Amsterdam, 26 February 2026
EMADOC-1829012207-29317
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fubelv

International non-proprietary name: Etanercept

Procedure No. EMEA/H/C/006738/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

List of abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of variance
AS	Ankylosing spondylitis
AUC	Area under the curve
BMI	Body mass index
BW	Body weight
CHF	Congestive heart failure
CHMP	Committee for Human Medicinal Products
CHO	Chinese Hamster Ovary
CI	Confidence Interval
Cmax	Maximum concentration
CRP	C-reactive protein
CSR	Clinical study report
CV	Cardiovascular
DAS	Disease Activity Score
DMARD	Disease-modifying anti-rheumatic drug
DP	Drug product
DS	Drug substance
DSC	Differential scanning calorimeter
ECG	Electrocardiogram
ECL	Electro-chemiluminescence
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPCB	End of production cell bank
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League against rheumatism
FAS	Full analysis set
Fc	Fragment crystallizable
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
h	hour
HAQ-DI	Health Assessment Questionnaire- Disability Index
HBV	Hepatitis B virus
HCP	Host cell protein
HMW	High Molecular Weight
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation
IGA	Investigator’s Global Assessment
IgG1	Immunoglobulin G1
INN	International Nonproprietary Name
ITT	Intention-to-treat
JIA	Juvenile idiopathic arthritis
Kel	Constant of elimination
kg	Kilogram
LIVCA	Limit of in vitro cell age
LMW	Low Molecular Weight
MAA	Marketing Authorisation Application
MCB	Master Cell Bank

mg	Milligram
MOR	Maximum operating range
MTX	Methotrexate
N	Number of Patients
nAB	Neutralizing Antibodies
NOR	Normal operating range
NRI	Non-response imputation
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAR	Proven Acceptable Range
PC	Placebo-controlled
PD	Pharmacodynamics
PFP	Pre-filled pen
PFS	Pre-filled syringe
PPS	Per-protocol set
PQR	Product quality review
PS	Plaque Psoriasis
PsA	Psoriatic Arthritis
RA	Rheumatoid arthritis
RMP	Reference Medicinal Product
RND	Subjects randomized set
SA	Scientific Advice
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Standard deviation
SDM	Scale down model
SE	Standard error
SEC	Size exclusion chromatography
SJC	Swollen Joint Count
SmPC	Summary of Product Characteristics
SpA	Spondyloarthropathy
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TFF	Tangential flow filtration
TJC	Tender Joint Count
Tmax	Time to maximum plasma concentration
TNFR	Tumour Necrosis Factor Receptor
TNFα	Tumour Necrosis Factor alpha
VAS	Visual Analogue Scale
Vd	Volume of distribution
WCB	Working Cell Bank

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Fubelv
Active substance	Etanercept
INN or common name	Etanercept
Applicant	Biosimilar Collaborations Ireland Limited Unit 35/36 Grange Parade Baldoyle Industrial Estate Dublin 13 D13 R20R IRELAND
EMA product number	EMEA/H/C/006738
ATC code and pharmacotherapeutic group	L04AB01 L2: l04 immunosuppressants, L3: l04a immunosuppressants, L4: l04ab tumor necrosis factor alpha (tnf-alpha) inhibitors
Pharmaceutical form(s) and strength (s)	Solution for injection 25 mg and 50 mg
Packaging	pre-filled syringe (glass) and pre-filled syringe (glass) in a pre-filled pen
Package size(s)	12 pre-filled pens, 12 pre-filled syringes, 24 (2 x 12) pre-filled syringes (multipack), 4 pre-filled pens, 4 pre-filled syringes and 8 (2 x 4) pre-filled syringes (multipack)
Route of administration	Subcutaneous use
Device or diagnostic	Fubelv 25 and 50 mg solution for injection in pre-filled syringe. The syringe is made from clear type 1 glass with a stainless steel 27-gauge needle with rigid needle shield and FluroTec coated bromobutyl rubber stopper containing 0.5 or 1 ml of solution. Fubelv 50 mg solution for injection in pre-filled pen. Pre-filled pen containing a pre-filled syringe of Fubelv.
Orphan designation	N
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation	Standard

Product data	
granted at opinion	
Legal basis	Article 10(4) of Directive 2001/83/EC
Final indication	<u>Rheumatoid arthritis</u> Fubelv in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate. Fubelv can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Fubelv is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Fubelv, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function. <u>Juvenile idiopathic arthritis</u> Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy. <u>Psoriatic arthritis</u> Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease- modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease. <u>Axial spondyloarthritis</u> *Ankylosing spondylitis* Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Product data	
	Non-radiographic axial spondyloarthritis Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs). Plaque psoriasis Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1). Paediatric plaque psoriasis Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.
New active substance status	Not applied for

1.2. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	*Topic (quality/ non-clinical/ clinical)*	*Reference number / Coordinator(s)*	*Brief summary of the advice*
20 November 2014	Quality, Non-clinical and Clinical.	EMEA/H/SA/ 2891/1/2014 /III	The Scientific advice pertained to the following quality, non-clinical, and clinical aspects: • the quality of the product that will be used in the planned Phase III clinical studies; • the completeness of the non-clinical programme conducted to date; and, • specific elements regarding the design of the Phase III study, including endpoints, immunogenicity data, and study population.

