Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Etanercept

Proprietary Product Names: Rymti/Etera

Sponsor: Lupin Australia Pty Ltd

February 2021

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
ACM	Advisory Committee on Medicines
ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADCC	Antibody dependent cell mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
AS	Ankylosing spondylitis
ASA	Australian-specific Annex
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
AUC_t	Area under concentration time curve from time zero to last measurable concentration
AusPAR	Australian Public Assessment Report
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	Body mass index
CCP	Cyclic citrullinated peptide
CHF	Congestive heart failure
CHMP	Committee For Medicinal Products For Human Use (European Union)
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CPD	Certified product details

Abbreviation	Meaning
CRP	C-reactive protein
DAS	Disease Activity Score
DLP	Data lock point
DMARD	Disease modifying anti-rheumatic drug
DP	Drug product
DS	Drug substance
ECG	Electrocardiogram
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency (European Union)
ESR	Erythrocyte sedimentation ratio
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full analysis set
Fc	Fragment crystallisable
FLR	Fluorescence
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
GMP	Good Manufacturing Practices
GVP	Good Pharmacovigilance Practices
HAQ-DI	Health Assessment Questionnaire-Disability Index
HILIC	Hydrophilic interaction liquid chromatography
HLA	Human leukocyte antigen
IFU	Instructions for Use
IgG	Immunoglobulin G
ISR	Injection site reaction
JIA	Juvenile idiopathic arthritis

Abbreviation	Meaning
K_d	Disassociation constant
LS	Least square
MI	Multiple imputation
MRI	Magnetic resonance imaging
MSD-ECL	Meso scale discovery bridging electro-chemiluminescence
MTX	Methotrexate
nAB	Neutralising antibodies
NP	Normal phase
nr-axial SpA	Non-radiographic axial spondyloarthritis
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PASI	Psoriasis Area and Severity Index
PFP	Prefilled pen
PFS	Prefilled syringe
PI	Product Information
PK	Pharmacokinetic
PPS	Per protocol set
PsA	Psoriatic arthritis
PSO	Plaque psoriasis
PSUR	Periodic safety update report
PT	Preferred Term
PY	Patient years
RA	Rheumatoid arthritis
RABBIT	Rheumatoid Arthritis: Observation of Biologic Therapy (German: *Rheumatoide Arthritis: Beobachtung der Biologika-Therapie*)

Abbreviation	Meaning
RH	Relative humidity
RMP	Risk management plan
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SPR	Surface plasmon resonance
TB	Tuberculosis
$T_{1/2}$	Terminal drug half life
TGA	Therapeutic Goods Administration
TNF	Tumour necrosis factor
TNFR	Tumour necrosis factor receptor
TEAE	Treatment emergent adverse event
TRAE	Treatment related adverse event
ULN	Upper limit of normal
UPLC	Ultra high performance liquid chromatography

I. Introduction to product submission

Submission details

Type of submission:	New biosimilar medicine
Product name:	Rymti/Etera
Active ingredient:	Etanercept
Decision:	Approved
Date of decision:	28 January 2020
Date of entry onto ARTG:	1 October 2020
ARTG numbers:	309829, 309831, 309830, 309834
, *Black Triangle Scheme:*[1]	No
Sponsor's name and address:	Lupin Australia Pty Ltd Suite 2 Level 2, 19-23 Prospect St, Box Hill, VIC, 3128
Dose form:	Solution for injection
Strengths:	25 mg (25 mg/0.5 mL) and 50 mg (50 mg/1.0 mL)
Container:	Prefilled syringe (PFS)
Pack size:	4
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). Rymti/Etera can be used in combination with methotrexate.* *Severe, active RA 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. Etanercept*

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

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 (AS) in adults.

Non-radiographic axial spondyloarthritis

Treatment of adults with active; non-radiographic axial spondyloarthritis (nr-axial SpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) change who have had an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs).*

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

Children and adolescents

Children and adolescents weighing less than 62.5 kg should not receive Rymti/Etera. These patients should be accurately dosed on a mg/kg basis with other etanercept products.[2]

Juvenile idiopathic arthritis

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

Active extended oligoarthritis in children and adolescents, aged two 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 two years.

Paediatric plaque psoriasis

Chronic, severe plaque psoriasis in children and adolescents from four 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 Psoriasis Area and Severity Index (PASI) response is not achieved.

[2] The wording of the indications for Rymti/Etera is not identical to the wording of the indications of the comparator (originator) product, Enbrel. These sentences are at variance with the Enbrel indications.

Route of administration:	Subcutaneous injection
Dosage:	Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patients may self inject only if their physician determines that it is appropriate and with medical follow up, as necessary, after proper training in injection technique. Patients treated with Rymti/Etera should be given the Patient Alert Card. **Adults: rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis and ankylosing spondylitis** The recommended dose of Rymti/Etera is 50 mg per week, given as a subcutaneous injection, either once weekly as a single 50 mg injection or twice weekly as two separate 25 mg injections given three to four days apart. Available data in non-radiographic axial spondyloarthritissuggest a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period. **Adults: plaque psoriasis** The recommended dose of Rymti/Etera is 50 mg per week, given once weekly (single 50 mg injection) or twice weekly (single 25 mg injections given three to four days apart) as a subcutaneous injection. Higher responses may be achieved from initial treatment for up to 12 weeks with a dose of 50 mg given twice weekly, after which, the dose should be reduced to the standard dose of 50 mg per week. Treatment should be discontinued in patients who do not show a significant Psoriasis Area and Severity Index (PASI) response after 12 weeks. If re-treatment with Rymti/Etera is indicated, the dose used should be 50 mg per week. **Use in elderly patients** Elderly rheumatoid arthritis patients (age ≥ 65 years) show similar safety, efficacy and pharmacokinetic profiles compared to younger adult patients treated with Rymti/Etera. Dose adjustment is not needed for the elderly. However, as with other medicinal products, greater sensitivity in some older patients cannot be ruled out. **Use in children and adolescents** Rymti/Etera is only available as 25 mg prefilled syringe and 50 mg prefilled syringe. Rymti/Etera should only be administered in children and adolescents weighing 62.5 kg or more. The dosage of Rymti/Etera is based on body weight for children and

adolescents. Patients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using other etanercept products (see below for dosing for specific indications). Patients weighing 62.5 kg or more and receiving once weekly doses may be dosed using a 50 mg (in 1 mL) fixed dose prefilled syringe.

Juvenile idiopathic arthritis (age two years and above)

The recommended dose for children 2 to17 years of age is 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly as a subcutaneous injection, or 0.4 mg/kg (up to a maximum of 25 mg), given twice weekly with an interval of three to four days between doses.

Paediatric plaque psoriasis (age four years and above)

The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose), given once weekly as a subcutaneous injection for up to 24 weeks. Treatment should be discontinued in patients who do not show a significant Psoriasis Area and Severity Index (PASI) response after 12 weeks. If re-treatment with Rymti/Etera is indicated, the above guidance on treatment duration should be followed.

For further information regarding dosage, refer to the Product Information.

Pregnancy 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.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Lupin Australia Pty Ltd (the sponsor) to register Rymti/Etera (etanercept) 25 mg/0.5 mL and 50 mg/1.0 mL, solution for injection prefilled syringe for the following proposed indications:

> *The proposed indications and dosage for Rymit/Etera are identical to those currently registered for Enbrel;[3] except for the weight restrictions for children and adolescents prescribed for the juvenile idiopathic arthritis and paediatric plaque psoriasis indications, as follows: Children and adolescents weighing less than 62.5 kg should*

[3] Enbrel (etanercept) was first registered in Australia on 18 March 2003 (ARTG number 90456). *Enbrel is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, juvenile idiopathic arthritis and paediatric plaque psoriasis.*

not receive Rymti/Etera. These patients should be accurately dosed on a mg/kg basis with other etanercept products.

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterised by polyarticular inflammatory synovitis, which is associated with cartilage breakdown, bony erosion and ultimately loss of function of the affected joints. It is the second most common form of arthritis and the most common autoimmune disease in Australia with a prevalence of 2%.

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and is more common in females. The estimated prevalence of JIA in Australia is one in 1000 children aged up to 16 years.

Ankylosing spondylitis (AS) affects approximately 0.5% of the population, mainly young to middle aged males. The characteristic clinical features of AS are inflammatory back pain with peripheral symptoms such as enthesitis or arthritis, and extra articular manifestations such as anterior uveitis, plaque psoriasis (PSO) and chronic inflammatory bowel disease. Most patients with active AS show objective signs of inflammation on imaging such as sacroiliitis and spondylitis, or findings via laboratory tests such as elevated C-reactive protein (CRP) or erythrocyte sedimentation rate. Furthermore, many patients with AS are positive for human leukocyte antigen (HLA) B27, have a positive family history of spondyloarthritis or related diseases. Non-radiographic axial spondyloarthritis (nr-axial SpA) is a related condition to AS in which patients have a similar clinical presentation (including inflammatory back pain), but radiographic sacroiliitis is not identified on plain X-rays. The prevalence of nr-axial SpA is similar to that of AS, but the former has a higher female preponderance. The rate of progression of nr-axial SpA to AS ranges from 10% to 20% over two years.

Plaque psoriasis (PSO) is an inflammatory immune based skin disorder with a genetic disposition, occurring in 3% of the adult Australian population. Though PSO can present at any age, the mean age of onset has a bimodal distribution at 15 to 20 years and 55 to 60 years. It is equally distributed across the genders. Approximately 15% of all cases of PSO begin in children before the age of 15 years, and the condition may start as young as infancy. About 25 to 30% of subjects with PSO develop a concurrent inflammatory arthritis, psoriatic arthritis (PsA).

The inflammatory arthritides (RA, PsA and JIA) are a group of heterogeneous conditions in terms of clinical presentation, natural history and drug responsiveness. Conventional synthetic disease-modifying antirheumatic drugs (DMARD), in particular, methotrexate (MTX), either alone or in combination with each other, are the initial recommended treatments for most types of inflammatory arthritis apart from AS. Biological DMARDs, either as add-on or single drug therapy, is the next recommended line of therapy in active inflammatory arthritis after conventional synthetic DMARD failure or intolerability. While anti-tumour necrosis factor (TNF) drugs and cytokine modulators have been shown to demonstrate significant efficacy in treating active inflammatory arthritis, a substantial proportion of patients are not achieving meaningful clinical responses.

