Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Etanercept

Proprietary Product Name: Erelzi

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

September 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
Ab	Antibody
ABN	Australian Biological Name
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
AE	Adverse event (not necessarily treatment-related)
Anti-CCP	Anti-cyclic citrullinated peptide
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate aminotransferase
ATE	Averaged treatment effect
BCC	Basal cell carcinoma
BDRM	Blinded data review meeting
BMI	Body-mass index
BSA	Body surface area
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CPU	Clinical pharmacology unit
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAS28-CRP	Disease Activity Score 28-CRP
DBL	Database lock
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying anti-rheumatic drug

Abbreviation	Meaning
ECG	Electrocardiogram
EQ-5D	EuroQoL five dimensions questionnaire
ESR	Erythrocyte sedimentation rate
IP	Investigational product
IV	Intravenous
HAQ-DI	Health assessment questionnaire disability index
Hb	Haemoglobin
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IMP	Investigational medicinal product
INN	International Non-proprietary Name
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LPLV	Last patient, last visit
mbTNF-α	Transmembrane TNF alpha
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OA	Overall analysis (in the Egality trial)
PASI	Psoriasis Area and Severity Index
PBRER	Periodic benefit-risk evaluation report

Abbreviation	Meaning
PsA	Psoriatic arthritis
PSUR	Periodic safety update report
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous (ly)
SCC	Squamous cell carcinoma
SD	Standard deviation
sPGA	Static Physician's Global Assessment
sTNF-α	Soluble tumour necrosis factor alpha
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TNF	Tumour necrosis factor
ULN	Upper limit of normal
UVB	Ultraviolet B
VAS	Visual analogue scale

I. Introduction to product submission

Submission details

Type of submission:	New biosimilar medicine
Decision:	Approved
Date of decision:	18 October 2017
Date of entry onto ARTG:	30 November 2017
ARTG number:	281780, 281783, 281784
Active ingredient:	Etanercept
Product name:	Erelzi
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road Macquarie Park NSW 2113
Dose form:	Solution for injection
Strengths:	25 mg (25 mg/0.5 mL), 50 mg (50 mg/1.0 mL)
Containers:	Pre-filled syringe, pre-filled autoinjector
Approved therapeutic use:	***Adults*** ***Rheumatoid Arthritis*** *Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Erelzi can be used in combination with methotrexate. Severe, active rheumatoid arthritis in adults to slow progression of disease- associated structural damage in patients at high risk of erosive disease.* ***Psoriatic Arthritis*** *The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. Erelzi has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.* ***Plaque Psoriasis*** *Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.* ***Ankylosing Spondylitis*** *The signs and symptoms of active ankylosing spondylitis in adults.* ***Non-radiographic Axial Spondyloarthritis***

Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change who have had an inadequate response to NSAIDs.*

**Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4.*

Children and Adolescents

Paediatric patients weighting less than 62.5 kg should not receive Erelzi. Paediatric patients weighting less than 62.5 kg should be accurately dosed on a mg/kg basis with other etanercept products.

Juvenile Idiopathic Arthritis

Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.

Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate. Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy. Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate. Etanercept has not been studied in children aged less than 2 years.

Paediatric Plaque Psoriasis

Chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.

Route of administration: Subcutaneous

Product background

This AusPAR describes the application by the sponsor to register Erelzi (etanercept) as a medicinal product biosimilar to Enbrel.

The innovator product, Enbrel solution for injection, was approved for registration in March 2003 as a composite pack containing 25 mg powder for injection vial and diluent syringe. Subsequent presentations have been approved; the most recent in 2009 was a 50 mg solution for injection auto-injector. Brenzys (etanercept) 50 mg solution for injection pre-filled syringe and 50 mg solution for injection auto-injector (Samsung Bioepis Pty Ltd) was the first biosimilar etanercept approved in Australia. It was registered in July 2016 and has only adult indications.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein. For both Enbrel and Erelzi, etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a protein genetically engineered by fusing the extracellular ligand-binding domain of human tumour

necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH2 and CH3 regions but not the CH1 region of IgG1.

Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. Both Enbrel and Erelzi are manufactured using a serum-free process.

The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNF receptors (TNFR), preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biological responses controlled by additional downstream molecules (for example, cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF. Etanercept is a fusion protein rather than a physiological TNF receptor in the bloodstream and has a longer half-life than naturally occurring soluble TNF receptors in the bloodstream.

The sponsor states that the proposed indications for Erelzi are aligned with those currently approved for Enbrel in Australia, namely:

- Rheumatoid Arthritis (adults);
- Psoriatic Arthritis (adults);
- Plaque psoriasis (adults);
- Ankylosing Spondylitis (adults);
- Non-radiographic Axial Spondyloarthritis (adults);
- Polyarticular Juvenile Idiopathic Arthritis (children and adolescents); and
- Paediatric plaque psoriasis (children and adolescents).

The proposed indications for Erelzi as outlined in the proposed Product Information (PI) document are as follows (identical to the approved indications for Enbrel):

Adults

Rheumatoid Arthritis

Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Erelzi can be used in combination with methotrexate.

Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease.

Psoriatic Arthritis

The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. Erelzi has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Plaque Psoriasis

Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.

Ankylosing Spondylitis

The signs and symptoms of active ankylosing spondylitis in adults.

Non-radiographic Axial Spondyloarthritis

Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change who have had an inadequate response to NSAIDs.*

**Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4.*

Children and Adolescents

Juvenile Idiopathic Arthritis

Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.

Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.

Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.

Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.

Etanercept has not been studied in children aged less than 2 years.

Paediatric Plaque Psoriasis

Chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.

Regulatory status

Table 1 shows the regulatory status at the time of this submission to TGA.

Table 1: Regulatory status of Erelzi at the time of this submission to TGA

Country/Region	Tradename	Submitted	Approved	Indication	Status
EU (centralised procedure)	Erelzi	11 Nov 2015	23 Jun 2017	See 1 below.	Approved 23 Jun 2017
US	Erelzi	30 Jul 2015	30 Aug 2016	See 2 below.	Approved 30 Aug 2016
Canada	Erelzi	31 Mar 2016	6 Apr 2017	See 3 below.	Approved 06 Apr 2017

1. Approved indications identical to reference medicine in the EU (Enbrel):
   - Rheumatoid arthritis
     - Erelzi in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.
   - Erelzi can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

- Erelzi is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.
- Etanercept, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X ray and to improve physical function.
- Juvenile idiopathic arthritis
    - Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.
    - Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.
    - Treatment of enthesitis related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.
    - Etanercept has not been studied in children aged less than 2 years.
- Psoriatic arthritis
    - Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X ray in patients with polyarticular symmetrical subtypes of the disease.
- Axial spondyloarthritis
- Ankylosing spondylitis (AS)
    - Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.
- Non radiographic axial spondyloarthritis
    - Treatment of adults with severe non radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to non steroidal anti inflammatory drugs (NSAIDs).
- Plaque psoriasis
    - Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet A light (PUVA) (see section 5.1).
- Paediatric plaque psoriasis
    - Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

2. Approved indications identical to reference medicine in the US (Enbrel) at the time of Erelzi approval:

2.1 Rheumatoid Arthritis

- Erelzi is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA). Erelzi can be initiated in combination with methotrexate (MTX) or used alone.

2.2 Polyarticular Juvenile Idiopathic Arthritis

- Erelzi is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 and older.

2.3 Psoriatic Arthritis

- Erelzi is indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA). Erelzi can be used in combination with methotrexate (MTX) in patients who do not respond adequately to MTX alone.

2.4 Ankylosing Spondylitis

- Erelzi is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis (AS).

2.5 Plaque Psoriasis

- Erelzi is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.

3. Approved indications identical to reference medicine in Canada (Enbrel), except those covered by patent-protection:
   - treatment of moderately to severely active rheumatoid arthritis (RA) in adults. Treatment is effective in reducing the signs and symptoms of RA, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function. Erelzi can be initiated in combination with methotrexate (MTX) in adult patients or used alone.
   - reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients aged 4 to 17 years who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Etanercept has not been studied in children less than 4 years of age.
   - reducing signs and symptoms of active ankylosing spondylitis (AS).

Product Information

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

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Registration timeline.

Description	Date
Submission dossier accepted and first round evaluation commenced	30 November 2016
First round evaluation completed	5 June 2017
Sponsor provides responses on questions raised in first round evaluation	10 July 2017
Second round evaluation completed	16 August 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	4 September 2017
Sponsor's pre-Advisory Committee response	18 September 2017
Advisory Committee meeting	5-6 October 2017
Registration decision (Outcome)	18 October 2017
Completion of administrative activities and registration on ARTG	30 November 2017
Number of working days from submission dossier acceptance to registration decision*	195

* Legislative timeframe is 255 working days

III. Quality findings

Introduction

State-of-the-art analytical methods were used to analyse and compare Erelzi, Enbrel/EU, and Enbrel/US on physico-chemical (identity, purity) and in vitro functional biological (potency) levels. Quality attributes were evaluated to detect variants and to quantify the levels of individual variants, leading to a comprehensive understanding of the characteristics of Erelzi and Enbrel/EU/US. The final comparability study confirmed that Enbrel/EU and Enbrel/US are indistinguishable with regard to physicochemical and in vitro functional attributes. Minor differences detected in the course of the analysis have been justified by the sponsor. The conclusion based on quality grounds is that Erelzi qualifies as a biosimilar.

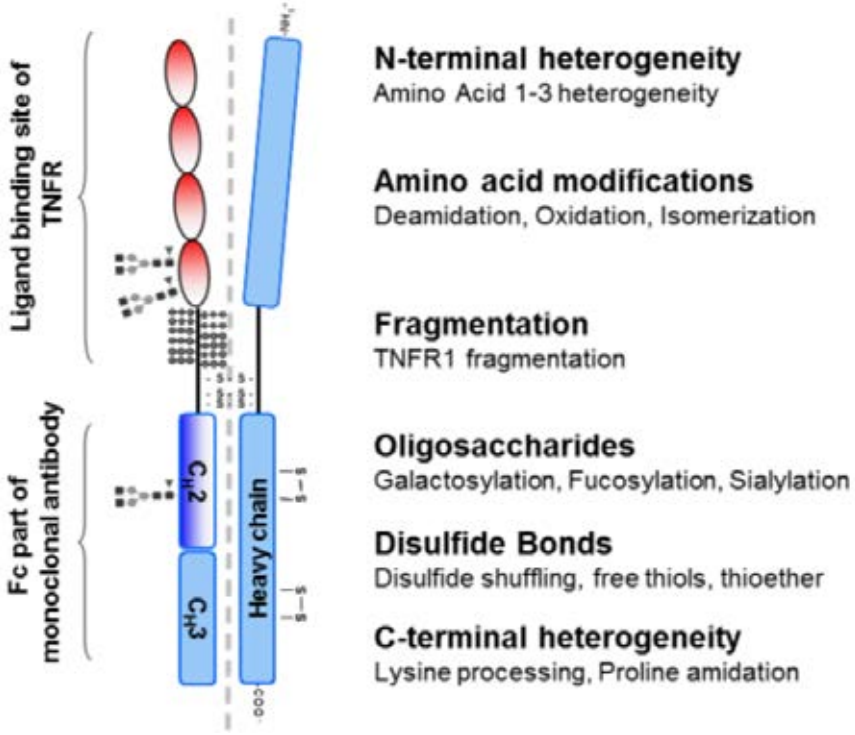
The pharmacological activity by which Enbrel (etanercept) modulates disease activity is the same in all indications, that is, inhibition of TNFα binding to its receptor. Enbrel is approved for the following conditions: rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis and paediatric plaque psoriasis. Erelzi is intended for subcutaneous use in the same posology as Enbrel, without dose adjustment in patients with renal and hepatic impairment and in elderly patients (≥ 65 years). All warnings, precautions for use, and contraindications approved for Enbrel are expected to apply also to Erelzi.

Drug substance (active ingredient)

Erelzi is a genetically-engineered dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton tumour necrosis factor receptor (TNFR) linked to the Fc portion of human immunoglobulin G (IgG1).

Erelzi is a genetically-engineered dimeric fusion protein which binds to TNF to reduce systemic inflammation. Erelzi binds TNF via the extracellular ligand-binding portion of the human 75 kilodalton TNFR, which is linked to the Fc portion of human immunoglobulin G (IgG1). The Fc component of Erelzi contains the CH2 domain, the CH3 domain, and the hinge region. However, the CH1 domain of IgG1 is absent.

Figure 1: Schematic representation of etanercept



Erelzi contains 934 amino acids (homo-dimer: 467) and has an approximate molecular mass of 125 kDa as determined by mass spectroscopy. The apparent molecular size of Erelzi (determined by SDS-PAGE) is 150 kDa and equal to the apparent molecular weight stated for EU-authorised and US-licensed Enbrel.

To determine compatibility with the innovator product and with Australian product, the following studies were done:

- The global originator product range was determined by analysis of etanercept sourced from a variety of regions. The majority of the analysed batches correspond to Enbrel/EU and Enbrel/US. Comparability of Enbrel/EU and Enbrel/US was confirmed showing that the two products are analytically indistinguishable and can therefore be regarded to originate from the same source.
- Comparability of Erelzi was evaluated and confirmed against this global originator product range in a comprehensive analytical study. The results of this analytical assessment did not reveal any significant differences between the products showing consistency between Erelzi batches as well as high comparability to the originator products with respect to their physicochemical properties and functional activity.
- The sponsor presents data describing the comparability of Enbrel/AUS with the global originator product range (that is, the combined range of Enbrel/EU and Enbrel/US) by analysis of batches of Enbrel/AUS. The data obtained from these batches is directly compared to the available data from Enbrel/EU and Enbrel/US, leading to the conclusion that Enbrel/AUS is indistinguishable from Enbrel batches sourced in other markets.

Drug product

Erelzi 25 mg/0.5 mL and 50 mg/1.0 mL solution for injection is a colourless to slightly yellowish solution comprising etanercept as drug substance, sodium citrate as buffer,

sodium chloride as tonicity agent, sucrose and L-lysine as stabilisers, and water for injection as diluent.

Erelzi drug product is adjusted to pH 6.3 with sodium hydroxide and hydrochloric acid as required, is supplied in pre-filled syringes (clear glass barrel with fixed needle) closed with a plunger stopper and is intended for SC administration.

To obtain an Erelzi formulation with an appropriate stability profile, the following approach was chosen. Formulation development was performed in three phases:

- Pre-formulation experiments
- Formulation screening I
- Formulation screening II

The manufacturing process of Erelzi 25 mg/0.5 mL and 50 mg/1.0 mL solution for injection is a standard aseptic manufacturing procedure. The batch size is flexible and defined by the exact amount and content of the protein etanercept in Erelzi drug substance solution.

Erelzi 25 mg/0.5 mL and 50 mg/1.0 mL solution for injection in pre-filled syringe (PFS) is produced using standard manufacturing steps, such as dissolving of excipients and active ingredient, compounding, sterile filtration and aseptic syringe filling.

For long term storage conditions (5 ± 3°C), all of the data provided are within the shelf-life specifications after 30 months (25 mg/0.5 mL) or 36 months (50 mg/1.0 mL), respectively. However, stability data for at least three batches were only available for 12 months for (25 mg/0.5 mL) and 24 months for (50 mg/1.0 mL) at that time. The sponsor should supply further data (up to 24 months) for the 25 mg/0.5 mL product.

Quality summary and conclusions

The evaluator asked questions of the sponsor relating to GMP certification of one manufacturing site, expiry dates for TGA certifications, stability data, and storage conditions. The sponsor provided responses, which were accepted by the Quality evaluator.