1.3. Eligibility to the centralised procedure

The applicant Biosimilar Collaborations Ireland Limited submitted on 29 July 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Fubelv (etanercept), through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Rheumatoid arthritis

Fubelv in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Fubelv can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Fubelv is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Fubelv, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis

Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

1.4. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products

The application submitted is composed of administrative information, complete quality data, and appropriate non-clinical and clinical data for a similar biological medicinal product.

This application is submitted as a multiple of Nepexto authorised on 20 May 2020 in accordance with Article 82.1 of Regulation (EC) No 726/2004.The chosen reference product is:

Medicinal product which is or has been authorised in accordance with European Union provisions in force for not less than 8 years in the EEA:

Product name, strength, pharmaceutical form:	Enbrel 25 mg solution for injection in pre-filled syringe Enbrel 50 mg solution for injection in pre-filled syringe Enbrel 50 mg solution for injection in pre-filled pen
Marketing authorisation holder:	Pfizer Limited
Date of authorisation:	03 February 2000
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/99/126

Medicinal product authorised in the European Union/Member States where the application is made for European reference medicinal product:

Product name, strength, pharmaceutical form:	Enbrel 25 mg solution for injection in pre-filled syringe Enbrel 50 mg solution for injection in pre-filled syringe Enbrel 50 mg solution for injection in pre-filled pen

Marketing authorisation holder:	Pfizer Limited
Date of authorisation:	03 February 2000
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/99/126

Medicinal product which is or has been authorised in accordance with European Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Product name, strength, pharmaceutical form:	Enbrel 25 mg solution for injection in pre-filled syringe Enbrel 50 mg solution for injection in pre-filled syringe Enbrel 50 mg solution for injection in pre-filled pen
Marketing authorisation holder:	Pfizer Limited
Date of authorisation:	03 February 2000
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/99/126

1.5. Information on paediatrics

Not applicable.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

rapporteur:	Janet Koenig
Co-rapporteur:	Ewa Balkowiec Iskra

The appointed CHMP Co-rapporteur had no prominent role in scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	29 July 2025
The procedure started on	18 August 2025
The CHMP rapporteur's first assessment report was received on	23 September 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	N/A
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	23 September 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	2 October 2025
The Biologics working party agreed on the Assessment Overview during their meeting on	8 October 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	16 October 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 January 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	12 February 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The Biologics working party agreed on the Assessment Overview during their meeting on	18 February 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fubelv on	26 February 2026

1.8. CHMP outcome

1.8.1. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Fubelv is favourable in the following indication(s):

Rheumatoid arthritis

Fubelv in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Fubelv can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Fubelv is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Fubelv, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who

have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis

Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.8.2. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Fubelv is considered biosimilar to Enbrel EU. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

1.8.3. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.8.4. Other conditions and requirements of the marketing authorisation

1.8.4.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

1.8.5. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.8.5.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.8.5.2. Additional risk minimisation measures

The MAH shall ensure that a patient reminder card regarding serious infections is implemented.

1.8.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

2.1. Therapeutic context

Fubelv, containing the active substance etanercept was developed as a biosimilar to the reference medicinal product Enbrel (etanercept).

The applicant applied for the same therapeutic indications as for Enbrel: moderate to severe rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis (non-radiographic axial spondyloarthritis), plaque psoriasis and paediatric plaque psoriasis.

2.2. Aspects of development

Fubelv was developed with the following strength and presentation:

- Fubelv 25 mg solution for injection in pre-filled syringe
- Fubelv 50 mg solution for injection in pre-filled syringe
- Fubelv 50 mg solution for injection in pre-filled pen

Nepexto was approved trough the centralised procedure on 20 May 2020. Fubelv is a duplicate application of the same product for co-marketing reasons.

2.3. Description of the product

Fubelv (etanercept) is a proposed biosimilar to Enbrel and a duplicate of Nepexto.

Etanercept is a recombinant human tumour necrosis factor receptor p75 Fc fusion protein. It interferes with the soluble TNF-α by mimicking the inhibitory effects of naturally occurring soluble TNF receptors that deactivate TNF-α and therefore down-regulate immune responses.

Fubelv is presented in single-use pre-filled syringes containing 25 mg or 50 mg etanercept and in pre-filled pen containing 50 mg etanercept to be administered via subcutaneous (SC) injection. The applicant did not apply for the paediatric formulation, 10 mg powder and solvent for solution for injection.

The recommended dose of etanercept is 25 mg administered twice weekly or 50 mg administered once weekly. For paediatric patients, the dosage is based on body weight. Since the proposed pre-filled syringe and pen presentations do not have scaled unit indications, these formulations are not suitable for flexible dosing per kg body weight (BW). Paediatric patients who require a dose other than a full 25 mg or 50 mg should not receive Fubelv. If an alternate dose is required, other etanercept products offering such an option should be used.