Current treatment strategies for nr-axial SpA are the same as for AS, and include non-steroidal anti-inflammatory drugs (NSAID), exercise based programs and anti-TNF inhibitors for refractory inflammatory spondyloarthritis.

Depending on severity, a stepwise approach is typically used when managing PSO. The first line strategy is topical therapy, which satisfactorily controls PSO in approximately 70% of all cases. Topical therapies include various corticosteroids, tar preparations, emollients, salicylic acid, vitamin D analogues, retinoids, and calcineurin inhibitors such as pimecrolimus. Various types of phototherapy are generally considered the next line of treatment in Australian guidelines, but their availability and potential limitations is a barrier to utilisation. Until recently, non-biological systemic therapies, in particular, weekly low dose MTX, have been the mainstay of treatment refractory moderate to severe PSO in adults. Other commonly used systemic therapies include oral cyclosporine and

acitretin. However, evidence indicates that conventional systemic therapies have limited efficacy in treating PSO (for example, MTX and ciclosporin achieve a Psoriasis Area and Severity Index (PASI) 75 response of 50 to 70% after 12 to 16 weeks of therapy), and carry significant toxicity and tolerability risks. The efficacy and safety of biologic therapies such as TNF and interleukin 17 inhibitors is established for patients with moderate to severe PSO (70 to 80% of patients achieve at least a PASI75 response at ten to 16 weeks). However, while biologic drugs have been shown to demonstrate significant efficacy in treating active PSO, loss of response over time may occur in up to 30% of patients and necessitate alternative treatment options.

TNF plays a central role in the molecular and cellular events occurring in the pathogenesis of several autoimmune inflammatory conditions. Elevated concentrations of TNF have been found in the synovium of those with active RA, PsA and AS, as well as in the skin lesions of PSO. Anti-TNF medicines work by neutralising the activity of soluble TNF and preventing its binding to the two main TNF receptors, p55 and p75. These receptors are expressed on the membrane of monocytes and T-lymphocytes, and circulate in the blood in soluble forms.

Etanercept is a recombinant human tumour necrosis factor receptor (TNFR) p75 fusion protein, which inhibits the binding of TNF to the surface of cells expressing TNFR such as T-lymphocytes in the synovium of patients with active RA. Enbrel (the reference medicinal product) is currently approved in Australia for use in seven treatment indications (five in adults and two paediatric indications). The central therapeutic effect of Enbrel in all these indications is mediated by TNF blockade. Reducing disease activity and slowing the progression of inflammatory disease are the key therapeutic goals in inflammatory autoimmune disease. Etanercept is well established and widely used in clinical practice for > 18 years, with a well characterised benefit-risk profile.

Regulatory status

This product is considered a new biosimilar medicine for Australian regulatory purposes.

At the time the TGA considered this application, similar applications were approved in Japan (approved: 26 March 2019) and India (approved: March 2019), and an application was under consideration in the European Union (EU) (submitted: 30 April 2018).

Table 1: International regulatory status for Rymti, Etera

Country /Region	Trade Name	Submission date	Status	Approved indications
Japan	Etanercept	30 March 2018	Approved 26 March 2019	*Rheumatoid arthritis (including prevention of structural damage of joints) insufficiently effective in existing treatments.* *Juvenile idiopathic arthritis with multi-joint activity with insufficient effect in existing treatment.*

Country /Region	Trade Name	Submission date	Status	Approved indications
EU	Nepexto	30 April 2018	Under consideration	Under consideration
India	Rymti/ Nepexto/ Etera	August 2018	Approved March 2019	*Rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), nonradiographic axial spondyloarthritis (nr-AxSpA), plaque psoriasis, pediatric plaque psoriasis and juvenile idiopathic arthritis (JIA)*

Product Information

The Product Information (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: Timeline for Submission PM-2018-03223-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	31 October 2018
First round evaluation completed	18 April 2019
Sponsor provides responses on questions raised in first round evaluation	18 June 2019
Second round evaluation completed	9 August 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 November 2019

Description	Date
Sponsor's pre-Advisory Committee response	18 November 2019
Advisory Committee meeting	6 December 2019
Registration decision (Outcome)	29 January 2020
Completion of administrative activities and registration on the ARTG	1 October 2020
Number of working days from submission dossier acceptance to registration decision*	226

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

The following guidance documents are of relevance to the submission:

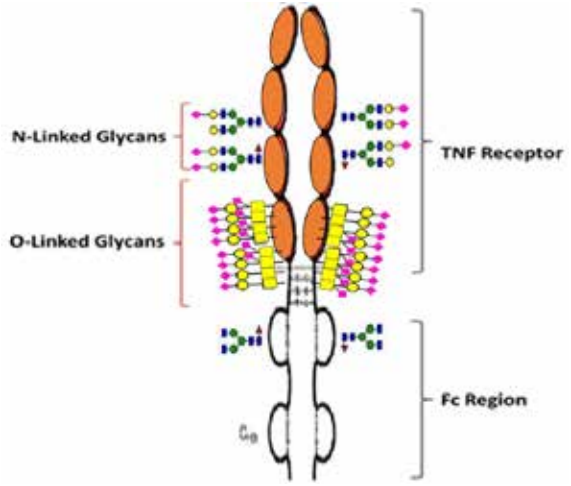
- Therapeutic Goods Administration: Regulation of biosimilar medicines (version 2.0; December 2015).
- **CPMP/EWP/556/95 Rev 1**: Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis. Effective: 29 January 2007
- **EMEA/CHMP/EWP/438/04**: Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis. Effective: 5 February 2008
- **CPMP/EWP/4891/03**: Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis. Effective: 23 February 2010
- **CPMP/EWP/2454**: Guideline on Clinical Investigation of Medicinal Products indicates for the treatment of Psoriasis. Effective: 28 July 2005
- **EMEA/CHMP/EWP/239770/2014 Rev 2**: Guideline on Clinical Investigation of Medicinal Products for the treatment of juvenile idiopathic arthritis. Effective: 10 November 2016
- **CHMP/437/04/Rev 1**: Guideline on Similar Biological Medicinal Products. Effective: 25 May 2015
- **EMA/CHMP/BMWP/86289/2010**: Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. Effective: 1 June 2014
- **EMA/CHMP/BMWP/403543/2010**: Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues. Effective: 17 August 2015

Quality

Etanercept is a fully humanised recombinant protein consisting of two soluble p75 TNFR molecules fused to the fragment crystallisable (Fc) fragment of human immunoglobulin G (IgG) subtype 1. A schematic presentation of the structure of etanercept is shown below in

Figure 1. It has an approximate molecular weight of 150 kDa. The proposed product (Rymti/Etera) uses the same amino acid sequence as the European reference product, Enbrel.

Figure 1: Structure of etanercept



This product is expressed in Chinese hamster ovary (CHO) cells and produced using a cell culture process. The culture then undergoes a series of filtration and chromatography steps. The drug product manufacturing steps include drug substance filtration and filling.

There are no outstanding issues with the drug substance and drug product specifications.

The fill volume of the prefilled syringe (PFS) is 1.0 mL for the 50 mg dose and 0.5 mL for the 25 mg dose. The recommended shelf life the drug product is 24 months stored at 2°C to 8°C. In-use stability data support a single period of up to four weeks of storage at 25°C.

Rymti/Etera was generally similar to Australian, EU, and United States (US) sourced Enbrel and Enbrel sourced from other geographical origins in a number of quality attributes, including amino acid sequence, higher order structures, binding kinetics with TNF-α and TNF-β, biological activity in neutralisation of TNF-α and TNF-β, degradation profile and stability.

A multi-step analytical similarity exercise was conducted to establish similarity between Rymti/Etera and the Australian registered Enbrel reference product. However, due to the differences in cell line and manufacturing processes, differences in some physicochemical characteristics and biological activities between the two products were expected. The secondary evaluations of infectious disease safety, container safety, microbiology (sterility) and endotoxin had no outstanding issues and the evaluations raised no objections to the registration on these quality grounds.

The quality evaluator has recommended approval of Rymti/Etera and proposed some changes to the specific conditions of registration.

Nonclinical

The nonclinical evaluator did not raise any objection to approval based on the nonclinical aspects, however this was contingent on the quality evaluator assessment of the comparability studies.

The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics (PK) and repeat dose toxicity, conducted from Enbrel sourced internationally (from India, Japan and the EU) with no nonclinical comparability studies between Australian sourced Enbrel and the international sources. The nonclinical evaluator noted the overall consistency of the dossier with the relevant EU guideline.

The PKs of Enbrel and Rymti/Etera were similar in mice.

The animal studies of efficacy compared Rymti and Enbrel in a RA model but not for other indications. The nonclinical evaluator noted higher levels of antibody dependent cell-mediated cytotoxic (ADCC) activity than Enbrel from other sources, attributed to higher levels of afucosylation. However, similar toxicity profiles between Enbrel and Rymti/Etera were shown in four week comparative repeat dose toxicity study in monkeys however the groups in the study were small and limited the safety information that could be derived.

Anti-drug antibodies (ADA) were detected in animals from low and high dose groups. In low doses ADA were associated with faster clearance.

Injection site reactions were similar across the treated groups.

No specific data were presented to support the pregnancy category and lactation information in the Rymti/Etera PI and the sponsor proposed to adopt the information from the Enbrel PI.

Following amendments during the evaluation phase the nonclinical aspects of the PI were considered acceptable.

Clinical

The clinical dossier consisted of:

- two Phase I studies, Study YLB113-001, and Study LBC-14-155; and
- one Phase III study, Study YLB113-003

Pharmacology

Study YLB113-001 was conducted in 60 Japanese healthy male volunteers and Study LBC-14-155 in 58 healthy Indian male volunteers. In the Japanese study, 58 patients were included in the PK analysis.

