scale will be documented as an AE.

Immunogenicity: Blood samples were collected pre-dose and 4 weeks after the first injection of the study drugs for determination of ADAs and NAbs to etanercept (single doses of Brenzys 50 mg SC, EU-Enbrel® 50 mg SC, US-Enbrel® 50 mg SC).

Statistical Analyses

Statistics Protocol for PK Equivalence

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

The statistical analysis of the $\log_e$-transformed primary endpoints was based on an analysis of variance model. The difference in least squares means (LSMean) of $\log_e(AUC_{inf})$ and $\log_e(C_{max})$ between the Brenzys and EU-Enbrel®, Brenzys and US-Enbrel®, and EU-Enbrel® and US-Enbrel® and the associated 90% confidence intervals (CIs) was determined. Back-transformation provided the ratio of geometric LSMeans and 90% CIs for these ratios.

PK similarity for the primary endpoints was to be concluded if the 90% CIs for the ratio of geometric LSMean of the test to the reference product was completely contained within the acceptance interval of 0.8 to 1.25.

Furthermore, in accordance with Health Canada guidance (Conduct and Analysis of Comparative Bioavailability Studies [12-105972-31]), PK similarity for AUC_{last} was demonstrated by using the same statistical analysis used to assess bioequivalence of the primary endpoints.

Rationale for the PK Equivalence Margins Used

The rationale for the bioequivalence testing procedures and equivalence margins used for the primary (i.e., C_{max} and AUC_{last}) as well as the secondary PK parameters followed the usual standards (Guideline on the Investigation of Bioequivalence, CHMP/EWP/QWP 1401/98 Rev. 1/Corr **) (44).

Analysis Sets (e.g., intention to Treat or Per-protocol)

Pharmacokinetic (PK) Population

The PK population included all randomised subjects who received at least one of the treatments to be compared, with evaluable primary PK parameters and without any major protocol deviation. All PK analyses were performed based on this analysis set.

Data might have been excluded from PK analysis (listed only) if any of the following criteria were fulfilled:

- Concomitant medication, which could render the serum concentration-time profile unreliable
- The pre-dose concentration was greater than 5% of the corresponding maximum serum concentration (C_{max}) in any given treatment period.

Safety Set consisted of all patients who received *at least one dose* of study drug during the study phase and were analyzed according to the treatment received.

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

- For the description of the statistics protocol for pharmacokinetic equivalence testing, please refer to CTD Modules 2.7.2 (p.11-12)
- For the description of the rationale for the therapeutic equivalence margins used, please refer to CTD Module 2.7.2 (p.7-8).
- For description of the analysis set, please refer to CTD Modules 2.7.4 (p.10); SB4-G11-NHV CSR, section 9.7.1.1.

b) Results

Baseline Characteristics

TABLE 23: MAJOR DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR STUDY SB4-G11-NHV BY DOSING SEQUENCE

Characteristics Mean (SD)	Part A			Part B			Part C		
	Brenzys-EU	EU-Brenzys	Total	Brenzys-US	US-Brenzys	Total	EU-US	US-EU	Total
N	23	23	46	23	23	46	23	23	46
Age (years)	38 (9.4)	41 (10.9)	39 (10.2)	38 (9.7)	42 (8.9)	40 (9.5)	40 (10.5)	41 (9.4)	41 (9.9)
Gender, no (%)									
Male	23 (100)	23 (100)	46 (100)	23 (100)	23 (100)	46 (100)	23 (100)	23 (100)	46 (100)
Race, n (%)									
White	23 (100)	23 (100)	46 (100)	23 (100)	22 (95.7)	45 (97.8)	23 (100)	21 (91.3)	44 (95.7)
Black or Africa American	0	0	0	0	0	0	0	1 (4.3)	1 (2.2)
Other	0	0	0	0	1 (4.3)	1 (2.2)	0	1 (4.3)	1 (2.2)
Ethnicity, no (%)									
Not Hispanic or Latino	23 (100)	23 (100)	46 (100)	23 (100)	23 (100)	46 (100)	23 (100)	23 (100)	46 (100)
Body Weight (kg)	81.3 (8.27)	77.8 (8.61)	79.5 (8.53)	79.6 (6.18)	76.0 (8.00)	77.8 (7.30)	79.8 (6.87)	77.6 (8.56)	78.7 (7.75)
BMI (kg/m^2)	24.9 (2.33)	23.9 (2.25)	24.4 (2.32)	24.7 (2.51)	24.2 (2.03)	24.5 (2.27)	24.4 (2.05)	24.7 (2.40)	24.6 (2.21)

Brenzys: Brenzys; EU: EU-Enbrel®; US: US-Enbrel®; BMI: Body Mass Index.
Source: CTD 2.7.4, Table 4.

Similarity/Differences

The average age, height, weight and BMI were generally comparable between the sequences. All subjects were male in this study and the majority of subjects were white.

Concomitant Conditions/Medications

All volunteers in this study were healthy individuals. As such, vast majority of the subjects did not experience any concomitant conditions throughout the study, with 7 instances of abnormal physical examinations after first dose administration. For all 3 parts (A-C) of the study, the number of subjects in each treatment sequence receiving concomitant medications was low (at most 2 subjects) with the most common concomitant medication being paracetamol taken by 2 subjects in Part A of the study.

Patient Disposition

In Part A (Brenzys vs. EU-Enbrel®), of all 46 subjects randomized, 1 subject discontinued from the study (due to AE) and 45 subjects were included in the PK population. Three patients had non-zero baseline concentrations of greater than 5% of C_{max} in Period 2. These subjects were excluded from the PK summaries and statistical comparison. In Part B (Brenzys vs. US-Enbrel®), of all 46 subjects randomized, 1 subject discontinued from the study (due to AE) and 45 subjects were included in the PK population. One patient had non-zero baseline concentration of greater than 5% of C_{max} in Period 2 and was excluded from the PK summaries and statistical comparison. In Part C (EU-Enbrel® vs. US-Enbrel®), of all 46 subjects randomized, 4 subjects discontinued from the study (3 due to AE). Overall, 42 subjects were included in the PK population.

TABLE 24: SUMMARY OF PATIENT DISPOSITION BY DOSING SEQUENCE FOR STUDY SB4-G11-NHV

Disposition	SB4-G11-NHV					
	Part A		Part B		Part C	
	Brenzys-EU	EU-Brenzys	Brenzys-US	US-Brenzys	EU-US	US-EU
Screened, N	Not available					
Randomized, N	23	23	23	23	23	23
Discontinued, N (%)	1 (4.3)	0 (0)	0 (0)	1 (4.3)	3 (13.0)	1 (4.3)
WDAEs, N (%)	1[a] (4.3)	0 (0)	0 (0)	1[b] (4.3)	1[c] (4.3)	1[b] (4.3)
Pathological lab, N (%)	0	0	0	0	1[c,d] (4.3)	0
Withdrawal due to SAEs, N (%)	0	0	0	0	0	0
Lost to follow-up, N (%)	0	0	0	0	0	0
Other	0	0	0	0	1 (4.3)	0
Pharmacokinetic Set, N	22	23	23	22	20	22
Safety, N	23	23	23	23	23	23

Brenzys: Brenzys; EU: EU-Enbrel®; US: US-Enbrel®; SAE; serious adverse event; WDAE: withdrawal due to adverse event.
[a] Occurred after Brenzys administration (Period 1).
[b] Occurred after US-Enbrel® administration (Period 1).
[c] Occurred after EU-Enbrel® administration (Period 1).
[d] Abnormal pathological laboratory value reported as AE.
Source: CTD 2.7.4, p.24; CSR SB4-G11-NHV, Table 10-1.

Efficacy Results

There were no clinical trials conducted with Brenzys in patients with ankylosing spondylitis. The use of Brenzys in ankylosing spondylitis is supported in consideration of the similar product quality characteristics of Brenzys and the reference product Enbrel® (see section *4.1 Quality Information*) and the similar pathophysiology of ankylosing to the studied populations. In addition, human PK (see section *4.3 Pharmacokinetics*) and clinical efficacy and safety studies (see section *4.2 Pivotal Clinical Studies*) have been conducted to demonstrate comparable clinical profiles between Brenzys and the Enbrel®.

Safety Results

Adverse Events

Part A (Brenzys vs. EU Enbrel®): TEAEs were experienced by 18 (39.1%) of Brenzys subjects and 16 (34.8%) of EU-Enbrel® subjects (Table 25). The TEAEs most frequently reported for volunteers in the Brenzys and EU-Enbrel® groups were nasopharyngitis, headache, and injection site reaction. Back pain was only reported in 1 subject in the Brenzys group (Table 35, Appendix 1).

The majority of reported TEAEs were mild (43 TEAEs), 3 were moderate (Brenzys: headache and neck pain; EU-Enbrel®: headache) and one was severe (EU-Enbrel®: diarrhoea). The severe TEAE of diarrhoea was considered not causally related to the study drug.

The proportion of subjects who experienced TEAEs considered causally related to the study drugs was 26.1% after Brenzys administration and 21.7% after EU-Enbrel® administration. The most frequently reported TEAEs suspected to be related to the study drugs were headache (6 subjects; Brenzys: 4; EU-Enbrel®: 2) and injection site reaction (5 subjects; Brenzys: 2; EU-Enbrel®: 3).

For US-Brenzys, the most commonly reported TEAEs included nasopharyngitis, headache, injection site reaction, as well as back pain and dizziness (Table 35**, Appendix 1).**

The majority of reported TEAEs were mild (60 TEAEs), 8 were of moderate intensity (Brenzys: dyspepsia, chest discomfort, gastroenteritis, alanine aminotransferase (ALT) increased and headache; US-Enbrel®: tooth abscess, influenza-like illness and postural dizziness) and none was severe.

The proportion of subjects who experienced TEAEs considered to be causally related to the study drugs was 37.0% after Brenzys administration and 32.6% after US-Enbrel® administration. The most frequently reported TEAEs suspected to be causally related to the study drugs were headache (5 subjects; Brenzys: 3; US-Enbrel®: 3; including 1 subject after both treatments) and injection site reaction (5 subjects; Brenzys: 3; US-Enbrel®: 3, including 1 subject after both treatments).

Part C (EU-Enbrel® vs. US-Enbrel®): TEAEs were experienced by 17 (37.0%) of EU-Enbrel® subjects and 14 (30.4%) of US-Enbrel® subjects (Table 25). The TEAEs most frequently reported for volunteers in the EU-Enbrel® group were nasopharyngitis and headache. For US-Brenzys, the most commonly reported TEAEs included headache and injection site reaction (Table 35**, Appendix 1).**
Overall, the most frequent TEAEs overall were headache, injection site reaction and nasopharyngitis. The majority of TEAEs reported was mild or moderate in severity and transient. The proportion of subjects with TEAEs suspected to be study drug-related was comparable between two treatments in each part. There were no SAEs in this study.

[redacted]

[redacted]

[redacted]

[redacted]

Laboratory Parameters: In each of the 3 parts (A, B, and C), mean and median values of haematology, blood chemistry, and urinalysis parameters did not show any changes over time. Minor alterations were similar to those usually seen in a healthy population. There were also no clinically meaningful differences in the changes from baseline for any the assessed parameter between the two treatments in any study part. In all, there were no clinically meaningful differences between Brenzys and the etanercept reference product (EU- and US-Enbrel®) in terms of notable laboratory values (see CTD 2.7.4, p.32-33 for details).

Vitals, Physicals, and ECGs: In each part, vital parameters did not show any large or clinically relevant changes over time for any of the treatments. There were no clinically significant changes from baseline of the vital sign parameters in both treatments in each part. Overall, there were no differences between the three study drugs in vital signs in any study part.

In each part, ECG parameters did not show any relevant changes over time. None of the subjects reached Fridericia-corrected QT intervals (QTcF) > 450 msec at any time point for any of the treatments. Overall, there were no differences between the three study drugs with regard to the ECG findings and evaluation in any study part (see CTD 2.7.4, p.37 for details).

4.2.5 Summary of Safety

a) Safety Evaluation Plan (CTD 2.5, Section 1.2; CTD 2.7.4, Section 1.1)

Brenzys has been developed a proposed subsequent entry biologic (SEB; hereafter "biosimilar") to Enbrel® having the TNF-α inhibitor etanercept as the active substance. Brenzys is presented in single-use PFS and pre-filled pens containing 50 mg/mL etanercept to be administered via subcutaneous injection.

The applicant intends to claim the same therapeutic indications for Brenzys as granted for Enbrel® in Canada, except psoriatic arthritis (PsA) and plaque psoriasis (PsO). In addition due to the proposed pharmaceutical form containing 50 mg etanercept per dose, the applicant does not intend to claim the approved pediatric indication (juvenile idiopathic arthritis [JIA]). Representing a biosimilar, the proposed dosing and the recommended posology of Brenzys correspond with Enbrel® (45).

Etanercept is well established and widely used in clinical practice for about 15 years, with a well-characterized safety profile. As to be expected for a TNF-α inhibitor, main safety issues are characterized by the immunosuppressive action of etanercept. Long-term inhibition of TNF-α could lead to a serious impairment of defense mechanisms against infections (in particular, opportunistic infections) and against the development of neoplasms (46).

The clinical development program of Brenzys was in alignment with respective EU and Canadian guidance. Scientific advice from the EMA/Scientific Advice Working Party (SAWP), as well as consultations with the FDA (pre-Investigational New Drug meeting) and Health Canada (pre-submission meeting) also provided input in the Brenzys development program.

Based on the supportive quality similarity exercises and the *in vitro* and *in vivo* non-clinical study results, a clinical Phase I study was conducted to compare the PK, **safety/tolerability**, and immunogenicity in order to demonstrate similarity between Brenzys and Enbrel®, subsequently followed by a clinical Phase III study in RA patients to demonstrate similarity in efficacy, **safety/tolerability**, immunogenicity, and patient PK profiles between Brenzys and Enbrel®.

b) Safety Populations Evaluated

RA Patients (CTD 2.7.4, Sections 1.2.2 and 2.1.1.2)

As this Phase III study was conducted in RA patients, a pooled safety analysis is not applicable due to the heterogeneity of study populations (RA patients vs. healthy subjects) and duration of treatment / exposure (long-term vs. single-dose). Please refer to Safety Results in section *4.2.1 SB4-G31-RA* above for detailed safety information.

Briefly, a total of 596 patients (Brenzys: 299; EU-Enbrel®: 297) received at least 1 injection of Brenzys or EU-Enbrel®; the mean duration of exposure was 338.9 days in the Brenzys and 323.5 days in the EU-Enbrel® treatment groups. 505 subjects (Brenzys: 259; EU-Enbrel®: 246) completed 52 weeks of treatment. Ninety-one (Brenzys: 40; EU-Enbrel®: 51) subjects discontinued the study mostly due to AE, withdrew consent, and investigator discretion. A total of 354 (59.4%) patients reported 1179 TEAEs at any time after the first dose of the study drugs: 533 TEAEs in 175 (58.5%)patients in the Brenzys treatment group vs. 646 TEAEs in 179 (60.3%) patients in the EU-Enbrel® treatment group. The majority of AEs were mild to moderate in severity.

Healthy Subjects (CTD 2.7.4, Section 1.2.1)

In the *Overview of Safety* section below, only results from study SB4-G11-NHV are discussed in which data for Brenzys, EU-Enbrel® and US-Enbrel® are pooled from across the 3 parts (A: Brenzys vs. EU-Enbrel®; B: Brenzys vs. US-Enbrel®; C – EU-Enbrel® vs. US-Enbrel®) of the study. This *post-hoc* analysis is developed specifically for this submission document.

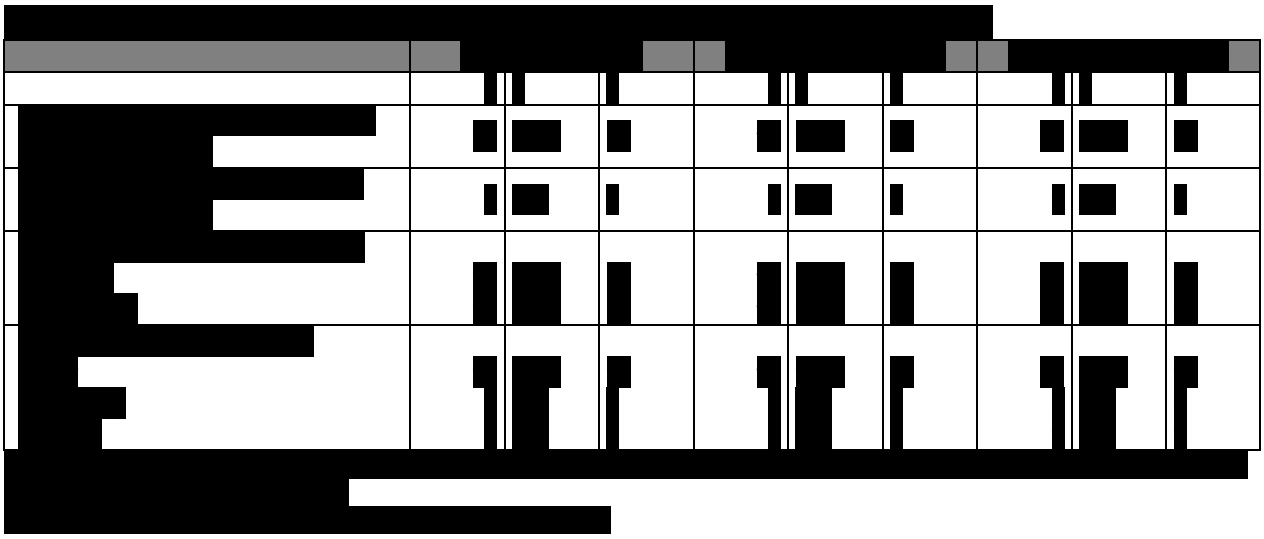
In the Phase I study, across the 3 study parts, 91 volunteers received 1 dose of Brenzys, 90 volunteers received 1 dose of EU-Enbrel®, and 89 volunteers received 1 dose of US-Enbrel®.

c) Overview of Safety

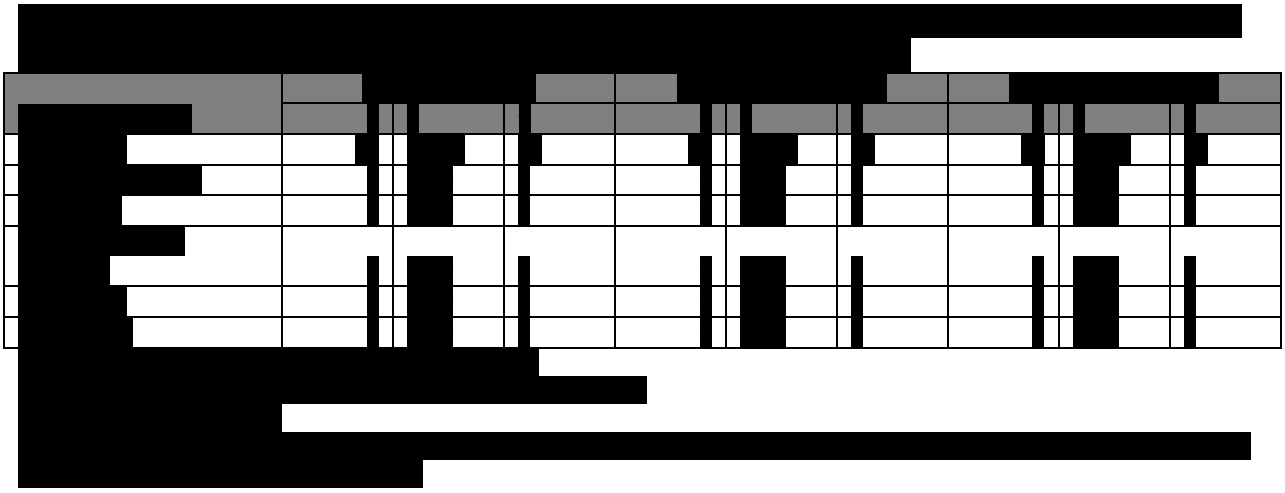
Adverse Events

Healthy Subjects

In study SB4-G11-NHV, pooled analysis of TEAE summaries revealed that the relatedness and severity of TEAEs were generally comparable across the 3 treatments with no obvious trend.