2.4. Inspection issues.

2.4.1. Good manufacturing practice (GMP) inspection(s)

A pre-approval GMP inspection was conducted for the active substance and finished product manufacturing site at Lupin Limited (Biotech Division), India. Conformance with EU GMP requirements has been confirmed. No further inspection is required to verify GMP compliance.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection is required to verify GLP compliance.

2.4.3. Good clinical practice (GCP) inspection(s)

A routine GCP inspection was carried out at two clinical sites of the pivotal phase III study YLB113-002. In addition, during the clock-stop of the Nepexto application, a triggered GCP inspection was performed for the clinical and analytical sites of the phase I study ETA.50/334 in order to verify the newly submitted pharmacokinetics data. It was concluded that the results of both GCP inspections were of sufficient quality to be used for the evaluation of the application. No further inspection is required to verify GCP compliance.

3. Quality aspects

3.1. Introduction

3.2. Introduction

Fubelv is a sterile, clear to opalescent and colourless to yellow liquid for subcutaneous administration presented as:

- 50 mg/ml of etanercept solution for injection in 1 ml pre-filled syringe (PFS)

- 25 mg/0.5 ml of etanercept solution for injection in 1 ml PFS

- 50 mg/ml of etanercept solution for injection in a disposable 1 ml pre-filled pen (PFP).

Other ingredients are sodium citrate, sodium dihydrogen phosphate dihydrate, glycine, sucrose, sodium chloride and water for injections.

The product is available as a pre-filled syringe which consists of a non-graduated clear type I glass with fluorotec-coated bromobutyl rubber stopper. The disposable pen is made by assembling the pre-filled syringe with the sub-assembly pen components.

Fubelv has been developed as biosimilar medicinal product to the reference product Enbrel.

3.3. Active substance

3.3.1. General information

The active substance, etanercept (INN), is a recombinant dimeric protein consisting of two soluble p75 TNFR (sTNFR2) molecules fused to the Fc fragment of human IgG1. The fusion protein is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. Etanercept consists of 934 amino acids and has an apparent molecular weight of approximately 150 kDa. The protein contains the IgG1-specific N-glycosylation sites, and the TNFR-related N-glycosylation sites and multiple O-glycosylation sites in the receptor portion. 29 disulphide bonds are present in the correctly folded molecule.

3.3.2. Manufacture, process controls and process development

The active substance is manufactured at Lupin Limited (Biotech division), Gat No. 1156, 1157, 1158, 1159 and 1160, Village Ghotawade, Taluka Mulshi, Dist. Pune – 412 115, Maharashtra, India. Satisfactory evidence of GMP compliance has been presented.

Etanercept is recombinantly expressed by CHO cells.

The active substance manufacturing process is a conventional process starting with the inoculum build-up based on one vial of working cell bank (WCB), comprising six stages of culture expansion using defined serum-free media with addition of methotrexate. Then, the main fermenter is inoculated and run in a fed-batch mode up to the harvest. The subsequent downstream process includes purification through a series of chromatographic steps and a refolding step, virus inactivation and filtration steps.

After the first chromatography step (affinity chromatography, protein A resin) the eluate is subjected to low pH treatment for viral inactivation and neutralisation. Further it is followed by refolding step to

convert product related variant (misfolded) to main form. Subsequent steps include hydrophobic interaction chromatography, followed by anion exchange chromatography. The last chromatography step (mixed mode) is run in the negative binding mode, i.e. etanercept is in the flow-through. The flow through is subjected to virus filtration followed by tangential flow filtration (TFF) for buffer exchange and concentration of the active substance. The final active substance is formulated with sucrose and stored in glass bottles at 2-8°C.

A satisfactory level of detail has been included in the process description.

Control of materials

The target fusion protein TNFR:Fc is expressed in a CHO-dhfr cell line. Sufficient information on the host cell line in terms of origin, culture and storage conditions has been provided. The generation of the expression plasmid has been described in sufficient detail and information on the generation of the parental cell line has also been provided.

Additional experiments have been carried out to demonstrate the clonality and genetic stability of the cell line. The cloning strategy has been sufficiently described.

A two-tiered cell bank system, comprising master cell bank (MCB) and WCB was established. Release specifications and characterisation data of MCB and WCB were provided. Adequate tests to confirm the genetic stability of the MCB and end of production cell bank (EPCB) have been performed. A protocol for future qualification of new WCBs has been provided.

A scale down production process was used to analyse end of production cells. The limit of in vitro cell age (LIVCA) for production is defined. Representativeness of scale down study for the production process is considered demonstrated and stability of EPCB is considered confirmed.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented.

Control of critical steps and intermediates

Critical and non-critical process parameters have been identified based on risk assessments and process characterisation studies. In-process controls and monitoring are employed to ensure product consistency. Safety relevant steps for the control of adventitious agents are largely controlled by critical process parameters and in-process controls.