The Rymti/Etera or Japanese sourced Enbrel ratios for area under the concentration time curve from time zero to last measurable concentration (AUC_t) and maximum serum concentration (C_{max}) were 1.12 and 1.13, respectively for 25 mg subcutaneous (SC) dosing. The mean AUC_t values of Rymti/Etera and Enbrel were comparable at 431.28 µg·h/mL and 380.84 µg·h/mL, respectively. The mean C_{max} values were also comparable between the two formulations of etanercept being 1.966 µg/mL following Rymti injection and 1.742 µg/mL following Enbrel. The Rymti or Enbrel ratios for AUC_t and C_{max} were 1.12 (90% confidence interval (CI) 1.03, 1.21) and 1.13 (90% CI 1.04, 1.22), respectively.

In the Indian study the Rymti/Etera or Indian sourced Enbrel reference ratios for AUC_t and C_{max} in this study were 1.08 and 1.05, respectively.

The half-life ($T_{1/2}$) of etanercept for both products in Japanese patients was 115 minutes and 69 and 74 minutes for Indian patients Enbrel and Rymti, respectively. The sponsor undertook a population PK analysis approach to further understand the differences. The concentration time profiles and PK parameters of etanercept were simulated in Japanese subjects at a dose of 50 mg and for Indian subjects at dose of 25 mg using derived input parameters and a one compartmental extravascular PK model. Simulations supported the observed data and revealed the differences in the terminal drug $T_{1/2}$ and area under concentration time curve (AUC) of etanercept between the two subject populations were due to a difference in the elimination phase of etanercept. Japanese subjects have a significant higher $T_{1/2}$ and AUC of etanercept compared to Indian subjects.

Historical profiles of Japanese and Indian patients suggest the Japanese PK profile is more similar to European patients and the Indian profile is more similar to American patients. Simulations based of the mean concentration data for each group produced similar results.

No multi-dose PK studies were conducted but this was justified on the basis of the linear PK profile of etanercept. From the sponsor's literature review there are no major differences across the indications for mean steady state etanercept concentrations.

Rymti/Etera and Enbrel had similar levels of TNFα inhibition in the Indian pharmacology study. Table 3 below shows a summary of the TNFα inhibition.

Table 3: Study LBC-14-155 Tumour necrosis factor inhibition in *in vitro* system; recovery of tumour necrosis factor α

Formulation	N	Mean	SD	Min	Max	P-value*
T	12	10.5414	1.2208	9.6272	14.2222	0.7672
R	12	10.5601	1.1142	9.6849	13.7769	

T is Rymti; R is Indian-sourced Enbrel; N = number of observations; SD = standard deviation; Min = minimum; Max = maximum.

*The obtained p-value is statically not significant at 0.05 level of significance.

Efficacy

Study YLB113-002

Study YLB113-002 was a multicentre, multinational, double blind, randomised, placebo controlled Phase III study conducted between 2015 and 2017. It included 528 adult patients with at least moderately active RA;[4] and with an inadequate response to at least three months of MTX at an optimum dose (6 to 25 mg/week, not exceeding local approved dose recommendations) but on a stable dose for at least six weeks before screening, and with no prior biological treatment for RA. It was conducted in three stages, and initial double blind randomised phase to a 24 week primary endpoint (Stage A). At the end of Stage A patients could either enter a 28 week double blind treatment extension to a 52 week endpoint then four week follow-up (Stage B) or Stage C in which patients switched from Rymti to Enbrel, or Enbrel to Rymti.

Patients were eligible for Stage B of Study YLB113-002 if they had completed Stage A without treatment related Grade 3 or higher treatment related adverse events (TRAE) and could tolerate the study medication. Patients were eligible for Stage C of Study YLB113-002 if they had a reduction in baseline Disease Activity Score (DAS) 28;[5] score of ≥ 0.6 at Week 12 and/or Week 24, had completed Stage A, and could tolerate the study treatment in Stage A without serious adverse events (SAE) or unresolved Grade 3 or higher TRAEs. In Stage C, subjects crossed over to the other etanercept treatment arm. Patients whose DAS28 score had either not improved sufficiently from Baseline or those inclined to participate in Stage B (despite DAS28 improvement), were encouraged to continue in Stage B of the trial. Stage C was a later amendment to the initial study design that

[4] Defined as at least 6 tender and swollen joints (of 68/66 joints examined) at screening and randomisation; as well as a DAS28 score of ≥ 3.2 mg/L and be ACR Global Functional Class I, II or III at screening.
[5] The **Disease Activity Score 28** (**DAS28**) is a system developed and validated by the European League Against Rheumatism (EULAR) to measure the progress and improvement of rheumatoid arthritis. Calculation of a DAS28 score involves the combination of an examination of 28 specified joints for tenderness upon touching and swelling, the erythrocyte sedimentation rate (ESR) via blood sample, and the patient's subjective assessment of disease activity during the preceding 7 days on a scale between 0 ('no activity') and 100 ('highest activity possible'. DAS28 is often used in clinical trials for the development of rheumatoid arthritis (RA). DAS28 values range from 2.0 to 10.0; higher values mean a higher disease activity.

contributed delays the sponsor considers may have affected the numbers in this part of the study.

Exclusion criteria were numerous and were divided into four main categories:

- receipt of prohibited therapies for RA including any conventional DMARD other than MTX within two weeks of randomisation or at least five drug $T_{1/2}$ (whichever is greater), alkylating agents within six months of randomisation, and systemic or intra-articular glucocorticoid within two weeks of screening;
- increased risk of significant infection, including active tuberculosis (TB) or latent TB; history of chronic or recurrent infection and receipt of live or live attenuated vaccine within four weeks of screening;
- significant laboratory abnormalities at screening including serum transaminases > three x upper limit of normal (ULN), serum total bilirubin > two x ULN, serum creatinine > 2 mg/dL, total white blood cell count < 3.5 x 10^9/L, lymphocyte count < 1.0 x 10^9/L, platelet count < 125 x 10^9/L and haemoglobin < 8.0 g/dL; and
- co-morbidities that increased the patient's risk when taking etanercept, for example, current or prior history of lymphoproliferative disease or clinically significant malignancy (except excised and cured squamous cell carcinoma of the uterine cervix and non-melanoma skin cancers), latex allergy history, New York Heart Association (NYHA) Class III or IV congestive cardiac failure;[6] uncontrolled diabetes mellitus or hypertension, substance abuse in ≤ two years, any history of demyelinating disorders; pregnancy and lactation.

Study medication (Rymti/Etera or Enbrel) was administered as a once weekly 50 mg subcutaneous injection into the thigh or abdominal wall. Up to Week 52, patients continued on a stable background dose of MTX 6 to 25 mg/week. Folic acid therapy was recommended. Oral glucocorticoids (≤ 10 mg prednisone per day or equivalent) and single agent NSAIDs were allowed if the dose was stable for at least two weeks before screening and was stable through the active treatment period. Dose reductions of background therapies were allowed for safety concerns or for NSAIDs and corticosteroids for improvement in RA disease activity. Doses of steroids and NSAIDs were discontinued 24 hours prior to joint evaluations.

The fixed effects meta-analysis of three studies of Enbrel versus placebo estimated a risk difference of 40.4% with a 95% CI of 31% to 50%. To preserve ≥ 50% of the Enbrel effect over placebo, an equivalence limit of 15% was set for the primary analysis. Assuming an American College of Rheumatology (ACR) 20;[7] response rate of 70% with etanercept plus MTX from published studies with the 15%, equivalence margin, a two sided statistical significance level of 5% and a power of 80%, the sponsor calculated it required a sample size of 392 allocated in a 1:1 randomisation ratio (196 per treatment) to test the therapeutic equivalence of Rymti/Etera and Enbrel.

[6] The **New York Heart Association** (**NYHA**) Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity: I. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath). II. Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath). III. Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea. IV. Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

[7] The **ACR** (**American College of Rheumatology**) **criteria** are a standardised measure of disease improvement widely used in rheumatology trials, but less so clinically. The **ACR20** is a composite measure defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in three of the following five criteria: patient global assessment, physician global assessment, a patient functional ability measure (most often the Health Assessment Questionnaire (HAQ), Visual Analog Scale (VAS) for Pain, and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). ACR50 and ACR70 are the same instruments with an improvement of 50% and 70% respectively.

Of the 874 patients screen, 528 were randomised into Stage A (266 to Rymti, 262 to Enbrel). The full analysis set (FAS) comprised 517 patients who received at least one dose of study medication. From the 497 patients who competed Stage A (247 Rymti, 250 Enbrel), 471 entered Stage B (236 Rymti, 235 Enbrel); 454 completed Stage B (227 Rymti, 227 Enbrel); 18 entered Stage C (eight switched from Rymti to Enbrel, ten from Enbrel to Rymti); and 17 patients completed Stage C.

Stage A

The median ages of enrolled subjects in the Rymti/Etera group and Enbrel groups were 53 years (ranged from 22 to 75 years) and 54 years (ranged from 18 to 74 years), respectively. About 16% were aged between 65 and 84 years. Most were female: (76.0% in the Rymti group and 79.9% in the Enbrel group). The mean baseline body mass index (BMI) was 24.8 kg/m^2 in the Rymti group and 25.0 kg/m^2 in the Enbrel group. Of the 517 patients 260 (50.3%) were recruited in Japan, 225 (43.5%) in Europe and 32 (6.2%) in India.

The mean (median) duration of RA prior to study inclusion was 6.3 (4.1) years in the Rymti/Etera group and 6.1 (3.6) years in the Enbrel arm. About 70% were rheumatoid factor seropositive and about 73% had anti-cyclic citrullinated peptide (CCP) antibodies.

The two groups were well matched for baseline RA disease activity. The mean swollen joint counts (maximum of 66) were 13.3 and 14.2 in the Rymti/Etera and Enbrel treatment groups, respectively; and the mean tender joint counts (maximum of 68) were 18.1 and 18.9 in the Rymti and Enbrel arms, respectively. The baseline mean health assessment questionnaire disability index (HAQ-DI) scores were 1.06 and 1.13 in the Rymti and Enbrel treatment groups.

All enrolled patients received low dose MTX weekly as a prior DMARD that was continued during the trial. MTX 6 to 10 mg weekly was received in 60.5% of the Rymti group and 55.1% of the Enbrel group, and 29.7% of the Rymti group and 31.5% of the Enbrel group received ≥ 15 mg MTX weekly with a median weekly dose of 10 mg about 95% took their MTX orally. About 60% also took folic acid. About 8% took one additional prior conventional DMARD and 3.3% had taken ≥ two or more, with sulfasalazine and leflunomide were the most frequently used non-MTX DMARDs. Around 44% of the Rymti group and 40.2% in the Enbrel group took a median daily dose of 4 mg dose prednisone at baseline, and about 62% were taking stable NSAID at Baseline.