Pooled analysis of the TEAEs further revealed that the type and incidence of TEAEs between Brenzys and both EU- and US- Enbrel® were generally similar and comparable, suggesting no new safety signals for Brenzys that are not observed in Enbrel® (Table 27).



4.3 Pharmacokinetics

PK similarity between Brenzys and Enbrel® was evaluated in both healthy volunteers (SB4-G11-NHV) and RA patients (SB4-G31-RA). The primary objective of study SB4-G11-NHV was to demonstrate PK similarity between Brenzys and EU-Enbrel® (Part A), between Brenzys and US-Enbrel® (Part B), and between EU- and US-Enbrel® (Part C). **For the primary PK endpoints of AUC_{inf} and C_{max}, the 90% CI of the ratios of the geometric means both lie within the acceptance equivalence range of 80-125%** for Parts A and B of the study (Table 25; see Appendix 1, Table 36 for Part C results). The comparative serum concentration-time profiles for Parts A-C are located in Appendix 1 (Figure 2, Figure 3, Figure 4, respectively). Other PK variables (AUC_{last}, T_{max}, $T_{1/2}$) were also highly similar between Brenzys and Enbrel® (Appendix 1, Table 37).

In study SB4-G31-RA, an exploratory analysis of PK parameters were conducted in a PK subset (n=79) of patients to provide supportive evidence of PK equivalence of Brenzys and EU-Enbrel®. As the PK analysis was exploratory, equivalence criteria were not used to compare the PK parameters. **Results showed that for all exposure parameters (AUC_{τ}, C_{max} and C_{min}), the range (Min, Max) of values were comparable between Brenzys and Enbrel®** at steady-state (Week 8) (Table 25; Table 38, in Appendix 1). The slightly higher mean values for these parameters for Brenzys compared to Enbrel® may be the result of the generally large inter-subject variability (%CV) seen for both etanercept products, which is typical for protein molecule drugs and is consistent with the results of a previous study with Enbrel® (47). Similar results were also seen for other PK parameters (Table 25; Table 38, in Appendix 1). Trough serum concentration (C_{trough}) prior to each dosing up to Week 24 were also measured; results showed that the trough levels were comparable at each time point between Brenzys and Enbrel® (Table 44, Appendix 1).

TABLE 25: SERUM PK PARAMETERS FOR STUDIES SB4-G11-NHV AND SB4-G31-RA (PK POPULATION)

Study SB4-G11-NHV (Normal Healthy Volunteers)					
	n	Brenzys 50 mg (N=45)	n	Enbrel® 50 mg (N=45)	Ratios of Geometric Means; 90% CI
AUC_{inf} (µg·h/mL), Mean (SD)	42[a]	769.069 (243.9039)	42[a]	771.680 (226.2874)	0.990 (0.947 – 1.036)
	44[b]	834.680 (242.7652)	44[b]	810.054 (195.9770)	1.011 (0.958 – 1.067)
C_{max} (µg/mL), Mean (SD)	42[a]	3.607 (1.4298)	42[a]	3.435 (1.2390)	1.037 (0.985 – 1.092)
	44[b]	3.869 (1.3251)	44[b]	3.613 (1.0252)	1.044 (0.977 – 1.114)
Study SB4-G31-RA (Rheumatoid Arthritis Subjects) (at Week 8)					
	n	Brenzys 50 mg (N=41)[c]	n	Enbrel® 50 mg (N=38)[c]	
AUC_{τ} (µg·h/mL) **Mean (SD)** **CV%** **Min, Max**	36	676.378 (255.065) 37.7 121.683, 1 142.107	34	520.899 (261.008) 50.1 98.092, 1145.019	
[redacted]					
[redacted]					

Study SB4-G11-NHV
AUC_{inf} = area under the curve to infinity; CI = confidence interval; C_{max} = maximum concentration; SD = standard deviation.
[a] Part A (three subjects were excluded due to carryover effect);
[b] Part B (one subject was excluded due to carryover effect.
[c] Four subjects in the Brenzys group and 2 subjects in the EU-Enbrel® group were excluded from the PK summary due to a data quality issue at the site.

Study SB4-G31-RA
AUC_{τ} = area under the concentration-time curve over the dosing interval; CV% = coefficient of variation.
Source: CTD 2.7.2, Tables 3-6, 10.

Overall, all pharmacokinetic endpoints in both healthy volunteers and RA patients demonstrated that Brenzys is highly comparable to Enbrel®, regardless of administration in both healthy and diseased subjects.

4.4 Immunogenicity

Brenzys tagged single-assay approach was used to detect immunogenicity. Overall immunogenicity results are presented for baseline, Weeks 8, 24, and 52 for the randomized, double-blind portion of study SB4-G31-RA (Table 26). Results for other time points are presented in Table 45 in Appendix 1. Brenzys was well-tolerated in RA patients, with 3 (1.0%) subjects vs. 39 (13.2%) subjects for Enbrel® ($p<0.001$) reported with an overall post-dose ADA-positive result at Week 52. Only one sample from Enbrel® group had neutralizing capacity.

TABLE 26: INCIDENCE OF ANTI-DRUG ANTIBODIES AND NEUTRALIZING ANTIBODIES TO ETANERCEPT IN STUDY SB4-G31-RA (RANDOMIZED, DOUBLE-BLIND PERIOD) IN RA PATIENTS (SAFETY POPULATION)

Timepoint		Brenzys 50 mg (N=299)			Enbrel® 50 mg (N=297)			Total (N=596)		
	Parameter	n'	n	(%)	n'	n	(%)	n'	n	(%)
W0 (baseline)	ADA-Pos	299	0	(0.0)	297	0	(0.0)	596	0	(0.0)
	NAb-Pos		0			0			0	
W8 overall*	ADA-Pos	299	2	(0.7)	296	38	(12.8)	595	40	(6.7)
	NAb-Pos		0			1			1	
W24 overall*	ADA-Pos	299	2	(0.7)	296	39	(13.2)	595	41	(6.9)
	NAb-Pos		0			1			1	
W52 overall*	ADA-Pos	299	3	(1.0)	296	39	(13.2)	595	42	(7.1)
	NAb-Pos		0			1			1	

ADA: anti-drug antibody; NAb: neutralizing antibody; N: number of patients in the safety set; n': number of patients with an ADA assessment; n: number of patients with antibodies to Brenzys or Enbrel®; W: Week.
* Overall ADA results at Week 8, Week 24 and Week 52 were determined as "Positive" if at least one ADA positive until the time point regardless the ADA result at Week 0 and "Negative" if no ADA positive until the time point regardless the ADA result at Week 0.
Source: CTD 2.7.2, Section 4.

Preliminary results from the open-label extension period of study SB4-G31-RA revealed only minor immunological events (1 subject in each group developed non-neutralizing antibody) (Table 46 in Appendix). In study SB4-G11-NHV, blood samples were collected at baseline and Day 29 for immunogenicity testing. Similar to RA patients, Brenzys is equally well-tolerated in healthy volunteers. Zero samples were positive for NAb (See Table 47 in Appendix 1).

The incidence of ADA shown in the Enbrel® group in both studies appeared higher compared to those reported in the previous studies (46). In the RA study, immunogenicity was measured more frequently and with a more sensitive assay (e.g., Week 4 showed highest incidence of ADA but this time point was not measured in previous studies (34, 38, 48)). The antibodies detected in this study were generally transient and non-neutralizing, consistent with those seen with Enbrel® in previous studies (38, 46). Since Brenzys tagged single-assay approach was used to detect immunogenicity, the assay method did not seem to have caused the lower incidence of ADA observed in Brenzys compared with Enbrel®. There are product-specific factors known to affect immunogenicity, such as product origin (foreign or human), product aggregates, impurities, container closure system (49-52). Among these factors the level of product aggregates (high molecular weight in size-exclusion high-performance liquid chromatography and peak 3 in hydrophobic interaction chromatography), impurities (host cell proteins) and glycosylation (%high mannose N-glycan) were slightly lower in Brenzys compared with Enbrel®. Although it is unclear why the incidence of ADA was lower in Brenzys compared with Enbrel®, the differences in product aggregates, impurities and glycosylation may have caused the lower incidence of ADA in Brenzys compared with Enbrel® (53-56). However, such minor differences did not translate into functional differences in various *in vitro* biologics assays that were conducted as part of the Brenzys development program. Furthermore, according to the EMA guideline on biosimilars (8) the lower immunogenicity of Brenzys does not preclude classification as biosimilar since clinical efficacy of Brenzys and Enbrel® were similar in patients with ADA-negative results and no apparent correlation between ADA and clinical response or safety was observed (8, 38, 57, 58).

5. CRITICAL APPRAISAL OF CLINICAL STUDIES

This review included two studies: SB4-G31-RA was a phase 3 RCT that evaluated the clinical equivalence of Brenzys (etanercept SEB) compared to Enbrel (the reference biologic) that also included an open-label extension phase. Study SB4-G11-NHV was a phase 1 controlled, randomized, single-blind, crossover study that compared the pharmacokinetics (PK), safety, tolerability, and immunogenicity of three formulations of etanercept (Brenzys, EU-Enbrel, and US-Enbrel), in healthy male subjects. The following information is based on an appraisal of the manufacturer's submission.

5.1 Internal Validity

5.1.1 Study SB4-G31-RA

The first phase of SB4-G31-RA was an equivalence, parallel-group, multicentre, controlled, double-blind RCT that evaluated the efficacy of Brenzys (etanercept SEB) versus Enbrel (the reference biologic) in patients with RA. The first phase of the trial continued for 52 weeks.

Overall, the trial was generally well designed, with a sufficient number of enrolled patients (N = 596) for a two-sided alpha level of 0.05, 80% power for the primary outcomes, given a two-sided 15% equivalence margin, and allowing for a 20% loss of patients.[1,2]

The calculation of the equivalence margin was briefly described, and the manufacturer stated that the choice of margin was agreed upon by the regulatory agencies, the US Food and Drug Administration and the European Medicines Agency. It was not clear if the equivalence margin was derived from a fully comprehensive systematic review of etanercept, or if it was based solely on the results of previous pivotal trials for etanercept. The equivalence margin aimed to preserve 50% of the treatment effect of etanercept compared to placebo, and it is not clear if this margin exceeds any clinically meaningful differences that might affect the decision-making process by clinicians. The clinical expert consulted for this review indicated that aiming to preserve 50% of the treatment effect is a generous margin.

The randomization procedure and allocation concealment were well conducted. Using a unique number, patients were registered using an Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS). Subsequently, a computer-generated randomization scheme centrally randomized patients to a 1:1 ratio to either Brenzys or Enbrel. For each visit, the investigator used the IWRS (or IVRS) to obtain an appropriate number of codes that indicated which pre-filled syringes were to be dispensed to the patient. Patients, investigators, joint assessors, and other study personnel were kept blinded to treatment until week 52.

Both Brenzys and Enbrel were self-administered at a dose level of 50 mg once weekly. Treatment compliance was measured based on the investigational drug accountability, documented by the site staff. Patients in both groups were also on either oral or parenteral methotrexate (10 mg to 25 mg per week), and were required to take folic acid (5 mg to 10 mg per week) while taking methotrexate during the study period. Except for four patients in the Brenzys group and two in the Enbrel group, all patients recorded a treatment compliance rate of 80% to 120%.

Demographic characteristics, body mass index, disease severity (as shown by physician global assessment of disease activity), patient pain assessment and global disease activity, disease duration, swollen joint count, tender joint count, Health Assessment Questionnaire–Disability Index (HAQ-DI), and erythrocyte sedimentation rate (ESR) were well balanced between groups. Small variations were noted

in the levels of C-reactive protein [redacted], between the groups; however, this was not identified as being of concern, according to the clinical expert consulted for this review.

The primary outcome in this study (ACR20 response), was evaluated at 24 weeks. The choice of the outcome and analysis point is appropriately conducted as a reflection of the Enbrel pivotal studies, from which the equivalence margin was derived. Secondary outcomes were sufficiently reported to provide a clear picture of the efficacy of Brenzys compared to Enbrel. One secondary outcome, the modified total Sharp score (mTSS), depends on a radiographic assessment by a radiologist. The method of scoring the mTSS was not comprehensively reported, nor was the number of assessors or the methods used to blind assessors clarified. If : if there was even one assessor who was not blinded, this could have biased the results in either direction.

At 24 weeks, more patients withdrew from the Enbrel group (9.8%) than the Brenzys group (5.4%). Similarly, at 52 weeks, more patients withdrew from the Enbrel group (17.2%) than the Brenzys group (13.4%). The study enrolled a sufficient number of participants to allow a dropout rate of up to 20% and maintain 80% power at a two-sided alpha level of 0.05. It is uncertain if the imbalance in the dropout rate between the two groups impacted the results.

All outcomes were assessed using a per-protocol population and were compared with the results of a sensitivity analysis based on the intention-to-treat population, where missing data were imputed using multiple imputation methods in a pattern-mixture analysis. The results of the sensitivity analysis were similar to the primary analysis.

All but one of the secondary efficacy end points at 52 weeks fell within the equivalence margins. The upper margin of American College of Rheumatology 70% response (ACR70) at 52 weeks exceeded the upper equivalency margin, but was not statistically significantly different.

The second phase of study SB4-G31-RA was an extension study of up to 100 weeks assessing the tolerability, safety, and PK of Brenzys. The study included only patients from two countries (the Czech Republic and Poland) [redacted] (N = 245); patients in the Enbrel group were switched to Brenzys. This study has recently concluded, and the data suggest continued improvements. However, the nature of the study restricts the value to assessing the tolerability, PK, and immunogenicity, and capturing possible safety-related red flags.

Although the safety data in the initial phase and the extension phase 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.

5.1.2 Study SB4-G11-NHV

SB4-G11-NHV was a phase 1 PK study that compared Brenzys and Enbrel in healthy participants. The study findings provide evidence that Brenzys and Enbrel have similar PK profiles. This study was a crossover, randomized, single-blind study that included three treatment comparisons (parts): Brenzys versus US-Enbrel, Brenzys versus EU-Enbrel, and US-Enbrel versus EU-Enbrel. Overall, the study was well conducted and well reported.

The study had sufficient participants (N = 138) in each part (n = 46) to meet the predetermined sample size of 32 that would provide at least 90% power to detect a 20% difference in PK. Participants were assigned to one of the two possible interventions in each part according to a computer-generated randomization code. Participants had similar baseline characteristics and received a 50 mg dose of Brenzys or Enbrel once every week for 21 days. Participants had a sufficient washout period of 28 days before crossing over.

The primary outcome (PK parameters) was sufficiently described and well conducted. A standard PK equivalence margin of 80% to 125% was used to indicate PK biosimilarity. Although this was a single-blind trial, and because PK is an objective outcome, it is unlikely that knowledge of the administered treatment by investigators would have influenced the result in any major way. Similarly, the immunogenicity testing was well conducted and did not show any statistically significant differences compared with EU-Enbrel, but did show statistically significantly fewer cases of anti-drug antibody (ADA)-positive participants in the SEB Brenzys group compared with US-Enbrel. These outcomes were not adjusted for multiple statistical testing.

5.2 External Validity

5.2.1 Study SB4-G31-RA

The trial recruited patients with RA from 73 centres across 10 countries in Europe, Asia, and Latin America. The participants had active RA and were taking concomitant methotrexate plus folic acid.

However, the applicability of the results to the Canadian population has the following limitations:

1. No North American sites were included in the trial; it is unclear how this may have affected outcomes.
2. Over 90% of the study population was white; generalizability of the results to other racial groups is unclear.
3. Because patients older than 75 years were excluded, generalizability of the results to those older than 75 years is unclear.
4. The applicability of the results to populations with more concomitant medications and comorbidities is unknown.

5.2.2 Study SB4-G11-NHV

SB4-G11-NHV was a phase 1 PK study and, as such, no clinical efficacy data can be generalized to the Canadian population. Safety data suggest little difference in the adverse events profiles between Brenzys and the different formulations of Enbrel; however, sample sizes were small, the follow-up period was relatively short to detect serious but uncommon adverse events, and it is unclear whether the results are generalizable to the target populations for Brenzys (e.g., based on potential differences in renal and hepatic function).

6. EXTRAPOLATION OF INDICATIONS

6.1 Manufacturer's Rationale for Extrapolation

6.1.1 Overview of Pathophysiology of RA and AS, and the Mechanism of Action of Etanercept

a) TNF-α Biology

TNF-α is a multipotent cytokine that occurs in monomeric and trimeric soluble and transmembrane forms. It exhibits a wide spectrum of activity, including coordinating host immune and inflammatory response to infectious, malignant and auto-immune conditions. Large amounts of TNF-α have been shown to be released in response to lipopolysaccharide, other bacterial components and interleukin-1 (IL-1). TNF-α exerts its biological functions by binding to the TNF receptor, of which two types have been identified: TNF-R1 and TNF-R2. TNF-R1 is expressed in most tissues and can be fully activated by both the membrane-bound and soluble trimeric forms of TNF, whereas TNF-R2 is found only in cells of the immune system. Whereas initial TNF-α expression in response to infection or injury is beneficial, sustained or excessive expression has been identified to be associated with several chronic inflammatory auto-immune disorders.

Elevated levels of TNF-α have been detected in both the synovial fluid and synovial tissues of patients with rheumatoid arthritis (RA), indicating a major role in inducing the inflammatory response in the synovial joints of these patients. Increased levels of TNF-α have also been detected in other auto-immune disorders, in particular psoriasis and psoriatic arthritis (PsA), in which raised levels have been identified in serum, skin blister fluids and skin lesions, and synovial tissues and fluid, respectively. See CTD 2.5, section 1.1 and below for additional details.

b) Pathophysiology — Rheumatoid Arthritis

RA is a chronic and progressive autoimmune inflammatory disease characterized by inflammation of the synovial lining of joints and periarticular structures (59). RA is a destructive disease, associated with joint deformities, pain, fatigue and disability (60, 61). Molecular characteristics of RA include presence of autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) (62).