In addition to the PARs (proven acceptance ranges), the Applicant states NORs (normal operating ranges) and MORs (maximum operating ranges) within the PARs. The actions taken, if the process is operated beyond the respective limits, have been clearly stated.

Overall, the proposed process control strategy is considered acceptable.

Process validation

The process validation batches were manufactured to demonstrate consistency of the process when run applying the defined NORs. In addition to the routinely performed in-process controls, additional tests were scheduled as per process validation protocol. The additional tests were performed to monitor depletion of misfolded forms, oxidised variants, host cell proteins (HCP), DNA, and residual protein A. The process parameters were held within the ranges as defined by NORs. The resulting active substance complied with the proposed specification.

The criticality classification has been revised after the process validation. To demonstrate that the process validation batches still comply with the revised control strategy, the Applicant has submitted comparative tables on in-process controls, in-process tests (for the upstream process) and testing of

quality attributes (for the down-stream process intermediates) of the process validation batches versus "consistency batches" that were manufactured according to the revised control strategy. These data support that the process was not altered by the revision of the control strategy, and that the process can be considered in a validated state.

Product Quality Reviews (PQR) of the last two years have been provided. The data provided support process consistency.

The process capabilities in depletion of some of the process related impurities has been demonstrated with spiking studies. DNA, HCP, and residual protein A are routinely tested at active substance release. Thus, additional information on the depletion studies is not considered necessary.

Upstream and downstream batch size is appropriately defined.

Manufacturing process development

Fubelv was developed as biosimilar to Enbrel. The process development, including several process versions, has been described. Changes during development include process optimizations and scale up. An analytical comparability study was performed, and no considerable differences were observed; to address residual uncertainty an additional PK study using the proposed commercial product has been performed.

All manufacturing extensions were adequately supported by respective comparability studies.

3.3.3. Characterisation and impurities

The etanercept active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a recombinant dimeric protein. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities.

Introduction of a refolding step established the molecular basis for correlation of biological activity with correctly folded (disulfide-bonded) molecules.

Criticality assessment was used to decide upon the need to perform clearance studies for process- and product-related impurities. Following this pre-assessment some clearance studies were conducted for HCP, HC DNA, media components, antifoam C, viruses, High Molecular Weight (HMW) forms, misfolded and degraded forms. Overall, no problems arise from residuals in the active substance as these are either cleared to acceptable/sufficient levels or/and are controlled at release of the active substance.

In summary, the characterisation is considered appropriate for this type of molecule.

3.3.4. Control of active substance

The active substance specification contains the following parameters: appearance/colour/clarity pH, identification, assay, purity, conformational variants, bacterial endotoxins test, quantitation of host-cell-derived protein, quantitation of host-cell derived DNA, quantitation of residual protein A, bioburden test, relative density, N-Glycan analysis, sialic acid analysis and TNF-α binding ELISA. The active substance specification is considered acceptable.

Analytical procedures and reference standards

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

The Applicant has provided batch data for 55 active substance lots from different scales and versions of the manufacturing process. The results were within specifications and confirm consistency of manufacturing process.

Reference materials

The approach to qualify in-house primary and secondary reference standards is acceptable. The provided specifications for qualification of reference standards (in-house primary and secondary reference standard) are based on the agreed ranges for quality attributes of etanercept.

3.3.5. Stability

The proposed shelf life of the active substance is 24 months when stored at 2 - 8°C.

Etanercept active substance is stored in reduced size container closure, Ph. Eur./USP type I glass, screw capped depyrogenated vials. The material of construction is similar to that of the actual active storage container.

The analytical methods used for stability testing are stability-indicating and the same as for release.

The applicant has provided long-term stability data from six stability studies, covering multiple development and commercial scale batches. Data for up to 60 months is available.

All batches were stable at accelerated conditions (25°C ± 2°C; 60 ± 5% RH).

Data from thermal stress studies at 40 °C ± 2°C have also been provided.

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

3.4. Finished medicinal product

3.4.1. Description of the product and pharmaceutical development

Description *the product*

Fubelv finished product is a sterile, clear to opalescent and colourless to yellow liquid for subcutaneous administration and is formulated at pH 6.3 ± 0.2. Fubelv is presented as:

- 50 mg/ml of etanercept solution for injection in 1 ml pre-filled syringe (PFS)

- 25 mg/0.5 ml of etanercept solution for injection in 1 ml PFS

- 50 mg/ml of etanercept solution for injection in a disposable 1 ml pre-filled pen (PFP).

Pharmaceutical development

Fubelv finished product consists of Etanercept as active substance and excipients are glycine, trisodium citrate dihydrate, sodium dihydrogen phosphate dihydrate, sucrose, sodium chloride and water for injections.