The study protocol allowed for discretion in selection of the serum inflammatory marker. Serum CRP was selected for 36.9% and erythrocyte sedimentation ratio (ESR) was used for 63.1%. Mean baseline CRP values were 1.299 mg/dL in the Rymti group versus 1.015 mg/dL in the Enbrel group. Mean baseline ESR was 35.5 mm/hr in the Rymti group versus 32.8 mm/hr in the Enbrel group. The mean DAS28-CRP score was 5.191 in the Rymti group and 5.237 in the Enbrel group, and the mean DAS28-ESR score was 6.108 in the Rymti group and 6.057 in the Enbrel group.

Early discontinuations Stage A occurred for 17 (6.4%) Rymti and ten (3.8%) Enbrel patients most commonly due to consent withdrawal in the Rymti group and adverse event (AE) in the Enbrel group. 33 major protocol deviations were reported in the FAS cohort of 517 subjects with 10.2% of the Rymti group and 9.2% of the Enbrel group excluded from the per protocol analysis due to major protocol deviations. Most were eligibility criteria breaches (3.4% Rymti and 2.4% Enbrel), significant medication compliance issues (3.0% Rymti and 0.8% Enbrel) and use of prohibited medications (1.9% Rymti and 1.2% Enbrel).

The primary endpoint was ACR20 response at Week 24. Results for the primary endpoint are shown in Table 4, below.

Table 4: Study YLB113-002 Stage A primary endpoint

FAS = 517 (PPS=477)	Etanercept Lupin		Enbrel
FAS population	**N=263**		**N=254**
ACR20 response at week 24	81.2%		86.8%
Treatment difference (95% CI)*		-5.6% (-11.6; 0.5)	
PPS population	**N=239**		**N=238**
ACR20 response at week 24	86.0%		90.6%
Treatment difference (95% CI)*		-4.6% (-10.1;0.8)	

Etanercept Lupin = Rymti/Etera; N = number of subjects in the analysis set with ACR20 results non-missing; PPS = per protocol set

*95% confidence internal for the estimated difference in proportions is produced using the binominal regression model.

Missing data have been imputed according to non-responder imputation (NRI) and/or multiple imputation (MI).

The rates of ACR20 response at Week 24 were similar between the two treatment groups for age (< 65 years versus > 65 years), gender and with a lower baseline level of disease activity (DAS28 score < 5.1) (see Table 5, below). However, in patients with higher disease activity at Baseline (DAS28 score > 5.1), the Enbrel group had a higher numerical ACR20 response rate at 88.0% compared with 79.0% in the Rymti group. Across the geographic regions there was considerable heterogeneity in the rates of ACR20 response (in particular, significantly lower in Indian subjects, especially with Enbrel therapy), but overall similar.

The secondary efficacy endpoints included:

- ACR20 response rates at Weeks 4, 8, and 12,
- ACR50;[7] and ACR70;[7] response rates at Weeks 4, 8, 12 and 24,
- improvement (least square (LS) mean change from Baseline) in DAS28 score at Weeks 4, 8, 12 and 24.

European League Against Rheumatism (EULAR) and DAS28 response rates at Weeks 4, 8, 12 and 24 were also reported as exploratory outcomes of Stage A. ACR-N at Week 24 was requested by the European Medicines Agency (EMA) as a post-hoc analysis.

The rates of ACR20 response at Weeks 4, 8 and 12 in the FAS (summarised below). The ACR20 increased over time in both treatment groups with no significant differences observed between the groups. The majority of clinical response was seen at 12 weeks of therapy, small incremental improvement (3.7 to 5.8%) in ACR20 thereafter to 24 weeks.

Table 5: Study YLB113-002 American College of Rheumatology 20 response rate by visit during Stage A (full analysis set)

				Difference in proportions (YLB113 50 mg – Enbrel 50 mg, %)	
Visit (Week)	Treatment Arm	N	Proportion	Estimate	95% Confidence Interval
Day 29 (Week 4)	YLB113 50 mg Enbrel 50 mg	263 254	55.8 53.9	1.9	(-6.3, 10.2)
Day 57 (Week 8)	YLB113 50 mg Enbrel 50 mg	263 254	67.5 74.0	-6.5	(-14.2, 1.2)
Day 85 (Week 12)	YLB113 50 mg Enbrel 50 mg	263 254	77.5 81.0	-3.5	(-10.0, 3.1)

The adjusted proportions of subjects with ACR20 response in each treatment group at each visit (week) are estimated using binomial regression.

The difference in proportions is calculated as the difference between the probabilities predicted by the model for both treatment groups on the original scale at each particular visit (week) (E (response to treatment at each visit (week)) = treatment + baseline DAS28 stratum + age + region).

The 95% confidence interval for the estimated difference in proportions is produced using the binominal regression model.

Missing data have been imputed according to NRI and/or MI.

N = Number of subjects in the analysis set with ACR20 results non-missing.

Protocol defined margins: (- 15.0% + 15.0%) for Week 24 95% confidence interval.

For subject [information redacted] has Day 1 pre-treatment missing components and thus, the baseline value is imputed using multiple imputation.

The ACR50 and ACR70 response rates at Weeks 4, 8 and 12 were similar for both treatment groups but the Week 24 ACR50 response rate was 56.3% in the Rymti group compared to 67.1% in the Enbrel group (treatment difference -10.7%, 95% CI (-18.9%, -2.6%)). The Week 24 ACR70 response rates were around 35% in each treatment group.

The DAS28 score used either ESR or CRP, with the results pooled. At Week 24 the LS means were -2.43 (95% CI -2.616, -2.239) and -2.48 (-2.668, -2.286), difference 0.05 (-0.129, 0.228). In this DAS28 ESR subgroup, the LS mean change from Baseline to Week 24 was -2.63 in the Rymti group (n = 161) and -2.62 in the Enbrel group (n = 165), with a treatment difference of -0.01 (95% CI -0.230, 0.214). For DAS28 CRP, the LS mean change from Baseline to Week 24 was -2.18 in the Rymti group (n = 102) and -2.25 in the Enbrel group (n = 89) with a treatment difference of 0.07 (95% CI -0.216, 0.365).

EULAR Responses (good, moderate and no response) based on pooled DAS28 responses at Weeks 4, 8, 12 and 24 were similar between the groups. At Week 24, 39.5% (104 over 263) of subjects in the Rymti group and 38.6% (98 over 254) of patients in the Enbrel group reached clinical remission. At Week 24, low disease activity was recorded in a slightly lower proportion of subjects in the Rymti group (15.2% (40 over 263) of subjects in the Rymti group versus 20.1% (51 over 254) of patients in the Enbrel group).

At Week 24 the mean percentage change from Baseline in ACR-N (using ESR) was -60.1 (95% CI -64.1, -56.1) with Rymti and -59.9 (95% CI -63.7, -56.1) with Enbrel. The mean percentage change from Baseline to Week 24 in ACR-N (using CRP) was -61.4 (95% CI -67.6, -55.2) with Rymti and -62.6 (95% CI -69.0, -56.3) with. Similar results were observed in the per protocol population.

Stage B

Patients in Stage B continued their assigned treatment from Stage A.

The baseline characteristics for this part of the study were similar to Stage A. Six major protocol deviations in this part of the study included 0.9% in each treatment group with inadequate compliance with study medication and 0.9% of the Rymti group using prohibited medications that may have influenced efficacy outcomes. Early discontinuation occurred in nine (3.4%) Rymti and eight (3.1%) Enbrel most commonly due to consent withdrawal three (1.1%) in the Rymti group and due to equal numbers of AEs 4 (1.5%) in each group.

The efficacy outcomes for Stage B of the trial were stated to have been collected, but were not included in the study report but a summary was provided in response to questions, and are summarised in Table 6.

Table 6: Study YLB113-002 (Stage B) American College of Rheumatology responses

Visit	Treatment Arm	N	Proportion	Difference in proportions	
				Estimate	95% Confidence Interval
ACR20					
Week 36	YLB113 50mg	235	85.4	-3.2	(-9.1, 2.7)
	Enbrel 50mg	229	88.6		
Week 44	YLB113 50mg	235	86.7	-3.6	(-9.4, 2.1)
	Enbrel 50mg	229	90.4		
Week 52	YLB113 50mg	235	89.6	0.2	(-5.4, 5.9)
	Enbrel 50mg	229	89.3		
ACR50					
Week 36	YLB113 50mg	235	70.5	-4.7	(-12.6, 3.2)
	Enbrel 50mg	229	75.2		
Week 44	YLB113 50mg	235	70.2	-4.0	(-12.0, 4.1)
	Enbrel 50mg	229	74.1		
Week 52	YLB113 50mg	235	73.1	-2.1	(-9.8, 5.6)
	Enbrel 50mg	229	75.2		
ACR70					
Week 36	YLB113 50mg	235	44.0	-2.1	(-11.1, 6.9)
	Enbrel 50mg	229	46.1		
Week 44	YLB113 50mg	235	49.0	0.8	(-8.2, 9.8)
	Enbrel 50mg	229	48.2		
Week 52	YLB113 50mg	235	50.8	-3.8	(-12.8, 5.1)
	Enbrel 50mg	229	54.6		

The DAS28 scores were also summarised in Table 7.

Table 7: Study YLB113-002 (Stage B) Mean change from Baseline in Disease Activity Score 28 results

Week	Treatment Arm	N	Mean Change from Baseline		Treatment Difference (YLB113 50mg – Enbrel 50mg)	
			LS Mean	95% CI	LS Mean	95% CI
Week 36	YLB113 50mg	235	-2.48	(-2.673, -2.284)	0.08	(-0.106, 0.260)
	Enbrel 50mg	229	-2.56	(-2.752, -2.359)		
Week 44	YLB113 50mg	235	-2.64	(-2.835, -2.450)	0.00	(-0.180, 0.182)
	Enbrel 50mg	229	-2.64	(-2.838, -2.449)		
Week 52	YLB113 50mg	235	-2.78	(-2.978, -2.586)	-0.04	(-0.227, 0.142)
	Enbrel 50mg	229	-2.74	(-2.938, -2.542)		

Stage C

Eighteen European based subjects (eight switched to Enbrel, ten switched to Rymti) with a median age of 55 years entered Stage C of the trial. There were seven female subjects in each treatment group with a mean BMI of 25.7 kg/m^2 (mean weight of 72.8 kg). One patient in the switching Stage C discontinued because of an RA exacerbation (Enbrel-Rymti group). One major protocol deviation was recorded in a subject treated with Rymti related to inadequate compliance with injectable study medication.