The sponsor provided data that support the proposed 30 month shelf life for both strengths of drug product, that is, 25mg/0.5mL and 50 mg/1.0 mL. The recommended shelf life for Erelzi is as follows:

- A total shelf-life of 30 months at the intended storage temperature of 5 ± 3°C including 28 days at 25 ± 2°C immediately before usage. An additional temperature excursion of not more than 10 days at > 8°C to ≤ 25 ± 2°C during shipping is allowed.

The product must be protected from light.

Apart from the need to confirm GMP certification for all sites, there were no further objections to the registration of Erelzi on quality grounds.

Request for draft CPD and samples

The Laboratories Branch of TGA manages post-market monitoring of quality aspects for Biological Medicines. A risk assessment process is used to determine the appropriate level of post-market monitoring. For products assigned to the Batch Release risk group, TGA Laboratories will request the sponsor to provide information, samples and other materials required to perform verification/validation of the relevant test methods and conduct Batch Release testing. As method verification/validation may take several weeks to

complete, this work is typically performed prior to registration, to facilitate timely release and distribution after registration.

Batch release testing & compliance with certified product details (CPD)

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

  The sponsor must supply:

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

IV. Nonclinical findings

Introduction

The scope of the submitted dossier was in accordance with the relevant guideline.[1] It was noted that none of the drug substance or drug product Erelzi batches featured in the comprehensive functional characterisation assessments were used in the in vivo nonclinical studies. In response to a post-first round evaluation query, the sponsor referred to the fact that one drug substance batch, which was used to manufacture the nonclinical drug product batch, was included in comparability assessments listed in the datapool used for calculations summary. These assessments were limited to demonstrations of comparability of TNFα and TNFβ reporter gene assays, CDC activity, glycosylation patterns and pH values between batches of Erelzi and Enbrel. Nevertheless, because the batch used in the nonclinical in vivo investigations was not represented in the more comprehensive assessments outlined, it is uncertain how relevant the findings from the in vivo studies are to assessing the overall safety profile of Erelzi. The in vivo animal studies have served more as a complement to the clinical demonstrations of efficacy rather than offered any meaningful insight into the safety profile of the biosimilar. Therefore, the conclusions of the quality evaluator will be more central to determining whether sufficient biosimilarity has been demonstrated between Erelzi and Enbrel.

[1] Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues: EMA/CHMP/BMWP/403543/2010

EU-sourced Enbrel was claimed to be the comparator that was used in the nonclinical studies. The comparability of EU- (as well as US-) Enbrel against Australian-sourced Enbrel was reported. Bridging studies demonstrated sufficient similar biological activity (as TNFα neutralisation) between EU- and US-sourced Enbrel comparators and the Enbrel product marketed in Australia.

Pharmacology

The pharmacological activity of Erelzi and EU- and US-sourced Enbrel were compared in a series of in vitro assays, which were all evaluated by the Quality evaluator. In general, studies on functional characteristics (binding to TNFα, neutralisation of TNFα and TNFβ, apoptosis assay, affinity for C1q, FcγRI-IIIa/b and CDC activities) of Erelzi and Enbrel showed similar (overlapping) ranges of activities across the different batches tested. The Erelzi drug product batch used in the nonclinical studies was not included in the in vitro comparability testing.

For in vivo comparability assessments of Erelzi, the sponsor used a human TNF transgenic mouse model of polyarthritis, which overexpresses human TNF and develops chronic polyarthritis by 7 weeks of age. An initial pilot study was conducted to characterise the anti-inflammatory effects of innovator Enbrel (EU-sourced) in this animal model in order to determine benchmark levels of improvement against biosimilar Erelzi. Three study designs were utilised (single bolus dosing at 7 weeks of age, repeat dosing for 3 weeks and repeat dosing for 5 weeks). In-life assessments consisted of the assignment of arthritic scores, while post-mortem assessments involved assigning histopathology scores for severity of arthritis of ankle joints. Dosing of Enbrel (3, 10, 30 mg/kg) was either by the SC or IP routes, although treatment-related improvements to scores were generally similar when either route was used. The longer repeat dosing regimen (5 weeks compared with 3 weeks) offered the most improvements in arthritic and histopathology scores, as well as body weight gain, in the Tg197 mice but the differences were small.

For the comparability study with Erelzi, the protocol design utilised three dosing regimens (a single bolus injection, 5 doses or 9 doses) to compare the anti-arthritic effects of Erelzi and Enbrel (both at 10 mg/kg, IP). Both dosing regimens of Erelzi improved body weights, with the group that received 9 doses reaching statistical significance relative to vehicle control groups. Improvements in arthritic scores relative to vehicle or untreated controls were similar for the Erelzi and Enbrel treated groups, using either dosing regimen. Improvements in histopathology scores (relative to vehicle group) were more apparent in the Erelzi groups than Enbrel. Scores for mice that received 9 doses of Erelzi were significantly different from vehicle controls. Overall, however, the findings from this study adequately demonstrate comparable anti-inflammatory activity (based on improvements in arthritis scores, joint histopathology assessments and body weight as a marker for general well-being) between etanercept biosimilar Erelzi and comparator EU-Enbrel in a mouse model of polyarthritis. No animal studies were submitted to support the use of Erelzi in the other proposed indications and as such no comment can be made from a nonclinical perspective to support the use of the biosimilar etanercept for these indications.

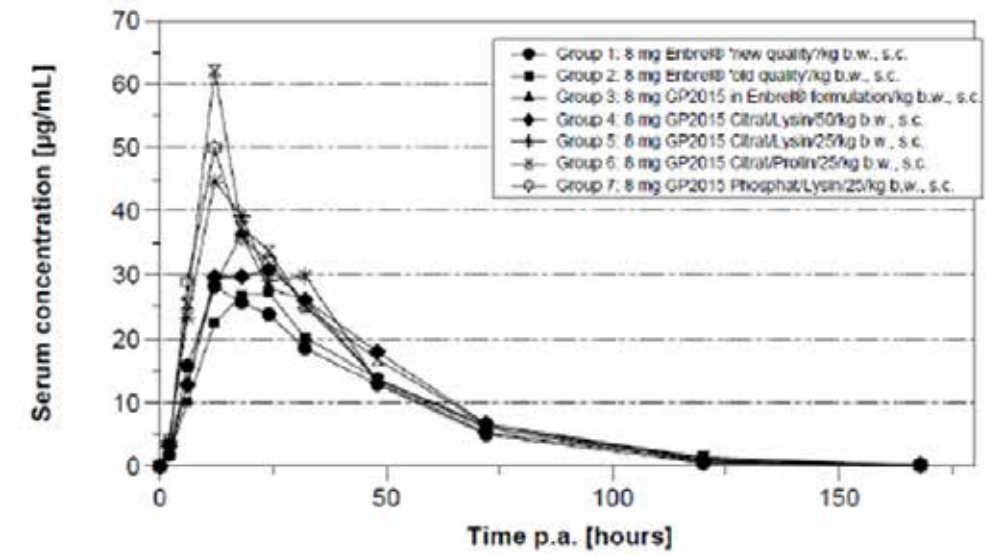
Pharmacokinetics

Pharmacokinetic parameters were assessed in single dose studies conducted in rabbits and in cynomolgus monkeys as part of toxicokinetic measurements in the 28 day repeat dose toxicity study. The objectives of the rabbit studies were primarily concerned with finding a formulation of Erelzi that exhibits comparable PK attributes to the originator

formulation. According to EMA guidance,[2] in vivo nonclinical studies may be conducted to provide complementary information that pertains to relevant differences in formulation. This may be in cases where a formulation includes excipients not commonly used for biotechnology-derived protein products. It is questionable whether these considerations apply to this submission as the excipients used in the different Erelzi formulations did not appear to be remarkably novel. Regardless, the data from these single dose rabbit studies were used to select the formulation used in the toxicity study and subsequently, the clinical formulation intended for registration.

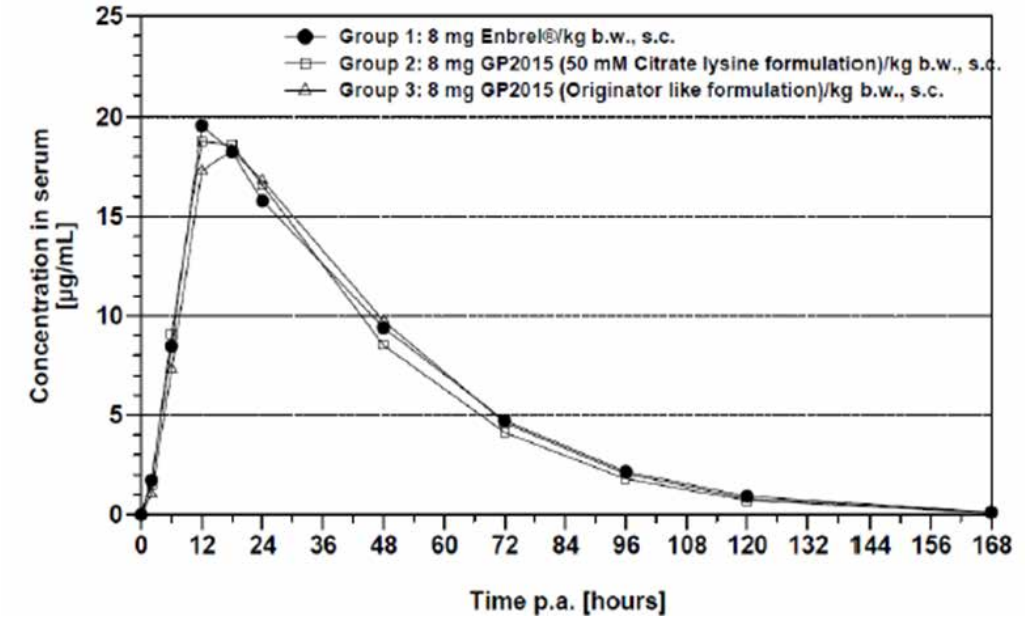
In the single dose studies, different Erelzi formulations were tested in which the excipient buffer salts and amino acids used in the Enbrel formulation were substituted with other salts and amino acids. The combinations tested included the phosphate/arginine combination used in the Enbrel formulation (Study GP15-001). The 50 mM citrate/lysine formulation combination of Erelzi exhibited PK characteristics that aligned the closest to the Enbrel formulation, as was confirmed in a second comparative study in rabbits (Study GP15-006). Quantitative differences in PK parameters were evident between the two rabbit studies whereby the second study showed marginally lower overall values for PK parameters. Since the same doses, routes and testing conditions were used for both studies, and particularly since lower values were consistently seen for all formulations in the second study (Study GP15-006), the reason for these discrepancies was not addressed. Differences are highlighted below.

Figure 2: Mean serum concentrations of etanercept in male rabbits after single 8 mg/kg, SC doses of Erelzi or Enbrel (Study GP15-001)



[2] CHMP/BMWP/42832/2005 Rev 1

Figure 3: Mean serum concentration of etanercept in male rabbits after single 8 mg/kg, SC doses of 2 formulations of Erelzi and Enbrel (Study GP15-006)



In response to a post-first round query, the sponsor acknowledged the difference and cited some possible reasons, including differences in group sizes, the slight difference in rabbit ages, seasonal variations and use of a different analytical method for detecting Erelzi to account for differences. As the observations in question did not relate to Erelzi batches that have clinical relevance (that is, no overlap with clinical batches), the sponsor justifications are noted and accepted.

Toxicokinetic parameters determined in cynomolgus monkeys as part of the 28 day toxicity study (Study GP15-003) showed comparable absorption profiles between Erelzi and Enbrel. However, sampling day 7 exposures (as $AUC_{0-\infty}$) to Erelzi etanercept were slightly lower than to Enbrel etanercept. On the last sampling day (day 28), exposures (as both Cmax and $AUC_{0-\infty}$) were substantially lower than respective measurements on days 1 and 7. The study authors confirmed the presence of anti-etanercept antibodies in 2 animals from each etanercept group, but indicated that high levels of free etanercept in the serum likely disguised the detection of anti-etanercept antibodies. Nevertheless, since ADAs were detected in animals from both groups, extent of immunogenicity is likely to be similar between the two forms of etanercept and therefore unlikely to be a factor in any potential qualitative differences in effects.

Toxicity

The sponsor submitted a comparative GLP-compliant repeat-dose toxicity study in cynomolgus monkeys of 4 weeks (28 days) duration. Duration of study and choice of species are acceptable. The clinical route (SC) and a dosing regimen (every 3 days) similar to the proposed clinical regimen were used in the study. Groups of 3 animals per sex received SC dose of placebo, Erelzi or EU-sourced Enbrel (15 mg/kg), every 3 days, which were administered into 4 rotated injection sites. Dose selection is acceptable, resulting in AUC exposures of up to 6 to 8 times clinical exposures that were reported in healthy subjects (clinical Study GP15-104).

Toxicity findings were generally minor and the nature, incidence and severity of findings in Erelzi treated animals were comparable to those observed with EU-sourced Enbrel. There were no mortalities and clinical signs were limited to injection site reactions that were seen in only a few etanercept-treated animals from both groups. There were no treatment-related effects on body weight gain, urinalysis, cardiovascular parameters (HR,

blood pressure, ECG parameters), organ weights or gross pathology. Haematology and serum chemistry parameters were similar between the etanercept groups.

Three animals (1 Erelzi treated male and 2 Enbrel treated males) exhibited changes that were attributed to treatment. These changes included injection site reactions (erythema, ecchymosis and erythematous blotches), which were most evident around the last injection day (day 28). These same animals also exhibited fluctuations in haematologic parameters (decreases in RBC, haemoglobin and haematocrit levels, corresponding increases in reticulocytes and variable changes to platelets levels) relative to placebo control group measurements. As well, the Erelzi male exhibited small elevations in body temperatures. These observations likely reflected immunogenic reactions elicited by ADAs against etanercept. Consistent with this, all three animals exhibited reduced serum levels (as $AUC_{0-\tau}$) of etanercept by day 28 (#5M: 358 µg.h/mL, #7M: 260 µg.h/mL, #8M: 159 µg.h/mL) compared to other animals of their treatment group or to measurements from day 1 ($AUC_{0-\tau}$ Day 1: Enbrel 4050 ± 463 µg.h/mL; Erelzi: 4020 ± 164 µg.h/mL).

Histopathology observations were limited to inflammatory lesions around the injection sites, which were generally seen in the etanercept-treated groups and included dermatitis, myositis and cellulitis. Incidences of these observations were tallied from four injection sites for the three groups, where for most findings incidences were comparable between Erelzi and EU-Enbrel treated groups. Myositis was seen in all Erelzi-treated females but none in EU-Enbrel treated females, and there were more Erelzi-treated males with myositis than EU-Enbrel treated males, thus it is likely to be associated with Erelzi treatment. Cellulitis was most frequent in Erelzi-treated females and EU-Enbrel-treated males. Perivascular mononuclear cell infiltration was only evident in injection sites from etanercept treated animals. Total incidents (injection sites) were similar in males from either etanercept group, while in females there were more frequent observations in Erelzi-treated animals than those that received Enbrel. Overall, these histopathology observations were confined to injection sites and observations were variable for both etanercept groups, thus a clear qualitative difference between Erelzi and Enbrel was not apparent.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[3] This matches the existing category for Enbrel and is considered appropriate.