The function of all formulation components is indicated and found acceptable. All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. Due to patent constraints a new etanercept

formulation different to the reference product Enbrel was developed. Based on the results of appropriate formulation development studies, finally arginine was replaced by glycine and di-sodium hydrogen phosphate dihydrate by sodium citrate. This formulation was demonstrated to ensure satisfactory stability of etanercept.

Manufacturing process development

During finished product manufacturing process development, the Applicant sufficiently evaluated the individual finished product manufacturing steps and their impact on product quality. Appropriate studies were conducted to confirm the compatibility between the finished product solution and the equipment used in the manufacturing process. Furthermore, the filters utilised for bulk filtration were appropriately validated with respect to bubble point, compatibility with the bulk product, bacterial retention capacity, potential adsorption of the active substance as well as extractables and leachables. The target fill volumes were appropriately evaluated for the filling process and are considered justified. Moreover, the integrity of the PFS after insertion of the plunger stopper was satisfactorily demonstrated by appropriate leakage tests. Finally, it was shown that freeze thaw cycles do not compromise Fubelv quality.

Extractables and leachables of the primary packaging were adequately studied by use of a set of analytical methods. The results confirm that no relevant leaching occurs which might affect the safety or quality of the finished product up to its end of shelf life.

The primary packaging is clear type I glass with a fluorotec-coated bromobutyl rubber stopper. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Container closure

The components of the primary packaging are a glass syringe (clear type I glass) with a staked stainless steel 27-gauge needle and a rigid needle shield consisting of a polyisoprene rubber and a polypropylene shield. Fluorotec coated bromobutyl rubber is used as plunger stopper. The components are purchased pre-sterilised. The sterilisation procedures and the manufacturers responsible for the sterilisation are stated. Furthermore, it is confirmed that sterilisation is conducted in line with the respective ISO standards.

Appropriate information on the disposable pen is presented which confirms conformance of the pen with the essential requirements of medical device legislation. It was further demonstrated that the pen complies with the requirements of the relevant quality standards (ISO 116081 and ISO 11608-5) with regard to functionality. The essential pen performance parameters are included in the pen specification and are routinely monitored at release and in the stability studies. The designed pen contains appropriate visual and audible features to assist the patients for proper handling. It is reported that the pen design was verified by Human Factor Studies with patients suffering from Rheumatoid Arthritis.

A major objection was raised during the procedure due to the absence of Notified Body Opinions for the PFS and PFP. The requested Notified Body Opinions have subsequently been provided, and the major objection is therefore considered satisfactorily resolved.

3.4.2. Manufacture of the product and process controls

Batch release is carried out by Biosimilar, Collaborations Ireland Limited, Block B, The Crescent Building, Santry Demesne Dublin, D09 C6X8, Ireland. Satisfactory evidence of GMP compliance has been presented for all sites involved in the manufacture, control and batch release of the finished

product.

The finished product manufacturing process consists of dispensing active substance lots, filtration and filling of the bulk solution into the syringes. The finished product manufacturing process is described with sufficient detail.

Holding times during the manufacturing operation are justified based on development data, as well as duration times for mixing, filtration and filling. Critical process parameters are defined. Their operating ranges were adequately evaluated by process characterisation studies. The classification of the process parameters according to their criticality is sufficiently justified.

Pre- and post-filtration filter integrity tests are conducted and their classification is justified.

Process validation was performed at both manufacturing sites using full scale consecutive batches of PFS and PFP. All samples collected across the manufacturing process and tested met the predefined acceptance criteria. Additional parameters that were measured for process validation purposes were also within the specified ranges. Validation data are also presented for the PFP assembly process. The results confirm consistent pen quality in terms of appearance and performance. Moreover, the aseptic part of the manufacturing process is adequately validated by media fill. Overall, the validation data demonstrate that the manufacturing processes are capable to consistently produce Fubelv PFS and PFP of intended quality.

3.4.3. Control of Finished Product

The specifications for the finished product include test parameters on appearance/colour/clarity (visual inspection), pH, extractable volume, osmolality, sub-visible particles, identification, assay (protein content, in vitro cell-based bioassay, potency, purity, conformational variants, bacterial endotoxins test, sterility, foreign insoluble matter and TNF-α binding ELISA. Pre-filled pen presentations additionally contain the following specifications: dose accuracy and functional characteristics.

The proposed finished product specification is adequate for a satisfactory control of the sterile finished product solution. All acceptance criteria have been appropriately justified. The in-house analytical procedures have been sufficiently described.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

During the procedure, a major objection was raised as the presented Nitrosamines Risk Assessment was not in line with the last version of the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" and not all potential sources of nitrosamines were discussed. In response the Applicant presented an updated risk assessment on the relevance of the potential source of nitrosamines in the finished product (raw materials & excipients used in processing, manufacturing process, packaging components and packaging materials etc.). Although the presence of substances (ammonia/ammonium) that could produce very small amounts of amines in the syringe stopper was confirmed, nitrites (NO2-), nitrates (NO3-), nitric acid or azide (N3-) were not present. Therefore, there is no possibility that N-nitrosamine is formed. For excipients used in formulation, sodium chloride has traces of nitrite (NO2-), trisodium citrate dihydrate and glycine have traces of ammonium. However, considering their amount in the final formulation, the presence of nitrosamine impurities is negligible. The updated nitrosamine risk assessment is considered satisfactory and the major objection is therefore resolved. Based on the information provided it is accepted that no risk was

identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical procedures and reference standards

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data of 53 finished product batches, covering various scales, were provided. Release results of finished product batches have been presented covering all strengths and presentations. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

An International reference standard (Compendial or International Bureau Standard) was not available for Etanercept. Therefore, the Reference product (Enbrel) was used as reference standard for all the tests during the initial stages of product development. Following that, the internal reference standard was prepared and qualified against the international reference standard (BRP) for potency assay.