The ACR20 response rate at Week 36, 44 and 52 was 57.9%, 67.5% and 69.0% in the Rymti group (n = 10) and 65.1%, 90.7% and 63.7% in the Enbrel arm (n = 8), at Week 44 was in the Rymti group (n = 10) and in the Enbrel arm (n = 8). The ACR50 responses at Weeks 36 and 44 were both 20.6% in the Rymti group versus 36.7% in the Enbrel arm, and at Week 52 was 47.1% in both treatment groups. The ACR70 responses at Weeks 36 and 44 were both 4.8% in the Rymti group and 19.0% in the Enbrel arm, and at Week 52 was 5.0% in the Rymti group and 19.3% in the Enbrel arm.

All 18 subjects contributed data to both DAS28 (ESR and CRP) score calculations. The LS mean improvements from Baseline for DAS28 scores at Weeks 36, 44 and 52 ranged from -2.2 to -2.8 in the Rymti group and -2.5 to -2.6 in the Enbrel arm. At Week 52, LS mean improvements from Baseline in DAS28 score using ESR were -2.9 for Rymti and -2.7 for Enbrel, and using CRP -2.0 for Rymti and -1.6 for Enbrel. At Week 52 using the mean percentage change from Baseline in ACR-N (using ESR) was -70.5 (95% CI -119, -22.1) with Rymti and -48.2 (95% CI -85.7, -10.7) with Enbrel.

Impact of anti-drug antibodies on efficacy

The incidence of positive ADA in Study YLB113-002 was very low in both treatment groups precluding a meaningful assessment.

Safety

Most of the safety data is from Study YLB113-002.

From Stage A, the safety dataset is from 517 of 528 randomised patients (263 in the Rymti group and 254 subjects in the Enbrel arm). Two patients from each treatment group) did not receive study treatment so were excluded from the safety set. Seven subjects (three in the Rymti group and four in the Enbrel arm) were excluded because of Good Clinical Practice (GCP) violations. The mean duration of exposure was 22.8 weeks in the Rymti

group and 23.1 weeks in the Enbrel group (range: 1 to 24 weeks for each). Most continuing subjects (93.9 to 95.3%) received all doses of study treatment up to 24 weeks with similar cumulative exposures in both treatment arms. Drug compliance was 97% for Rymti and 99.2% for Enbrel.

The overall incidence and number of treatment emergent adverse events (TEAE) up to Week 24 was higher in the Enbrel arm (65.7% (167 over 254) reported a total of 794 AEs compared to the Rymti group (55.5% (146 over 263) reported a total of 364 AEs). The incidence of TEAEs was 865 per 1000 patient years (PY) (193.07 PY of exposure) in the Enbrel group and 726.5 per 1000 PY in the Rymti group (200.95 PY of exposure).

Most TEAEs in both groups were of mild or moderate severity with the main difference being an almost three fold increased incidence of general disorders and administration site conditions in the Enbrel (31.1% (79 over 254), total of 465 AEs) versus Rymti group (11% (29 over 263), total of 79 AEs). Other AEs by System Organ Class (SOC) reported in ≥ 5% included for the Rymti and Enbrel arms, respectively:

- Infections and Infestations: 24.0% (63 over 263) versus 27.2% (69 over 254)
- Gastrointestinal Disorders: 9.5% (25 over 263) versus 10.2% (26 over 254)
- Musculoskeletal and Connective tissue disorders: 8.0% (21 over 263) versus 10.6% (27 over 254)
- Skin and Subcutaneous Tissue Disorders: 7.6% (20 over 263) versus 8.3% (21 over 254)
- Injury, Poisoning and Procedure Complications: 6.5% (17 over 263) versus 6.3% (16 over 254)
- Respiratory, Thoracic and Mediastinal Disorders: 6.5% (17 over 263) versus 4.7% (12 over 254)
- Nervous System Disorders: 2.7% (seven over 263) versus 6.7% (17 over 254).

The most frequently occurring AE at the Preferred Term (PT) level was Nasopharyngitis, (11.4% of subjects (30 over 263) versus 9.8% (25 over 254) in the Rymti versus Enbrel groups.

Injection site reactions (ISRs) were reported in 3.8% versus 13.8% in the Rymti versus Enbrel groups. Injection site erythema was reported in 1.9% versus 9.8% in the Rymti versus Enbrel groups. Other ISR descriptor proportions were: Injection site pruritus (1.1% versus 3.1%), and Injection site bruising (1.1% versus 1.2%).

The other common types of AEs by PT occurred at a similar frequency between the two groups (Rymti versus Enbrel) and included: Abnormal hepatic function (2.4 to 4.2%), Pharyngitis (1.9 to 2.0%), Bronchitis (1.2 to 1.5%), Upper respiratory tract infection (1.5 to 2.0%), Rheumatoid arthritis flare (1.9 to 2.8%), Back pain (1.1 to 3.1%), Headache (1.1 to 3.5%) and Nausea (1.6 to 1.9%).

In Stage B, TEAEs occurred in 52.8% (124 over 235) versus 63.3% (145 over 229) in the Rymti versus Enbrel groups but the exposure adjusted incidence for AEs was 812.54 per 1000 PY (152.63 PY of exposure) in the Rymti group versus 658.6 per 1000 PY (220.15 PY of exposure) in the Enbrel group.

The most frequently recorded TEAE by SOC was infections and infestations a higher frequency and exposure adjusted incidence of 25.5% (60 over 235), total of 76 AEs, rate of 365.1 per 1000 PY) versus 35.4% (81 over 229) of subjects reported a total of 118 AEs at rate of 573.2 per 1000 PY of exposure) for Rymti versus Enbrel. The most frequent infection was Nasopharyngitis, (14.9% (35 over 235) of subjects reported a total of 42 AEs at a rate of 248 per 1000 PY of exposure) versus 19.2% (44 over 229) of subjects in the Enbrel group (total of 55 AEs at rate of 362.4 per 1000 PY of exposure) for Rymti versus

Enbrel. A more than a two fold increased rate of administration site AEs occurred with Enbrel (6.4% (15 over 235), 109.5 per 1000 PY) versus 14.8% (34 over 229), 321 per 1000 PY) for Rymti versus Enbrel). The largest difference was for ISRs, 1.3% (3 over 235), 23.1 per 1000 PY versus 7.4% (17 over 229), 180.8 per 1000 PY for Rymti versus Enbrel. Injection site erythema (0% versus 4.4% (10 over 229) 103.7 per 1000 PY for Rymti versus Enbrel. Injection site bruising was reported in five versus one patients for Rymti versus Enbrel.

In Stage C, the overall incidence and number of treatment emergent AEs was similar in the treatment groups: TEAEs in 30% versus 37.5% in the Rymti switch group versus the Enbrel crossover arm. In the Rymti treatment group, for Infections there were single reports of respiratory tract infection, urinary tract infection, neutropaenia (in one patient with infection) and first degree atrioventricular heart block. In the Enbrel crossover treatment group, there were single reports of leukopenia with neutropenia, RA exacerbation and injection site erythema and no infections.

In Study YLB113-001, TEAEs occurred in 10.2% (6 over 59) versus 20.0% (12 over 60) Rymti versus Enbrel. In the Enbrel group one subject had Grade 1 injection site haematoma and four subjects had infections (two cases of herpes simplex, one case of sinusitis and one case of gonorrhoeal urethritis). In the Rymti group one subject each had sore throat and forearm rash.

A total of 14 AEs (in 11 subjects) were recorded in Study LBC-14-155, three of which occurred during the study and 11 during the post-study evaluation. The three AEs (in three separate subjects) during the study were all related to multiple injuries as a consequence of various types of accidents and were unrelated to study medication. Of the 14 AEs, six were reported following Rymti injection and eight were recorded following Enbrel injection and were laboratory abnormalities of mild severity.

Treatment related adverse events

In Study YBL113-002 Stage A TRAEs occurred in 14.8% versus 12.2% for Rymti versus Enbrel. Most TRAEs in both groups were generally similar between the treatment arms and of either mild or moderate severity, however various types of administration site AEs occurred in 6.8% ((18 over 263), a total of 62 AEs) versus 21.7% ((55 over 254), a total of 379 AEs) for Rymti versus Enbrel.

In Stage B, TRAEs occurred in 2.6% versus 13.5% for Rymti versus Enbrel. Most TRAEs in both groups were assessed as being of either mild or moderate severity with no discernible differences between the two treatment arms apart from the approximate two fold increased incidence of various types of ISRs in the Enbrel arm. Treatment related infections of various types were also common in both treatment groups at an equal and approximate incidence of 4%.

In Stage C, one patient in each treatment group experienced two AEs that were considered to be possibly related to study medication. A Rymti treated subject recorded leukopenia and neutropenia. A subject treated with Enbrel reported injection site erythema and neutropaenia.

In Study YLB113-001, 8.5% versus 15% of Rymti versus Enbrel were TRAEs. The Rymti TRAEs were sore throat, skin eruption, gingival pain, oral paraesthesia, increased blood triglycerides and increased serum gamma glutamyl transpeptidase (GGT). The Enbrel TRAEs were four infections, one ISR, enteritis, three minor blood abnormalities (abnormal liver function, increased serum GGT and raised serum urate) and one case of sore throat. In Study LBC-14-155 two subjects recorded two TRAEs of increased serum transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)). One resolved without sequelae, with the other outcome unknown.

No deaths occurred during any of the Rymti studies.