In patients with underlying immune hyperreactivity (evidenced by autoantibody production), the earliest phases of the disease mechanism are driven by the innate immune system activating macrophages (Mϕ), dendritic cells (D cells) and fibroblast-like synoviocytes (FLS). Costimulation-dependent interactions between D cells, T cells and B cells (wherein D cells present antigens and activate T cells, which, in turn activate B cells) occur in central lymphoid organs (primarily lymph nodes) (62, 63). Activated lymphocytes can migrate back to the synovium, triggering adaptive responses. Many positive feedback loops exist in the pathogenesis of RA (involving interactions between osteoclasts, chondrocytes, leukocytes, and synovial fibroblasts) and fuel the chronic inflammation associated with the disease and its progression (62, 63).

Bone erosion, resulting from a prolonged inflammatory attack on the synovial membrane, is an indicator of irreversible damage. At the molecular level, the association between inflammation and bone erosion is underpinned by the enzymes such as matrix metalloproteinases and aggrecanases, which degrade articular cartilage and bone, whilst promoting osteoclast differentiation (64).

Tumor necrosis factor (TNF) overexpression is a key inflammatory cascade associated with bone destruction and synovial inflammation in RA. This may be triggered by several factors, including interactions between T and B cells, synovial-like fibroblasts and Mϕ. **Increased TNF levels trigger an**

increase in many cytokines, including interleukin (IL) 6, which drives inflammation and bone destruction (65).

c) Pathophysiology — Ankylosing Spondylitis

AS is part of the axial spondyloarthritis family. It is a chronic axial spondyloarthropathy involving the spine and sacroiliac joint. AS, which can lead to spine deformities and disability (66), is characterized by sacroiliiitis (inflammation of the sacroiliac joint), spinal inflammation and enthesitis. Inflammatory back pain is the predominant symptom presented by patients with AS together with reduced spinal mobility (67).

Although not extensively studied, the pathophysiology of AS is thought to involve the inflammatory CD68+ and CD3+ T cells (68, 69). **Like many other chronic inflammatory diseases TNF-α, IL-1 and IL-6 have been found around the inflammatory lesions of the spine.** The presence of transforming growth factor- beta is associated with advanced AS (69). Furthermore, an interrelation between AS and inflammatory bowel disease suggests that the immune response in AS is triggered by the prolonged exposure of bacterial enteritis (70).

In summary, the importance of TNF-α as a centrally important cytokine in the pathogenesis of RA and AS has been stressed by experimental data showing the down-regulation of IL-1 and other pro-inflammatory cytokines by anti-TNF-α agents in *in vitro* synovial cell cultures, the up-regulation of TNF-α and TNF-α receptors in the rheumatoid synovium and in the sacroiliac joints (in AS) (71). Ultimately, the central role of TNF-α in RA and AS disease pathogenesis have been demonstrated by the success of anti-TNF-α agents in the treatment of these diseases.

d) Mechanism of Action of Etanercept

Etanercept is a recombinant human tumour necrosis factor receptor p75Fc fusion protein. It interferes with the soluble TNF-α by mimicking the inhibitory effects of naturally occurring soluble TNF receptors that deactivate TNF-α and therefore down-regulate immune responses. Etanercept acts as a decoy receptor for TNF-α, reducing TNF-α effects and hence represents a competitive TNF-α inhibitor (EPAR Enbrel®, 2014; Goffe and Cather, 2003). Etanercept may also modulate biological responses controlled by molecules further down the inflammatory cascade (e.g., cytokines, adhesion molecules, proteinases etc.) that are induced or regulated by TNF-α (CTD 2.5 section 1.1).

Due to the high affinity of etanercept towards TNF-α, its use in chronic inflammatory diseases such as RA and AS is particularly appropriate. The downstream effect of TNF-antagonism is complex. Generally speaking, antagonism of TNF-α in RA results in different outcomes. Specifically, anti-TNF therapy has impact on: 1) immunology (depressed T-cell response restored; reduction in rheumatoid-factor levels), 2) inflammation (diminished cytokine [IL-1, IL-6, TNF] production in joints and chemokines; reduction in serum levels of vascular endothelial growth factor (VEGF), IL-1, IL-6, chemokines and acute-phase proteins) and, 3) reduced levels of VEGF and angiogenesis. All of which results in the diminished damage to both cartilage and bone (72).

VEGF is the predominant cytokine regulating angiogenesis, which is a prominent feature in RA and other chronic inflammatory diseases in which increased blood vessel density facilitates cell trafficking in and out of the inflamed tissue. Elevated VEGF expression is seen in RA synovial tissue and elevated serum VEGF concentrations are seen in patients with RA. Serum VEGF concentrations were reduced in RA patients following etanercept treatment. Markers of endothelium or neovasculature showed reduced vascularity in the synovial tissue of etanercept-treated patients with RA (12).

In addition to binding to TNFR1 and TNFR2, TNF gains additional complexity from the distinct signaling pathways mediated through transmembrane-TNF (tmTNF), which can function as a ligand and a receptor. Receptor-mediated effects of sTNF and tmTNF can lead alternatively to activation of nuclear NF-κB or to apoptosis, depending on the metabolic state of the cell. TNF antagonists may induce cytotoxicity of tmTNF-bearing cells by Fc-dependent mechanisms, including ADCC and CDC. However, as previously discussed, these latter mechanisms are not thought to be important for the pathogenesis of RA and AS, therefore, they will not be discussed in this submission (12).

6.1.2 Justification of Extrapolation — Clinical Experience

Enbrel® etanercept is one of the first anti-TNF molecules marketed for which there has been nearly 18 years of clinical experience. As such, extensive clinical experience has been gathered from both the safety and efficacy perspective (14). It is expected that Brenzys will be equally as safe and effective as Enbrel® based on the demonstrated biosimilarity.

6.1.3 Justification of Extrapolation — Analytical Similarity

The development program of Brenzys involved an extensive series of physiochemical and *in vitro* biological/functional assays. These assays demonstrated comparability in all aspects the primary and higher order structures. At the functional level, TNF-α and LT-α3 binding assays demonstrated highly comparable binding affinities between Brenzys and Enbrel®. Although minor difference existed in terms of afucosylation level leading to small difference in FcγRIIIa binding, highly sensitive cell-based activity assays (ADCC, CDC) revealed that this had no impact on the function of Brenzys relative to Enbrel®. Furthermore, these mechanisms (ADCC, CDC) were not considered to be important for etanercept's mechanism of action in the indications of RA and AS.

6.1.4 Justification for Extrapolation — PK Similarity

In accordance with guideline EMA/CHMP/BMWP/403543/2010, healthy subjects were selected as appropriate population for demonstrating equivalence in exposure in a comparative single-dose study as this population showed good tolerability and is considered more homogeneous and hence more sensitive as compared to patient populations. Furthermore, the design of study SB4-G11-NHV conducted in healthy subjects was endorsed as the pivotal PK study by the Committee for Medicinal Products for Human Use (CHMP) scientific advice. This study demonstrated that the PK is equivalent between Brenzys and EU-Enbrel® in Part A, Brenzys and US-Enbrel® in Part B and EU-Enbrel® and US-Enbrel® in Part C. Supportive PK data in RA patients was also provided from study SB4-G31-RA. The results are consistent across both clinical studies and provide a robust evidence for a similar PK profile between Brenzys and Enbrel®.

Etanercept 25-mg twice weekly dosage regimen generates systemic exposures comparable to 50 mg once weekly, as predicted by PK modelling and simulation and confirmed by clinical studies (73, 74). As the PK of etanercept is comparable in patients with RA, AS, psoriasis, and healthy subjects (74-77), the PK results obtained with Brenzys, demonstrating biosimilarity between Brenzys and the reference product Enbrel® in healthy subjects with supportive evidence in RA patients, can be reasonably extrapolated to the other approved therapeutic indications of Enbrel®. An integrated population PK analysis found that health status or disease type did not significantly affect etanercept PK (77) (CTD 2.7.2, p.7,26). Therefore, extrapolation to the indication of AS is further justified.

6.1.5 Justification of Extrapolation — Clinical Efficacy of Brenzys in RA

The indication of RA has received marketing authorization by the EMA at the beginning of 2016 (11). The approval of this indication was granted on the basis of the results of a pivotal safety/efficacy/PK study

SB4-G31-RA (described in section *4.2.1 SB4-G31-RA* above). Briefly, this study compared Brenzys to Enbrel® in RA subjects with moderate to severe RA despite MTX therapy. Results of the primary endpoint of ACR20 response at Week 24 were highly comparable for both PPS1 (78.1% vs. 80.5%) and FAS (73.6% vs. 71.1%) between Brenzys and Enbrel®, respectively. The 95% CIs of the adjusted difference rates fell within the predefined equivalence margin of ±15% for both PPS1 and FAS (-9.54%, 4.80% and -5.50%, 8.82%, respectively). In addition, all other efficacy, safety, immunogenicity, and PK endpoints were also highly comparable.

Thus, based on the highly comparable clinical data demonstrating the therapeutic similarity between Brenzys and Enbrel®, Brenzys is expected to have similar efficacy in other diseases where TNF-α is the primary driver of disease etiology. In other words, Brenzys is expected to function equally well as Enbrel® in the extrapolated indication of AS.

6.1.6 Justification for Extrapolation — Safety/Immunogenicity

Etanercept is well established and widely used in clinical practice with a well-characterized safety profile. As to be expected for a TNF-α inhibitor, main safety issues are characterised by the immunosuppressive action of etanercept. Long-term inhibition of TNF-α could lead to a serious impairment of defence mechanisms against infections (in particular, opportunistic infections) and against the development of neoplasms (CTD 2.7.4, section 1.1). Overall, safety analyses of the studies conducted in both RA subjects and healthy volunteers did not identify any differences in the safety profile of Brenzys and Enbrel®.

Immunogenicity analyses in both RA subjects and healthy volunteers revealed that Brenzys was less immunogenic compared with Enbrel® although this had no impact on the PK and safety profile. In addition, almost all ADAs were transient and rarely neutralizing except for one patient in the Enbrel® treatment group (RA study). Furthermore, the clinical impact of the lower ADA formation / immunogenicity of Brenzys compared with Enbrel® appeared to be negligible as subgroup analysis revealed no difference in terms of safety and efficacy (CTD 2.7.2, section 4.3). Therefore, it is expected that Brenzys will be equally as safe as Enbrel® in AS patients.

6.1.7 Justification For Extrapolation — Dosing

In alignment with the concept of biosimilarity, the recommended doses of Brenzys are identical to the doses of the reference product Enbrel®, namely, 50 mg for both the RA and AS indications. This identical posology between Brenzys and Enbrel® for these indications is justified by the demonstrated highly comparable biosimilarity (efficacy/safety/PK in RA subjects and PK in healthy volunteers) between these two products.

The Brenzys dose of 50 mg SC corresponds to the highest labeled dose for Enbrel® and is as such in line with the suggestions made in guideline EMA/CHMP/BMWP/403543/2010. The dose proportionality of Enbrel® was well-established in single-dose PK studies. Comparable exposure between 25 mg twice weekly (approved for Enbrel®) and 50 mg once weekly (approved for Brenzys and Enbrel®) was demonstrated both after a single dose and at steady-state. Furthermore, the 50 mg once weekly dosing was shown to be therapeutically equivalent to 25 mg twice weekly at Week 8. Thus, additional studies with difference dosing schedule was not needed (CTD 2.7.2, p.8). **Thus, based on the above evidence, the extrapolation of indication to AS is justified.**

6.1.8 Justification of Extrapolation — International Regulatory Agencies Endorsement

Uncontrolled inflammatory process is common to all approved therapeutic indications of Enbrel®. Based on the primary mechanism of action of etanercept as well as the corresponding dosing among therapeutic indications, extrapolation of biosimilarity from RA to other approved indications is reasonably justified, which is further corroborated by a similar safety profile for Enbrel® across the granted therapeutic indications (46, 78). This approach has been endorsed by the Health Canada, EMA (EMA/CHMP/SAWP/9771/2012) and the US FDA (US FDA Meeting Minutes PIND 113462, 2012) (CTD 2.5, section 1.1).

6.2 Health Canada's Conclusion on Extrapolation

Health Canada considered extrapolation of clinical effects and adverse events to the ankylosing spondylitis population as appropriate.

6.3 International Regulatory Conclusions on Extrapolation

As per EMA CHMP Assessment Report's discussion on the benefit-risk balance (p.74-75):

"Extrapolation of the pharmacokinetic, efficacy and safety data generated in the two clinical trials in healthy volunteers and RA to the other authorised indications of Enbrel® is sufficiently justified.

As the PK of etanercept is comparable in patients with RA, ankylosing spondylitis (AS), psoriasis, and healthy subjects (McCormack and Wellington, 2004; Nestorov et al., 2006; Zhou, 2005; Zhou et al., 2011), **the PK results obtained with Benepali, demonstrating its biosimilarity with the reference product Enbrel® in healthy subjects can be reasonably extrapolated to the approved therapeutic indications of Enbrel®**.

With regards to the efficacy, it is well established that an uncontrolled inflammatory process is common to all therapeutic indications of Enbrel®. These indications share a common mechanism of action, i.e. the competitive inhibition of TNF-α binding and blockade of the ensuing inflammatory processes. **Therefore, and in line with the EMA guidelines on the similar biological medicinal products, the efficacy results obtained with Benepali, demonstrating equivalence of Benepali and Enbrel® in RA patients can be reasonably extrapolated to the other approved therapeutic indications of Enbrel®**.

Finally, with regards to safety, the adverse event profiles, clinical laboratory data, and other safety parameters did not show any significant safety issues which are not expected with etanercept treatment. There were no obvious relevant differences in the safety profile of Benepali as compared to Enbrel® with no obvious no indication of any safety imbalance in disadvantage of Benepali. **The safety outcomes obtained with Benepali in RA patients can be reasonably extrapolated to the other approved therapeutic indications of EU Enbrel®. There appears to be no relevant differences in the safety profile of etanercept throughout the approved therapeutic indications. As a biosimilar, the safety-related product information for Enbrel® also applies to Brenzys.**" (10)

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

In summary, following the above demonstration of pharmacokinetic and therapeutic similarity of Brenzys and Enbrel® in the clinical development program and the key involvement of TNF-α in RA and AS disease pathophysiology, this submission provided sufficient evidence to support the recommendation of Brenzys for all the requested indications, under the same labeling as Enbrel®.

6.4 CDR Comments on Extrapolation

The rationale supporting the extrapolation of clinical study data from patients with RA to patients with AS can be summarized with the following points:

1. The results of a phase 3 randomized controlled trial suggest the equivalence in clinical efficacy, PK profile, immunogenicity, and safety profile; of Brenzys to Enbrel; the consistency of Brenzys is further supported by the results of an extension study phase. A phase 1 trial in healthy volunteers further supports similarity in PK profile.
2. Clinicians' experience with the use of the reference etanercept product, Enbrel, for AS is extensive.
3. RA and AS share common inflammatory cytokines.
4. The role of TNF is important across both indications.

Other factors that should be taken into consideration when determining the appropriateness of the extrapolation of data to AS include:

1. Immunogenicity: Patients in the phase 3 clinical trial were all receiving methotrexate, which inhibits the immune response. According to the clinical expert consulted for the review, the concomitant use of methotrexate with an anti-TNF biologic in AS is not common. As such, there is a concern that immunogenicity of Brenzys compared with Enbrel cannot be extrapolated to the AS indication.
2. Calculation of equivalence margin: The manufacturer did not provide a clinical opinion or justification for the basis of choosing a 50% preservation of the ACR20 treatment effect of etanercept versus placebo as the basis for calculating the equivalence margin. The manufacturer has claimed the choice of margin was developed in consultation with regulators, and the granted indication by the EMA shows the calculation of the margin was sufficient to demonstrate equivalence in the opinion of the EMA. It is unclear if the equivalence margin calculated for the RA indication can also be applied to the AS indication.

The evidence presented in this submission suggested equivalence of Brenzys and the reference etanercept (Enbrel) according to the primary outcome (ACR20) in RA. In the absence of clinical evidence for patients with AS, the above points suggest that extrapolation of the safety and efficacy results from the rheumatoid studies may be reasonable. Beside the Health Canada NoC, Brenzys was also approved by the EMA and Therapeutic Goods Administration for both RA and AS indications, in addition to PsA and plaque arthritis.

7. COST COMPARISON

The Brenzys 50 mg PFS/auto-injector drug product will carry a price ($305.0000) approximately 25% lower relative to the publicly available Ontario Drug Benefit Formulary price of $405.9850 for the Enbrel 50 mg PFS/auto-injector. Consequently, the approximate 25% cost differential equates to $100.9850 in savings per 50 mg PFS/auto-injector.

In addition, the Brenzys 50 mg PFS/auto-injector drug product will carry a price of $305.0000, which is approximately 25% lower than the publicly available Ontario Drug Benefit Formulary price of $405.8600 for two vials of Enbrel (2 × $202.9300). Consequently, the approximate 25% cost differential equates to $100.8600 in savings per 50 mg PFS/auto-injector.

TABLE 27: COST COMPARISON OF SEB AND THE REFERENCE PRODUCT FOR RHEUMATOID ARTHRITIS

Drug/ Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost/Year[c] ($)
Brenzys	50 mg/mL PFS/auto-injector	Sterile solution for injection	$305.0000	50 mg/week	$15,860.00
Enbrel	50 mg/mL PFS	Sterile solution for injection	$405.9850		$21,111.22
	50 mg/mL auto-injector				
	25 mg/vial[d]	Lyophilized powder for reconstitution	$202.9300 (25 mg) $405.8600 (2 × 25 mg)		$21,104.72

PFS = pre-filled syringe; SEB = subsequent entry biologic.
[a] Ontario Drug Benefit Formulary (January 14, 2016).
[b] Brenzys and Enbrel product monographs.
[c] Fifty-two weeks per year.
[d] A 50 mg dose can also be given as two 25 mg subcutaneous injections. When administering Enbrel as two 25 mg injections, the injections should be given either on the same day once weekly or three or four days apart.

TABLE 28: COST COMPARISON OF SEB AND THE REFERENCE PRODUCT FOR ANKYLOSING SPONDYLITIS

Drug/ Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose[b]	Average Drug Cost/Year[c] ($)
Brenzys	50 mg/mL PFS/auto-injector	Sterile solution for injection	$305.0000	50 mg/week	$15,860.00
Enbrel	50 mg/mL PFS	Sterile solution for injection	$405.9850		$21,111.22
	50 mg/mL auto-injector				
	25 mg/vial[d]	Lyophilized powder for reconstitution	$202.9300 (25 mg) $405.8600 (2 × 25 mg)		$21,104.72

PFS = pre-filled syringe; SEB = subsequent entry biologic.
[a] Ontario Drug Benefit Formulary (January 14, 2016).
[b] Brenzys and Enbrel product monographs.
[c] Fifty-two weeks per year.
[d] A 50 mg dose can also be given as two 25 mg subcutaneous injections. When administering Enbrel as two 25 mg injections, the injections should be given either on the same day once weekly or three or four days apart.