3.4.4. Stability of the product

A shelf life of 36 months at 2°C - 8°C is claimed for the finished product.

Stability data from PFS 50 mg/mL batches representative of the proposed commercial finished product are available covering the proposed shelf life of 36 months. All these batches contain active substance from different lots. The stability data provided is sufficient to provide evidence on PFS 50 mg/mL stability. This data also supports PFP shelf life of 36 months as the stability results of the physicochemical parameters of the PFS are considered representative for the PFP. For the PFS 25 mg/0.5 mL data from two stability batches has initially been presented, one of them only for 12 months. However, a shelf life of 36 months is accepted for PFS 25 mg/0.5 mL based on data of the 50 mg/mL strength as the two presentations do not differ in protein concentration but only in fill volume.

Multiple batches of finished product manufactured at the commercial manufacturing sites have also been introduced into the stability studies, for PFS 25 mg/0.5 mL and PFS 50 mg/mL. All batches were manufactured by using the same active substance lot, at least in parts, and thus, cannot be considered completely independent. To comply with the requirements of ICH Q5C, additional commercial scale batches manufactured at the Lupin manufacturing site were put on storage. Based on the results of these additional studies at recommended storage conditions and at accelerated conditions, a shelf life of 36 months for the product manufactured at the Lupin site is supported.

Results from studies performed at accelerated stability condition at 25°C ± 2°C; 60 ± 5% RH show parameters within specifications but with various trends for increase of impurities and decrease of potency.

The finished product was subjected to various stress conditions to understand degradation pathways and underlying impurities. Results from this study suggest that Etanercept is susceptible to exposure to light, oxidizing agents, agitation and high temperature stress factors.

Temperature excursion studies were initiated using representative finished product lots to support a storage of 4 weeks at room temperature for ambulant use as described in the SmPC. Currently, stability data of 12 months storage at 25.0 ± 2.0°C/60.0 ± 5.0%RH are available. The results confirm satisfactory stability of the product under these conditions. Finally, the results of the photostability studies confirm that the finished product is susceptible to light and must be stored in the secondary

packaging. A respective storage instruction is included in the SmPC.

Based on the presented data, the claimed shelf life of 36 months at 2°C - 8°C is considered acceptable.

3.4.5. Biosimilarity exercise

To establish biosimilarity of Fubelv to EU Enbrel on the quality level, a comprehensive analytical comparability exercise, split into two Parts and three Campaigns, was performed comparing Fubelv to EU Enbrel and Enbrel Japan. Biosimilarity studies were performed with material representative of the proposed commercial Fubelv.

A "historical" similarity evaluation (Part A) was conducted during various developmental stages of the active substance and finished product and included for comparison of reference product (Enbrel) from EU, Japan and India. Some basic structural elucidation studies were completed and evaluated. No remarkable concerns were identified; the Applicant presented the correct amino acid sequence and correct pattern of the 29 disulfide bonds along with the most frequently observed "misbonded" bridge positions that lead to misfolded forms of etanercept.

The "Side-by-Side" analytical similarity exercise which is the process-relevant biosimilarity exercise comprises several analytical campaigns.

Generally, inherent structural quality attributes related to the protein backbone (such as amino acid sequence, disulfide bonding, secondary, tertiary and higher order structure) are comparable between Fubelv and Enbrel. Differences exist in the glycosylation profiles (N- and O-glycans).

As regards N-glycan structures, differences exist in the amount of total mannosylated glycoforms (mostly outside the Enbrel range) and the amount of afucosylated forms (at or above the upper Enbrel range). The amount of galactosylated glycoforms is shifted to the upper Enbrel range and outside the range. The amount of sialylated glycoforms is considered similar. The differences in high mannose content and afucosylated structures could be assigned to the Fc part of the molecule while the slight differences in galactosylated forms are located on the TNFR-part of the molecule. The overall sialylation is fairly comparable between test and reference product. Investigations on the N-glycosylation profiles were adequately performed; the new comparability exercise confirmed the results of the first exercise based on a more representative data pool.

Data presented on comparability of O-glycosylation have been sufficiently amended by new data and justification. In the comparability exercises, the level of disialylated glycans is slightly higher for Fubelv compared to Enbrel while the level of monosialylated O-glycans is conversely slightly lower. The potential impact of the differences in glycosylation is addressed in the various biological assays as detailed below.