Serious adverse events

In Stage A of Study YLB113-002A, 13 SAEs were reported in 12 subjects (2.3% of 517) up to Week 24; eight (3.0% of 263, 48.5 per 1000 PY) subjects reported nine SAEs in the Rymti group, and four (1.6% of 254, 25.1 per 1000 PY) subjects reported four SAEs in the Enbrel arm. The most frequently SAE (in ≥ two patients in either treatment group) by SOC was Infection (three SAEs in three subjects (1.1 to 1.2%) in each treatment group). The three infectious SAEs in the Rymti group were one each of *Pneumocystis jirovecii* pneumonia, pneumonia and *Escherichia coli* urinary tract infection. The three infectious SAEs in the Enbrel arm were two cases of pneumonia and one case of *Pneumocystis jirovecii* pneumonia. A case of lobular breast carcinoma in situ was reported in the Rymti group. The other SAEs in the Rymti group included single reports of ankle fracture, adult onset Still's disease, uterine polyp, interstitial lung disease and pleurisy. The non-infectious SAE recorded in the Enbrel arm was gastritis. Four of the SAEs reported in the Rymti group (three infections plus one case of adult onset Still's disease) and one of the SAEs in the Enbrel arm (pneumonia) were considered treatment related.

In Stage B, a total of 13 SAEs were reported in 13 subjects (2.8% of 464): eight (3.4% of 235) patients reported 11 SAEs (1120.4 per 1000 PY) in the Rymti group, and five (2.2% of 229) patients reported five SAEs (1644.7 per 1000 PY) in the Enbrel arm.

By SOC, the most frequent SAE affecting ≥ two patients in either treatment group was Infection (three SAEs in two subjects (0.9%) in the Rymti group and two SAEs in two subjects (0.9%) in the Enbrel group). In the Rymti group these were one case each of bacterial pneumonia, rhinitis and sinusitis, and in the Enbrel arm there was one case each of herpes zoster infection and renal abscess. One patient in the Rymti group recorded pancreatic carcinoma with liver and lung metastases (three SAEs in total) and one patient in the Rymti group developed uterine cancer. The other types of SAEs recorded in the Rymti group included single reports of deep vein thrombosis, positional vertigo, headache, interstitial lung disease and pleural cyst. The other SAEs recorded in the Enbrel arm were sixth cranial nerve paresis and angina pectoris. Four of the SAEs reported in the Rymti group (three infections plus one case of interstitial lung disease) and one of the SAEs (herpes zoster infection) in the Enbrel arm in Stage B were considered to be treatment related.

No treatment emergent SAEs were reported during Stage C of the trial.

The SAE in the Study YLB113-001 was not considered to be related to study medication based on prior history. No SAEs were reported in Study LBC-14-155.

Discontinuations due to adverse events

In Stage A of Study YLB113-002 up to Week 24, seven AEs led to treatment discontinuation in 1.4% of 517patients: two AEs in two (0.8% of 263) subjects in the Rymti group and five AEs in five (2.0% of 254) patients. In the Enbrel arm two discontinuations were due to ISR, two were due to skin rash and urticaria (treatment related) and the other was an ovarian cyst (unrelated). The two AEs resulting in treatment cessation in the Rymti group were adult onset Still's disease (possibly related) and lobular carcinoma in situ (unrelated).

In Stage B of Study YLB113-002, four subjects (1.7% of 229 to 235) in each treatment group permanently discontinued treatment due to AEs. In the Rymti group these were single cases of perirectal abscess (considered to be treatment related), interstitial lung disease (possibly treatment related), pneumonia (deemed unrelated) and metastatic pancreatic carcinoma (unrelated). In the Enbrel arm these were single cases of pustular PSO, renal abscess, uterine cancer and Moya disease (all considered to be either not or unlikely to be related to treatment).

No discontinuation of study medication due to an AE was reported in Stage C of the study.

In Study YLB113-001, one subject discontinued one day before the second administration period (Day 28) due to persistent Grade 2 sinus inflammation (treatment related), 16 days after the first administration of Enbrel.

One subject discontinued from Study LBC-14-155 due to multiple injuries from an accident in period 1.

Liver function and liver toxicity

All abnormalities of liver enzymes were graded mild or moderate and none were considered clinically significant by the investigator.

In Study YLB113-002 Stage A, an elevated ALT value, was recorded in 8.0% (21 over 263) of the Rymti group and 9.8% (25 over 254) of the Enbrel group. Increased AST readings were observed in 15 patients in each group (5.7 to 5.9%). One patient in each treatment group had increases in serum total bilirubin. In Stage B, elevated serum AST value was reported in 3.0% (7 over 235) in the Rymti group and no cases in the Enbrel group, elevated serum ALT values in 1.7% (4 over 235) of subjects in the Rymti group and 1.3% (3 over 229) of patients in the Enbrel arm and elevated serum total bilirubin in one patient in Rymti group. In Stage C, one Enbrel treated subject developed a temporary minor increase in serum AST. No potential Hy's law cases observed in any stage of the study.[8]

Following each injection in Study YLB113-001, one patient was recorded to have increased serum GGT, which was considered to be treatment related. Following Enbrel injection in the first study period, a subject was observed to have an AE of abnormal hepatic function, a combination of mildly raised serum transaminases and GGT (considered to be treatment related).

Two subjects in Study LBC-14-155 (one following each treatment) developed a two to three fold increase in serum transaminases following study medication that was considered to be possibly related to treatment. The elevation in the Rymti patient resolved but the outcome for the Enbrel patient is unknown.

Blood chemistry

Four subjects (1.5% of 263) treated with Rymti and with six subjects (2.4% of 254) treated with Enbrel in Stage A, and three to four subjects (1.3 to 1.7%) in each treatment group of Stage B developed new increases from Baseline in serum total cholesterol. Two Enbrel treated subjects (0.9% of 229) recorded transient increases in serum creatinine phosphokinase levels in Stage B and one subject developed raised serum uric acid in Study YLB113-001. One subject Rymti patient recorded an elevation in blood triglycerides in one subject developed raised serum uric acid.

Haematology and haematological toxicity

Four patients in each treatment group recorded neutropaenia and one to two subjects in each treatment group were identified as having thrombocytopenia in Stage A of Study YLB113-002. In Stage B, four Enbrel patients (1.7% of 229) had neutropaenia and one to two subjects in each treatment group had thrombocytopenia. In Stage C, one Enbrel treated subject (12.5% of 8) developed mild thrombocytopenia.

In the post-study period of Study LBC-14-155, one subject recorded a lymphocytosis (Rymti was the second injection given) that resolved without sequelae. Four patients who

[8] **Hy's Law**: Evidence of hepatocellular injury with a rise in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN) and total bilirubin > 2 x ULN, and no other reason to explain rise in aminotransferases and total bilirubin. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury with jaundice.

received Enbrel as their second study drug, and in two who received Rymti as their second treatment.

Immunogenicity

The assays for ADA differed between the studies in this submission. In Study YLB113-002 meso scale discovery bridging electro-chemiluminescence (MSD-ECL) immuno-assay was used for the determination of ADA, however in the Phase I Study YLB113-001 an enzyme linked immunosorbent assay (ELISA) was used. The clinical evaluator was satisfied that each of these methods was appropriately developed and validated, however the MSD-ECL method is less affected by drug present in the sample than the ELISA. Results from these assay methods are not directly comparable.

By 24 weeks (Stage A), only two patients (0.8% of 263) treated withYLB113 (Rytmi) developed positive ADA, neither of which had neutralising activity. In contrast, a total of 21 patients (21 over 254) in the Enbrel arm recorded a positive ADA result and for two of those subjects the ADA was neutralising (see Table 8, below).

Table 8: Study YLB113-002 Anti-drug antibodies

	YLB113 50 mg				Enbrel 50 mg			
	N	Total Reportable n	ADA Positive n (%)	nAB Positive n (%)	N	Total Reportable n	ADA Positive n (%)	nAB Positive n (%)
Stage A	263	263	2 (0.8)	0	254	254	21 (8.3)	2 (0.8)
Stage B	235	233	0	0	229	229	2 (0.9)	0
Stage C	10	10	0	0	8	8	1 (12.5)	0
Long-term immunogenicity	235	235	2 (0.9)	0	229	229	21 (9.2)	1 (0.4)

N = number of subjects in the analysis set for each column.

n = number of subjects in each particular category.

Total reportable = total number of subjects in the analysis set with ADA data.

% = percentage of subjects with sampling results 'positive' calculated relative to the total reportable number of subjects.

ADA positive: subjects who test positive at any time point after first administration of study during particular stage of study.

Long term immunogenicity: subjects who test positive at any time point after first administration of study during till Week 52 (Stage A and B combined)

At Baseline, no subjects enrolled in Study YLB113-002 tested positive for ADA. At Week 4, nine subjects (3.6% of 254) in the Enbrel group versus no subjects in the Rymti group tested ADA positive. At Week 8, nine patients in the Enbrel group (3.6% of 254, one neutralising antibodies (nAB)) and one patient (0.4% of 263) in the Rymti group. At Week 12, seven in the Enbrel group (2.8% of 254, two nAB) and one patient (0.4% of 263) in the Rymti group. At Week 24, none of the Rymti group and only one subject in the Enbrel arm (0.4% of 254) tested positive for ADA suggesting formation of ADA may have been transient. No clear relationship of ADA status by treatment group was seen in analysis of AEs of special interest including permanent treatment discontinuations, ISRs, hypersensitivity reactions and infection.

In Stages B and C of Study YLB113-002, includes immunogenicity results from Weeks 36, 44 and 52. In Stage B, two Enbrel treated subjects (0.9% of 229) but no Rymti patients recorded positive ADA but no nABs. One ADA positive Enbrel treated patient had a persistently positive ADA test at all time points in Stage B. In Stage C, only one Enbrel treated patient (12.5% of 8) developed ADA without nAB test at Week 36 that was subsequently negative at Weeks 44 and 52. An analysis of AEs of special interest (Stage A

events plus malignancy) and ADA status did not reveal any clear association between certain types of AEs and positive ADA status.

In Study YLB113-001, blood samples for immunogenicity testing were collected on Day 1 (prior to any investigational drug administration), as well as 21 days after each drug administration (or at the time of discontinuation from the trial if the subject prematurely withdrew). No subject tested positive for ADA in either treatment period of this trial. No immunogenicity testing was performed in Study LBC-14-155.