Nonclinical summary and conclusions

- The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat dose toxicity. The scope of the nonclinical program was in general accordance with guidelines on the nonclinical assessment of biological medicines.[4] The sponsor stated that all nonclinical studies used EU-sourced Enbrel as reference product. Bridging studies, conducted to demonstrate the adequacy of the Enbrel comparators used in nonclinical and clinical studies to the product marketed in Australia, confirmed comparability between EU- (as well as US-) sourced Enbrel and Australian-supplied Enbrel.
- No overall meaningful differences between Erelzi/Erelzi and EU-sourced Enbrel were observed in the comparative in vivo pharmacology, pharmacokinetic and toxicity studies.

[3] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[4] EMEA/CHMP/BMWP/42832/2005 Rev 1

- The demonstration of comparative in vivo pharmacological, pharmacokinetic and toxicological attributes between Erelzi/Erelzi and EU-sourced Enbrel was generally sound. However, the nonclinical drug substance and drug product batches used in these studies were not included in the panel of batches evaluated in the in vitro comparability assessments. Without full concordance of batches used in the in vitro and in vivo testing, the relevance of the findings from the nonclinical in vivo studies to the overall safety profile of Erelzi/Erelzi is limited. Therefore, from a nonclinical perspective, the comparable safety profile of Erelzi/Erelzi relative to Enbrel is uncertain, meaning that the conclusions of the Quality Evaluator will be more central to establishing biosimilarity between Erelzi/Erelzi and Enbrel.
- The draft PI document should be amended as directed.

V. Clinical findings

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

Introduction

Clinical rationale

Erelzi has been developed by the sponsor as a similar biological product to the reference product Enbrel. It can serve as an alternative to the reference product, if found to be biosimilar.

Guidance

The following guidelines have been considered in relation to this submission.

- General guidelines
  - CPMP/ICH/135/95: Note for guidance on good clinical practice (CPMP/ICH/135/95 - Annotated with TGA comments)
- Guidelines regarding similar biological medicinal products
  - TGA guidance on regulation of biosimilar medicines, Version 2.0, December 2015
  - CHMP/437/04 Rev. 1: Guideline on similar biological medicinal products.
  - EMEA/CHMP/BMWP/42832/2005 Rev1: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.
  - EMA/CHMP/BWP/247713/2012: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)
  - EMA/CHMP/BMWP/403543/2010: Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues.
  - CPMP/EWP/QWP/1401/98 Rev. 1/ Corr: Guideline on the Investigation of Bioequivalence.
- General guidelines regarding biological medicinal products/therapeutic proteins

- EMEA/CHMP/BMWP/101695/2006: Guideline on Comparability of Biotechnology-Derived Medicinal Products after a change in the Manufacturing Process - Non-Clinical and Clinical Issues.
- EMEA/CHMP/BMWP/14327/2006: Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins.
- CHMP/EWP/14327/2004: Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins.

· Guidelines regarding products containing monoclonal antibodies

- EMA/CHMP/BMWP/86289/2010: Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use.
- CPMP/ICH/5721/03: ICH Topic Q 5 E: Comparability of Biotechnological/ Biological Products (Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process).

· Indication-specific guidelines

- CHMP/EWP/2454/02 corr: Guideline on clinical investigation of medicinal products indicated for the treatment of Psoriasis.

· Guidelines regarding products for long-term use

- Rules 1998 (3C) - 3CC6a: Clinical Investigation of Medicinal Products for Long-Term Use.

· Specific guidance for this submission: Pre-submission advice was sought in August 2016. The main items included:

- There were no objections to the trade name Erelzi at the time of the meeting.
- The bridging study report comparing the Australian batches to overseas-sourced batches of the reference product (Enbrel).
- The proposed PI will state that powder for injection vials of Erelzi will not be available for use in weight-based dosage adjustments for children and adolescents weighing below 62.5 kg.

Contents of the clinical dossier

The dossier does not contain a full development program. The sponsor supports their biosimilar application with bioequivalence and equivalence studies that compare their product, Erelzi, to the reference product, Enbrel.

· Four pharmacokinetic studies (in healthy subjects); and

· One efficacy study in patients with plaque psoriasis.

Clinical study reports were included for:

· PK studies

- Study GP15-101: A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of Erelzi and Enbrel (EU-licensed) following a single subcutaneous injection in healthy subjects.
- Study GP15-102: A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of Erelzi and Enbrel (US-licensed) following a single subcutaneous injection in healthy subjects.
- Study GP15-103: A randomized, open label, two-way cross-over study to determine the pharmacokinetics and safety of Erelzi following a single

subcutaneous injection by an auto-injector and by a pre-filled syringe in healthy male subjects.

- Study GP15-104 (Pivotal): A randomized, double blind, two-way cross-over study to determine the pharmacokinetics and safety of Erelzi and Enbrel (EU-licensed) following a single dose of 50 mg subcutaneous injection in healthy male subjects.

· Efficacy studies

- GP15-302 (Pivotal): A randomized, double-blind, multicentre study to demonstrate equivalent efficacy and to compare safety and immunogenicity of a biosimilar etanercept (Erelzi) and Enbrel in patients with moderate to severe chronic plaque type psoriasis (Egality).

Paediatric data

The provided studies did not include paediatric patients.

Good clinical practice

All studies contained a statement claiming compliance with good clinical practice guidelines or ethical principles of the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

Studies GP15-101, GP15-102, GP15-103, GP15-104, and GP15-302 provided PK data. Studies GP15-101, GP15-102, GP15-103, GP15-104 were dedicated PK studies in healthy subjects. Study GP15-302 was an equivalence study that compared Erelzi to Enbrel with regard to efficacy in plaque psoriasis. The PK component of that study was limited to a comparison of steady state trough concentrations.

Table 3: Summary of clinical pharmacology studies of Erelzi

Study No.	Study title	Study population	Study duration	Dosage [batch number]	PK/PD endpoints
Pivotal PK study					
GP15-104	A randomized, double blind, two-way crossover study to determine the pharmacokinetics and safety of GP2015 and Enbrel/EU following a single dose of 50 mg s.c. injection in healthy male subjects	Healthy volunteers Total: N (m)=54	Up to 3 months from screening to follow-up including 35 days of washout between doses	GP2015 [DR0917 (S0014)] or Enbrel/EU [H76640] 2 single doses, 50 mg s.c.	• Primary PK: C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of etanercept • Secondary PK: $CL_{0\text{-inf}}$, t_{max}, k_{el} and $t_{1/2}$ of etanercept
Supportive PK studies[1]					
GP15-101	A randomized, double-blind, two-way crossover study to determine the PK and safety of GP2015 and Enbrel/EU following a single s.c. injection in healthy subjects	Healthy volunteers Total: N (m/f)=54 (33/21)	Up to 3 months from screening to follow-up including 35 days of washout between doses	GP2015 [2G27062011] or Enbrel/EU [E88057]: 2 single doses, 50 mg s.c.	• Primary PK: $AUC_{0\text{-last}}$, C_{max} of etanercept • Secondary PK: $AUC_{0\text{-inf}}$, t_{max}, k_{el} and $t_{1/2}$ of etanercept
GP15-102	A randomized, double-blind, two-way crossover study to determine the PK and safety of GP2015 and Enbrel/US following a single 50 mg s.c. injection in healthy subjects.	Healthy volunteers Total: N (m/f)=57 (42/15)	Up to 3 months from screening to follow-up including 35 days of washout between doses	GP2015 [2G27062011] or Enbrel/US [1026663]: 2 single doses, 50 mg s.c.	• Primary PK: $AUC_{0\text{-last}}$, C_{max} of etanercept • Secondary PK: $AUC_{0\text{-inf}}$, t_{max}, k_{el} and $t_{1/2}$ of etanercept
GP15-103	A randomized, open label, two-way crossover study to determine the PK and safety of GP2015 following a single s.c. injection by an AI and by a PFS in healthy male subjects.	Healthy volunteers N (m)=51	Up to 3 months from screening to follow-up including 35 days of washout between doses	GP2015 PFS [DR0919 (S0016)] or GP2015 AI [30771670 (S0016)]: 2 single doses, 50 mg s.c.	• Primary PK: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max} of etanercept • Secondary PK:$AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}, by weight category, t_{max}, k_{el} and $t_{1/2}$ of etanercept
Study No.	**Study title**	**Study population**	**Study duration**	**Dosage [batch number]**	**PK/PD endpoints**
Confirmatory efficacy and safety study					
GP15-302	A randomized, double-blind, multicenter study to demonstrate equivalent efficacy and to compare safety and immunogenicity of GP2015, a proposed biosimilar etanercept, and Enbrel/EU in patients with moderate to severe chronic plaque-type psoriasis.	Patients with moderate to severe chronic plaque-type psoriasis Total: N=531 (329m/202f) GP2015: 264 (157m/107f) Enbrel/EU: 267 (172m/95f PK sub-study: N=147 (95m/52f)	52 weeks (data included in this dossier up to cut-off date of 29-Oct-2014 i.e. LPLV for Week 30)	GP2015 [S0011, S0012, S0014] or Enbrel/EU [G75422, H76640]: GP2015 or Enbrel/EU: 50 mg s.c., twice-weekly up to 12 weeks, then once weekly up to 52 weeks	PK: trough serum concentrations at baseline and Weeks 2, 4, 8 and 12 PD: high sensitivity C-reactive protein (hsCRP) concentrations at baseline and Weeks 4 and 12

AI=autoinjector; Enbrel/EU=EU-authorized Enbrel; Enbrel/US=US-licensed Enbrel; f=female; hsCRP=high sensitivity C-reactive protein; N=number of patients or subjects; m=male; PD=Pharmacodynamic; PFS=pre-filled syringe; PK= pharmacokinetic; s.c.=subcutaneous(ly).
For definitions of $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, k_{el}, t_{max}, $t_{1/2}$ refer to List of abbreviations.
[1] GP15-101 and GP15-102 have identical study designs and were performed in the same phase I unit. Additionally, prospectively planned cross-study comparison of the studies GP15-102 (using Enbrel/US) and GP15-101 (using Enbrel/EU) was performed (denoted as study GP15-105).
Source: [Module 5.3.3.1 GP15-101], [Module 5.3.3.1 GP15-102], [Module 5.3.3.1 GP15-103], [Module 5.3.3.1 GP15-104] and [Module 5.3.5.1 GP15-302 Week 30]

Evaluator's conclusions on pharmacokinetics

Overall, the bioequivalence criteria for Erelzi were met. The main results were within the prescribed bioequivalence margins and are acceptable.

Enbrel is currently approved in Australia and its PK study data and their description in the PI document have previously been accepted by the TGA. Consequently, the PI document of any approved biosimilar to Enbrel without separate PK studies should contain the identical information with regard to pharmacokinetics. The proposed PI document for Erelzi fulfils this requirement. However, in the 'Pharmacology' section, in the 'Pharmacokinetics' subsection, under a 'Comparability of Erelzi with Enbrel' subheading, comparability data should be added.

Nearly no subjects in the PK studies developed ADAs. More detail and questions are directed to the sponsor.

As stated above, the clinical efficacy study reporting did not show the trough concentration mean ratios and associated 90% CIs. All of the information necessary is presented in tables.

Pharmacodynamics

Pharmacodynamic data pertaining to Enbrel are proposed to be included in the Erelzi PI. In the proposed PI for Erelzi, the section with regard to pharmacodynamic data is identical to the corresponding section in the reference product PI document. However, in the 'Pharmacology' section, in the 'Pharmacodynamics' subsection, under a 'Comparability of Erelzi with Enbrel' subheading, comparability data should be added.

Study GP15-302 had a small pharmacodynamic component, in which high sensitivity C-reactive protein (hsCRP) was used as a pharmacodynamic marker. This marker was compared between the treatment groups at baseline, and at Weeks 4 and 12.

The mean hsCRP levels (± SD) (Erelzi versus Enbrel) were 4.390 ± 5.8540 mg/L versus 4.529 ± 12.0969 mg/L, 1.993 ± 3.5787 mg/L vs 1.810 ± 2.6836 mg/L, and 1.889 ± 2.7920 mg/L versus 1.747 ± 3.0309 mg/L at baseline, Week 4, and Week 12, respectively. The proportions of patients with high hsCRP levels as well as the mean hsCRP levels were similar between the Erelzi and Enbrel groups.

The results are generally supportive of biosimilarity, but a pharmacodynamic assessment was not necessarily required to establish this.

Dosage selection for the pivotal studies

The doses used in clinical equivalence study were identical to the usual recommended dosing regimen for the respective adult indications in the reference product Enbrel.

Efficacy

Studies providing efficacy data

One study provided evaluable efficacy data for plaque psoriasis:

- Study GP15-302: a Phase III, double-blind, randomised, active comparator-controlled study in 531 subjects with moderate to severe psoriasis evaluating the efficacy and safety of Erelzi compared with Enbrel (EU).

Evaluator's conclusions on efficacy

The submission relies on one efficacy study to demonstrate biosimilarity, namely Study GP15-302 (Egality) (a Phase III, double-blind, randomised, active comparator-controlled study in 531 subjects with moderate to severe plaque psoriasis evaluating the efficacy and safety of Erelzi compared with Enbrel (EU)). 531 patients were part of the study, and this number was sufficient. The study was set up to follow patients for up to 52 weeks, with the primary assessment being conducted at the end of Week 12 (identical to the pivotal psoriasis trials with Enbrel).

The doses used in Study GP15-302 were at the upper end of clinically used adult doses for Enbrel (50 mg twice weekly for 12 weeks, then 50 mg weekly). This dosage regimen was also used in the pivotal trials (in at least one treatment arm). This is considered appropriate. The study design was acceptable overall.

The characteristics of the Egality study population were sufficiently similar to the populations in the Enbrel pivotal trials, as well as a general psoriasis population. This supported the internal and external validity of the study.

EGALITY appropriately used a per-protocol population as the main analysis population. PASI75 response at Week 12 was the primary endpoint which was also used by both pivotal reference product trials (Leonardi, et al. (2003) and Papp, et al. (2005)).[5] Arguably, for an equivalence trial, the use of a continuous PASI variable, e.g. Percentage change from baseline, is more suitable to detect smaller differences in treatment effect than a categorical variable. The sponsor has also included continuous PASI variables as secondary endpoints. This is considered favourable, as this made both a comparison to pivotal trial endpoints and a suitable accommodation for equivalence trial design through use of continuous variables possible.

Only descriptive statistics were provided for the endpoints other than those involving PASI scores. Given that any psoriasis trial assessment should not solely rely on PASI scores, it is important to also provide an appropriate statistical analysis of the other endpoints, that is, data comparing the treatment groups, and comparing the pooled continued group and the pooled switched group (difference and 95% CIs).

Most trials of TNF-α antagonist biosimilars used rheumatoid arthritis as their main study indication (Lai and La Noce, 2016).[6] For Erelzi, the sponsor has chosen psoriasis as the target indication for their equivalence Study GP15-302. There are advantages and disadvantages with regard to that choice.

The investigation of medicines for rheumatoid arthritis has a better choice of endpoints: the ACR score, for example, is highly validated and is also a composite endpoint. Additionally, biomarkers and radiographic evidence can be used for rheumatoid arthritis.

The psoriasis assessment tools are often considered a limitation of clinical trials in psoriasis patients. Psoriasis assessments appear to be more subjective with clinicians often overestimating body surface area affected. The patient experience of severity is also rather subjective. The PASI is still considered the gold standard and widely used in psoriasis clinical trials, including the reference product pivotal trials. The PASI's disadvantages are that the upper end of the scale is rarely used (the highest score in Study GP15-302 was 55.2/72), and may have low response distribution and no consensus on

[5] Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB; Etanercept Psoriasis Study Group 2003. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 349(21):2014-22; Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, Zitnik R, van de Kerkhof PC, Melvin L; Etanercept Psoriasis Study Group 2005. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 152(6):1304-12.