For functional characterisation of TNFR and Fc the number of lots investigated was significantly increased in the new comparability exercise to support the representativeness of product and process. The comparability studies showed that the difference in afucosylated structures resulted in a difference in the ADCC assay. However, as the assay was designed as a hypersensitive assay the result was rated as "over-discriminatory" and the Applicant showed in additional assay formats with ADCC-positive and -negative antibody controls that the overall ADCC could be disregarded for etanercept compared to the positive controls. This is also in line with previous evaluations of etanercept products. Thus, the structural differences observed for glycan structures do not have any impact on functional parameters tested.

Generally, in comparability exercises the difference in glycosylation did not translate into any other

remarkable difference in the various potency and binding assays.

Differences are observed in N- and C-terminal heterogeneity of Fubelv and Enbrel. Etanercept is almost fully processed to the C-1 variant missing lysine and this impacts the charge profile of Fubelv compared to Enbrel that has a small proportion of lysine-carrying variants. Fubelv also has lower amounts of N-terminal variants (N-1, N-2). Similarity can be concluded on this attribute as no impact is expected from variability in N- and C-termini for etanercept. This is confirmed by both similarity studies.

Comparable or lower amounts of oxidized methionines, deamidated asparagines, of aggregates or misfolded forms are found for Fubelv. As regards the charge profile a lower number of basic variants is found for Fubelv consequential to the almost fully processed C-terminal variant without lysine. This has been concluded above to have no impact on the molecular function of etanercept.

A small study of similarity of finished product related attributes (protein content, extinction coefficient, subvisible particles) was conducted and did not result in any remarkable difference between Fubelv and Enbrel.

The comparability exercise is based on a sufficiently large sample size and uses independent batches of active substance that were not pooled. Results are sufficiently representative of the commercial process. Hence, a positive conclusion on biosimilarity can be drawn.

Table 2: Overview of analytical comparability exercise

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Primary structure	Amino acid sequence	Reducing peptide mapping, LC-MS/MS, Intact and reduced mass (MALDI) Deglycosylated intact and reduced Mass by LC/MS Amino acid composition Determination of extinction coefficient	Identical primary sequence
Higher order structure	Secondary and tertiary structure	Far UV Circular Dichroism spectroscopy Fourier transform infrared spectroscopy Near UV Circular Dichroism Intrinsic Fluorescence spectroscopy (280 nm and 295 nm) Second derivative UV spectroscopy Free thiol group analysis, DSC disulphide linkage analysis TNFR II conformational assay by ELISA NMR	Comparable higher order structure
Glycosylation	Post translational modifications	Glycosylation sites by LC-MS/MS, Glycan site occupancy by LC-MS	Overall comparable, some minor differences observed

Molecular parameter	Attribute	Methods for control and characterization	Key findings
		N-glycan profiling by NP-UPLC N-glycan profiling by LC-MS/MS N-glycan profiling by HILIC-MS Alpha-Gal by LC-MS from enriched glycopeptides O-glycan by LC-MS TNFR:Fc by LC-MS Sialic acid estimation Monosaccharide analysis	
	Functional characterisation of TNFRII moiety	TNF-α neutralization assay TNF-β neutralization assay Apoptosis bioassay TNF-α ligand binding assay by ELISA TNF-α binding kinetics by SPR TNF-β binding kinetics by SPR	No differences detected

3.4.6. Adventitious agents

There are no animal-derived materials used in the manufacturing process except one raw material used in cell line establishment. The cell banks (MCB, WCB and EOPCs) have been comprehensively characterized regarding adventitious agents. A virus validation study analyzing the viral clearance capacity of the etanercept manufacturing process has been performed comprising several process steps (AEX, HIC, MMC, Protein A chromatography, low pH, viral filtration) in small scale models. The virus validation study reports and the qualification of the models have been provided and support the validity and adequacy of the virus clearance capacity of the manufacturing process.

3.5. Discussion and conclusions on quality aspects

Based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for Fubelv is approvable from the quality point of view.

The provided Module 3 dossier is well-structured and data presentation is consistent.

The active substance manufacturing process control strategy is properly justified. The overall choice of manufacturing process parameters and their acceptance criteria is substantiated with development data. The active substance is thoroughly characterised, specifications are set according to ICHQ6B, and stability is demonstrated. Data to support the viral safety of finished product for commercial use according to ICHQ5A is provided.

The development, manufacture and control of Fubelv finished product is adequately described. Overall, the quality of Fubelv finished product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

Major objections were raised during the procedure relating to an incomplete nitrosamine risk assessment and absence of Notified Body Opinions for the PFS and PFP. These major objections were satisfactorily addressed through the submission of an updated nitrosamine risk assessment and the requested Notified Body Opinions.

EU GMP certificates or MIAs have been provided for all active substance and finished product manufacturing sites.