Other

There was no safety signal for renal toxicity, or electrocardiogram (ECG) abnormalities in the submission, consistent with the previous findings for etanercept. There were no pregnancies in the clinical trial programme. A higher incidence of AEs for infection was seen in elderly patients (> 65 years).

Post-marketing safety data

At the time the Delegate overview was written Rymti has not yet been approved or marketed in any country.

Clinical evaluators recommendation regarding authorisation

The clinical evaluator recommended approval of this biosimilar etanercept for all the approved indications of the reference product Enbrel, with the proposed dosing instructions that direct the prescriber to other etanercept products for patients weighing less than 62.5 kg.

Risk management plan

The sponsor has submitted draft EU-RMP version 0.3 (undated; data lock point (DLP) 28 August 2018) and Australian-specific Annex (ASA) version 0.1 (25 September 2018) in support of this application. In the response to the first round, the sponsor submitted EU-RMP version 0.3 (14 March 2019; DLP 28 August 2018) and ASA version 0.2 (28 May 2019). In the response to the second round, the sponsor submitted EU-RMP version 0.4 (30 June 2019; DLP 29 May 2019) and ASA version 0.3 (21 August 2019). Prior to ACM consideration, the sponsor withdrew the applications for the auto-injector presentation.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 9.[9]

[9] 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;

Table 9: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Malignancy (including lymphoma and leukaemia)	ü	ü	ü	–
	Serious and opportunistic infections (including tuberculosis, legionella, listeria and parasitic infections)	ü	ü	ü	ü *
	Lupus-like reactions	ü	ü	ü	–
	Sarcoidosis and/or granulomas	ü	ü	ü	–
	Allergic reactions	ü	ü	ü	–
	Severe cutaneous adverse reactions, including toxic epidermal necrolysis and Stevens Johnson Syndrome	ü	ü	ü	–
	Systemic vasculitis, including anti-neutrophil cytoplasmic antibodies positive vasculitis	ü	ü	ü	–
	Macrophage activation syndrome	ü	ü	ü	–
	Central demyelinating disorders	ü	ü	ü	–
	Peripheral demyelinating events (chronic inflammatory demyelinating polyneuropathy and Guillain Barré syndrome)	ü	ü	ü	–
	Aplastic anaemia and pancytopenia	ü	ü	ü	–
	Interstitial lung disease (including pulmonary fibrosis and pneumonitis)	ü	ü	ü	–
	Autoimmune hepatitis	ü	ü	ü	–
	Liver events in patients with viral hepatitis (including hepatitis B virus reactivation)	ü	ü	ü	–
	Change in morphology and/or severity of psoriasis in adult and paediatric populations	ü	ü	ü	–
	Congestive heart failure (CHF) in adult subjects	ü	ü	ü	ü *
	Inflammatory bowel disease in JIA subjects	ü	ü	ü	ü
Important potential risks	Autoimmune renal disease	ü	ü	–	–
	Pemphigus/pemphigoid	ü	ü	ü	–
	Amyotrophic lateral sclerosis	ü	ü	–	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Myasthenia gravis	ü	ü	–	–
	Encephalitis/ leukoencephalomyelitis	ü	ü	ü	–
	Progressive multifocal leukoencephalopathy	ü	ü	–	–
	Liver failure	ü	ü	ü	–
	Hepatic cirrhosis and fibrosis	ü	ü	ü	–
	Severe hypertensive reactions	ü	ü	–	–
	Adverse pregnancy outcomes	ü	ü	ü	–
	Potential for male infertility	ü	ü	ü	
	Impaired growth and development of juvenile subjects	ü	ü	ü	–
	Paediatric off-label use - administration to child or adolescent who weighs less than 62.5 kg	ü		ü	ü *
	Weight gain	ü	ü	–	–
	Acute ischaemic cardiovascular events in adult subjects	ü	ü	–	–
Missing information	None				

* Patient Alert Card

Routine pharmacovigilance measures are proposed. The sponsor has provided targeted follow-up questionnaires for the safety concerns identified during the European evaluation, and included non-melanoma skin cancer within the malignancy follow-up questionnaire.

The additional pharmacovigilance activity will recruit 1200 patients with a five year follow-up per patient within the German rheumatoid arthritis: observation of biologic therapy (RABBIT) patient registry to monitor all safety concerns.

Routine risk minimisation measures include the PI and CMI, which are generally consistent with the reference product, and Instructions for Use (IFU).

Additional risk minimisation in the form of a patient alert card is proposed to mitigate the risks of serious infections, congestive heart failure in adults, and administration to child or adolescent who weighs less than 62.5 kg.

The PI, CMI, IFU and the Patient Alert Card will be included in each carton.

The sponsor will no longer be obligated to supply the following additional risk minimisation tools (which are implemented for the reference product) to reduce medication errors, as the submission for auto-injection presentation has been withdrawn: teaching guide to facilitate training of the patients in the safe self-injection; a needle-free demonstration device; and instructional materials to share with patients.

Risk-benefit analysis

Delegate's considerations

This is the third biosimilar for etanercept. In general terms, the EU guidelines have been followed in the development program for this biosimilar however there are some challenges for this submission. The current proposal is to register a 25 mg and 50 mg PFS and the sponsor is claiming all indications that have been approved for the Australian reference product Enbrel.

Physicochemical similarity of Rymti/Etera with Australian Enbrel is a standard requirement, however to link all the clinical data presented for Rymti with Australian Enbrel multiple comparisons of similarity of Japanese, Indian and European versions of Enbrel with Australian Enbrel was necessary. With each comparison there is a degree of uncertainty, however the quality evaluator was satisfied the requirements were met. The quality evaluator however noted differences in the physicochemical characteristics of Rymti that were unlikely to have negative clinical consequence. These differences obviate the need for clinical data to support the submission.

The comparisons of the PKs of Enbrel and Rymti were conducted in Japan with the 25 mg strength and India with the 50 mg strength. While in each comparison Enbrel and Rymti had similar kinetics and could be considered bioequivalent, the subject populations differed with a lower clearance in the Japanese population resulting in a higher exposure and longer $T_{1/2}$ than seen in the Indian population. A population PK approach was used to explore this further. Simulations of the untested doses showed similar results for each population. Comparisons of historical outcomes for Enbrel showed the results for the Japanese population more closely aligned with European patients and Indian populations aligned more closely with US patients. Given the diversity of ethnicities within Australia this provides some reassurance that the PKs of Rymti should be generalisable to Australian patients receiving Enbrel.

The clinical trial was adequately powered, and had an acceptable primary endpoint for comparison. Adequate justification was provided for the equivalence margin although it is noted that ± 15% would be considered just within the acceptable limits from a clinical perspective. The confidence limits of the point estimate ratio for ACR20 for Rymti versus Enbrel was within those margins. The population demographics raise some challenges for generalisability to the Australian context given approximately half the patients were Japanese, however the aim of an equivalence trial in a biosimilar submission is to demonstrate therapeutic equivalence of the test and reference products.

The dosing of MTX received comment from the clinical evaluator. Lower median doses of MTX were given than are usually administered in the Australian clinical context. This is expected because the recommended starting dose in Japan is 6 to 8 mg/week with an escalation to 10 to 12 mg/week and a maximum of 16 mg/week which the Japanese guidelines note is tolerated by only about 30% of patients. Again, the aim of the study is to detect differences in efficacy that may be due to differences in the physicochemical characteristics of the etanercept versions rather than to assess the efficacy of etanercept as it may be used in the Australian context, noting etanercept is currently approved in Australia.

Other background therapies included NSAIDs and corticosteroids that could be down titrated according to patient response to the etanercept. While this is reasonable for the safety of the patients in the study and consistent with clinical practice, variations in background therapy add some uncertainty to the comparisons of the two etanercept products.

Of concern is the relatively high protocol deviation rate, which coupled with the early discontinuations reduces the power of the study to detect differences between the treatments. It is, however, noted the results from the per protocol analysis were in concordance with the primary analysis.

The primary endpoint of the study of ACR20 at Week 24 was met with the treatment difference of -5.6% and a 95% CI of -11.6%, 0.5%, within the pre-defined equivalence range of -15% to 15%. By geographic region the proportions of responders differed although the difference between the groups favoured Enbrel in Japan and Europe in similar proportions to the overall result of the study, noting the study was not powered for comparison between regions. The small number of Indian patients (16 in each treatment group) limit the interpretation of the data for this region. The results for ACR20, 50 and 70 were generally similar between the groups. For the DAS28 score of disease activity the main analysis at 24 were derived from pooled data from DAS28 calculated using either ESR or CRP depending on the investigator's nominated measure of acute phase reactant. The scales differ (lower scores can be seen in DAS28 CRP compared with DAS28 ESR for the same disease activity) so pooling limits the interpretation of the magnitude of the differences between the two treatments however a sensitivity analysis for the DAS28 calculated using each method were in general agreement. Other measures of disease activity were consistent with the primary endpoint. Efficacy data for the Stage B of the pivotal study were not provided in the submission, and although a summary of the data show the efficacy is generally sustained over a 52 week period these data were not fully evaluated. The switching part of the study Stage C is very small and the results are inconclusive.

The safety profile of etanercept is well established. The Stages A and B provide safety data up to Week 52. The data mainly show differences in injection site reactions of various types with higher rates with Enbrel, although the rates seen for Enbrel in the pivotal study are similar to or lower than those reported in the PI for Enbrel. The immunogenicity data interpretation is challenges by the use of two assays at different points in the clinical development program. A highly sensitive drug insensitive assay used for the immunogenicity analysis in the pivotal study showed a significantly lower rate of ADA formation, particularly in the first 24 weeks of therapy, and few patients developed nAB. The formation of ADA does not appear to have an impact on efficacy, but it is unclear whether there is any contribution to the differences in ISR. Another difference between Enbrel and Rymti is the latex cover on the needle of Enbrel, which may also have contributed to injection site reactions.

As noted above, the sponsor proposes to extrapolate the findings of the study to all indications based on a common mechanism of action of etanercept in all indications: a binding of soluble TNF to cell surface receptors and through binding transmembrane TNF, inhibiting subsequent signal transduction and adhesion molecule expression. The sponsor provided a rationale and justification around the use of the RA model as suitably sensitive model for the indications requested that was considered acceptable by the clinical evaluator. RA has been previously accepted as a suitable model for assessing the therapeutic equivalence of biosimilar TNF inhibitors and the rationale based on mechanism is reasonable and acceptable.