[6] Lai Z, La Noce A 2016. Key design considerations on comparative clinical efficacy studies for biosimilars: adalimumab as an example. RMD Open 2(1):e000154.

interpretability, whereas PGA/IGA may not necessarily discriminate small change and may not have a robust range (Feldman and Kruger, 2005; Spuls et al., 2010).[7] In the relevant EU guideline,[8] a combination of endpoint measures is recommended (for example, PASI and sPGA or PASI and BSA) which was used in Study GP15-302. The use of the combination eliminates many of the disadvantages associated with psoriasis assessments.

The advantage of a psoriasis trial is that the population will be comparatively younger with fewer co-morbidities and fewer co-medications, and thus providing a better signal-to noise ratio. Therefore, the use of a psoriasis target population can be considered as a valid population for the purposes of assessing biosimilarity and especially with regard to extrapolation.

As outlined, based on the evidence available, the approval of extrapolation to the other reference product indications is considered reasonable in conjunction with appropriate pharmacovigilance activities (for example, participation in relevant disease registries) and risk minimisation activities.

There is sufficient evidence to support clinical efficacy of Erelzi in psoriasis, and also biosimilarity of Erelzi to the reference product Enbrel, pending a satisfactory sponsor response to the outstanding issues.

Safety

Studies providing safety data

All five studies (four PK bioequivalence studies and one equivalence study in psoriasis patients) included in this submission provided safety data:

- Study GP15-302: a phase 3, double-blind, randomised, active comparator-controlled study in 531 subjects with moderate to severe psoriasis evaluating the efficacy and safety of Erelzi compared with Enbrel (EU).
- Study GP15-104: a randomized, double blind, two-way cross-over study to determine the pharmacokinetics and safety of Erelzi and Enbrel (EU-licensed) following a single dose of 50 mg subcutaneous injection in healthy male subjects.
- Study GP15-101: a randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of Erelzi and Enbrel (EU-licensed) following a single subcutaneous injection in healthy subjects.
- Study GP15-102: A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of Erelzi and Enbrel (US-licensed) following a single subcutaneous injection in healthy subjects.
- Study GP15-103: A randomized, open label, two-way cross-over study to determine the pharmacokinetics and safety of Erelzi following a single subcutaneous injection by an auto-injector and by a pre-filled syringe in healthy male subjects.

A summary of the studies providing safety data is shown.

[7] Feldman S, Krueger G 2005. Psoriasis assessment tools in clinical trials. Ann Rheum Dis 64(Suppl 2): ii65–ii68; Spuls PI, Lecluse LL, Poulsen ML, Bos JD, Stern RS, Nijsten T 2010. How good are clinical severity and outcome measures for psoriasis?: quantitative evaluation in a systematic review. J Invest Dermatol 130(4):933–943.
[8] CHMP/EWP/2454/02 corr

Table 4: Overview of studies providing evaluable safety data

Study No.	Study title	Study population	Study duration	Dosage [batch number]	Safety endpoints
Pivotal PK study					
GP15-104	A randomized, double blind, 2-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel/EU following a single dose of 50 mg s.c. injection in healthy male subjects	Healthy volunteers Total: N (m)=54	Up to 3 months from screening to follow-up including 35 days of washout between doses	GP2015 [DR0917 (S0014)] or Enbrel/EU [H76640] 2 single doses, 50 mg s.c.	• AEs and SAEs • hematology parameters (including coagulation), blood chemistry and urine • local tolerance at the injection site • vital signs • physical condition • 12-lead ECG • antibody formation against etanercept
Supportive PK studies[1]					
GP15-101	A randomized, double-blind, 2-way crossover study to determine the PK and safety of GP2015 and Enbrel/EU following a single s.c. injection in healthy subjects	Healthy volunteers Total: N=54 (33m/21f)	Up to 3 months from screening to follow-up including 35 days of washout between doses	GP2015 [2G27062011] or Enbrel/EU [E88057]: 2 single doses, 50 mg s.c.	• AEs and SAEs • hematology parameters (including coagulation), blood chemistry and urine • local tolerance at the injection site • vital signs • physical condition • 12-lead ECG • antibody formation against etanercept

GP15-102	A randomized, double-blind, 2-way crossover study to determine the PK and safety of GP2015 and Enbrel/US following a single 50 mg s.c. injection in healthy subjects	Healthy volunteers Total: N=57 (42m/15f)	Up to 3 months from screening to follow-up including 35 days of washout between doses	GP2015 [2G27062011] or Enbrel/US [1026663]: 2 single doses, 50 mg s.c.	• AEs and SAEs • hematology parameters (including coagulation), blood chemistry and urine • local tolerance at the injection site • vital signs • physical condition • 12-lead ECG • antibody formation against etanercept
GP15-103	A randomized, open label, 2-way crossover study to determine the PKs and safety of GP2015 following a single s.c. injection by an AI and by a PFS in healthy male subjects	Healthy volunteers N (m)=51	Up to 3 months from screening to follow-up including 35 days of washout between doses	GP2015 PFS [DR0919 (S0016)] or GP2015 AI [30771670 (S0016)]: 2 single doses, 50 mg s.c.	• AEs and SAEs • hematology parameters (including coagulation), blood chemistry and urine • local tolerance at the injection site • vital signs • physical condition • 12-lead ECG • antibody formation against etanercept
Pivotal confirmatory efficacy and safety study					
GP15-302	A randomized, double-blind, multicenter study to demonstrate equivalent efficacy and to compare safety and immunogenicity of a biosimilar etanercept (GP2015) and Enbrel/EU in patients with moderate to severe chronic plaque-type psoriasis	Patients with moderate to severe chronic plaque-type psoriasis Total: N=531* (329m/202f) GP2015: 264 * (157m/107f) Enbrel/EU: 267* (172m/95f)	52 weeks (including all the data)	GP2015 [S0011, S0012, S0014] or Enbrel/EU [G75422, H76640, H18066, H12012]: 50 mg s.c., twice-weekly up to 12 weeks, then once weekly up to 52 weeks	• AEs and SAEs • hematology parameters (including coagulation), blood chemistry and urine • local tolerance at the injection site • vital signs • physical condition • 12-lead ECG • antibody formation against etanercept

* Number of patients included in the Treatment Period 1 (TP1) safety set, defined as all patients who took at least 1 dose of study treatment during TP1.

AE=adverse event; ECG=electrocardiogram; Enbrel/EU=EU-authorized Enbrel; f=female; m=male; N=number of total patients; SAE=serious adverse event; s.c.=subcutaneously.

No formal hypotheses were tested in the safety parts of the studies. The safety endpoints mainly related to overall safety, local tolerance, and immunogenicity.

The Medical Dictionary for Regulatory Activities (MedDRA) was used for coding (v14.1 for Studies GP15-101 and GP15-102; v17.0 for Studies GP15-104, GP15-103, and GP15-302).

As this is a biosimilar application, the main purpose of the clinical safety section was to evaluate whether there were significant differences between the biosimilar and the reference product. The efficacy and safety of the reference product has been previously established for the currently approved indications. The list of TEAEs of special interest is acceptable.

Patient exposure

All subjects in the PK studies were exposed to single 50 mg doses of Erelzi and Enbrel (EU). The baseline demographics were reasonably balanced in the studies. Subjects were exposed to both treatments; hence the treatment groups were balanced automatically (subject to no dropouts after period I).

Table 5: Exposure to Erelzi and comparators in PK studies

	GP2015	Enbrel/US	Enbrel/EU
Duration of drug exposure	single injection	single injection	single injection
Dose administered	50 mg	50 mg	50 mg
Subjects			
enrolled	216	54	138
withdrawals	8	3	3
Subjects dosed	216	54	138

Source: [Module 5.3.3.1 GP15-101], [Module 5.3.3.1 GP15-102], [Module 5.3.3.1 GP15-103], [Module 5.3.3.1 GP15-104]

All patients in the clinical equivalence study had plaque psoriasis and were exposed to 50 mg of Erelzi or Enbrel (EU) twice weekly. The baseline demographics were reasonably balanced between the treatment groups.

Table 6: Exposure to Erelzi and comparators in the clinical equivalence study.

Exposure	Erelzi	Enbrel (EU)
Randomisation (Erelzi: N = 264; Enbrel (EU): N = 267)		
Any exposure	264	267
Exposure ≥ 2 weeks	263	263
Exposure ≥ 4 weeks	262	258
Exposure ≥ 8 weeks	257	257
Re-randomisation at Week 12 (Erelzi: N = 150; Enbrel (EU): N = 151)		
Exposure ≥ 18 weeks	147	148
Exposure ≥ 24 weeks	143	146
Exposure ≥ 36 weeks	138	139
Exposure ≥ 42 weeks	137	139
Exposure ≥ 48 weeks	133	137
Exposure = 52 weeks	118	120

The maximum duration of IMP exposure was 52 weeks in the clinical psoriasis study (GP15-302) which was reached by 118 patients (Erelzi) and 120 patients (Enbrel). Within the OA Safety Set, patients were exposed (Erelzi versus Enbrel) for a mean 318.3 days (vs. 309.9 days), for a median 358.0 days (vs. 358.0 days). Within the OA Safety Set, patients were exposed (pooled continued group versus pooled switched group) for a mean 314.0 days (vs. 346.2 days), for a median 358.0 days (vs. 358.0 days). The exposure was sufficient for comparability purposes. The clinical studies were not powered to detect rarer adverse events.

Comment: Patient exposure was adequate to show comparability to the reference product. Furthermore, a subset of study GP15-302 switched three times from one product to the other between Week 12 and Week 30 providing data for a small group of subjects until week 52 (40 weeks of data after the first switch).

Safety issues with the potential for major regulatory impact

TEAEs of special interest

The sponsor defined adverse events of special interest based on special warnings and precautions given in the Enbrel product label.

Specific adverse events of interest for the safety analysis of the phase 3 study are listed.

Table 7: TEAEs of special interest.

System organ class (SOC)	High level group term (HLGT)/ High level term (HLT)/Preferred term (PT)
Infections and infestations	Tuberculous infections (HLT)
	Atypical mycobacterial infections (HLT)
	Hepatitis B (PT)
	Acute hepatitis B (PT)
	Chronic hepatitis B (PT)
	Hepatitis C (PT)
	Acute hepatitis C (PT)
	Chronic hepatitis C (PT)
	Sepsis, bacteremia, viremia and fungemia NEC (HLT)
	Listeriosis (PT)
	Legionella infection (PT)
	Pneumonia legionella (PT)
	Fungal infectious disorders (HLGT)
	Pneumocystis infections (HLT)
	Aspergillus infections (HLT)
	Herpes viral infections (HLT)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	All PTs
Allergic/anaphylactic reactions	Angioedema and urticarial (HLGT)
	Hypersensitivity (PT)
	Drug hypersensitivity (PT)
	Bronchospasm (PT)
	Rubber sensitivity (PT)
	Rashes, eruptions and exanthemas NEC (HLT)
Immune system disorders/ Autoimmune events	Acute and chronic sarcoidosis (HLT)
	Autoimmune pancytopenia (PT)
	Autoimmune hepatitis (PT)
	Autoantibody positive (PT)
	Lupus-like syndrome (PT)
	Vasculitides (HLT)
	Vasculitides NEC (HLT)
Neurological events	Demyelinating disorders (HLGT)
Hematological events	Pancytopenia (PT)
	Thrombocytopenia (PT)
	Anemia (PT)
	Aplastic anemia (PT)
	Leukopenia (PT)
	Neutropenia (PT)
	White blood cell count decreased (PT)
Congestive Heart Failure	Cardiac failure congestive (PT)
	Interstitial lung disease (PT)

Source: [Module 5.3.5.1 GP15-302 Week 30-Table 9-6]
HLGT=high level group term; HLT=high level term; NEC=not elsewhere classified; PT=preferred term; SOC=system organ class

Adverse events of special interest (AESIs) were relatively infrequent in all treatment groups. Individual AESIs did not occur in more than one patient in any group. Overall, even though the numbers are too small to determine a trend, infections and neoplasms/malignancies appeared to occur more frequently in the continued Erelzi group, whereas hypersensitivity and associated reactions occurred more often in the continued Enbrel group.

Table 8: Study GP15-302. Summary comments on TEAEs of special interest.

Set	Comment
TP1	There were slightly more patients with TEAEs of special interest in the Erelzi group (9 (3.4%) versus 5 (1.9%), mainly due to a slightly bigger number of neoplasms (only 1 malignant) in the Erelzi group (5 (1.9%) patients versus 1 (0.4%) patient) with low absolute numbers. However, here appear to be no overt clinically significant differences between the two groups~.
TP2	Infections and infestations (herpes simplex, blastomycosis, oral candidiasis, and tinea) occurred in the Erelzi group, and urticaria and hypersensitivity in the Enbrel group. The absolute numbers were rather low (one patient for each condition).
TP2^	This set essentially combines the results for TP1 and TP2.
EP*	As per TP1 and TP2 results, infections were more frequent in the continued Erelzi group (additionally onychomycosis and single case of sepsis in the Erelzi group, and herpes zoster in the Enbrel group).
EP#	There appear to be no overt clinically significant differences between the two groups~.
OA*	There appear to be no overt clinically significant differences between the two groups~, even though as for the previous sets, infections (mostly mild) and neoplasms (only 1 malignant) occurred more frequently in the continued Erelzi group, whereas hypersensitivity and associated reactions occurred more often in the continued Enbrel group. Absolute numbers were small.
OA#	There appear to be no overt clinically significant differences between the two groups~.

^ *Post hoc* analysis comparing TP2 continued treatment groups from baseline to the end of TP2; * Continued Erelzi population versus continued Enbrel population comparison; # Pooled continued population versus pooled switched population comparison; ~ The study was not powered to detect rarer adverse events or to make meaningful conclusions about incidence and this should be taken into consideration.

Liver function and liver toxicity

Pivotal efficacy study

There were a small number of liver-related events, the most significant of which are described below:

- One patient (treatment sequence in Group 2: Enbrel) experienced a severe event of drug induced toxic hepatitis (suspected to be related to study drug) apparent through deranged liver function tests in TP1. Hepatitis B surface antigen (HBsAg), IgM toxoplasma (blood IgM), and anti-hepatitis C virus (HCV) testing showed negative results. The study drug was discontinued. The event resolved with treatment. This was an isolated incidence that did not occur in Erelzi, but in Enbrel.
- One patient (treatment sequence in Group 1b: Erelzi > Enbrel > Erelzi) experienced a moderate event of hepatic steatosis (suspected to be related to study drug) in TP2. The study drug was discontinued. The event resolved.
- One patient (Group 1: Erelzi) experienced a mild event of hepatic steatosis (suspected to be related to study drug) in EP. The study drug was discontinued. The event was considered ongoing at the end of the study.
- There was another liver event not deemed related to the study drugs: cholelithiasis in Group 1b.

PK studies in healthy volunteers

In the PK studies, some liver function test derangements occurred: 1 subject experienced an elevation of AST on Day 14 after dosing with Erelzi (deemed related to IMP); 1 subject experienced elevated ALT and AST approximately 41 days after Enbrel treatment in Period I (deemed unrated to IMP); 1 subject had elevated AST and ALT values on Day 7 of Period II following Erelzi treatment. In GP15-103, several values outside the reference range were observed, but none were considered to be clinically significant.