7.1 CDR Reviewer Comments Regarding Cost Information

7.1.1 Summary of the Manufacturer's Analysis

The SEB etanercept (Brenzys) is available as a 50 mg/mL pre-filled syringe (PFS) and auto-injector for subcutaneous injection at a manufacturer-submitted price of $305.00 per 50 mg injection. The manufacturer submitted a cost comparison between Brenzys and the reference product etanercept (Enbrel) for two indications: adult patients with moderate-to-severe active RA, and patients with active AS. For this comparison, the manufacturer considered the recommended dose of 50 mg/week for both versions of etanercept, for both indications reviewed, as outlined within the product monographs. Under the assumption of similar clinical effects and dose, the manufacturer reported that Brenzys is 25% less costly than Enbrel, based on the manufacturer-submitted price for Brenzys ($305.00) and the Ontario Drug Benefit Formulary price for Enbrel ($405.9850) (May 2016).[3]

7.1.2 CADTH Common Drug Review Assessment of 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.
- Using the Ontario Drug Benefit price for Enbrel as a reference, the annual cost of Brenzys is 25% lower ($100.985 less per PFS) than Enbrel (Table 29).

TABLE 29: ETANERCEPT DOSING BASED ON THE MANUFACTURER'S COST COMPARISON

Treatment/Indications	Recommended Dose[a]	Number of Treatments per Year[a]	Price per 50 mg Syringe ($)[b]	Annual Cost($)
Brenzys/rheumatoid arthritis and ankylosing spondylitis	50 mg/week	52	$305.0000	$15,860
Enbrel/rheumatoid arthritis and ankylosing spondylitis	50 mg/week	52	$405.9850	$21,111

[a] Brenzys and Enbrel product monograph.
[b] Manufacturer-submitted price for Brenzys;[4] Ontario Drug Benefit price for Enbrel.[3]

7.1.3 Issues for Consideration

- The clinical expert indicated that patients may start or switch to the etanercept SEB Brenzys, but noted that additional clinical evidence would be helpful to support switching.
- Enbrel is also available for the following indications: moderate-to-severe active polyarticular juvenile idiopathic arthritis, adult patients with PsA, and adult patients with chronic moderate-to-severe plaque psoriasis. While these are not covered under the NoC application for Brenzys, there is the potential for off-label use of Brenzys in these indications.
- Enbrel is additionally available as a 25 mg per vial lyophilized powder for reconstitution, while Brenzys is available only as a 50 mg/mL PFS/auto-injector. The clinical expert indicated that a 25 mg per vial lyophilized powder for reconstitution is rarely used in clinical practice for adult patients; therefore, there would not be a preference to have Brenzys available in this dosage form.
- The reimbursement criteria for Enbrel differ across publicly funded drug plans in Canada as Enbrel is available as a restricted benefit with specific reimbursement criteria (Appendix 2). The expected savings from Brenzys compared with Enbrel are based on the assumption that the existing reimbursement criteria for Enbrel would be applied to Brenzys.

Conclusion

At the submitted price, the cost of Brenzys is 25% less than the reference product etanercept (Enbrel), when using the Ontario Drug Benefit price for Enbrel ($405.9850 per 50mg/mL PFS) as a reference.

8. DISCUSSION

The manufacturer provided one phase 3 RCT that evaluated the clinical equivalence of Brenzys and Enbrel in patients with RA (SB4-G31-RA) that also included an extension phase, as well as a phase 1 PK study that enrolled healthy volunteers (Study SB4-G11-NHV). In general, both studies were well conducted and well reported. SB4-G31-RA demonstrated that various outcomes for Brenzys fell within the equivalence margin for the reference etanercept. This included the primary outcome ACR20 at 24 weeks, and secondary outcomes of ACR20 at 52 weeks, ACR50 at 24 and 52 weeks, ACR70 at 24 and 52 weeks, DAS28 at 24 and 52 weeks, and European League Against Rheumatism (EULAR) response at 24 and 52 weeks. The extension phase provided supportive, non-comparative evidence of longer-term efficacy and tolerability of Brenzys. SB4-G11-NHV provided evidence of equivalence of the PK profiles of Brenzys and the reference etanercept.

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 no representation of a geriatric population older than 75 years. It is important to take into consideration, however, that the aim of the submitted evidence was to support the notion of equivalence between Brenzys and the reference product etanercept, rather than to generalize the results to the Canadian population.

Given the similarity in some inflammatory pathways in both diseases, the important role of TNF in both diseases, the extensive clinical experience with the reference etanercept, and the provided evidence of clinical and PK equivalence, the extrapolation of evidence for equivalency between the Brenzys and the reference etanercept from studies conducted in patients with RA to patients with AS is likely reasonable. Extrapolating the immunogenicity data, however, is limited due to concomitant use of methotrexate in the phase 3 trial.

Patient groups expressed a concern for those who are currently taking the reference biologic product, Enbrel, and may be required to be switched to the SEB (Brenzys). They speculated that this could occur 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 SEB given the lack of longer-term data on safety and sustainability. The extension phase of SB4-G31-RA switched all patients who were treated originally with the reference etanercept to the SEB Brenzys, and initial data suggested that these patients continued to improve. However, these results are not compared statistically against a group of patients who remained on the reference product etanercept, and as such, any results obtained are considered descriptive and exploratory in nature and offer limited evidence upon which conclusions regarding the appropriateness of switching patients from the reference product to the SEB could be drawn.

8.1 Potential Place in Therapy[2]

The reference product, etanercept (Enbrel), has been widely used for patients with RA, PsA and AS for more than 10 years. In terms of biologic drugs, anti-TNF drugs have been the first-line treatment option for all three of these indications, and etanercept has been one of the most frequently chosen. Typically, anti-TNF drugs are used after an inadequate trial of two NSAIDs for patients with AS, and after an inadequate trial of DMARD monotherapy or combination therapy in patients with RA. Etanercept has the advantage of having the longest observation period for safety and efficacy for a subcutaneous anti-TNF drug. It may be used with or without methotrexate, which is often poorly tolerated.

The etanercept SEB would be an appropriate choice for any biologic-naive or biologic-experienced patient who would receive the reference product, Enbrel, for treatment of both indications under review (RA and AS). At this time, there is limited evidence to support switching a patient from the reference product, Enbrel, to the etanercept SEB.

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

9. CONCLUSION

Overall, the manufacturer provided sufficient data from one phase 3 clinical equivalence trial and one phase 1 pharmacokinetic trial to demonstrate similar efficacy across the primary and secondary outcomes, as well as safety outcomes, between the SEB Brenzys and the reference drug, Enbrel. The extrapolation of the evidence to support equivalence of these outcomes in RA patients to AS patients also appears to be reasonable. There is currently limited evidence available to support switching a patient from the reference product, Enbrel, to the etanercept SEB Brenzys.

APPENDIX 1: ADDITIONAL DATA

TABLE 30: DETAILED SUMMARY OF PHYSICOCHEMICAL TEST METHODS AND RESULTS FOR THE COMPARABILITY OF BRENZYS (BRENZYS) DRUG PRODUCT (DP) AND ENBREL® (ETN)

Test Method(s)	Summary of Results	Reference(s)
Primary structure		CTD 2.3.R, section 5.2.1
Molecular weight (MW)	• MW was determined using mass spectrometry. • **MW of Brenzys and the reference ETNs were similar.**	
Amino acid (full) sequencing	• The full amino acid sequence of Brenzys DP was compared to the amino acid sequence encoded by the proposed DNA sequence. • **The amino acid sequence of Brenzys was identical to that of EU-ETN.**	
N-terminal sequence analysis	• N-terminal sequencing was performed by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) to determine the integrity of Brenzys and EU-ETN. • **Three forms of N-terminal peptide were found for Brenzys and ETN:** ▪ Intact (1-LPAQVAFTPYAPEPGSTCR-) ▪ Leu deleted (1-PAQVAFTPYAPEPGSTCR-) ▪ Leu-Pro deleted (1-AQVAFTPYAPEPGSTCR-) • ETN sourced from different countries possessed different contents of the N-terminal peptides. • The relative levels of the N-terminal peptides in Brenzys differed to the levels of these peptides in ETN sourced from the different countries. • **It is understood that the heterogeneity of the N-terminal sequence is induced by an unknown mechanism of truncation, and cannot be controlled during the manufacturing process.** • **TNF-α binding assay and TNF-α neutralization assay demonstrated that these differences had no effect on the biological activity.** • This finding has been substantiated in conference presentations of the Sandoz (FDA Advisory Committee on Pharmaceutical Science and Clinical Pharmacology) where it was shown that the N-terminus was observed to be variable depending on the source of the reference and this had no effect on the biological function of the molecule. • **Although differences were observed, it has been concluded that these differences do not affect the determination that Brenzys is similar to ETN.**	
C-terminal sequence analysis	[redacted]	
Peptide mapping	• Peptide mapping for Brenzys and EU-ETN was performed using LC-ESI-MS/MS after digestion with different proteases (trypsin, Lys-C, and aspartic acid [Asp]-N). • The resulting peptides were analyzed with respect to their post-translational modifications, sequence variants, and whole sequence. • The chromatograms showed identical patterns between Brenzys and EU-ETN, irrespective of protease used. • **Therefore, the peptide map for Brenzys was considered similar to that of the ETN.**	
Methionine (Met) oxidation	[redacted]	

Test Method(s)	Summary of Results	Reference(s)
	[redacted]	
Deamidation	• The deamidation level of Asn was quantified using LC-ESI-MS/MS after digestion with trypsin. • Minor differences were observed between the relative deamidation levels of the 7 possible Asn residues for Brenzys and ETN. • **FcRn binding assay showed that these minor differences had no effect on FcRn binding affinity and therefore considered not significant and should not affect the assessment of biosimilarity.**	
Disulphide bond	• The disulphide bonds were analyzed using LC-ESI-MS/MS. • **The disulphide linkage patterns are similar for Brenzys and EU-ETN.**	
C-terminal Lys variant analysis	• The relative level of the Lys variant at the heavy chain C-terminus was determined from the peptide mapping results. • The relative level of the Lys variant in Brenzys was lower than that in EU-ETN indicating that most of the Lys on the C-terminus of Brenzys was found cleaved. • The heterogeneity of C-terminal residues is a characteristic of therapeutic monoclonal antibodies and C-terminal Lys variation that is known not to impact PK profiles (79). • It has been suggested that there is no relationship between the presence of C-terminal Lys and the biological activity of the Fc fusion protein, and that the C-terminus is oriented away from the Fc receptor epitope (80). • In addition, the C-terminal Lys does not possess any physiological effect as it is cleaved by carboxypeptidase as it enters the blood (81). • **TNF-α binding functional assay demonstrated that C-terminal Lys content did not impact TNF-α binding activity. Therefore, the difference in C-terminal Lys content is not considered significant.**	
Free sulfhydryl group quantification	• The free sulfhydryl group in Brenzys and ETN was quantified [redacted] • Minor differences were seen in the concentration of free sulfhydryl and the percent free sulfhydryl between Brenzys and EU-ETN. • However [redacted], the result suggests that essentially all 58 Cys residues (29 residues per monomer) were linked by disulphide bonds and there was practically no free Cys residue. • **Therefore, the minor difference in free sulfhydryl group content is not considered significant.**	
Physicochemical: Chromatography		CTD 2.3.R, section 5.2.2
Size Exclusion Chromatography (SEC)	• Size exclusion-high performance liquid chromatography (SEC) under native conditions was used to determine the percent aggregate and percent main peak in Brenzys and was used to determine the similarity of Brenzys with ETN. • Slight differences were observed in the chromatograms for Brenzys with ETN. • The HMW in EU-ETN were double peaks, whereas there was a single peak in Brenzys. • From the results of high pressure (HP)-SEC with multiangle laser light scattering (MALLS)	

Test Method(s)	Summary of Results	Reference(s)
	analysis and sedimentation velocity-analytical ultracentrifugation (SV-AUC) analysis, **the HMW in both Brenzys and ETN were identified mainly as dimers and therefore the difference in peak appearance was not considered significant**. [redacted] • [redacted]	
Hydrophobic Interaction Chromatography (HIC)	[redacted] • [redacted] • **The differences in the HIC peaks were characterized through the Structure-Activity Relationship (SAR) study, which supported that the difference in relative peak contents between Brenzys and the reference product was not considered significant.**	
CEX-HPLC [redacted]	• Cation exchange chromatography (CEX) was used to evaluate the charge heterogeneity of Brenzys and ETN. • The level of %Main + %Acidic variants in Brenzys was higher than that of ETN and the level of %Basic in Brenzys was lower than the ETN. • SAR studies revealed that the difference in the content of the basic charge variant was mainly caused by the difference in the content of C- terminus with Lys. • [redacted] • Therefore, it is appropriately considered that the difference in basic variant content will not influence the binding activity of Brenzys. • The charge variant of the originator ETN itself has changed substantially following a process change (82) [redacted]. • **In the Schiestl publication, it is stated that despite the change in charge variant content, all tested products remained on the market and the observed changes were predicted not to result in an altered clinical profile and this was seen as acceptable by the health authorities.** • **Therefore, it is considered that the difference in relative charge variant content is not a significant difference, and will not be associated with clinical differences between Brenzys and EU-ETN.**	

Test Method(s)	Summary of Results	Reference(s)
Physicochemical: Electrophoresis		CTD 2.3.R, section 5.2.3
Capillary Electrophoresis-Sodium Dodecyl Sulfate (CE-SDS): Reducing	• [redacted]. • The purity of Brenzys was shown to be similar to that of EU-ETN. • [redacted]	
CE-SDS: Non-Reducing	• [redacted] • The purity of Brenzys was shown to be similar to that of EU-ETN. • [redacted]	
Charge Heterogeneities by Imaged Capillary Isoelectric Focusing (icIEF)	• The similarity range for the charge variants established was 16.4 to 31.1% for acidic variants, 45.8 to 57.0% for main portion, and 17.6 to 32.2% for basic variants. • Although Brenzys was found to possess a higher content of acidic isoform and lower content of basic isoform when compared with ETN [redacted] • SAR studies using CEX-HPLC showed that the charge variant content did not affect TNF-α binding activity and thus the variation in charge variants did not translate to differences in the biological activity of Brenzys. • Therefore, the differences in charge variants were not considered significant.	
Physicochemical: Glycan Profile		CTD 2.3.R, section 5.2.4
N-linked Glycosylation Site	• The N-linked glycosylation sites of Brenzys and ETN were determined using LC-ESI-MS/MS. • The N-linked glycosylation sites of Brenzys were [redacted] which were identical to those of EU-ETN.	
N-glycan Identification	• The N-glycan structures of Brenzys and ETN were identified by procainamide labeling using LC-ESI-MS/MS. • The N-glycan profile of Brenzys was similar to EU-ETN.	

N-glycan Profile by 2-aminobenzamide (2-AB) by UPLC	• Hydrophilic Interaction Ultra-performance Liquid Chromatography (HILIC-UPLC) was used to determine the relative quantity of N-glycan species.
	• [redacted]
	• The N-glycan profiles of Brenzys batches were different from those of EU-ETN:
	  • **The afucosylated glycan content in Brenzys was higher than observed for EU-ETN.** The afucosylated glycan level in therapeutic proteins is associated with FcγRIIIa binding activity and ADCC. <u>However, ADCC is not considered to be a mechanism of action of etanercept so these differences would not be clinically meaningful</u>.
	  • **ADCC analysis demonstrated absence of ADCC activity in both Brenzys and ETN**.
	  • [redacted]
	  • [redacted]	

Test Method(s)	Summary of Results	Reference(s)
	• **The neutral galactosylated glycan content in Brenzys was shown to be more variable than observed for EU-ETN.** The content of neutral galactosylated glycan is generally associated with CDC activity for monoclonal antibodies (Rituximab Product Approval Information, FDA). However, CDC is not known to be a mechanism of action of etanercept • **CDC analysis demonstrated similar CDC activity between Brenzys and ETN.** • Overall, results demonstrated that the N-glycan profile of Brenzys was generally similar to that of pre-change ETN and, therefore, **the difference between the N-glycan profiles of Brenzys and the reference products was not considered to have any impact on the clinical profile of Brenzys.** • In a recent publication (82), the N-glycan profile of several batches of ETN were analyzed and the results showed that there was an abrupt change in the N-glycan profile of ETN, most probably caused by changes in the manufacturing process. • These differences were not considered clinically meaningful and no clinical studies were required to demonstrate comparability as part of the variation submission. • **Therefore, the differences in N-glycan profiles of Brenzys and EU-ETN are not considered significant.**	
Fc Specific Glycan Profile	• Overall, the results indicated that the charged glycan content (%charged) was similar for Brenzys (slightly wider range) and EU-ETN. • The afucosylated glycan content (%afucose) and the neutral galactosylated glycan content (%gal; slightly wider range) were slightly higher in Brenzys than EU-ETN. • For monoclonal antibodies, afucosylated glycans in the Fc region are generally associated with ADCC and the neutral galactosylated glycans are associated with CDC (84). As previously discussed, ADCC and CDC are not considered to be mechanisms of action of etanercept. Moreover, **ADCC assays and CDC assays demonstrated absence of ADCC activity and similar CDC activity in Brenzys and ETN**. • Overall, the difference in contents of afucosylated glycan and galactosylated glycan are not considered to be significant.	
O-glycan Site by LC-MS	• O-linked glycosylated peptides were analyzed using reverse phase (RP)-UPLC coupled to ESI-MS/MS. • All O-linked glycosylated sites identified in Brenzys were identical to those found in EU-ETN. • **Therefore, Brenzys was considered to be similar to EU-ETN in terms of O-linked glycosylation sites.**	
O-glycan Profile by β-elimination	• The O-linked glycans were analysed by alkaline β-elimination with sodium hydroxide and sodium borohydride. • There was an abundant of sialylated O-glycans in Brenzys. • All O-glycan peaks that were detected in EU-ETN were detected in the Brenzys and the patterns between Brenzys and EU-ETN were also identical with respect to the retention times of the detected peaks, differing only in peak areas. • The intensity of each peak of O-glycosylated peptide was slightly different between Brenzys and EU-ETN indicating that Brenzys showed lower O-glycan occupancy. • Peak 1 and Peak 2 contents were similar between Brenzys and EU-ETN but the content of Peak 3 in Brenzys was shown to be slightly higher than EU-ETN. • The di-sialylated O-glycan (Peak 3) content of Brenzys is higher than that of EU-ETN and this high level of di-sialylated O-glycan compensates for the low level of O-glycan occupancy seen in Brenzys. **Overall, this results in similar TSA contents between Brenzys and EU-ETN**. • The above results are supported by the Schiestl paper, which analyzed the differences in ETN following a change to the manufacturing process (82): • When O-glycan profiles of the pre- and post-change ETN were compared, it was	