The indications proposed include radiographic claims. The inclusion of the radiographic claims has been justified on the basis of the consistency of the reduction in other markers

of clinical disease activity that would equate with a reduction in risk of bony erosion and joint destruction and has been accepted by the clinical evaluator.

The indications proposed include monotherapy based on the mechanism of action and that monotherapy has been demonstrated for etanercept. There is no indication in the submission that Rymti would behave differently in the monotherapy setting, therefore this proposal is considered reasonable.

The indications proposed include the paediatric indications for etanercept however the full dosing for these indications is not possible because the sponsor only proposes to register the fixed dose PFS for each strength. These syringes are not graduated and are intended for delivery of the full dose. The paediatric indications are dosed according to weight, so for the majority of children the proposed 25 mg and 50 mg strengths are unsuitable. In the indications section of the proposed Rymti PI the sponsor proposes to limit the use of Rymti for the paediatric indications to children and adolescents who weight > 62.5 kg. This would seem reasonable given the constraints of the chosen strengths. The currently proposed dosing instructions have some inconsistency with this limitation of the paediatric indications by weight however these could be easily amended by the sponsor.

The artwork of the cartons proposed is unacceptable from a clinical perspective. Although generally compliant with the labelling order the colour scheme and two of the three dimensions of the cartons are identical by strength. These products will be stored in a pharmacy refrigerator rather than on a shelf. There is the potential for confusion and medication error because of their similarity. In addition, there are no stability data to support any temperature excursions if an error were to be detected. The 25°C stability data are for a one time removal from refrigeration only. The sponsor should address this issue in the pre-Advisory Committee on Medicines (ACM) response.

Proposed action

Subject to the ACM's advice and the sponsor's responses to questions no specific issues are identified that indicate a negative benefit risk profile for Rymti and that would preclude registration.

Questions for sponsor

1. ***Please provide an update on the international regulatory status of Rymti internationally. Please include in your response an account of issues raised by the EMA and how the sponsor has or proposes to address those issues.***

As requested, the international regulatory status of Rymti is provided in Table 10. The same is also provided in the updated sequence 0003 section 1.11; foreign regulatory information section.[10]

[10] Inclusion of these is beyond the scope of the AusPAR.

Table 10: International regulatory status of Rymti

Country	Product Name	Submission Date	Current Status	Approved Indications
Japan	Etanercept BS PFS: • 10 mg/ml • 25 mg/0.5 ml • 50 mg/ml Etanercept BS PFP: • 50 mg/ml	March 2018	Approved March 2019	• Rheumatoid arthritis (including prevention of structural damage of joints) insufficiently effective in existing treatments. • Juvenile idiopathic arthritis with multi-joint activity with insufficient effect in existing treatment
EU [Information redacted]	Nepexto (Etanercept) PFS: • 25 mg/0.5 ml • 50 mg/ml Nepexto (Etanercept) PFP: • 50 mg/ml	April 2018	[Information redacted]	Under consideration
India	Rymti/Nepexto/Etera (Etanercept) PFS: • 25 mg/0.5 ml • 50 mg/ml Rymti/Nepexto/Etera (Etanercept) PFP • 50 mg/ml	August 2018	Approved March 2019	• Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), • Ankylosing Spondylitis (AS), Nonradiographic Axial Spondyloarthritis (nr- • AxSpA), Plaque Psoriasis (PsO), Pediatric Plaque Psoriasis and Juvenile • Idiopathic Arthritis (JIA)

BS: Biosimilar

Deferrals, withdrawals and rejections: none. Assurance is given that this application has not been refused for market approval or withdrawn in any region or country.

The account of issues (outstanding) raised by EMA and their addressal is provided under the sponsor's response to question 2.

2. Please briefly outline the issues raised by the EMA and how the sponsor proposes to address these.

Lupin received questions from the Committee For Medicinal Products For Human Use (CHMP) as part of the second Day 180 list of outstanding issues. The issues raised by the EMA during the second set of Day 180 list of outstanding issues are provided below, along with sponsor's responses for their resolution:

[Information redacted]

3. Please provide amended artwork to address Delegate and the RMP evaluator share concern regarding the potential for medication errors because of the similarity of the cartons proposed for the 25 mg and 50 mg strengths.

As per the Delegate's and RMP evaluator's request, the sponsor has amended the carton and label proposed for the 50 mg strength to a different colour tone to avoid potential medication errors. Clean and annotated copies of the amended 50 mg strength artwork is provided under section 1.3.1 in sponsor submitted dossier.[10]

4. Is the sponsor undertaking further studies of the stability of the Rymti formulation to establish whether an in use temperature excursion can be permitted?

The sponsor provides the assurance that, stability study is already in progress to support the in use temperature excursion covering the duration up to end of shelf life (that is 24 months) with temperature excursion at 1, 12, 18 and 24 months' time points at 25.0 ± 2.0°C / 60.0 ± 5.0 % relative humidity (RH). The sponsor also would like to inform the agency that results from 12 months stability time point after the temperature excursions at one month and 12 months (two points temperature excursion) has already been submitted, as a reply to question 20 of the quality evaluation report, in the response to a TGA request for information submitted 30 May 2019.

The sponsor additionally provides a commitment to submit the results of this study up to the end of shelf life, 24 months data, as a post approval activity using an appropriate variation route.

Furthermore, we would like to inform the agency that currently, 18 months temperature excursion data is completed with three times point of temperature excursion at one, 12 and 18 months. This data can be submitted to the agency upon request.

Request for Advisory Committee on Medicines

The Delegate requested advice from ACM with the following questions.

1. Please comment on the clinical trial evidence presented to support the efficacy and safety of Rymti, including whether sufficient data have been presented. Does the committee have any specific concerns about the approach of the sponsor?
2. Switching statements are not routinely included in the PI for biosimilars. Does the committee have any concerns about the data on switching between Rymti and Enbrel? Is the precautionary statement warranted?
3. 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.

Advisory Committee considerations[11]

The ACM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

[11] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (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 January 2010. ACM encompass 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.

1. ***Please comment on the clinical trial evidence presented to support the efficacy and safety of Rymti, including whether sufficient data have been presented. Does the committee have any specific concerns about the approach of the sponsor?***

The ACM was of the view that the supporting evidence for safety of Rymti was adequate, but less robust than the data supplied for other applications of a similar nature. The ACM noted that in the sponsor's pre-ACM response, the sponsor has undertaken the conduct of a further study to address concerns about misfold levels of the etanercept investigation medicinal product for the EMA, and agrees with the Delegate that this data should also be supplied to the TGA for consideration. Despite this, the ACM agreed overall that the data provided fulfils the EU criteria for biosimilar products and adequately supports the efficacy of the product.

2. ***Switching statements are not routinely included in the PI for biosimilars. Does the committee have any concerns about the data on switching between Rymti and Enbrel? Is the precautionary statement warranted?***

The ACM noted that numerous small differences existed in terms of quality and manufacturing between Rymti and other etanercept products. The ACM expressed concern that, as the number of biosimilar products increases, each with small and distinct differences from the originator, there is a theoretical risk that switching between multiple products could compound the effect of those differences, leading to unanticipated therapeutic effects. However, the ACM concluded that, as limited switching data have been provided in the dossier, there is limited evidence to show that switching between Rymti and other etanercept products would adversely impact treatment outcomes. For this reason, the ACM expressed support for the sponsor's proposal for inclusion of a switching statement that outlines the limitations of the data in the precautions section of the PI on this occasion, although a switching statement is not routinely required for biosimilars.

3. ***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.***

The ACM discussed the use of Rymti in paediatric patients despite the population not being included in the clinical studies. The ACM was concerned the product as presented is not suitable for use in weight based dosing for younger children. The ACM was of the view that while use in younger children was not recommended, it was reasonable to support the use of Rymti in adolescents provided their weight exceeds 62.5 kilograms.

General advice

The ACM noted the sponsor's withdrawal of its request for registration of the auto-injector pen late in the submission. The ACM was of the view that enabling the product to be self administered using an auto-injector pen would be highly desirable and that the sponsor should be encouraged to address any impediments to the registration of Rymti in such a dose form.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Rymti/Etera for 25 mg and 50 mg for subcutaneous injection, 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). Rymti/Etera can be used in combination with methotrexate.

Severe, active RA 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. Etanercept 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 (AS) in adults.

Non-radiographic axial spondyloarthritis

Treatment of adults with active; non-radiographic axial spondyloarthritis (nr-axial SpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) change who have had an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs).*

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

Children and adolescents

Children and adolescents weighing less than 62.5 kg should not receive Rymti, Etera. These patients should be accurately dosed on a mg/kg basis with other etanercept products.[2]

Juvenile idiopathic arthritis

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

Active extended oligoarthritis in children and adolescents, aged two 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 two years.

Paediatric plaque psoriasis

Chronic, severe plaque psoriasis in children and adolescents from four 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 psoriasis area and severity index (PASI) response is not achieved.

Specific conditions of registration applying to these goods

- All batches of Rymti/Etera (etanercept) imported into or manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the certified product details (CPD).

  The CPD, as described in Guidance 7: certified product details of the Australian regulatory guidelines for prescription medicines (ARGPM) (http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self assessable change.

- Up to five initial batches of Rymti/Etera (etanercept) imported into or 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. Outcomes of laboratory testing are published biannually in the TGA database of laboratory testing results http://www.tga.gov.au/ws-labs-index.

  This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until sponsor are notified in writing of any variation.

- The following clinical study report must be submitted to the TGA, as soon as possible after completion, for evaluation as Category 1 submission: Study CTRI/2019/01/016851.

- The etanercept EU-RMP (version 0.4, dated 20 June 2019, data lock point 29 May 2019), with Australian specific annex (version 0.3, dated 21 August 2019), included with submission PM-2018-03223-1-3, and any subsequent revisions, as agreed with the TA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the EMA's guideline on Good Pharmacovigilance Practices (GVP) Module VII periodic safety update report (Rev 1), Part VII.B structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Rymti 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>. The PI for Etera is identical except for the product name.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au