There appears to be no evidence for Erelzi to be different to Enbrel with regard to liver function and liver toxicity events.

Renal function and renal toxicity

There were a small number of haematuria events in GP15-302, e.g. 3 (1.8%) in the continued Erelzi group, and 1 (0.6%) in the continued Enbrel group (OA Set). One acute renal failure event occurred:

- One patient (treatment sequence in Group 1b: Erelzi > Enbrel > Erelzi > Enbrel) experienced several severe events of acute renal failure with anaemia, respiratory failure, and acid-base balance disorder. The acute renal failure (and the other severe adverse events) in this patient were not suspected to be related to the study drug.

There appears to be no evidence for Erelzi to be different to Enbrel with regard to renal function and renal toxicity events.

Other clinical chemistry

Pivotal efficacy study

Overall, there were also no notable differences between the treatment groups.

PK studies in healthy volunteers

In the PK studies, some liver function test derangement occurred.

Haematology and haematological toxicity

Pivotal efficacy study

Overall, there were also no notable differences between the treatment groups, and only a small number of neutropaenia events.

PK studies in healthy volunteers

In GP15-104, there were 18 occurrences of mild TEAEs of neutropenia (related to the IMP) which resolved. GP15-102 and GP15-103 had a small number of neutropaenia. In GP15-101, there was a case of clinically significant neutropenia which resolved 2 months after dosing.

Electrocardiograph findings and cardiovascular safety

The onset of new or the worsening of existing congestive heart failure is associated with TNF blockers, including etanercept. The reference product PI states:

> *There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking Enbrel. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease.*

Pivotal efficacy study

A standard 12-lead ECG was performed at screening, Week 12 and Week 52. Therefore, only limited ECG data were available. ECG findings were comparable for the Erelzi and Enbrel treatment groups.

One death occurred during study GP15-302. One patient in the Enbrel group died during TP1 as a result of cardiopulmonary failure. The patient had a history of type II diabetes mellitus and was receiving concomitant glimepiride and metformin treatment. The death was considered unrelated to the study medication.

There appears to be no evidence for Erelzi to be different to Enbrel with regard to cardiovascular safety.

PK studies in healthy volunteers

In the PK studies in healthy volunteers, 12-lead ECGs were performed at screening, pre-dose (only pre-dose of period II in GP15-103 study) and the follow-up visit. No clinically important findings in ECG morphology, heart rate or intervals were apparent in any of the studies.

Vital signs and clinical examination findings

In both the PK studies and the efficacy study, there were no clinically meaningful differences with regard to vital signs and clinical examination findings in the different treatment groups.

Immunogenicity and immunological events

Pivotal efficacy study

The lower limit of quantification (LLOQ) for immunogenicity purposes was 150 ng/mL. All patients in the Erelzi treatment group had negative ADA results and a total of 5 patients (1.9%) in the Enbrel group had a confirmed positive ADA result in TP1. None of the ADAs were neutralising. No new patients with ADAs were detected in TP2. One ADA positive result was detected at one time-point during the treatment with Erelzi in the EP, in a patient from the pooled switched group.

PK studies in healthy volunteers

No binding ADAs were detected in the GP15-101, GP15-102, and GP15-103 studies. In the GP15-104 study, 3 subjects had confirmed binding ADAs at the follow-up visit (Day 65) with titres slightly above the detection limit. All 3 subjects were in the treatment sequence of Erelzi > Enbrel (EU) (that is, Erelzi in period I and Enbrel (EU) in Period II). None of the ADAs were neutralising.

The sponsor stated that the binding ADA positive results were not considered clinically meaningful due to the very low titres and that there were no other safety concerns with respect to the ADA results.

Comment: Immunogenicity is one of the most important safety concerns in a biosimilar evaluation. Immunogenicity (through both neutralising and non-neutralising anti-drug-antibodies (ADAs)) has the potential to alter both efficacy and safety. However, the clinical significance of ADAs remains uncertain. Limited data shows that ADA positive patients are more likely to experience infusion reactions. The development of ADAs is not necessarily linked to non-responder patients. However, when comparing etanercept to adalimumab in rheumatoid arthritis patients, it appears that adalimumab patients who develop ADAs have worse clinical outcome compared to those who do not develop ADAs (Krieckaert et al., 2012).[9] Consequently, ADAs in etanercept do not seem to be as clinically significant as in adalimumab in rheumatoid arthritis.

[9] Krieckaert CL, Jamnitski A, Nurmohamed MT, Kostense PJ, Boers M, Wolbink G 2012. Comparison of long-term clinical outcome with etanercept treatment and adalimumab treatment of rheumatoid arthritis with respect to immunogenicity. Arthritis Rheum 64(12):3850–3855.

The psoriasis study population (no RA equivalence study was conducted) was better suited to detect any potential differences between treatment groups. A small literature review of anti-etanercept antibodies (Hsu et al., 2014)[10] revealed a proportion range of 0–18.3% of subjects tested. However, when considering larger RCTs only, the range was 2.7–18.3%. The immunogenicity results from EGALITY seem to be within the data provided by the literature, albeit on the lower end of the spectrum. Different testing methods in the literature review studies may have contributed to different ADA proportions.

With regard to the methodology, the sponsor stated the following:

> *Immunogenicity of etanercept as determined by the formation of antibodies against the drug will be evaluated by using validated immunoassays. The validation procedure and serum sample analysis will follow international guidelines. The study samples will be screened for anti-etanercept antibodies. Evaluation of potential anti-etanercept antibodies will be done by testing specificity and neutralizing effect. The assays will be performed by the study sponsor. A detailed description of the analytical method will be further described in the laboratory manual.*

Serious skin reactions

Local tolerability was generally comparable between treatment groups in both PK studies and the efficacy study.

In GP15-302 (EGALITY), injection site reactions were reported in a lower proportion of patients in the Erelzi group (4.9%), compared with the Enbrel group (14.2%) in TP1, with the majority being mild. The proportion of patients with a reaction was reasonably balanced in TP2 and the EP. No injection site reactions were classified as an SAE.

Post-marketing data

In the Summary of Clinical Safety, the sponsor states:

> *There are no data on post-marketing exposure as Erelzi has not yet been marketed in any region.*

Evaluator's conclusions on safety

The reference product, etanercept (Enbrel) has been marketed for more than a decade and the efficacy and safety has been established for the currently approved indications.

As this is a biosimilar application, the main purpose of the clinical safety section is to evaluate whether there are significant differences between the biosimilar and the reference product.

The sponsor has not provided an integrated safety summary, but presented the safety data for each study individually. The safety results from the clinical study was considered more representative with regard to target population and administration duration compared to the PK study which only administered a single dose in healthy subjects.

The maximum duration of IMP exposure was 52 weeks in the clinical psoriasis study (GP15-302) which was reached by 118 patients (Erelzi) and 120 patients (Enbrel). Within the OA Safety Set, patients were exposed (Erelzi versus Enbrel) for a mean 318.3 days (vs. 309.9 days), for a median 358.0 days (vs. 358.0 days). Within the OA Safety Set, patients were exposed (pooled continued group versus pooled switched group) for a mean 314.0

[10] Hsu L, Snodgrass BT, Armstrong AW 2014. Antidrug antibodies in psoriasis: a systematic review. Br J Dermatol 170(2):261–73.

days (vs. 346.2 days), for a median 358.0 days (vs. 358.0 days). The exposure was sufficient for comparability purposes. The clinical studies were not powered to detect rarer adverse events though.

Overall, the adverse event profile was fairly similar in all treatment groups. The safety data from the clinical studies and the PK study demonstrated that there were no clinically meaningful differences between Erelzi and the reference product Enbrel. Furthermore, there appears to be no evidence of clinically meaningful differences between the pooled continued group and the pooled switched group, indicating no apparent safety disadvantages from switching. However, the clinical studies were not powered sufficiently to provide statistical evidence of differences in less common adverse events.

The proportion of patients that developed ADAs was rather low.

The absence of a difference in the studies not powered for uncommon events does not provide evidence for the absence of safety concerns. There may be the possibility that the following are different in Erelzi (Erelzi) and this should be particularly monitored in the post-market environment and presented in PBRERs/PSURs: infections; malignancies (in particular in children and adolescents). Post-market monitoring is essential and the role of the risk management plan crucial in that regard. Furthermore, disease registries should be utilised as well.

First round benefit-risk assessment

First round assessment of benefits

See below.

Table 9: First round assessment of benefits.

Psoriasis	
Benefits	**Strengths and Uncertainties**
Equivalence of Erelzi to Enbrel was shown for patients in moderate to severe plaque psoriasis (efficacy and safety).	**Strengths** Study GP15-302 (EGALITY) was very similar to the reference product pivotal trial with regard to study population and endpoints. The study design and its endpoints were mainly based on the current gold standard for psoriasis clinical trials, the PASI score. The primary endpoint, most of the primary endpoint sensitivity analyses, and the PASI secondary endpoints were supportive of equivalence based on a 15% margin. The primary endpoint was identical to the reference product pivotal trial primary endpoint. Continuous PASI based endpoints were also used and supportive of equivalence. Longer term data were available, namely until Week 52. The study did not allow subjects to use concomitant systemic immunomodulators. The placebo-adjusted response rate (that is, signal-to noise ratio) with regard to treatment effect was larger than in a study that allowed

Psoriasis	
Benefits	**Strengths and Uncertainties**
	concomitant immunomodulators. The equivalence is supported by the PK study results. The study provided sufficient data on switching from Enbrel to Erelzi (and vice versa; this included 3 switches in the switching group). **Uncertainties** The psoriasis assessment tools are often considered a limitation of psoriasis clinical trials. Psoriasis assessments appear to be more subjective with clinicians often overestimating body surface area affected. The patient experience of severity is also rather subjective. The PASI's disadvantages are that the upper end of the scale is rarely used and may have low response distribution and no consensus on interpretability, whereas PGA/IGA may not necessarily discriminate small change and may not have a robust range. However, the combination of validated psoriasis scores can mitigate most of the limitations. No data beyond 52 weeks are available.

Table 10: Indications approved for the reference product Enbrel (other than psoriasis).

Indications approved for the reference product Enbrel (other than psoriasis)	
Benefits	**Strengths and Uncertainties**
Efficacy can be reasonably extrapolated from the conducted studies to the other indications approved for the reference product Enbrel	**Strengths** A high signal-to noise ratio indication (psoriasis) was used to detect potential differences between treatments, that is, to evaluate for equivalence. The dosing regimen used in the clinical studies was within the recommended dose range for all approved reference product adult indications. The other approved indications have a similar mechanism of action (e.g. no approved IBD indication). **Uncertainties** Not all indications were investigated. The dosing regimen used in the clinical studies differed from the approved reference product paediatric indications. Malignancies (in particular lymphoma) have been associated with children and adolescents treated with TNF-α antagonists, including etanercept.

First round assessment of risks

See below.

Table 11: First round assessment of risks.

Risks	Strengths and Uncertainties
Concerns that efficacy and safety are not equivalent to the reference product in a real world setting	**Strengths** The clinical studies provided robust efficacy and safety data in the target indications. Appropriate pharmacovigilance and risk minimisation measures should be implemented to detect, monitor and mitigate the risks. **Uncertainties** The clinical studies were not powered to detect more rare adverse events. Uncertainties remain with regard to extrapolation to paediatric indications. No data beyond 52 weeks are available. Other unknown risks not detected in the provided studies, including loss of efficacy or new emerging safety signals.

First round assessment of benefit-risk balance

Overall, the benefit-risk balance of Erelzi (etanercept) for the proposed usage is favourable. This assessment is based on data evaluated from a clinical point of view. The assessment was made by weighing up the risks and benefits as outlined in this evaluation report and summarised in the previous section. However, the favourable assessment is dependent on the satisfactory response to the evaluator questions, the agreement to implement an appropriate RMP, and a favourable assessment by the quality, toxicology, and RMP evaluators.

First round recommendation regarding authorisation

Approval of Erelzi (etanercept) is recommended for the following indications (as per proposed Erelzi PI document):

Rheumatoid Arthritis

Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Erelzi can be used in combination with methotrexate.

Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease.

Psoriatic Arthritis

The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. Erelzi has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Plaque Psoriasis

Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.

Ankylosing Spondylitis

The signs and symptoms of active ankylosing spondylitis in adults.

Non-radiographic Axial Spondyloarthritis

Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change who have had an inadequate response to NSAIDs.*

**Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4.*

Children and Adolescents

Juvenile Idiopathic Arthritis

Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.

Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.

Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.

Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.

Etanercept has not been studied in children aged less than 2 years.

Paediatric Plaque Psoriasis

Chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.

However, the approval recommendation is dependent on the satisfactory response to the evaluator questions, the agreement to implement an appropriate risk management plan, and a favourable assessment by the quality, toxicology, and RMP evaluators.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Erelzi in the proposed usage are unchanged from those identified in the first round.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Erelzi in the proposed usage are unchanged from those identified in the first round.

Second round assessment of benefit-risk balance

The benefit-risk balance of Erelzi, given the proposed usage, is favourable. This assessment is based on the data evaluated from a clinical point of view. The assessment was made by weighing up the risks and benefits as outlined in this evaluation report.

Second round recommendation regarding authorisation

Approval of Erelzi (etanercept, Erelzi) is recommended for the following indications (as per proposed Erelzi product information document):

Rheumatoid Arthritis

Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Erelzi can be used in combination with methotrexate.

Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease.

Psoriatic Arthritis

The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. Erelzi has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Plaque Psoriasis

Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.

Ankylosing Spondylitis

The signs and symptoms of active ankylosing spondylitis in adults.

Non-radiographic Axial Spondyloarthritis

Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change who have had an inadequate response to NSAIDs.*

**Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4.*

Children and Adolescents

Juvenile Idiopathic Arthritis

Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.

Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.

Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.

Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.

Etanercept has not been studied in children aged less than 2 years.

Paediatric Plaque Psoriasis

Chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.

However, the approval recommendation is dependent on the agreement to implement an appropriate risk management plan, and a favourable assessment by the quality, toxicology, and RMP evaluators.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[11]

- The proposed indications are identical to the reference product. However, the proposed presentations do not support use of Erelzi in the majority of the paediatric population.
- The sponsor has submitted EU-RMP version 1.3, 19 April 2017; DLP 19 April 2017 and ASA version 0.2 (draft, 26 June 2017) in support of this application.
- The proposed list of safety concerns and their associated risk monitoring and mitigation strategies are summarised below.

[11] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 12: Summary of safety concerns (ASA v0.2).