Test Method(s)	Summary of Results	Reference(s)
	determined that the O-glycan profile of Brenzys was similar to that of pre-change reference product. • **Overall, the slight difference in Peak 3 content was not considered significant.**	
Total Sialic Acid	• The TSA content of Brenzys and ETN was analyzed using ion-exclusion chromatography. [redacted] • The TSA contents of all Brenzys batches were within similarity range defined for the similarity study. [redacted] • [redacted]	
Biophysical: Higher-Order Structure		CTD 2.3.R, section 5.2.5
Hydrogen / Deuterium Exchange (H/DX)	• H/DX analysis provides information about the solvent accessibility of various parts of the molecule, and thus the tertiary structure of the protein. • **Results indicated that Brenzys is similar to EU-ETN.**	
Differential Scanning Calorimeter [redacted]	• [redacted]DSC was used to determine the heat-induced protein denaturation pattern of Brenzys and ETN. • **The shapes of the thermal scans for Brenzys and ETN were comparable and the results obtained of T_m1, T_m2 and T_m3 values are considered similar for Brenzys and EU-ETN.** [redacted]	
Micro-Flow Imaging (MFI)	• MFI was used for the quantification and visualization of sub-visible particles in the µm-size range. [redacted] • [redacted] • **Overall, the results from MFI were similar between Brenzys and EU-ETN.**	
Dynamic Light Scattering (DLS)	• DLS was used to analyze sub-visible aggregates in the nm-size range. • [redacted] • **Overall, the DLS results indicated that the main peak diameter was similar between Brenzys and EU-ETN and Brenzys was shown to be as mono-disperse as ETN.**	
High Pressure Size-Exclusion Chromatography (HP-SEC) with MALLS Detection	• HP-SEC with MALLS detection was used to determine the relative content of HMW, monomer, and LMW protein. [redacted] • [redacted]	

Test Method(s)	Summary of Results	Reference(s)
	[redacted] • HP-SEC with MALLS detection indicated that chromatograms from UV detection and MW estimation of monomer peak are similar for Brenzys and EU-ETN.	
Fluorescence Spectroscopy: Intrinsic Fluorescence	[redacted] • **As the spectra for Brenzys were within the range of the spectra for EU-ETN, the intrinsic fluorescence spectrum of Brenzys was considered to be similar to that of EU-ETN.**	
Fluorescence Spectroscopy: Extrinsic Fluorescence	[redacted]	
Fourier Transform Infrared Spectroscopy	• FTIR analysis of the secondary structure of Brenzys and ETN showed similar spectra. [redacted] Therefore, the FTIR spectra of Brenzys were considered to be similar to those of EU-ETN.	
Far-UV CD Spectroscopy	[redacted] the products have similar high order structures.	
Sedimentation Velocity-Analytical Ultra-centrifugation (SV-AUC)	• AUC provides information on the size and shape of macromolecules in solution with very few restrictions on the sample or the nature of the solvent. • SV-AUC was used as an orthogonal method to HP-SEC MALLS to investigate the monomer content, the presence of aggregates and fragments, as well as the molecular weight of the main molecule in Brenzys and ETN. [redacted] The aggregate content range for ETN was higher than seen for Brenzys but this was not considered to be significant [redacted]	
[redacted]	• [redacted]	

TABLE 31: DETAILED SUMMARY OF *IN VITRO* FUNCTIONAL TEST METHODS AND RESULTS FOR THE COMPARABILITY OF Brenzys (Brenzys) DRUG PRODUCT (DP) AND ENBREL® (ETN)

Test Method(s)	Summary of Results	Reference(s)
Mechanism of Action-related Biological Assays		CTD 2.3.R, section 5.2.6
TNF-α Binding Assay	• The relative binding activity of Brenzys and ETN to TNF-α was determined by fluorescence resonance energy transfer (FRET) based competitive binding assay. • The ranges for the binding activity of Brenzys and EU-ETN relative to the bioassay standard [redacted] were similar within the similarity range. **Therefore, the TNF-α binding activity of Brenzys and EU-ETN was considered to be similar.**	
LT-α3 Binding Assay	• LT-α3 binding to Brenzys and ETN was determined by a FRET assay. • The ranges for the binding activity of Brenzys and EU-ETN relative to the bioassay reference standard [redacted] were similar and the LT-α3 binding activity results for Brenzys DS and DP were within the similarity range. **Therefore, the LT-α3 binding activities of Brenzys and EU-ETN were considered to be similar.**	
TNF-α Neutralization Assay [redacted]	• By measuring luciferase activity, the inhibitory effect of Brenzys and ETN was assessed. [redacted] • [redacted] • **Overall, the potencies of Brenzys and EU-ETN determined by the TNF-α neutralization assay were considered to be similar.**	
Fc-Related Biological Activities		CTD 2.3.R, section 5.2.7
FcγRIa Binding Assay	• The binding activity of Brenzys and ETN to FcγRIa was determined by the FRET assay. [redacted] • [redacted]	
FcγRIIa Binding Assay by Surface Plasma Resonance (SPR)	• The binding affinity of Brenzys and ETN to FcγRIIa was determined by SPR. • The range of FcγRIIa binding affinity data for Brenzys was within the range observed for EU-ETN and the results for Brenzys DS and DP were within the pre-defined similarity range. • **Therefore, FcγRIIa binding affinities of Brenzys and ETN were considered to be similar.**	
FcγRIIb Binding Assay	• The binding affinity of Brenzys and ETN to FcγRIIb was determined by SPR. • The range of FcγRIIb binding affinity data for Brenzys was slightly different to the range observed for EU-ETN. However, the results for Brenzys DS and DP were within the pre-defined similarity range. • **Therefore, FcγRIIb binding affinities of Brenzys and ETN were considered to be similar.**	
FcγRIIIa Binding Assay (V158 allotype)	• The binding affinity of Brenzys and ETN to FcγRIIIa was determined by SPR. • The range of FcγRIIIa binding affinity data for Brenzys was within the range observed for EU-ETN and the results for Brenzys DS and DP were within the pre-defined similarity range. • A trend was observed where the binding affinity of Brenzys to FcγRIIIa was found to be slightly higher than that of ETN.	

Test Method(s)	Summary of Results	Reference(s)
	• This could have been attributable to the higher afucosylated N-glycan levels of Brenzys. The binding activity to FcγRIIIa is associated with ADCC activity, therefore differences in FcγRIIIa binding activity could potentially affect ADCC activity. **However, analysis has shown that ADCC activity was absent in both Brenzys and EU-ETN.** • **Therefore, FcγRIIIa binding affinities of Brenzys and ETN were considered to be similar and the minor differences were not considered to be clinically meaningful.**	
FcRn Binding Assay	• The binding affinity of Brenzys and ETN to FcRn was determined by SPR. • The binding affinity of Brenzys DS and DP were within the similarity range. **Therefore, the FcRn binding affinities of Brenzys and EU-ETN were considered to be similar.**	
Additional Biological Assays		CTD 2.3.R, section 5.2.8
TNF-α Binding Assay from Different Species	• It is well known that TNF-α is highly conserved [redacted] To confirm whether Brenzys and ETN have binding activity to TNF-α of different species, a binding assay was performed by enzyme-linked immunosorbent assay (ELISA). • There was no difference in binding activity between Brenzys DP and EU-ETN. • Similar trends were observed in different species [redacted], which show that there were no differences across species. • **These results indicate that Brenzys DP and EU-ETN had similar TNF-α binding activity across species.**	
FcγRIIIa Binding Assay (F158 allotype)	• The binding affinity of Brenzys and EU-ETN to FcγRIIIa (F158) was determined by SPR. • **The binding affinity of Brenzys DP to FcγRIIIa (F158) was slightly higher than that of EU-ETN.** • However, the V158 allotype of FcγRIIIa has a higher binding affinity for the Fc region of antibodies compared to the F158 allotype. The difference in binding affinity of the F158 allotype is thought to contribute *less* to ADCC compared to the V158 allotype. • **Therefore, it is considered that the difference in binding affinity to FcγRIIIa (F158) is not significant, as the binding affinity of Brenzys to FcγRIIIa (V158) was similar to ETN.**	
FcγRIIIb Binding Assay	• The binding affinity of Brenzys and EU-ETN to FcγRIIIb receptors was determined by SPR. • The average binding affinity of Brenzys DP to FcγRIIIb was slightly higher than that of EU-ETN, similar to the results found in the FcγRIIIa binding assay for both V158 and F158 allotypes. Since FcγRIIIb is highly homologous to FcγRIIIa, it is expected that the binding affinity of FcγRIIIb is similar to that of FcγRIIIa. • **Although differences were observed, this should not be clinically relevant.**	
C1q Binding Assay	• The binding activity of Brenzys and EU-ETN to the complement component C1q was assessed by sandwich ELISA. • The C1q binding activity of Brenzys DP was similar to the results for ETN and no statistically significant differences were observed. • **Therefore, the C1q binding activities of Brenzys and EU-ETN were similar.**	
CDC Assay	• The CDC activity of Brenzys and EU-ETN was analyzed by an enzyme reaction-based CDC assay. For comparison of CDC activity, Remicade was analyzed concurrently as CDC is considered to be a mechanism of action of Remicade. • The CDC activity results for Brenzys DP were within the CDC activity range for EU-ETN and no statistical difference was observed. • [redacted]	
ADCC Assay	• To confirm the absence of ADCC activity in Brenzys and EU-ETN, ADCC activity was analyzed using a modified natural killer (NK) cell line and the results were presented as the ADCC activity relative to Remicade. • **Relative to Remicade, the ADCC activity of Brenzys and EU-ETN was lower than < 5%,**	

Test Method(s)	Summary of Results	Reference(s)
	demonstrating the absence of ADCC activity in both Brenzys and EU-ETN.	
Apoptosis	• The apoptosis activity of Brenzys and EU-ETN was measured using a Caspase-Glo® 3/7 kit. • [redacted] • **Therefore, the apoptosis activities of Brenzys and EU-ETN were considered to be similar.**	

TABLE 32: SUBGROUP ANALYSIS OF ACR20 RESPONSE AT WEEK 24 BY ANTI-DRUG ANTIBODY STATUS AND BASELINE CRP LEVEL IN STUDY SB4-G31-RA (PPS1)

ACR20 Response at Week 24	Treatment (Brenzys 50 mg) (EU-Enbrel® 50 mg)	n/n'	(%)	Adjusted Difference Rate	95% CI
Post-dose Anti-drug Antibody Status					
Negative	Brenzys	191/245	78.0	-3.74%	-11.27%, 3.79%
	Enbrel®	169/207	81.6		
Positive	Brenzys	2/2	100	22.14%	-54.79%, 99.07%
	Enbrel®	21/29	72.4		
Baseline CRP Level					
≥ 10 mg/L	Brenzys	[redacted]	[redacted]	[redacted]	[redacted]
	Enbrel®				
< 10 mg/L	Brenzys	[redacted]	[redacted]	[redacted]	[redacted]
	Enbrel®				

n': number of patients with an assessment; n: number of responders.
Source: CTD 2.7.3, Section 3.3.

TABLE 33: NUMBER (%) OF PATIENTS WITH TEAES AND NUMBER OF EVENTS BY PREFERRED TERM THAT OCCURRED IN ≥ 2% OF PATIENTS IN ANY TREATMENT GROUP IN STUDY Brenzys-GB31-RA (SAFETY SET)

Treatment	Brenzys 50 mg N=299			EU-Enbrel® 50 mg N=297			Total N=596		
Preferred term	n	(%)	E	n	(%)	E	n	(%)	E
Any TEAEs	175	(58.5)	533	179	(60.3)	646	354	(59.4)	1179
Upper respiratory tract infection	24	(8.0)	28	16	(5.4)	18	40	(6.7)	46
Alanine aminotransferase increased	18	(6.0)	25	17	(5.7)	26	35	(5.9)	51
Nasopharyngitis	15	(5.0)	17	16	(5.4)	17	31	(5.2)	34
Headache	13	(4.3)	15	8	(2.7)	16	21	(3.5)	31
Hypertension	11	(3.7)	16	11	(3.7)	12	22	(3.7)	28
Rheumatoid arthritis	9	(3.0)	10	10	(3.4)	11	19	(3.2)	21
Aspartate aminotransferase increased	8	(2.7)	13	9	(3.0)	10	17	(2.9)	23
Viral infection	7	(2.3)	7	5	(1.7)	5	12	(2.0)	12
Injection site erythema	6	(2.0)	16	33	(11.1)	85	39	(6.5)	101
Bronchitis	6	(2.0)	6	6	(2.0)	6	12	(2.0)	12
Rash	6	(2.0)	6	4	(1.3)	4	10	(1.7)	10
Rhinitis	6	(2.0)	6	4	(1.3)	5	10	(1.7)	11
Leukopenia	6	(2.0)	7	3	(1.0)	4	9	(1.5)	11
Pharyngitis	5	(1.7)	5	8	(2.7)	9	13	(2.2)	14
Diarrhoea	5	(1.7)	5	7	(2.4)	8	12	(2.0)	13

Treatment	Brenzys 50 mg N=299			EU-Enbrel® 50 mg N=297			Total N=596		
Urinary tract infection	5	(1.7)	5	7	(2.4)	9	12	(2.0)	14
Cough	4	(1.3)	4	10	(3.4)	11	14	(2.3)	15
Lymphocyte count decreased	4	(1.3)	4	6	(2.0)	8	10	(1.7)	12
Erythema	2	(0.7)	4	10	(3.4)	10	12	(2.0)	14
Dizziness	2	(0.7)	3	7	(2.4)	7	9	(1.5)	10
Injection site rash	2	(0.7)	2	6	(2.0)	11	8	(1.3)	13
Injection site reaction	1	(0.3)	1	8	(2.7)	13	9	(1.5)	14

TEAE: treatment-emergent adverse event. Adverse events were coded by system organ class and preferred term using the MedDRA Version 16.0 coding dictionary. Percentages were based on the number of subjects in the safety set.
Source: CTD 2.7.4, Table 8.

TABLE 34: TEAES OF ADMINISTRATION SITE REACTIONS BY SYSTEM ORGAN CLASS, PREFERRED TERM IN STUDY SB4-G31-RA (SAFETY SET)

System Organ Class Preferred Term	Brenzys 50 mg N=299			Enbrel® 50 mg N=297			Total N=596		
	n	(%)	E	n	(%)	E	n	(%)	E
Any TEAE	11	(3.7)	22	52	(17.5)	157	63	(10.6)	179
General Disorders And Administration Site Conditions	11	(3.7)	22	52	(17.5)	157	63	(10.6)	179
Injection Site Erythema	6	(2.0)	16	33	(11.1)	85	39	(6.5)	101
Injection Site Rash	2	(0.7)	2	6	(2.0)	11	8	(1.3)	13
Injection Site Haematoma	1	(0.3)	1	0	(0.0)	0	1	(0.2)	1
Injection Site Hypersensitivity	1	(0.3)	1	2	(0.7)	10	3	(0.5)	11
Injection Site Pruritus	1	(0.3)	1	4	(1.3)	6	5	(0.8)	7
Injection Site Reaction	1	(0.3)	1	8	(2.7)	13	9	(1.5)	14
Application Site Erythema	0	(0.0)	0	3	(1.0)	18	3	(0.5)	18
Application Site Reaction	0	(0.0)	0	1	(0.3)	1	1	(0.2)	1
Injection Site Bruising	0	(0.0)	0	1	(0.3)	1	1	(0.2)	1
Injection Site Dermatitis	0	(0.0)	0	1	(0.3)	2	1	(0.2)	2
Injection Site Inflammation	0	(0.0)	0	2	(0.7)	2	2	(0.3)	2
Injection Site Oedema	0	(0.0)	0	3	(1.0)	6	3	(0.5)	6
Injection Site Pain	0	(0.0)	0	1	(0.3)	1	1	(0.2)	1
Injection Site Swelling	0	(0.0)	0	1	(0.3)	1	1	(0.2)	1

TEAE: treatment-emergent adverse event under the high-level group term, Administration Site Reactions. - E: frequency of TEAEs; Percentages were based on the number of subjects in the Safety set.
Source: CSR SB4-G31-RA, Table 14.3.1-1.13.

[redacted]

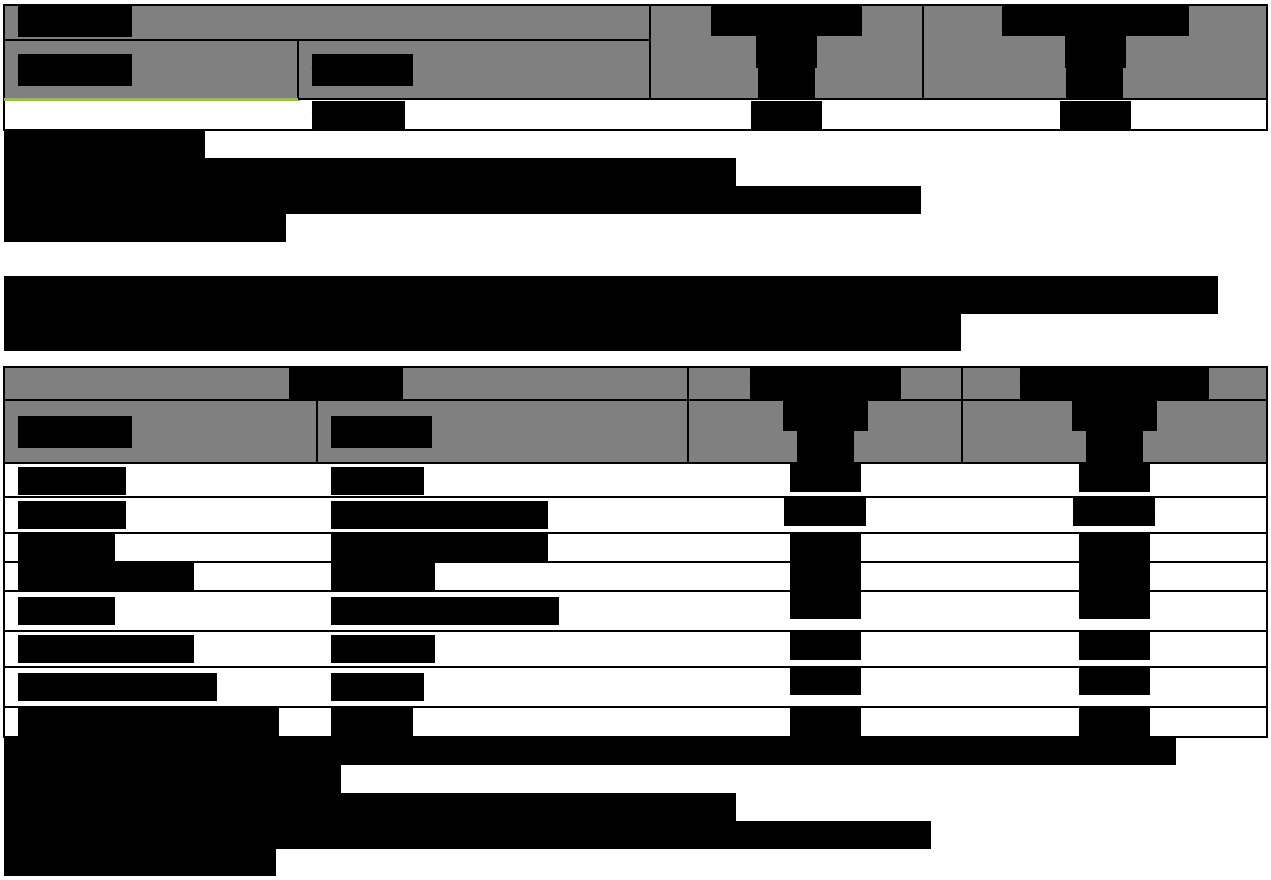


TABLE 35: NUMBER (%) OF SUBJECTS WITH TEAES AND NUMBER OF EVENTS BY PREFERRED TERM OCCURRED IN ≥ 5% OF SUBJECTS IN ANY TREATMENT IN STUDY SB4-G11-NHV (SAFETY SET)

Preferred Term[a]	Part A				Part B				Part C			
	Brenzys		EU-Enbrel®		Brenzys		US-Enbrel®		EU-Enbrel®		US-Enbrel®	
	N=46		N=46		N=46		N=46		N=46		N=46	
	n (%[c])	E	n (%[c])	E	n (%[c])	E	n (%[c])	E	n (%[c])	E	n (%[c])	E
Any TEAEs[b]	18 (39.1)	26	16 (34.8)	21	23 (50.0)	35	20 (43.5)	33	17 (37.0)	30	14 (30.4)	22
Nasopharyngitis	5 (10.9)	5	2 (4.3)	2	2 (4.3)	2	2 (4.3)	2	2 (4.3)	2	1 (2.2)	1
Headache	4 (8.7)	5	2 (4.3)	2	3 (6.5)	3	4 (8.7)	4	4 (8.7)	6	3 (6.5)	3
Injection site reaction	2 (4.3)	2	3 (6.5)	3	3 (6.5)	3	3 (6.5)	3	1 (2.2)	1	3 (6.5)	3
Back pain	1 (2.2)	1	0 (0.0)	0	1 (2.2)	1	3 (6.5)	3	0 (0.0)	0	0 (0.0)	0
Dizziness	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	3 (6.5)	3	1 (2.2)	1	0 (0.0)	0

[a] Preferred terms are sorted in descending frequency of Brenzys-related TEAEs in Part A and Part B, and of EU-Enbrel®-related TEAEs in Part C.
[b] Adverse events were coded by preferred term using the MedDRA Version 15.1 coding dictionary. N: number of subjects in the safety set; Subjects n: number of subjects who experienced each event.
[c] Percentage is Subjects n divided by N. E: number of events experienced.
Source: CTD 2.7.4, Table 7.