Summary of safety concerns (ASA v0.2)		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Malignancies (including lymphoma and leukaemia)	✓*	✓	✓	-
	Serious and opportunistic infections	✓	✓	✓	✓
	Lupus-like reactions	✓	✓	✓	-
	Sarcoidosis and/or granulomas	✓	✓	✓	-
	Injection site reactions	✓	✓	✓	-
	Allergic reactions	✓	✓	✓	-
	Severe cutaneous adverse reactions (including TEN/SJS)	✓	✓	✓	-
	Systemic vasculitis (including ANCA+ vasculitis)	✓	✓	✓	-
	Macrophage activation syndrome	✓	✓	✓	-
	Central demyelinating disorders	✓*	✓	✓	-
	Peripheral demyelinating events (CIDP, GBS)	✓*	✓	✓	-
	Aplastic anaemia and pancytopaenia	✓	✓	✓	-
	Interstitial lung disease (including pulmonary fibrosis, pneumonitis)	✓	✓	✓	-
	Autoimmune hepatitis	✓	✓	✓	-
	Liver events in patients with viral hepatitis (including HBV reactivation)	✓	✓	✓	-
	Change in morphology and/or severity of psoriasis in adults and paediatric populations	✓	✓	✓	-
	Worsening of congestive heart failure in adults (with rheumatoid arthritis)	✓	✓	✓	✓
	Inflammatory bowel disease in JIA patients	✓	✓	✓	-
Important potential risks	Autoimmune renal disease	✓	✓	-	–
	Pemphigus/pemphigoid	✓	✓	-	-
	Amyotrophic lateral sclerosis	✓*	✓	-	-
	Myasthenia gravis	✓	✓	-	-
	Encephalitis/leukoencephalomyelitis	✓	✓	-	-
	Progressive multifocal leukoencephalopathy	✓*	✓	-	-
	Liver failure	✓	✓	-	-
	Hepatic cirrhosis and hepatic fibrosis	✓	✓	-	-
	Severe hypertensive reactions	✓	✓	-	-
	Adverse pregnancy outcomes	✓*	✓	✓	-
	Potential for medication error (prefilled pen)	✓	✓	✓	†
	Potential for male infertility	✓	✓	✓	-
	Weight gain	✓	✓	-	-
	Impaired growth and development in juvenile patients (ie JIA, paediatric plaque psoriasis)	✓*	✓	✓	-
	Acute ischaemic cardiovascular events in adults (ie all except JIA, paediatric plaque psoriasis)	✓	✓	-	-
	Uveitis and scleritis	✓	✓	✓	-
Missing information	Use in hepatic and renally impaired patients	✓	✓	✓	-
	Use in different ethnic origins	✓	✓	-	-
	Use in pregnant women	✓	✓	✓	-

* Targeted follow-up questionnaires proposed for use in selected safety concerns. These are enhanced routine pharmacovigilance measures. Questionnaires are not considered to be additional PV measures (as the sponsor has designated in the ASA) by the RMPE.

†: Needleless demonstration device, Educational material relating to correct use of the auto-injector

Pharmacovigilance activities

- Routine Pharmacovigilance measures are proposed, with selective use of targeted follow-up questionnaires for enhanced routine pharmacovigilance – including follow-up of non-melanoma skin cancer (NMSC) in patients of all ages.
- Registry based Post-market surveillance through the European Rheumatology patient registries (RABBIT, ARTIS, BSRBR, BADBIR) is proposed for monitoring all the safety concerns.

Risk minimisation activities

- Routine risk minimisation measures include the PI, CMI, and pack inserts, which include 'Instructions for use of the Erelzi Pre-filled syringe' or 'Instructions for use of the Erelzi auto-injector'

- Additional risk minimisation includes
  - Patient alert card proposed to mitigate the risks of 'serious and opportunistic infections' and 'worsening of CHF in adults with rheumatoid arthritis'
  - Additional risk minimisation tools to reduce medication error with the pre-filled pen (Auto-injector):
    - Teaching guide to facilitate training of the patients in the safe use of the pre-filled pen
    - A needle-free demonstration device
    - Instructional materials to share with patients.

New and outstanding recommendations from second round evaluation

There are outstanding recommendations as follows:

- The malignancy targeted follow-up questionnaire must include targeted questions specific to skin cancer specific risk factors and treatments (e.g. PUVA, chronic sun/sunlamp/sunbed use, if chronic sun exposure was sun protection used, previous skin cancers and precancerous skin lesions, fair skin colour).
- The targeted follow up questionnaires must be adapted to collect Australian-specific patient ethnicity information, including Aboriginal and Torres Strait Islander identity status recorded as one of the following options: 'Aboriginal', 'Aboriginal and Torres Strait Islander', 'Torres Strait Islander', or 'neither'.
- In the CMI, a statement that Erelzi should not be used in children weighing less than 62.5 kg should be included under 'What Erelzi is used for' – add 'Erelzi is not available in a dose suitable for use in children weighing less than 62.5 kg'.

Outstanding commitments

Australian adapted educational materials including a Patient Alert Card and step-by-step instruction guide must be submitted to be evaluated and agreed to be implemented prior to launch.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *Implement the EU-RMP for etanercept (Erelzi) version 1.3, 19 April 2017; DLP 19 April 2017 with ASA version 0.2 (draft); 26 June 2017, and any future updates as a condition of registration.*

Other advice to the Delegate

The following recommendations are made to the Delegate for inclusion in the PI:

- The PI should state prominently, in relevant locations, that Erelzi cannot be safely administered to persons ≤62.5 kg bodyweight. It is recommended that the following statement 'Erelzi is not formulated for use in children weighing less than 62.5 kg. Other etanercept products with appropriate dosage forms for children are available' or similar should be included immediately after the following headings:
  - 'Paediatric Use' in the Precautions section, and

– ‘Children and Adolescents’ in the indications section (for JIA and plaque psoriasis).

VII. Overall conclusion and risk/benefit assessment

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

Quality

Apart from the need to confirm GMP certification for all sites there are no current objections to the registration of Enbrel on quality grounds.

Erelzi is a genetically-engineered dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton tumour necrosis factor receptor (TNFR) linked to the Fc portion of human immunoglobulin G (IgG1). Since the sponsor is pursuing a global biosimilar development, both the reference product Enbrel/EU and the comparator product Enbrel/US, as well as Enbrel AUS have been used in different stages of the development of Erelzi.

The evaluator has noted that the pharmacological activity by which Enbrel (etanercept) modulates disease activity is the same in all indications that is, inhibition of TNFα binding to its receptor.

Nonclinical

While there was no objection to approval of Erelzi on nonclinical grounds, the evaluator noted that the nonclinical drug substance and drug product batches used in the nonclinical studies were not included in the panel of batches evaluated in the in vitro comparability assessments, with the exception of one drug substance batch used to manufacture the nonclinical product batch. Without concordance of batches used in in vitro and in vivo testing it is uncertain if findings from the nonclinical in vivo studies are relevant to the overall safety profile of Erelzi. Therefore, the evaluator considered that, the comparable safety profile of Erelzi relative to Enbrel is uncertain and that the conclusions of the Quality evaluator would be more central to establishing biosimilarity between Erelzi and Enbrel.

EU-sourced Enbrel was stated to be the comparator that was used in the nonclinical studies. The comparability of EU- (as well as US-) Enbrel against Australian-sourced Enbrel was reported (in Local Comparability with Reference Product). Bridging studies demonstrated sufficient similar biological activity (as TNFα neutralisation) between EU- and US-sourced Enbrel comparators and the Enbrel product marketed in Australia. Given that no nonclinical batches were included in the in vitro comparability assessments, conclusions on whether Erelzi and Enbrel are sufficiently similar will be based on assessments by the Quality evaluator. The Delegate notes that the Quality evaluator did not object to approval.

Clinical

Pharmacology

Four PK studies were submitted, a pivotal PK study and 3 supportive studies.

The initial study designed to shown bioequivalence between Erelzi and Enbrel, Study GP15-101 did not meet its primary endpoint and a subsequent study, GP15-104 was

conducted. Methodological issues were considered to be the cause of failure of Study GP15-101 in which bioequivalence margins were met for Cmax and not for AUC $_{0\text{-tlast}}$. However, the bioequivalence criteria were met between Erelzi and Enbrel for both Cmax and AUC $_{0\text{-tlast}}$ when the actual dose administered was taken into account. A post-hoc analysis of Study GP15-101 data, taking into account the different operators (that is, the people who dosed the study drug) who administered study drug to individual subjects in different periods, bioequivalence could also be demonstrated.

Study GP15-104 was a randomised, two-way crossover study to determine the pharmacokinetics and safety of Erelzi and Enbrel/ EU following a single dose of 50 mg s.c. injection in 54 healthy male subjects aged from 18 to 49 years. Unlike in Study GP15-101 the study drug was administered to each individual subject by the same administrator in the 2 periods of study. The between dose washout period was at least 35 days.

The primary objective of this study was to determine bioequivalence between ERALZI and Enbrel in terms of the PK parameters Cmax, AUC $_{0\text{-tlast}}$, AUC $_{0\text{-inf}}$ following a single SC administration of 50 mg. The PK parameters of tmax, kel, and t½, as well as immunogenicity of both products and overall safety, tolerability and local tolerance of Erelzi and Enbrel were also compared.

The criteria for bioequivalence were met in this study with the mean ratio Erelzi/Enbrel for Cmax being 1.03 (90%CI 0.98 – 1.09); for $AUC_{0\text{-last}}$ 0.92 (90%CI 0.88 – 0.95) and for $AUC_{0\text{-inf}}$ 0.90 (90%CI 0.87 – 0.94).

Study GP15-102 compared the pharmacokinetics of Erelzi and US sourced Enbrel and was of similar design. It demonstrated bioequivalence of Erelzi with US sourced Enbrel.

Study GP15-103 compared the pharmacokinetics and safety of Erelzi following a single subcutaneous injection by an auto-injector and by a pre-filled syringe in healthy male subjects. This study showed bioequivalence if Erelzi administered by an auto-injector and via a pre-filled syringe. Trough serum concentration data were obtained from a subgroup of 147 patients (Erelzi n = 72; Enbrel n = 75) participating in the clinical equivalence study GP15-302.

After multiple dosing of Erelzi 50 mg or Enbrel 50 mg at Weeks 2, 4, 8 and 12, trough serum concentration levels appeared to be similar in the two treatment groups.

Efficacy

One study provided evaluable efficacy data for plaque psoriasis. Study GP15-302 was a Phase 3, double-blind, randomised, active comparator-controlled study in subjects with moderate to severe chronic plaque-type psoriasis to evaluate the efficacy and safety of Erelzi compared with Enbrel (EU-authorised).

This study had a treatment period of up to 52 weeks per patient and consisted of 4 periods:

- Screening period of at least 2 weeks and up to 4 weeks for eligibility assessment;
- Treatment Period 1 (TP1) of 12 weeks;
- TP2 of 18 weeks; and
- Extension Period (EP) of 22 weeks.

The primary assessment of clinical equivalence was conducted at the end of TP1 when subjects had received 12 weeks of randomised treatment with either Erelzi or Enbrel. During TP1 (Day 1 to Week 12) patients continuously received treatment with either Erelzi or Enbrel. The effect of repeated switching between the 2 treatments was assessed during TP2 (Week 13 to Week 30).

The EP from Week 30 to Week 52 was a long-term follow-up period during which the patients received the treatment they had last received during their last switch in TP2.

The primary objective was to demonstrate equivalent efficacy of Erelzi and Enbrel in patients with moderate to severe chronic plaque-type psoriasis with respect to Psoriasis Area and Severity Index (PASI) 75 response rate at Week 12.

Patients were randomised into 2 groups to receive either Erelzi (Group 1) or Enbrel (Group 2) for 12 weeks (TP1). Patient randomisation was stratified by body weight and prior systemic therapy at Day 1. Each group self-administered a 50 mg subcutaneous (s.c.) injection of study drug (Erelzi or Enbrel) twice each week until Week 12.

Patients who did not achieve at least PASI 50 response at the end of TP1 were not further treated with Erelzi or Enbrel. Only patients who achieved at least a PASI 50 response at Week 12 were re-assigned to progress to TP2. Re-assignment at Week 12 was not stratified. Approximately 75% of the patients in each of Groups 1 and 2 were to remain on their initial treatment throughout the study (Groups 1a and 2a), and approximately 25% of the patients were to receive alternating treatment with Erelzi or Enbrel for 3 periods of 6 consecutive weeks, that is,, switching after Week 12 and again switching back to the original treatment after Week 18 followed by a third switch of treatment regimens after Week 24 (Groups 1b and 2b).

The re-assignment scheme at Week 12 was changed to a ratio of 3:1 instead of 1:1 after the study had commenced. These measures were taken on advice from national European Health Authorities, to increase in the size of the safety database for continuous treatment with Erelzi in comparison to the originator.

Eligibility for the study and efficacy required assessment of the Psoriasis Area and Severity Index (PASI) score. To calculate this score the total Body Surface Area (BSA) affected by plaque-type psoriasis was estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs. Each reported percentage was multiplied by its corresponding factor for the respective body region (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages were added up to estimate the total BSA affected by plaque-type psoriasis. To derive the PASI score the head, trunk, upper limbs and lower limbs were assessed separately for erythema, thickening (plaque elevation, induration), and scaling desquamation). The average degree of severity of each sign in each of the 4 body regions was assigned a score of 0–4. The area covered by lesions on each body region was estimated as a percentage of the total area of that particular body region. PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretical maximum of 72.0. A PASI score > 20 is considered severe disease.

The following definitions were used in this study:

- PASI 50 response (partial response): patients who achieved ≥ 50% improvement (reduction) in PASI score compared to baseline were defined as PASI 50 responders.
- PASI 75 response: patients who achieved ≥ 75% improvement (reduction) in PASI score compared to baseline were defined as PASI 75 responders.
- PASI 90 response: patients who achieved ≥ 90% improvement (reduction) in PASI score compared to baseline were defined as PASI 90 responders.
- PASI 100 response / remission: complete clearing of psoriasis (PASI=0).

The major inclusion criteria were:

- age ≥ 18 years at screening;
- chronic plaque-type psoriasis diagnosed at least 6 months before baseline;

- moderate to severe psoriasis as defined at baseline by:
  - PASI score of 10 or greater and,
  - Investigator's Global Assessment (IGA) score of 3 or greater, based on a scale of 0 – 4 and,
  - BSA affected by plaque-type psoriasis of 10% or greater.
- chronic plaque-type psoriasis patients who had previously received phototherapy or systemic psoriasis therapy at least once or who were candidates for such therapies in the opinion of the investigator.

The major exclusion criteria were:

- Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic, and guttate psoriasis).
- Drug-induced psoriasis (that is,, new onset or current exacerbation from e.g., beta-blockers, or lithium).
- Ongoing use of prohibited psoriasis treatments (e.g., topical corticosteroids, UV-therapy). Washout periods detailed in the protocol had to be adhered to.
- Ongoing use of other non-psoriasis prohibited treatments. All other prior non-psoriasis concomitant treatments had to be on a stable dose for at least 4 weeks before baseline.
- Previous exposure to etanercept.
- Active ongoing inflammatory diseases other than psoriasis that could confound the evaluation of the benefit of treatment with etanercept.

After the screening period, the use of concomitant treatment for psoriasis in all body regions was to be restricted to bland emollients and other non-medicated interventions. Anti-histamines and corticosteroid drops required for use in the eye or ear during the study were permitted. Patients were to be advised to limit exposure to UV light during the study.

The equivalence margin was 18% was used to test equivalence on the primary variable, which was the proportion of PASI 75 responders at Week 12 using a 2-sided 95% confidence interval. An equivalence margin of 15% was used for the secondary efficacy variable of PASI % improvement from baseline to end Week 12. The sponsor's justification for the choice of equivalence margins was provided. The equivalence margin for the comparison of Enbrel with Erelzi with respect to PASI 75 response at Week 12 was based on response rates reported in published, double-blind, placebo controlled trials. In a similar population, the following response rates for PASI 75 after 12 weeks of treatment with etanercept 50mg twice weekly were observed:

- 49% (81 out of 164) versus placebo: 4% (6 out of 166) (Leonardi et al 2003)[12]
- 49% (96 out of 194) versus placebo: 3% (6 out of 193) (Papp et al 2005)[13]

Based on that observed effect size of 45-46%, an equivalence margin of 18% was chosen, so that at least 60% of the treatment effect seen for Enbrel was maintained. A response rate of 49% was assumed for the comparator treatment Enbrel. Therapeutic equivalence

[12] Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB; Etanercept Psoriasis Study Group 2003. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 349(21):2014-22.
[13] Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, Zitnik R, van de Kerkhof PC, Melvin L; Etanercept Psoriasis Study Group 2005. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 152(6):1304-12.

in terms of PASI 75 was to be concluded if the exact 95% confidence interval for the difference in the PASI 75 rates was completely contained within the interval [−18%; 18%].