TABLE 36: SERUM PK PARAMETERS FOR PART C IN STUDY SB4-G11-NHV (PK POPULATION)

	n	EU-Enbrel® 50 mg (N=42)	n	US-Enbrel® 50 mg (N=42)	Ratios of Geometric Means; 90% CI
AUC_{inf} (µg·h/mL), Mean (SD)	42	790.110 (274.2535)	42	768.228 (238.1251)	1.005 (0.915 – 1.104)
C_{max} (µg/mL), Mean (SD)	42	3.720 (1.5444)	42	3.575 (1.4833)	1.033 (0.947 – 1.127)
AUC_{last} (µg·h/mL), Mean (SD)	42	752.277 (259.2088)	42	727.820 (229.8597)	1.013 (0.923 – 1.111)
T_{max} (h), Median	42	60.017 (23.933-143.800)	42	60.025 (24.000-120.033)	Not Applicable
$T_{1/2}$ (h), Mean (SD)	42	95.363 (17.8670)	42	100.198 (19.3456)	Not Applicable

AUC_{inf} = area under the curve to infinity; AUC_{last}: area under the concentration-time curve from time zero to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum concentration; SD = standard deviation.
Source: CTD 2.7.2, Tables 7,8; CSR SB4-G11-NHV, Table 14.2.4c.

TABLE 37: ADDITIONAL PHARMACOKINETIC RESULTS FOR STUDY SB4-G11-NHV (PK POPULATION)

Parameter	n	Brenzys (N=45)	n	Enbrel® (N=45)	Ratios of Geometric Means; 90% CI
AUC_{last} (µg·h/mL), Mean (SD)	42[a]	728.169 (234.7621)	42[a]	734.015 (220.2722)	0.986 (0.942 – 1.033)
	44[b]	788.773 (232.4636)	44[b]	765.187 (184.5046)	1.010 (0.954 – 1.069)
T_{max} (h), Median (range)	42[a]	72.025 (35.933-145.817)	42[a]	71.992 (35.983-143.583)	Not Applicable
	44[b]	71.933 (24.017-144.017)	44[b]	60.050 (36.033-120.033)	Not Applicable
$T_{1/2}$ (h), Mean (SD)	42[a]	105.782 (11.6924)	42[a]	100.340 (16.1335)	Not Applicable
	44[b]	106.188 (9.0884)	44[b]	101.400 (17.4656)	Not Applicable

[a] Part A (three subjects were excluded due to carryover effect); [b] Part B (one subject was excluded due to carryover effect
AUC_{last}: area under the concentration-time curve from time zero to the last quantifiable concentration; SD: standard deviation; $T_{1/2}$: terminal half-life; T_{max}: time to C_{max}.
CTD 2.7.2, Tables 3-6.

FIGURE 2: MEAN SERUM CONCENTRATIONS VERSUS NOMINAL TIMES ON SEMI-LOGARITHMIC SCALE IN PART A (BRENZYS VERSUS EU-ENBREL®) IN STUDY SB4-G11-NHV (PK POPULATION). BRENZYS: BRENZYS

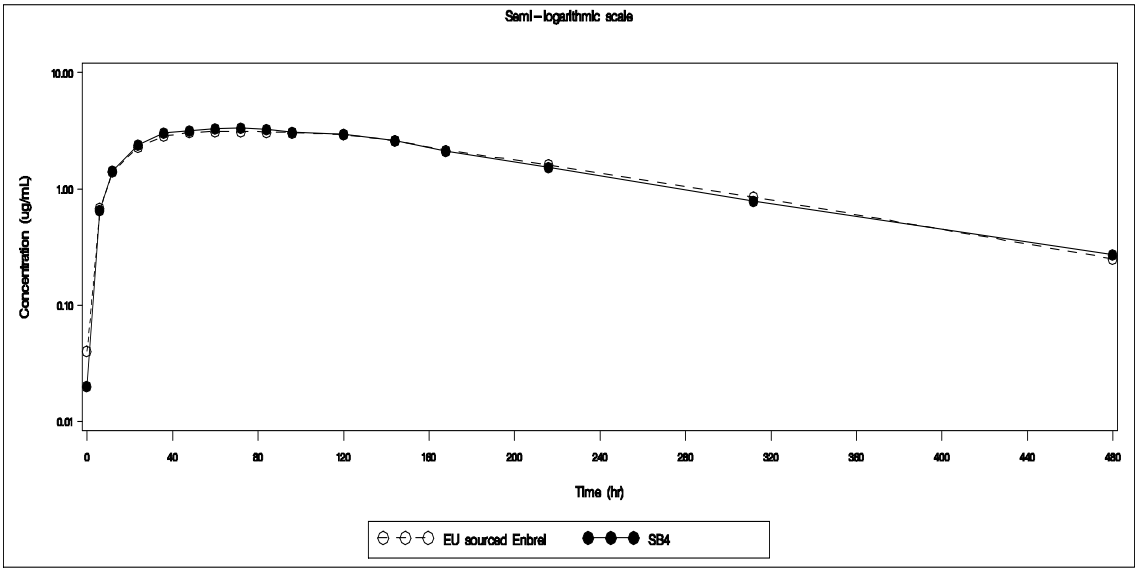


FIGURE 3: MEAN SERUM CONCENTRATIONS VERSUS NOMINAL TIMES ON SEMI-LOGARITHMIC SCALE IN PART B (BRENZYS VERSUS US-ENBREL®) IN STUDY BRENZYS-G11- NHV (PK POPULATION). BRENZYS: BRENZYS

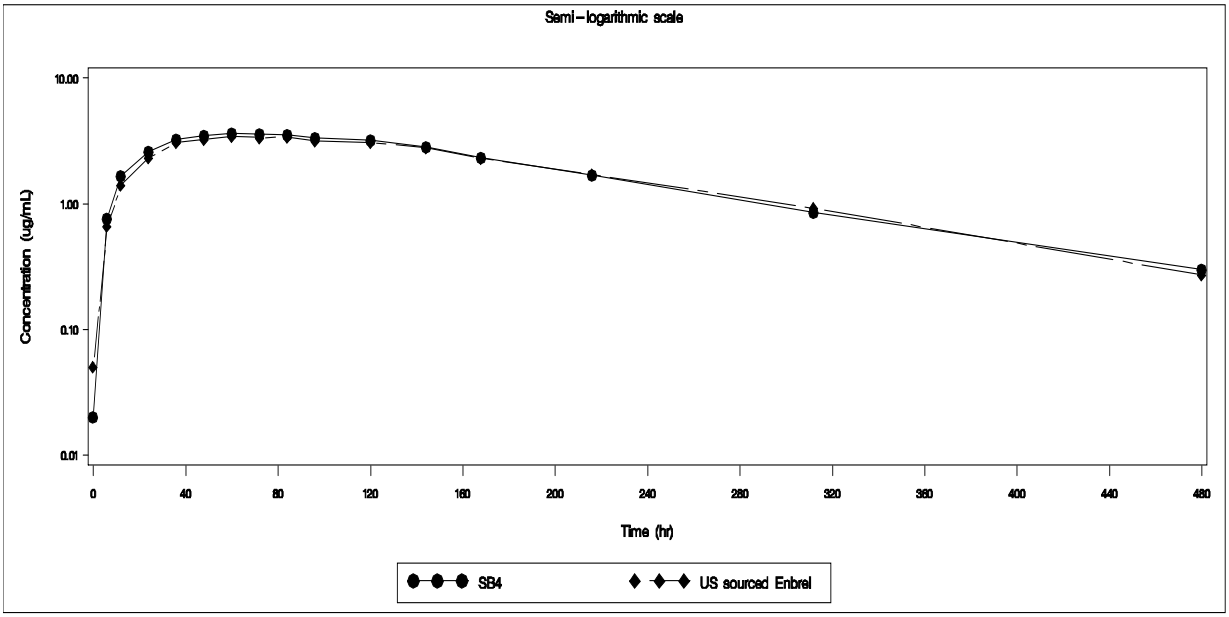


FIGURE 4: MEAN SERUM CONCENTRATIONS VERSUS NOMINAL TIMES ON SEMI-LOGARITHMIC SCALE IN PART C (EU-ENBREL® VERSUS US-ENBREL®) IN STUDY SB4-G11-NHV (PK POPULATION)

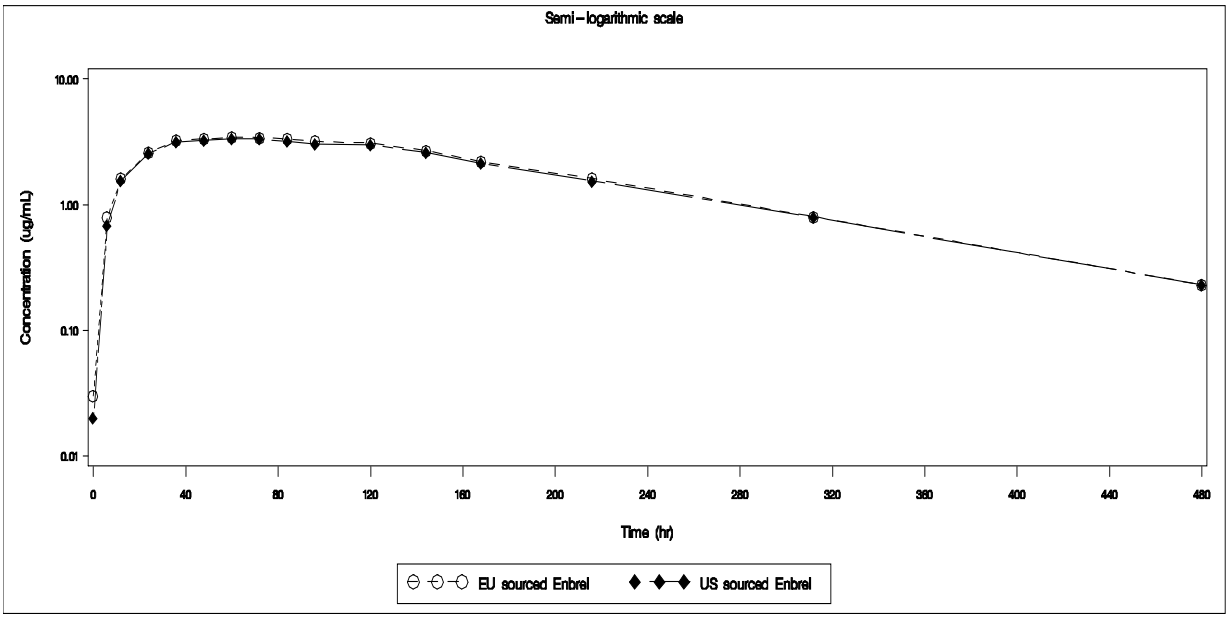
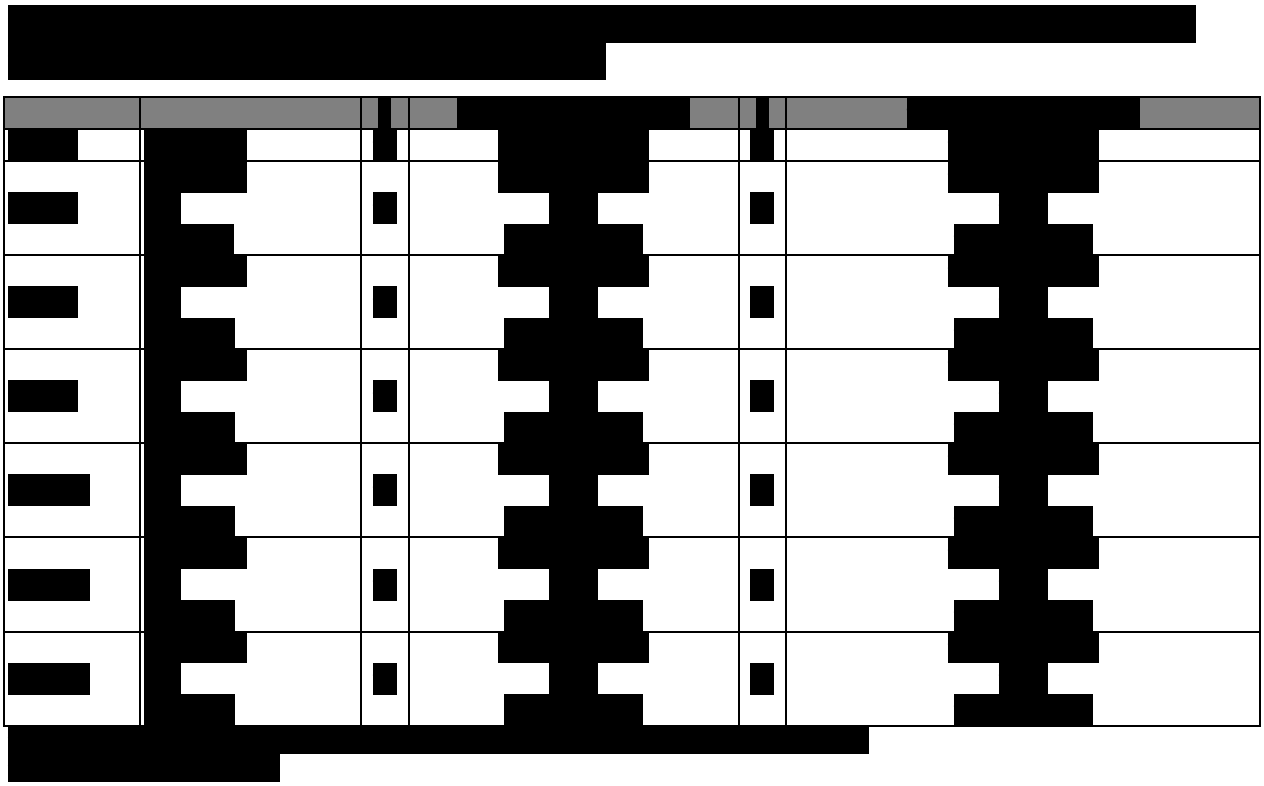
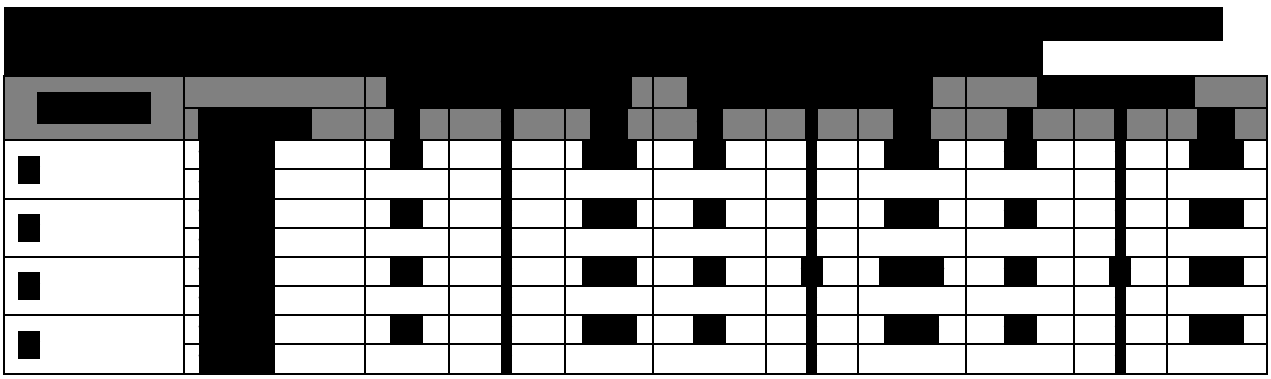


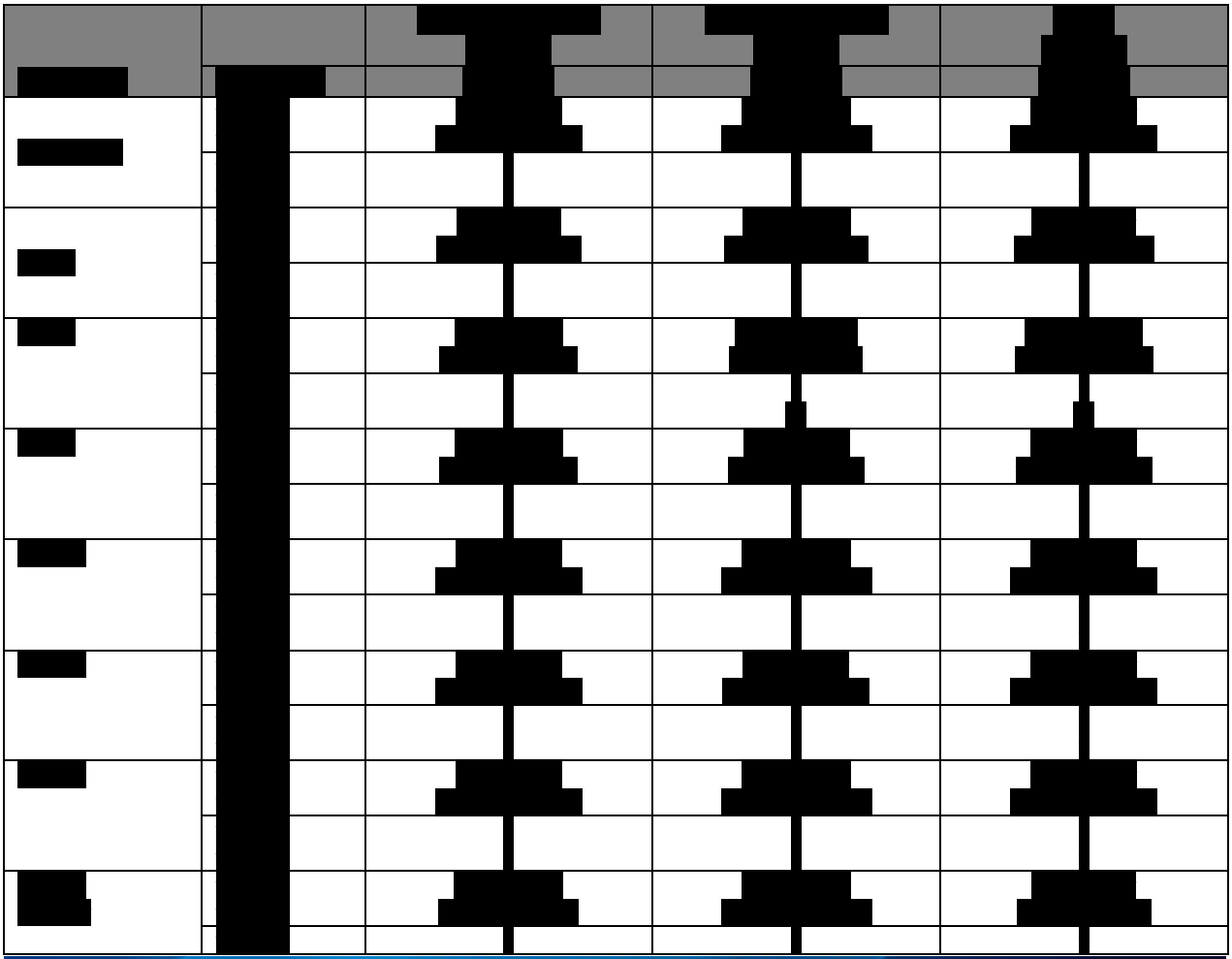
TABLE 38: ADDITIONAL KEY PHARMACOKINETIC PARAMETERS FOR ETANERCEPT FOLLOWING Brenzys OR ENBREL® AT WEEK 8 FOR STUDY SB4-G31-RA (PK POPULATION)

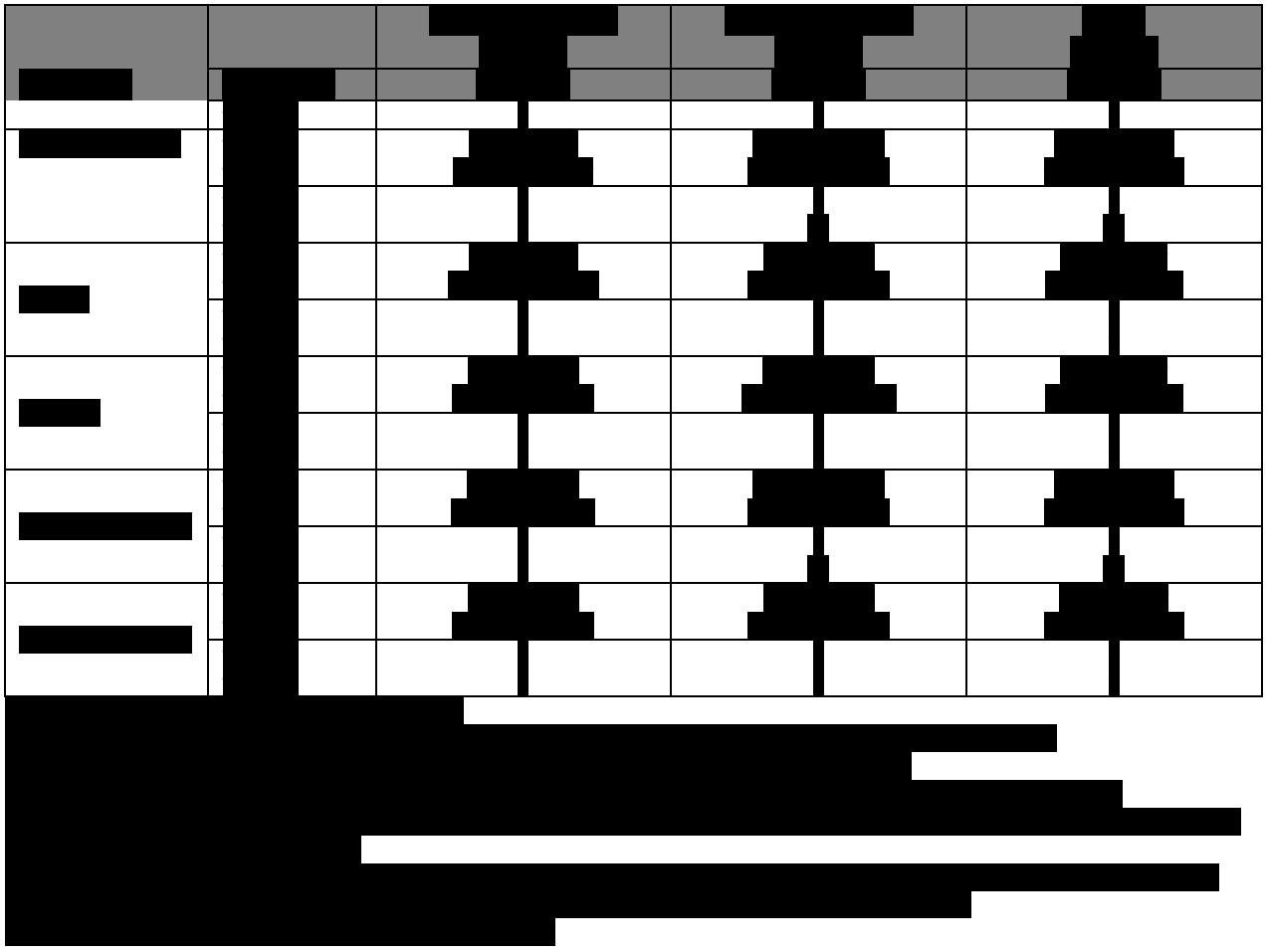
Parameter		n	Brenzys 50 mg (N=41)	n	Enbrel® 50 mg (N=38)
C_{min} (µg/mL)	Mean (SD) CV% Min, Max	36	2.599 (1.383) 53.2 0.000, 5.231	34	1.826 (1.087) 59.5 0.000, 5.244
CL/F (L/h)	Mean (SD) CV% Min, Max	36	0.093 (0.067) 71.5 0.044, 0.411	34	0.126 (0.084) 67.0 0.044, 0.510
Fluctuation (%)	Mean (SD) CV% Min, Max	36	65.851 (27.151) 41.2 25.546, 136.377	34	72.681 (22.530) 31.0 33.792, 124.448

C_{min}: minimum serum concentration; CL/F: apparent total body clearances; CV%: coefficient of variation; Max: maximum; Min: minimum; Fluctuation = 100*(C_{max} – C_{min})/C_{av}; SD: standard deviation.
Source: CTD 2.7.2, Table 10.









APPENDIX 2: DRUG PLAN LISTING STATUS FOR REFERENCE PRODUCT

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

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

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

LISTING STATUS OF ENBREL® FOR CDR-PARTICIPATING PLANS

Indication(s)	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Rheumatoid Arthritis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	-/RES
Ankylosing Spondylitis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	-/RES

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

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

RESTRICTED BENEFIT CRITERIA FOR ENBREL® FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

Drug Plan	Criteria for Restricted Benefit
BC	Treatment of rheumatoid arthritis according to established criteria when prescribed by a rheumatologist (note, criteria are extracted from SA form). Dose: 25 mg twice weekly or 50 mg weekly <u>Initial/Switch</u> Must have tried and failed/intolerant/contraindicated to: MTX (parenteral 25 mg [15 mg for over 65 years], minimum 8 weeks required)

Drug Plan	Criteria for Restricted Benefit
	PLUS two or more of the following: a. leflunomide (20 mg daily for 10 weeks) b. gold (weekly injections for 20 weeks) c. sulfasalazine (≥ 2 gm daily for 3 months) d. azathioprine (2-3 mg/kg/day for 3 months) e. other – specify drug, dose, duration f. other – specify drug, dose, duration PLUS at least one DMARD combination (NOTE: antimalarial in combination with one other DMARD is not acceptable): a. methotrexate with cyclosporine (minimum 4 months) b. methotrexate with hydroxychloroquine and sulfasalazine (O'Dell protocol) (minimum 4 months) c. methotrexate with gold (minimum 20 week trial) d. methotrexate with leflunomide (minimum 10 week trial) e. other — specify drugs, duration <u>Renewal</u> No specific criteria defined
AB	"Special authorization coverage may be provided for use in combination with methotrexate for the reduction in signs and symptoms of severely active Rheumatoid Arthritis (RA) in adult patients (18 years of age or older) who are refractory or intolerant to: • Methotrexate at 20 mg (PO, SC or IM) or greater total weekly dosage (15 mg or greater if patient is 65 years of age or older) for more than 12 weeks. Patients who do not exhibit a clinical response to PO methotrexate or experience gastrointestinal intolerance to PO methotrexate must have a trial of parenteral methotrexate before being accepted as refractory; AND • Methotrexate with other disease modifying antirheumatic agent(s) (minimum 4-month trial). [e.g., methotrexate with hydroxychloroquine or methotrexate with sulfasalazine]; AND • Leflunomide (minimum 10 week trial at 20 mg daily). Special authorization coverage of this agent may be provided for use as monotherapy in adult patients for whom methotrexate is contraindicated and/or for those patients who have experienced serious adverse effects. 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. For coverage, this drug must be initiated by a Specialist in Rheumatology who agrees to and continues to actively and consistently participate in the Alberta Post-Marketing Study ("Study") as required by Alberta Health and Wellness or its agent, throughout the special authorization approval period ("RA Specialist"). The patient must also provide all consents and authorizations required to permit the RA Specialist to actively and consistently participate in the Study. Special authorization approval for the patient may be revoked if the RA Specialist does not continually, actively and consistently participate in the Study. • Initial coverage may be approved for 50 mg per week for 8 weeks. • Patients will be limited to receiving a one-month supply of etanercept per prescription at their pharmacy.

Drug Plan	Criteria for Restricted Benefit
	• Patients will be permitted to switch from one 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 dosing (e.g. initial coverage period). • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. • Patients will not be permitted to switch from anakinra to other biologic agents except under exceptional circumstances. • Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. For continued coverage beyond 8 weeks, the patient must meet the following criteria: 1. The patient must be assessed by an RA Specialist after 8 weeks, but no longer than 12 weeks after treatment to determine response. 2. The RA specialist must confirm in writing that the patient is a 'responder' that meets the following criteria: • ACR20 OR an improvement of 1.2 units in the DAS28 score [reported to one (1) decimal place]; AND • An improvement of 0.22 in HAQ score [reported to two (2) decimal places]. It should be noted that the initial score for the DAS28 or HAQ score on record will be rounded to the correct number of decimal places as indicated above. Following this assessment, continued coverage may be approved for 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: 1. The patient has been assessed by an RA Specialist to determine response; 2. The RA specialist must confirm in writing that the patient has maintained a response to therapy as indicated by: • Confirmation of maintenance of ACR20, or • Maintenance of a minimum improvement of 1.2 units in DAS28 score [reported to one (1) decimal place] from baseline. 3. A current HAQ score [reported to two (2) decimal places] must be included with all renewal requests. It should be noted that the initial score for the DAS28 or HAQ score on record will be rounded to the correct number of decimal places as indicated above." All requests (including renewal requests) for etanercept for Rheumatoid Arthritis must be completed using the Abatacept/Adalimumab/Anakinra/Etanercept/Golimumab/Infliximab/Tocilizumab for Rheumatoid Arthritis Special Authorization Request Form (ABC 30902).
SK	For treatment of active rheumatoid arthritis in patients who have failed or are intolerant to methotrexate and leflunomide. This product should be used in consultation with a specialist in this area.
MB	For treatment of patients over 18 years of age who have moderate to severe active rheumatoid arthritis who have failed treatment with at least 3 DMARD therapies, one of which is methotrexate and/or leflunomide unless intolerance or contraindications to these agents is documented. One combination therapy of DMARD's must also be tried. Initial application information should include information on disease activity such as the number of tender joints, swollen joints, erythrocyte sedimentation rate and C-reactive protein value.

Drug Plan	Criteria for Restricted Benefit
	Request for coverage must be by a specialist in rheumatology.
ON	For the treatment of rheumatoid arthritis in patients who have: • Severe active disease (≥ 5 swollen joints and rheumatoid factor positive and/or, anti-CCP positive, and/or radiographic evidence of rheumatoid arthritis) despite the optimal use of various formulary disease-modifying antirheumatic drugs (DMARDs).* *Optimal use of DMARDs include: • Methotrexate (20 mg/week) for at least 3 months and leflunomide (20 mg/day) for at least 3 months in addition to an adequate trial (3 months) of at least one combination of DMARDs; or • Methotrexate (20 mg/week) for at least 3 months and leflunomide in combination with methotrexate for at least 3 months. • If the patient could not receive adequate trial(s) of methotrexate and/or leflunomide due to contraindication(s) or intolerance(s), the nature of contraindication(s) or intolerance(s) must be provided along with details of trials of other DMARDs or clear rationale why other DMARDs cannot be considered. OR • Methotrexate (20 mg/week), sulfasalazine (2 GM/day) and hydroxychloroquine (400 mg/day)* for at least 3 months. If the patient could not receive an adequate trial of methotrexate, sulfasalazine and hydroxychloroquine due to intolerance, then the above DMARD trial criteria must be met. *Hydroxychloroquine is based by weight up to 400 mg per day. **Renewal** will be considered for patients with objective evidence of at least a 20% reduction in swollen joint count and a minimum of improvement in 2 swollen joints over the previous year. For renewals beyond the second year, objective evidence of preservation of treatment effect must be provided. The planned dosing regimen for the requested biologic should be provided. The recommended doses for the treatment of rheumatoid arthritis are as follows: • Etanercept 25 mg twice weekly or 50 mg once weekly

NB	• For patients with moderate to severe active rheumatoid arthritis who:
	  • Have not responded to, or have had intolerable side effects with, an adequate trial of combination therapy of at least two traditional DMARDs (disease modifying antirheumatic drugs). Combination DMARD therapy must include methotrexate unless contraindicated or not tolerated,
	OR
	  • Are not candidates for combination DMARD therapy must have had adequate trial of at least three traditional DMARDs in sequence, one of which must have been methotrexate unless contraindicated.
	
	Claim note:
	• Must be prescribed by a rheumatologist.

Drug Plan	Criteria for Restricted Benefit

NS	• for patients with a diagnosis of active rheumatoid arthritis (RA) who:
	  • have not responded or who have had intolerable toxicity to an adequate trial[1] of combination therapy of at least two traditional DMARDs[2] or
	  • if combination therapy is not an option, an adequate trial[1] of at least three traditional DMARDs2 in sequence as monotherapy and
	  • patients must have had an adequate trial[1] of leflunomide. Exceptions can be considered in cases where leflunomide is contraindicated or not tolerated.
	
	• Therapy must include methotrexate alone or in combination unless contraindicated or not tolerated.
	• Written request of a rheumatologist or prescriber with a specialty in rheumatology.
	• After initial coverage period, can be reassessed for yearly coverage dependent on patient achieving an improvement in symptoms of at least 20%.
	
	Initial Coverage Duration and Maximum Dosage approved:
	• initial coverage period 6 months
	
	*Please note that the concurrent use of anti-TNF agents will not be approved.
	
	[1] An adequate trial is 5 months for IM gold, 6 months for penicillamine, 4 months for hydroxychloroquine and 3 months for all other traditional DMARDs as well as leflunomide, infliximab and etanercept.
	[2] Traditional agents include methotrexate, IM gold, sulfasalazine, hydroxychloroquine, azathioprine, chloroquine, penicillamine and cyclosporine.

PE	Maximum adult dose is 50 mg weekly or 25 mg twice weekly. Pediatric patients 4–17 years of age, coverage is for 0.8 mg/kg/weekly to a maximum of 50 mg weekly. For the treatment of rheumatoid arthritis in patients who: 1. Have not responded to a trial of at least 3 months of Leflunomide, AND 2. Have not responded to or have had intolerable toxicity to an adequate trial of Methotrexate and at least one of the following DMARDs (disease modifying antirheumatic drugs): IM Gold, Sulfasalazine, Hydroxychloroquine, Azathioprine, 3. Chloroquine, or Penicillamine, OR 4. Are intolerant to or have a contraindication to Methotrexate and are refractory to at least two of the following DMARDs (disease modifying antirheumatic drugs): IM Gold, Sulfasalazine, Hydroxychloroquine, Azathioprine, Chloroquine, or 5. Penicillamine, OR 6. Are not a candidate for combination DMARD therapy but have had an adequate trial of Methotrexate and at least two of the following DMARDs in sequence: IM Gold, Sulfasalazine, Hydroxychloroquine, Azathioprine, Chloroquine, or Penicillamine. An adequate trial is considered to be 5 months for IM Gold, 6 months for Penicillamine, 4 months for Hydroxychloroquine, and 3 months for all other traditional DMARDs. Unless limited by toxicity, the Methotrexate dosage should be increased up to 25mg/week unless a response is achieved at a lower dose. Renewal of coverage will require reassessment of the patient and submission of a new Special Authorization form. Initial approval* will be for a 6-month period.