This is statistically equivalent to calculating 2 independent 1-sided tests at a 2.5%-alpha level (1 in each direction), of which both had to be successful.

The primary analysis was performed adjusting for stratification factors using logistic regression. For TP1 only, stratification factors were: body mass (< 90 kg; ≥ 90 kg) and prior systemic therapy (no prior systemic therapy, any prior systemic therapy including biologic immunomodulating agents but no prior treatment with a TNF antagonist, or prior treatment with a TNF antagonist). Additionally, summary tables were stratified descriptively by country. No imputation for missing PASI scores and components of PASI score was performed for the main analysis; for a sensitivity analysis, missing data were imputed as non-response.

The primary analysis was repeated on the Full Analysis Set (FAS) as a sensitivity analysis. Missing values were imputed. Missing PASI 75 responses were imputed with non-response regardless of the reason for the missing data (e.g., premature study discontinuation, missed visit, administrative issues or worsening of the disease under investigation).

The primary analysis based on the Per-Protocol Set (PPS) was to be repeated excluding patients identified as having taken any rejected study drug during TP1 including patients who experienced some temperature excursions at home. Rejected refers to study drug that was subjected to temperature excursions outside of the normal range while in transit or at the study site, but was provided to patients prior to the decision to reject upon re-evaluation.

A total of 774 subjects with moderate to severe psoriasis were screened with 531 subjects randomised to treatment and 511 completing TP1 (FAS). A total of 497 subjects were treated in TP2:

- 150 continued Erelzi
- 151 continued Enbrel
- 100 subjects who received Erelzi during TP1 switched to the treatment sequence Enbrel – Erelzi – Enbrel
- 96 subjects who received Enbrel during TP1 switched to the treatment sequence Erelzi – Enbrel – Erelzi.

A total of 465 subjects continued into the Extension Period with the last treatment received in TP2 as follows:

- 139 subjects continued to receive Erelzi from TP2
- 141 subjects continued to receive Enbrel from TP2
- 95 subjects who switched to the treatment sequence Enbrel – Erelzi - Enbrel in TP2 continued treatment with Enbrel in the EP
- 90 subjects who switched to the treatment sequence Erelzi – Enbrel - Erelzi in TP2 and continued treatment with Erelzi in the EP.

The overall mean age was 42.4 years (range 18 to 78 years), 62.0% were male, 99.2% were Caucasian. Mean BMI was 28.509 ± 5.7809 kg/m^2. The mean (SD) time since diagnosis of psoriasis was 17.688 ± 11.5623 years. The mean (SD) PASI score was 22.51 ± 9.218 (median score 20.3). 68.9% of subjects did not have prior systemic therapy for psoriasis, 30.1% had some prior systemic therapy, and 0.9% had prior systemic therapy with a TNF antagonist.

There were 480 subjects included in the PPS assessment of the primary efficacy endpoint, a PASI75 response at Week 12 was achieved by 176 (73.4%) subjects given Erelzi and by 182 (75.7%) given Enbrel with an adjusted response rate difference of -2.3% (95%CI for difference -9.85, 5.30). Clinical equivalence was demonstrated within the definition of the study. Sensitivity analyses also supported clinical equivalence. Results for secondary efficacy endpoints in TP1 – these also show very similar results for the two treatment groups. Of particular note the difference in mean % change in PASI from baseline to Week 12 Per Protocol analysis (MMRM) was -0.64% (95%CI -3.474, 2.204) which was well within the specified equivalence margin of ±15%.

The Delegate notes that the clinical evaluator does not consider the ±18% equivalence margin for PASI 75 at Week 12 to be acceptable. In the study report it was stated that the equivalence margin for the comparison of Enbrel with Erelzi with respect to PASI 75 response at Week 12 was based on response rates reported in earlier double-blind, placebo- controlled trials. In a similar population, the following response rates for PASI 75 after 12 weeks of treatment with etanercept 50mg twice weekly were observed:

- 49% (81 out of 164) versus placebo: 4% (6 out of 166) (Leonardi et al 2003)[14]
- 49% (96 out of 194) versus placebo: 3% (6 out of 193) (Papp et al 2005)[15]

Based on this observed effect size of 45-46%, an equivalence margin of 18% was chosen, so that at least 60% of the treatment effect seen for Enbrel was maintained.

Arguably the demonstration of clinical equivalence using chronic plaque psoriasis allows assessment of smaller potential between-treatment differences than does rheumatoid arthritis as many subjects in RA studies are also taking methotrexate which may reduce apparent differences between other immunomodulatory treatments, both for efficacy and for immunogenicity. No studies were performed with paediatric subjects. This is consistent with the guidelines for biosimilar medicines.

Safety

The mean exposure to Erelzi was 318 days for 164 patients with 118 patients exposed to Erelzi for 52 weeks. The PK studies were conducted with healthy volunteers and safety information from these studies was presented separately from that of the clinical equivalence study.

Treatment emergent AEs in the PK studies in healthy volunteers – the most frequent were: neutropenia, headache, nasopharyngitis and oropharyngeal pain. The TEAEs were reasonably balanced between Erelzi and Enbrel (EU/US) treatment groups. Most TEAEs were of mild or moderate severity. The overall number of treatment emergent AEs was comparable between Erelzi and Enbrel.

Safety information from the clinical equivalence study was presented in an overall analysis and by treatment period (TP1, TP2, EP and Overall Analysis). In TP1, 99/187 (37.5%) patients given Erelzi and 96/267 (36%) patients given Enbrel reported at least one TEAE. Similar proportions of patients discontinued the study due to TEAEs (1.9% and 1.5% in the Erelzi and Enbrel groups, respectively). The incidence of SAEs was low with 4 patients (1.5%) given Erelzi and 3 patients (1.1%) given Enbrel reporting such events. The most frequently reported AEs were in the SOC of infections and infestations (18.6% Erelzi and 16.9% Enbrel). The incidence of AEs by SOC and for individual AEs were comparable

[14] Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB; Etanercept Psoriasis Study Group 2003. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 349(21):2014-22
[15] Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, Zitnik R, van de Kerkhof PC, Melvin L; Etanercept Psoriasis Study Group 2005. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 152(6):1304-12.

except for neoplasms benign, malignant and unspecified including polyps with 5 (1.9%) reported in patients given Erelzi versus 1 (0.4%) in a patient given Enbrel.

These were: skin papilloma (1 in each group), colon neoplasm (tubular-villous adenoma with low grade dysplasia), lipoma (1), malignant melanoma in situ (1) and melanocytic nevus (1). Only one of these was malignant (the melanoma) and it had been excised prior to study treatment commencing and was diagnosed as malignant after commencement of the study.

There was one death during this study. A patient in the Enbrel group died during TP1 as a result of cardiopulmonary failure. The patient had a history of type II diabetes mellitus and was receiving concomitant glimepiride and metformin treatment. The death was considered unrelated to study medication.

In TP2 there were 4 treatment groups, 2 continuing groups and 2 groups where switching occurred on 2 occasions. Safety comparisons of AEs for the continuing Erelzi and Enbrel groups were performed and showed comparable total frequency of AEs, type of AEs, serious AEs and discontinuation due to AEs for the continuing groups in TP2. Other AE comparisons for the continuing groups in TP2 and EP establish the similarity of AEs responses for the two products.

For the Overall Analysis safety set, the incidence of SAEs was low and comparable between the continued Erelzi and continued Enbrel groups (7 patients, 4.3% versus 7 patients, 4.1%) over the entire study period from baseline to Week 52. Similarly the incidence of SAEs was comparable for the pooled continued treatment patients and pooled switched patients at 4.2% and 6.1% respectively. There was no clustering of individual SAEs.

The safety of the continuing groups was then compared with safety in the groups that were switched both for the TP2 period only and for the TP and EP period. These comparisons also showed no substantial difference in incidence or type of AE or in discontinuations due to AEs between these pooled groups.

In the EP the assessment of AEs in the 4 groups continued, allowing further comparison of AEs between Erelzi and Enbrel continuing groups and between the pooled continuing and switched groups. In the EP there were some differences in incidence of AE parameters in the treatment periods, particularly in the EP (weeks 30 to 52) where 104 TEAEs were reported in 60 (42.9%) of patients continuing Erelzi compared with 74 TEAEs in 39 (27.5%) continuing Enbrel. Additionally, there were slightly higher discontinuation rates due to TEAEs in patients continuing Erelzi compared with those continuing Enbrel. There was no clustering of individual TEAEs.

TEAEs of special interest were identified based on warnings and precautions in the labelling of Enbrel. These included infections and infestations, neoplasms, allergic/anaphylactic reactions, immune system disorders/autoimmune events, neurological events, haematological events and congestive heart failure. The overall analysis showed no clinically significant differences in incidence of AEs for patients given continuing Erelzi or Enbrel compared with the patients who were switched. Infections and infestations were reported in 7 (4.7%) of patients given Erelzi versus 3 (2.0%) given Enbrel. Overall, infections and neoplasms/malignancies appeared to occur more frequently in the continued Erelzi group in TP1. Hypersensitivities were reported in 2 patients given continuing Enbrel and none given continuing Erelzi.

Local tolerability was generally comparable between treatment groups in both PK studies and the efficacy study. In the clinical equivalence study, injection site reactions were reported in 4.9% of patients given Erelzi versus 14.2% given Enbrel in TP1, with the majority being mild. The proportion of patients with a reaction was reasonably balanced in TP2 and the EP. No injection site reactions were classified as a SAE.

There were few hepatic or renal AEs and no suggestions these were more frequent with one product compared with the other.

Immunogenicity

The LLOQ for ADA was 200 ng/mL in all clinical studies except Study 302 where it was 150 ng/mL At the end of TP1 all patients given Erelzi had negative ADA results and 5 patients (1.9%) given Enbrel had a confirmed positive ADA result in TP1. None of the ADAs were neutralising. No new patients with ADAs were detected in TP2. One ADA positive result was detected at one time-point during the treatment with Erelzi in the EP, in a patient from the pooled switched group.

Risk management plan

While there were no objections to approval based on the RMP the RMP evaluator has recommended the PI be amended in multiple sections to highlight the lack of suitability of this product for children and adolescents. The CMI should be similarly amended.

The RMP evaluator has recommended the following condition of registration:

> *Implement the EU-RMP for etanercept (Erelzi) version 1.3, 19 April 2017; DLP 19 April 2017 with ASA version 0.2 (draft); 26 June 2017, and any future updates as a condition of registration.*

It is noted that the Australian adapted educational materials including a Patient Alert Card and step-by-step instruction guide must be submitted to be evaluated and agreed to be implemented prior to launch.

Risk-benefit analysis

Delegate's considerations

Bioequivalence of single doses of Erelzi and the innovator product, Enbrel, sourced from the EU and from the USA has been demonstrated. Trough serum concentrations from the multiple dosing in the clinical equivalence study suggest that exposure remains similar on multiple dosing.

The clinical equivalence study (GP15-302; EGALITY) was well designed and used the highest etanercept dose regimen approved for the treatment of chronic plaque psoriasis with Enbrel. The primary efficacy endpoint and severity of psoriasis at baseline for inclusion in the study were the same as were applied in the pivotal clinical studies supporting approval of Enbrel for the treatment of chronic plaque psoriasis. While cross-study comparisons have limitations it is of interest to note that the PASI75 response rates at Week 12 for the 50 mg twice weekly doses of etanercept achieved in Study GP15-302 were in the region of 50% higher than those achieved in the clinical studies for Enbrel described in the current PI for Enbrel and used to calculate the clinical equivalence margin. This occurred even though the selection criteria and baseline severity for study entrance were similar.

It is notable that in the chronic plaque psoriasis studies described in the PI for Enbrel for all treatment groups and in both studies the median baseline PASI score ranged from 15 to

In Study GP15-302 the median baseline PASI score was 20.3. This suggests that PASI75 response after 12 weeks treatment may be more likely to be achieved in individuals with more severe and/or extensive plaque psoriasis prior to treatment

The evaluator was concerned regarding the selection of the equivalence margin of ±18% for Week 12 PASI 75 response. Given the actual confidence interval for Week 12 PASI 75 response was much smaller than ±18%, that the sensitivity analyses also supported clinical equivalence and the justification for equivalence margin was based on previously demonstrated efficacy results, the equivalence margin for Week 12 PASI 75 response in the clinical equivalence study is not of concern.

The secondary efficacy endpoint of mean PASI% improvement from baseline to Week 12 also showed clinical equivalence with a 95%CI well within its ±15% equivalence margin. Equivalence of efficacy is accepted.

This submission included a more comprehensive assessment of the effects of switching between the test and innovator products than has been the case for earlier biosimilar TNFα antagonists assessed by this Delegate. This switching assessment is more readily undertaken with etanercept due to its twice weekly dosing regimen. For the treatment of psoriasis infliximab maintenance doses are given every 8 weeks and for adalimumab maintenance doses are given every 2 weeks. Those dose regimens would require longer studies for a similar assessment of the effects of switching. No indication of changes in ADA was shown in these studies for patients who switched treatments or for those who continued with either Erelzi or Enbrel, though the LLQ may have contributed to this outcome. Other safety assessments did not indicate that changing between Erelzi or Enbrel presented changes to the adverse event profile.

Extrapolation to other indications, including the paediatric indications is accepted and is consistent with the approach taken for other biosimilar TNFα antagonists.

Summary of issues

- In the innovator PI, the age range for children and adolescents is specified for the two paediatric indications and the sponsor is proposing to include the same wording for its paediatric indications. This is potentially misleading given the products can only be used in children and adolescents with body weights ≤62.5 kg.
- Likewise the 'Dosage and Administration' section of the draft PI has proposed wording to disclose the lack of mg/kg dosing with these products but given the limited paediatric population that could use these products it may be confusing to include them at all in either the indications or dosage sections of the PI.
- A clinical equivalence study has been conducted in patients with plaque psoriasis only.

Proposed action

The Delegate has no reason to say, at this time, that the application for Erelzi etanercept (rch) solution for injection 0.5 mg/ 0.5 mL and 1 mg/ 1 mL pre-filled syringe and 1 mg/1 mL auto-injector should not be approved for registration subject to satisfactory negotiation of the PI and RMP.

Request for ACM advice

The Advisory Committee on Prescription Medicines (ACM) is requested to provide advice on the following specific issues:

1. The sponsor is proposing to include the entire paediatric age range in its paediatric indications though the majority of children in the lower years of that age range will not be able to use the product due to having a body weight <62.5 kg. Does the Committee consider that there should be an amendment to the paediatric indications to acknowledge the inadequacy of this product for use in children and adolescents with body weight <62.5 kg? If so, what wording does the Committee recommend?

2. What are Committee's views on the efficacy of Erelzi and to what extent is there sufficient clinical trial evidence of similarity with the innovator product (Enbrel) to support the indication relating to plaque psoriasis for Erelzi?
3. Does the Committee consider there is sufficient evidence and/or justification to support extrapolation of the data in patients with plaque psoriasis to the other indications for Enbrel, including the paediatric indications?
4. What are the Committee's views on the comparability of the safety profiles of Erelzi and Enbrel?
5. Does the Committee consider the proposed wording in the draft PI regarding the lack of dose adjustments to allow for mg/ kg dosing is adequate? If not does the Committee recommend alternative wording?
6. The sponsor does not wish to include a statement of batch traceability in the PI at this time. What are the committee's view on this approach (please refer to 'Precautions').