Drug Plan	Criteria for Restricted Benefit
	Coverage will NOT be considered for use in combination with other biologic agents.
NL	For patients who have not responded or who have had intolerable toxicity to an adequate trial*of combination therapy of at least two traditional DMARDs,** OR if combination therapy is not an option, an adequate trial of at least three traditional DMARDs in sequence as monotherapy, AND patients must have had an adequate trial* of leflunomide. Exceptions can be considered in cases where leflunomide is ineffective or contraindicated. Therapy must include methotrexate*** alone or in combination unless contraindicated or not tolerated. Coverage will be approved initially for 6 months. Can be reassessed for yearly coverage dependent on patient achieving an improvement in symptoms (ACR) of at least 20%. * An adequate trial is 5 months for IM gold, 6 months for penicillamine, 4 months for hydroxychloroquine, and 3 months for all other traditional DMARDs as well as leflunomide, infliximab, and etanercept. ** Traditional agents include methotrexate, IM gold, sulfasalazine, hydroxychloroquine, azathioprine, chloroquine, D-penicillamine and cyclosporine. *** Unless limited by toxicity, methotrexate dosage should be increased up to 25 mg/wk unless response is achieved at a lower dose. Written request of a rheumatologist only.
YK	For severely active rheumatoid arthritis on recommendation of RA specialist. Specialist's consult to be provided. For patients refractory or intolerant to parenteral methotrexate after at least a 12-week trial. AND Methotrexate with other disease modifying antirheumatic agent(s) after at least a 4 month trial (e.g., methotrexate with hydroxychloroquine or methotrexate with sulfasalazine etc.) AND a minimum 10 week trial of Leflunomide at 20 mg daily.
NT	Same criteria as those listed in NIHB
NIHB	The coverage of etanercept in adult patients ≥ 18 years is set at a MAXIMUM dose of 50 mg weekly. Criteria for initial one year: • Prescribed by a rheumatologist. Coverage is provided for use, in combination with methotrexate (MTX) or other disease modifying antirheumatic drugs (DMARDs), for the reduction in signs and symptoms of severely active RA in adult patients ≥ 18 years who have failed: • MTX (oral or parenteral a dose ≥ 20mg weekly (≥ 15 mg weekly if patient is ≥ 65 years) for a minimum of 12 weeks of continuous treatment. Note: Patients who do not exhibit a clinical response to oral MTX or who experience gastrointestinal intolerance may consider a trial of parenteral MTX. AND • MTX in combination with at least two other DMARDs, such as sulfasalazine and hydroxychloroquine, for a minimum of 12 weeks of continuous treatment.

Drug Plan	Criteria for Restricted Benefit
	OR, if the patient has a contraindication or intolerance to MTX and has failed: • Combination of at least two DMARDs, such as sulfasalazine, hydroxychloroquine, azathioprine, leflunomide, cyclosporine or gold, for a minimum of 12 weeks of continuous treatment, or are refractory to a combination of at least 2 DMARDs
DND	When prescribed by a rheumatologist or a prescriber with a specialty in rheumatology for patients with moderate to severe active rheumatoid arthritis despite treatment with at least 2 DMARDs [including methotrexate unless contraindicated] in mono or combination therapy after 3 months at target dose. Note: Methotrexate at 20mg (PO, SC, IM) or greater total weekly dosage for more than 12 weeks. Patients who do not exhibit a clinical response to PO methotrexate or experience gastrointestinal intolerance to PO methotrexate must have a trial of parenteral methotrexate before being accepted as refractory AND One or more of the following: • Leflunomide 20mg daily for 10 weeks • Gold weekly injections for 20 weeks • Sulfasalazine ≥ 2gm daily for 3 months • Azathioprine 2-3mg/kg/day for 3 months
VAC	Special Authorization – criteria not available

Restricted Benefit Criteria for Enbrel® for the Treatment of Ankylosing Spondylitis

Drug Plan	Criteria for Restricted Benefit
BC	Treatment of ankylosing spondylitis according to established criteria when prescribed by a rheumatologist (note, criteria are extracted from SA form). Dose: 25 mg twice weekly or 50 mg weekly **Initial/Switch** A. Medication is being prescribed by a rheumatologist or medical specialist in rheumatology. B. Diagnosis of moderate to severe ankylosing spondylitis. C. Active ankylosing spondylitis with a BASDAI score ≥ 4; Copy of BASDAI required. D. For predominantly axial disease, treatment failure or intolerance to three NSAIDS for a minimum of two weeks each at accepted maximum dosage, **OR,** for predominantly peripheral disease, patient is refractory to minimum 3 month trials of each of the following: 1. Methotrexate up to 25 mg (15 mg over 65 years) parenteral weekly 2. Sulfasalazine up to 3 g daily. If no positive imaging, please confirm patient is HLA B27+ and provide at least two additional SpA features below. ☐ Confirmation Patient is HLA B27+ Additional SpA Features: ☐ inflammatory back pain ☐ dactylitis ☐ good response to NSAIDs ☐ arthritis ☐ psoriasis ☐ family history for SpA ☐ enthesitis ☐ Crohn's / colitis ☐ elevated CRP ☐ uveitis

Drug Plan	Criteria for Restricted Benefit
	Renewal No specific criteria defined
AB	"Special authorization coverage may be provided for the reduction in the signs and symptoms of severely active Ankylosing Spondylitis, as defined by the Modified New York criteria for Ankylosing Spondylitis, in adult patients (18 years of age or older) who have active disease as demonstrated by: • a BASDAI greater than or equal to 4 units, demonstrated on 2 occasions at least 8 weeks apart AND • a Spinal Pain VAS of greater than or equal to 4 cm (on a 0-10 cm scale), demonstrated on 2 occasions at least 8 weeks apart AND • who are refractory or intolerant to treatment with 2 or more NSAIDS each taken for a minimum of 4 weeks at maximum tolerated or recommended doses. 'Refractory' is defined as lack of effect at the recommended doses and for duration of treatments specified above. 'Intolerant' is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs. For coverage, this drug must be initiated by a specialist in rheumatology ("RA specialist"). • Initial coverage may be approved for 50 mg per week for 12 weeks. • Patients will be limited to receiving a one-month supply of etanercept per prescription at their pharmacy. • Patients will be permitted to switch from one biologic agent to another following an adequate trial of the first biologic agent if unresponsive to therapy, or due to serious adverse effects or contraindications. An adequate trial is defined as at a minimum the completion of induction dosing (e.g. initial coverage period). • Patients will not be permitted to switch back to a previously trialed biologic agent if they were deemed unresponsive to therapy. • Patients are limited to receiving one biologic agent at a time regardless of the condition for which it is being prescribed. For continued coverage beyond 12 weeks, the patient must meet the following criteria: 1. The patient must be assessed at week 12 by an RA specialist after the initial twelve weeks of therapy to determine response. 2. The RA specialist must confirm, in writing, that the patient is a 'responder' that meets the following criteria: • Reduction of the BASDAI score by at least 50% of the pre-treatment value or by 2 or more units, AND • Reduction of the spinal pain VAS by 2 cm or more. Following this assessment, continued coverage may be approved for 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 (2) above." All requests (including renewal requests) for etanercept for Ankylosing Spondylitis must be completed using the Adalimumab/Etanercept/Golimumab/Infliximab for Ankylosing Spondylitis Special Authorization Request Form (ABC 31195).
SK	For treatment of ankylosing spondylitis (A.S.) according to the following criteria: 1. For patients who have already been treated conventionally with two or more NSAIDs taken sequentially at maximum tolerated or recommended doses for four weeks without symptom control. AND

Drug Plan	Criteria for Restricted Benefit
	2. Satisfy New York diagnostic criteria: a score > 4 on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) AND a score of > 4 cm on the 0-10cm spinal pain VAS on two occasions at least 12 weeks apart without any change of treatment. AND 3. Adequate response to treatment assessed at 12 weeks defined as at least 50% reduction in pre-treatment baseline BASDAI score or by > 2 units AND a reduction of > 2 cm in the spinal pain VAS. NOTE: Coverage will not be provided when a patient switches to another anti-TNF agent if the patient fails to respond or if there is loss of response to the first agent. Requests for coverage for this indication must be made by the rheumatologist. A second application would also be required after 12 weeks to assess and would need to show an improvement to the patient's condition on either of these medications. Please refer to the Formulary website for the application form. Subsequent annual renewal requests (beyond 15 months) will be considered for patients whose BASDAI scores do not worsen (i.e. remains within two points of the second assessment). This product should be used in consultation with a specialist in this area.
MB	For the treatment of patients with active ankylosing spondylitis who have failed to respond to an adequate trial of at least three different nonsteroidal anti-inflammatory drugs (NSAIDs) and, in patients with peripheral joint involvement, have failed to respond to methotrexate or sulfasalazine. Request for coverage must be made by a specialist in rheumatology.

ON	For the treatment of ankylosing spondylitis (AS) OR psoriatic spondylitis (PS) in patients who have severe active disease with:
	• Age of disease onset ≤ 50; AND
	• Low back pain and stiffness for > 3 months that improves with exercise and not relieved by rest; AND
	• Failure to respond to or documented intolerance to adequate trials of 2 non-steroidal anti-inflammatory drugs (NSAIDs) for at least 4 weeks each; AND
	• BASDAI score of ≥ 4 for at least 4 weeks while on standard therapy; AND
	
	The information submitted with the request must include the following:
	• A list of current concomitant medications related to the AS/PS, including pain medications (if relevant). Please include dosing regimens.
	• Details of review of radiographic reports for severe active disease.
	  • X-ray or CT scan report stating the presence of "SI joint fusion" or "SI joint erosion" OR
	  • MRI report stating the presence of "inflammation" or "edema" of the SI joint
	  • Actual radiographic reports must be submitted with the request. If the radiographic reports do not specify the above, the request will be reviewed by external medical experts.
	
	Additional information that should be provided if applicable:
	• Schober measurement and chest expansion measurement
	• Evidence of restricted spinal mobility
	• If the patient has AS/PS with predominantly peripheral joint involvement, additional information pertaining to trials of DMARDs must be provided, and these requests will be reviewed by external medical experts.
	
	Renewal will be considered for patients with objective evidence of at least a 50% reduction in BASDAI score or ≥ 2 absolute point reduction in BASDAI score. Please provide an update on concomitant medications for AS/PS and whether there has been a reduction in pain medication for AS/PS since initiating the biologic (if applicable).

Drug Plan	Criteria for Restricted Benefit
	For renewals beyond the second year, objective evidence of preservation of treatment effect must be provided. The planned dosing regimen for the requested biologic should be provided. The recommended doses for the treatment of AS/PS are as follows: • Etanercept 25 mg twice weekly or 50 mg once weekly

NB	• For the treatment of patients with moderate to severe ankylosing spondylitis (e.g. Bath AS Disease Activity Index (BASDAI) score ≥ 4 on 10 point scale) who:
	  • have axial symptoms* and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation or in whom NSAIDs are contraindicated
	  OR
	  • have peripheral symptoms and who have failed to respond to, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD.
	
	• Requests for renewal must include information showing the beneficial effects of the treatment, specifically:
	  • a decrease of at least 2 points on the BASDAI scale, compared with the pre-treatment score;
	  OR
	  • patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as HAQ or “ability to return to work”)
	
	<u>Clinical Notes:</u>
	1. * Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication to axial, disease do not require a trial of NSAIDs alone.
	2. ETANERCEPT will not be reimbursed in combination with other anti-TNF agents.
	
	<u>Clinical Notes:</u>
	• Must be prescribed by a rheumatologist or internist
	• Approval will be for a maximum of 6 months
	• Approvals will be for a maximum dose of 50 mg per week.

NS	• For the treatment of patients with moderate to severe ankylosing spondylitis (e.g., Bath AS Disease Activity Index (BASDAI) score ≥4 on 10 point scale) who:
	  • have axial symptoms** and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation, or in whom NSAIDs are contraindicated OR
	  • have peripheral symptoms and who have failed to respond to, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD
	  • must be prescribed by a rheumatologist or prescriber with a specialty in rheumatology
	  • requests for renewal must include information showing the beneficial effects of the treatment, specifically:
	• a decrease of at least 2 points on the BASDAI scale, compared with the pre-treatment score; OR
	• patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as HAQ or "ability to return to work")
	
	**Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication of axial disease, do not require a trial of 2 NSAIDs.

Drug Plan	Criteria for Restricted Benefit
	Initial coverage duration and maximum dosage approved: • Etanercept – initial period 6 months, maximum dose of 50 mg per week and not in combination with other anti-TNF agents.
PE	Approvals will be for a maximum adult dose of 50 mg per week or 25mg twice weekly. For the treatment of patients with moderate to severe ankylosing spondylitis (Bath AS Disease Activity Index (BASDAI) score ≥4 on 10 point scale who: a. have axial symptoms* and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation or in whom NSAIDs are contraindicated OR b. have peripheral symptoms and who have failed to respond to, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD. * Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication to axial disease, do not require a trial of NSAIDs alone. Approvals for Ankylosing Spondylitis anti-TNF agents will be for a maximum of six months, and will NOT be considered in combination with other biologic agents. Requests for renewal must include information showing the beneficial effects of the treatment, specifically: a. a decrease of at least two points on the BASDAI scale, compared with pre-treatment score OR b. patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as Health Assessment Questionnaire (HAQ) or ability to return to work). The request for coverage must be made by a rheumatologist or prescriber with a specialty in rheumatology, using the Ankylosing Spondylitis Special Authorization form available from the Drug Programs office or online at http://healthpei.ca/pharmacareforms. Patients must also apply for coverage through the High-Cost Drug Program. The patient application is available from the Drug Programs Office or online at http://healthpei.ca/pharmacareforms .
NL	For the treatment of patients with moderate to severe ankylosing spondylitis (e.g. Bath AS Disease Activity Index (BASDAI) score ≥ 4 on 10 point scale) who: • have axial symptoms* and who have failed to respond to the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation or in whom NSAIDs are contraindicated, OR • have peripheral symptoms and who have failed to respond to, or have contraindications to, the sequential use of at least 2 NSAIDs at the optimum dose for a minimum period of 3 months observation and have had an inadequate response to an optimal dose or maximal tolerated dose of a DMARD. Patients with recurrent uveitis (2 or more episodes within 12 months) as a complication to axial disease, do not require a trial of NSAIDs alone. Must be prescribed by a rheumatologist or internist. Approval will be for a maximum of 6 months.

Drug Plan	Criteria for Restricted Benefit
	Requests for renewal must include information showing the beneficial effects of the treatment, specifically: • a decrease of at least 2 points on the BASDAI scale, compared with the pre-treatment score; OR • patient and expert opinion of an adequate clinical response as indicated by a significant functional improvement (measured by outcomes such as HAQ or "ability to return to work"). Approvals will be for a maximum dose of 50mg per week and NOT be reimbursed in combination with other anti-TNF agents.
YK	For Ankylosing Spondylitis 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 maximal dosage. OR for predominantly peripheral disease, patients refractory to a 3 month trial of parenteral methotrexate and a 3 month trial of sulfasalazine. Rheumatologists consult to be provided.
NT	Same criteria as those listed in NIHB
NIHB	Criteria for initial one year: • Prescribed by rheumatologist Client who meets all of the following criteria: • BASDAI > 4 AND • patient is refractory to a three month trial of at least 3 NSAIDs at maximum tolerated dose AND • for peripheral joint involvement, patient is refractory to weekly parenteral (SC or IM) at 20mg or greater (15mg or greater if patient is > 65 years of age) for more than 8 weeks AND • sulfasalazine 2g/day for four months. Note: For axial involvement, patient does not need to be tried on MTX or sulfasalazine.
DND	• when prescribed by a rheumatologist or a prescriber with a specialty in rheumatology and meets the following criteria: • A diagnosis of moderate to severe Ankylosing Spondylitis as demonstrated by a BASDAI greater than or equal to 4 units. • Treatment failure or intolerance to three NSAIDs each taken for a minimum of 4 weeks sequentially and at maximum tolerated or recommended dosage. AND • If peripheral involvement, patient is refractory to a minimum 3 month trial of an optimal dose or maximum tolerated dose of methotrexate or sulfasalazine.
VAC	Special authorization – criteria not available

APPENDIX 3: SUMMARY OF PATIENT INPUT

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

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

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

ACE is a national organization that provides science-based information, education, and support programs to people with arthritis. CAPA 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 that raises awareness of spondyloarthritis and supports, educates, and advocates for those living with the condition.

None of the four patient groups declared any conflict of interest regarding any organization playing a significant role in compiling their submission. ACE declared receiving funding in the form of unrestricted grants-in-aid from the following private- and public-sector organizations: AbbVie Corporation, Amgen Canada, Arthritis Research Canada, BIOTECanada, Canadian Institutes of Health Research, Celgene Inc., Eli Lilly Canada Inc., Hoffman-La Roche Canada Ltd., Janssen, Merck & Co., Inc., Pfizer Canada, Sanofi Canada, UCB Canada Inc., and the University of British Columbia. CAPA declared receiving funding within the last year from AbbVie, Amgen Canada, Eli Lilly, Hoffman-La Roche, Janssen, Novartis, and UCB Canada Inc. The Arthritis Society has accepted funding from the following members of the pharmaceutical industry: AbbVie, Amgen, Bayer, Bristol-Myers Squibb, Celgene, Eli Lilly, Hospira, Janssen, Merck & Co., Inc., Novartis, Pfizer, Purdue, Roche, and UCB Canada Inc. The Canadian Spondylitis Association has received restricted educational and developmental grants from AbbVie, Amgen, and Janssen, and restricted travel grants from UCB Canada Inc.

2. Condition-Related Information

Patient groups gathered information from a variety of sources: Personal experience of board members living with the diseases, 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. The feedback request from CADTH was distributed and contact was made with responders, providing information via a survey of 700 people in Canada living with inflammatory arthritis.

Ankylosing Spondylitis

The onset of ankylosing spondylitis typically occurs between the ages of 15 and 45 years. 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 years. The wide range of symptoms affects work, recreational activity, and social activity, causes hardships for the patient's family, and places a strain on relationships.

Patients consider pain, fatigue, and stiffness to be the most important symptoms to control, as they can have debilitating effects on a patient's life. One patient was quoted as saying, "These (symptoms) 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 ankylosing spondylitis, rheumatoid arthritis is usually diagnosed during the most productive period of a person's life: Between the ages of 25 and 50 years. Rheumatoid arthritis can affect any and 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 rheumatoid arthritis 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. 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 have a normal, well-rounded lifestyle. For this, many patients consider joint swelling, fatigue, and flare-ups as the most important symptoms to control.

For both conditions, families and caregivers are affected; they have to compensate for loss of income, undertake ever-increasing efforts to help patients in their day-to-day activities, and deal with many of the psychological manifestations from the pain and reduced quality of life caused by AS and RA.

3. Current Therapy–Related Information

The current treatment objectivefor both RA and AS is symptom control and slowing the progression of the disease. Patients usually have to try several treatments before finding an effective regimen. Many patients end up receiving several drugs at once, each with its own set of potential side effects. Patients taking NSAIDs 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 they are "life-changers" that allowed them to largely resume a normal lifestyle. Although many patients have seen improvements using biologics, there are some who see no improvement at all, while others develop serious adverse effects that require the withdrawal of the medication; some reported the efficacy lasted only a few years. The most common adverse effects cited included infections, allergic reactions, and injection-site reactions, and 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 was 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 with a 10% co-pay.

4. Expectations About the Drug Being Reviewed

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

Patient groups, however, have highlighted the importance of the support programs that are currently offered to patients by the manufacturer of Enbrel. In addition, 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 their physician.

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

5. Key Messages

- Patients exhibited concerns about being switched without their consent from the reference drug to the SEB — even if they are doing well on the reference drug.
- Although patients have pointed to 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 support having several choices available to best address individual patients' response.
- Patients see SEBs as an advantage in improving access to the medication and reducing the burden on public plans.

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