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

Response from sponsor

Presented here are the sponsor's comments to the TGA's Delegate's Overview (DO) and request for ACM's advice on issues related to our submission to register Erelzi as a biosimilar medicinal product to the reference product Enbrel (etanercept). The sponsor welcomes the Delegate's preliminary assessment recommending the approval of the registration of Erelzi in the proposed indications, including the paediatric indications. The sponsor is hereby providing comments to the consolidated issues raised and advice sought from the Committee by the Delegate, particularly in relation to use of Erelzi in paediatric patients and the totality of evidence including the clinical level demonstrating similarity with the innovator product, Enbrel, to support use in all approved Enbrel indications. Additionally, the sponsor brings to the attention of the Committee clarification on a concern noted in the Delegate's narrative on the Non-Clinical evaluation. Where appropriate, our comments have been cross-referenced to the DO or to the original submission for marketing authorisation application (MAA).

Paediatric indications and dosage

The sponsor welcomes the Delegate's recommendation to approve Erelzi for the same indications as the reference product Enbrel, including the paediatric indications. The extrapolation to paediatric indications and a label in line with the reference product's label is justified based on the totality of evidence demonstrating the biosimilarity of Erelzi and Enbrel in line with TGA-adopted EMA guidelines.

We note though that the Delegate questions whether the paediatric indications should be included at all, given the dosage forms' limitation to enable weight-based dosing. The sponsor firmly believes that it is important to include the entire age range covering the paediatric indications as there is no clear correlation between age and weight especially in JIA and paediatric PsO patients. Studies have shown that paediatric patients with systemic arthritis or plaque psoriasis are at risk of weight gain compared to the general paediatric population; 1 in 3 have risk of obesity within 3 years of diagnosis and/or prolonged systemic corticosteroid use.[16] It is therefore conceivable that some paediatric patients suffering from systemic juvenile arthritis or plaque psoriasis will have a body weight of 62.5 kg or more. Moreover, the sponsor considers that any potential confusion on the correct paediatric dosing is suitably and sufficiently managed by abundantly including

[16] Growth and weight gain in children with juvenile idiopathic arthritis results from the ReACCh-Out cohort, Pediatr Rheumatol Online J. 2017; 15: 68.

instructions across multiple sections in the PI (Indications, Dosage and Administration, and Precautions) that adequately communicate instructions for weight-based dosage and administration. Additionally, the proposed PI clearly states that paediatric patients weighing less than 62.5 kg should not receive Erelzi but instead should be accurately dosed on a mg/kg basis with other etanercept products. It is of note that paediatric indications with the same age range as the reference product have been approved by the FDA, EMA and Health Canada, and respective labels include similar appropriate weight-based dosing instruction to allow for effective communication on the correct usage of Erelzi to Healthcare Professionals and care givers.

We also believe it will be useful for clinicians that would welcome an etanercept biosimilar option for paediatric patients who meet the weight criterion for the greater good of the Australian healthcare system. It is noted that the only other biosimilar version of etanercept (Brenzys) is limited to use in adult patients.

Totality of data presented demonstrates biosimilarity of Erelzi and Enbrel

Demonstration of biosimilarity is based on a concept that considers the "totality of the data": similarity with respect to a specific property or area of testing (e.g. physicochemical, biological, functional, nonclinical, or clinical) is not decisive in isolation, but only the evaluation of the complete data package is appropriate to conclude that the proposed product is approvable as a biosimilar according to applicable legislations. Biosimilarity of Erelzi and Enbrel was demonstrated by data encompassing the confirmation of similarity in highly sensitive assays on physicochemical and functional level, which is supported by nonclinical data and substantiated by comparable PK properties and similar efficacy and similar safety and immunogenicity profiles of Erelzi and Enbrel.

Study GP15-302 in patients with moderate to severe plaque psoriasis confirms biosimilarity of Erelzi and Enbrel on a clinical level

The sponsor believes that the choice of psoriasis as a model to confirm similar efficacy of Erelzi and Enbrel in a clinical setting is adequate as psoriasis lesions are sensitive to change by the treatment with etanercept, and the response is specifically related to TNF-inhibition by etanercept, as known from historical data. As the Delegate has noted, the demonstration of similar efficacy and similar safety and immunogenicity profiles using chronic plaque psoriasis allowed for a more definitive assessment of any potential clinically meaningful differences in contrast to rheumatoid arthritis where subjects are also taking methotrexate which may reduce apparent differences between other immunomodulatory treatments, both for efficacy and for immunogenicity. This is consistent with the guidelines for biosimilar medicines.[17]

No clinically meaningful differences between Erelzi and Enbrel were observed in terms of efficacy, safety, and immunogenicity profiles, even after multiple switching. A clinical equivalence margin of +/- 18% was pre-defined for the primary outcome (PASI75 response rates) and a margin of +/-15% was pre-defined for the key secondary outcome (mean percentage change from baseline (BL) in PASI scores) based on treatment effect sizes from historical data. Although the acceptance criteria may seem to be broad, this was not seen as an issue as the actual 95% Confidence Intervals of these outcomes fell between smaller ranges (<10%). The number and nature of adverse events between Erelzi and Enbrel were broadly comparable as well. The immunogenicity of Erelzi and Enbrel was similarly low in the clinical program, and there were no notable differences between patients treated in the plaque psoriasis study following repeat-dosing without background immunosuppression. In summary, the pivotal study GP015-302 in patients with plaque psoriasis demonstrates similar efficacy and similar safety and immunogenicity profiles of

[17] EMEA/CHMP/BMWP/42832/2005 Rev1

Erelzi and Enbrel and that there are no clinically meaningful differences. Thus, GP15-302 finally confirms biosimilarity of Erelzi and Enbrel.

Biosimilarity of Erelzi to Enbrel justifies a label consistent with the reference product including all indications

The scientific justification for extrapolation is based on the argument that, if Erelzi has been shown to be highly similar to Enbrel through multiple lines of evidence, and confirmed by a clinical trial in a sensitive indication to detect potential differences between the biosimilar and the reference product, Erelzi and Enbrel are expected to have similar activity and a similar safety profile in all clinical (adult and paediatric) settings in which Enbrel has been evaluated. Data established with Enbrel in various subpopulations (such as those based on age, gender, ethnicity, comorbidities, concurrent therapies, etc.) as well as data with the use of Enbrel at different dosages and in combination regimens are also extrapolated from Enbrel to Erelzi.

In view of the totality of evidence demonstrating high similarity of the molecules, similar nonclinical results, similar clinical PK, similar efficacy and similar safety, and immunogenicity profiles confirmed in the clinical program, and supported by the same of action in all indications (PsO, RA, PsA, AS, and JIA), a label for Erelzi consistent with that of Enbrel, with all indications including the paediatric indications for which Enbrel is currently approved, is therefore considered justified.

Other matters - Batch traceability

On the basis of the Delegate's comments, the industry's submission to the recent consultation on the Nomenclature of Biological Medicines (version 1.0, July 2017), and to further ensure patient safety, the sponsor has accepted the inclusion of the proposed batch traceability statement under the Precaution section of the PI as well. It is believed that the revised texts appropriately address the concern raised and that no further changes are required.

Sponsor's comments on the delegate's summary of the nonclinical evaluation

The sponsor would like to respectfully address the Delegate's summary of the non-clinical evaluation report. For clarity and completeness, as noted in the Section 31 response and review of evaluation reports, the inclusion of one drug substance batch (B056401) used to manufacture the nonclinical drug product batch was subject to comparability assessments that confirmed biosimilarity, including TNF-α and TNF-β reporter gene assays for functional characterization. Moreover, it is the sponsor's viewpoint that the provided nonclinical in vivo studies should be considered as a demonstration of biosimilarity given that there was no provision to use identical batches in the in vitro and the in vivo nonclinical tests in the TGA adopted guidance.[18]

Concluding remarks

The sponsor welcomes the Delegate's recommendation to approve Erelzi based on the totality of quality, nonclinical, clinical pharmacokinetic, efficacy, safety, and immunogenicity data demonstrating similarity of Erelzi and Enbrel and submitted from the biosimilar's robust development program. The sponsor acknowledges the limitation of use in paediatric patients due to fixed-dose dosage forms. However, key messages are prominently included in the product information to guide clinicians and care givers on the suitability of use in this patient population and to mitigate any concerns on medication errors. Erelzi offers patients and prescribers a safe and effective choice for all approved uses of Enbrel. The sponsor believes that the availability of biosimilar medicines provide the opportunity to make a significant positive impact on the Australian healthcare system by reducing the cost of subsidised biological medicines to government.

[18] EMEA/CHMP/BMWP/42832/2005 Rev 1

Advisory Committee Considerations[19]

The ACM taking into account the submitted evidence of efficacy, safety and quality; agreed with the delegate and considered Erelzi solution for injection containing 25 mg/0.5 mL and 50 mg/1 mL of etanercept (rch) to have an overall positive benefit-risk profile, with modification to the following indications which were taken to the ACM.

Sponsor's proposed indications for consideration by the ACM:

The proposed indications for Erelzi are aligned with those currently approved for Enbrel in Australia, namely:

- Rheumatoid Arthritis (adults);
- Psoriatic Arthritis (adults);
- Plaque Psoriasis (adults);
- Ankylosing Spondylitis (adults);
- Non-radiographic Axial Spondyloarthritis (adults)
- Polyarticular Juvenile Idiopathic Arthritis (children and adolescents 2 to 17 years); and
- Paediatric Plaque Psoriasis (children and adolescents 4 to 17 years).

ACM resolved to recommend the following indications:

- Rheumatoid Arthritis (adults);
- Psoriatic Arthritis (adults);
- Plaque Psoriasis (adults);
- Ankylosing Spondylitis (adults)
- Non-radiographic Axial Spondyloarthritis (adults).

In making this recommendation, the ACM:

- noted concerns with the two paediatric indications given the fixed dose form in which the product is presented means it potentially would only be administered to children and adolescents with body weight greater than 62.5 kg ,
- noted concerns with proposed wording in the sponsor's draft PI ("Dosage and Administration" section) to disclose the lack of mg/kg dosing of the products given the limited paediatric population that could potentially use the products, and
- noted that a clinical equivalence study has been conducted only in adult patients with plaque psoriasis.

[19] The ACM provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in 2010. ACM encompasses pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Proposed conditions of registration

The ACM agreed with the delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Subject to satisfactory implementation of the RMP most recently negotiated by the TGA,
- Negotiation of the PI and CMI to the satisfaction of the TGA.

Specific advice

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

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

- ***1. The sponsor is proposing to include the entire paediatric age range in its paediatric indications although the majority of children in the lower years of that age range will not be able to use the product due to having a body weight <62.5 kg. Does the Committee consider that there should be an amendment to the paediatric indications to acknowledge the inadequacy of this product for use in children and adolescents with body weight <62.5 kg? If so, what wording does the Committee recommend?***

The ACM noted the lack of any clinical data from the paediatric population. The ACM also noted previous discussions about the evaluation of biosimilar products and also discussed the application of the most recent TGA and EMA guidelines (2015) on biosimilar products to the consideration of this application.

The ACM recommended that the following proposed indications with respect to the paediatric population should be removed:

- Polyarticular Juvenile Idiopathic Arthritis (children and adolescents 2 to 17 years); and
- Paediatric Plaque Psoriasis (children and adolescents 4 to 17 years).

- ***2. What are the Committee's views on the efficacy of Erelzi and to what extent is there sufficient clinical trial evidence of similarity with the innovator product (Enbrel) to support the indication relating to plaque psoriasis for Erelzi?***

The ACM agreed that the efficacy for plaque psoriasis in adults has been demonstrated. The ACM noted that the trial design was strong and the standard outcome of PASI75 at 12 weeks was not statistically different between the two arms of the study. The ACM also noted that in the context of similar decisions made in relation to biosimilars, Erelzi is non-inferior to Enbrel for this indication.

- ***3. Does the Committee consider there is sufficient evidence and/or justification to support extrapolation of the data in patients with plaque psoriasis to the other indications for Enbrel, including the paediatric indications?***

The ACM considered that the principle of extrapolation has been established for other biosimilars and that there was sufficient evidence to support extrapolation of the data in patients with plaque psoriasis.

- ***4. What are the Committee's views on the comparability of the safety profiles of Erelzi and Enbrel?***

The ACM noted that the safety profiles from the phase 3 study and from other data in the application for adults do not demonstrate any clear toxicity difference between the two products, including the short two-way switching phase in the study design. However, the ACM also noted that the overall frequency of adverse effects was higher with Erelzi

compared to Enbrel and that the pattern of some adverse effects appeared slightly different between Erelzi and Enbrel groups. It was noted, however, that the sample size was small, and safety issues in larger numbers and in the longer term are unknown. The ACM also noted the lack of any safety data for the paediatric population.

- ***5. Does the Committee consider the proposed wording in the draft PI regarding the lack of dose adjustments to allow for mg/kg dosing adequate? If not does the Committee recommend alternative wording?***

The ACM recommended that the two indications referring to the paediatric population be removed, therefore the dose adjustments in the draft PI are no longer relevant.

- ***6. The sponsor does not wish to include a statement of batch traceability in the PI at this time. What are the Committee's view on this approach (please refer to PRECAUTIONS).***

The ACM agreed with the Delegate's proposal to include a statement of batch traceability and with the Delegate's suggested changes to the wording in the PI under 'Precautions'.

> *In order to improve the traceability of biological medicines, the trade name and the batch number of the administered product should be clearly recorded in the patient's medical record and/or dispensing record.*

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Erelzi [etanercept (rch)] (50 mg in 1 mL solution for injection auto-injector, 25 mg in 0.5 mL solution for injection pre-filled syringe, 50 mg in 1 mL solution for injection pre-filled syringe) indicated for:

> ***Adults***
>
> ***Rheumatoid Arthritis***
>
> *Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Erelzi can be used in combination with methotrexate. Severe, active rheumatoid arthritis in adults to slow progression of disease- associated structural damage in patients at high risk of erosive disease.*
>
> ***Psoriatic Arthritis***
>
> *The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. Erelzi has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.*
>
> ***Plaque Psoriasis***
>
> *Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.*
>
> ***Ankylosing Spondylitis***
>
> *The signs and symptoms of active ankylosing spondylitis in adults.*
>
> ***Non-radiographic Axial Spondyloarthritis***

Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change who have had an inadequate response to NSAIDs. *Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4.*

Children and Adolescents

Paediatric patients weighting less than 62.5 kg should not receive Erelzi. Paediatric patients weighting less than 62.5 kg should be accurately dosed on a mg/kg basis with other etanercept products.

Juvenile Idiopathic Arthritis

Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.

Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate. Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy. Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate. Etanercept has not been studied in children aged less than 2 years.

Paediatric Plaque Psoriasis

Chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.

Specific conditions of registration applying to these goods

- The EU-RMP, version 1.3, dated 19 April 2017, DLP 19 April 2017 with ASA version 0.2 (draft); 26 June 2017 and any future updates, as agreed with TGA will be implemented in Australia
- It is a condition of registration that all batches of Erelzi [etanercept (rch)] imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- It is a condition of registration that each batch of Erelzi [etanercept (rch)] imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

  The sponsor must supply:

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

- It is a specific condition of registration for Erelzi that the PI and CMI documents be updated within one month of safety-related changes made by the innovator.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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