The provided data demonstrate that Fubelv and the EU reference product Enbrel are similar in terms of quality attributes, compared in a comprehensive analytical similarity exercise. Biosimilarity is considered fully demonstrated from a quality point of view.

4. Non-clinical aspects

4.1. Introduction

The non-clinical programme for Fubelv (also referred as the company code YLB113 in the report) consisted of comparative *in vitro* studies with Enbrel sourced from India, Europe and Japan, comparative *in vivo* pharmacology (PD), pharmacokinetics (PK) and toxicity studies with Enbrel sourced from India and Japan and non-comparative toxicity studies conducted with YLB113 (etanercept) alone.

Scientific advice regarding the product development program of YLB113 (etanercept) was given by the EMA (EMA/CHMP/SAWP/693250/2014; Procedure EMEA/H/SA/2891/1/2014/III). The package of non-clinical *in vivo* studies provided by the applicant was not supported and was not considered necessary in the frame of a comparability exercise for a biosimilar as proposed in the current EU biosimilar guidelines.

In accordance with the requirements of the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical issues' (EMEA/CHMP/BMWP/42832/2005 Rev1), the comparative *in vitro* studies carried out with Enbrel from EU or Japan are considered paramount relevant for the present MA application, while the other studies are considered informative only.

Table 3: List of in vitro pharmacology studies performed for YLB113 (etanercept)

Sr. No.	**Title of Test**
Binding and Neutralisation Assays	
1.	TNF-α neutralisation assay
2.	TNF-β neutralisation assay
3.	TNF-α ligand binding assay by ELISA
4.	TNF-α binding kinetics by SPR
5.	TNF-β binding kinetics by SPR
Fc Effector functional Assays:	
6.	FcRn binding kinetics by SPR
7.	FcγRIIIa: V158 binding kinetics by SPR
8.	FcγRIIIa: F158 binding kinetics by SPR
9.	FcγRI binding kinetics by SPR
10.	FcγRIIa: His131 binding kinetics by SPR
11.	FcγRIIb binding kinetics by SPR
12.	Antibody Dependent Cell Cytotoxicity (ADCC)
13.	Complement Dependent Cytotoxicity (CDC)

Table 4: List of *in vivo* pre-clinical studies performed for YLB113 (etanercept)

No.	Study No	Title of the Study	Batch Number	GLP
1.	BIO-BN 019	Single Dose Comparative Pharmacokinetic Study of Lupin's Etanercept with Enbrel in Swiss Albino Mice	Etanercept: ETPR1412/DP and ETPR1412/DPN Enbrel: G67313	Yes
2.	ABD-2994	Evaluation of Efficacy of Etanercept Biosimilar in an animal model of collagen induced Arthritis	Etanercept: ET/PR03/11 Enbrel: F17194	Yes
3.	457-1-05-1401	Single dose subcutaneous toxicity study of TNFR:Fc Fusion Protein (Etanercept) in Swiss Albino Mice	Etanercept: ETPR03/11	Yes
4.	457-1-05-1402	Single dose subcutaneous toxicity study of TNFR:Fc Fusion Protein (Etanercept) in Wistar Rats	Etanercept: ETPR03/11	Yes
5.	456-1-05-1403	Single dose intravenous toxicity study of TNFR:Fc Fusion Protein (Etanercept) in Swiss Albino Mice	Etanercept: ETPR03/11	Yes
6.	457-1-05-1404	Single dose intravenous toxicity study of TNFR:Fc Fusion Protein (Etanercept) in Wistar Rats	Etanercept: ETPR03/11	Yes
7.	418-1-02-1405	28-Day Repeated dose subcutaneous toxicity study of TNRF:Fc Fusion Protein (Etanercept) in Swiss Albino Mice	Etanercept: ETPR03/11 Enbrel: E37625	Yes
8.	418-1-02-1406	28-Day Repeated dose subcutaneous toxicity study of TNRF:Fc Fusion Protein (Etanercept) in New Zealand White Rabbits	Etanercept: ETPR03/11	Yes
9.	S48117	Etanercept Drug Substance: 4 week Toxicity Study in the Cynomolgus Monkey by Subcutaneous Administration with a 2-week Recovery Period	Etanercept: 005-002-13/1 Enbrel: 13B03A	Yes

4.2. Analytical methods

The pharmacokinetic profile of YLB113 (etanercept) was investigated and compared with Enbrel in a 4-week repeat dose toxicity and toxicokinetic study in Cynomolgus monkeys (S48117, versus Japan-sourced Enbrel, considered pivotal) and in a single dose study conducted in Swiss albino mice (study BIO-BN019, versus India-sourced Enbrel, therefore considered informative only). In both studies, etanercept (YLB113 (etanercept), Enbrel) plasma levels were determined by an ELISA assay, validated in accordance with the EMA 'Guideline on Bioanalytical Method Validation' (EMEA/CHMP/EWP/192217/2009).

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

***In vitro* studies**

TNF is an important cytokine in the inflammatory process of RA. The primary mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive.

The comparability of YLB113 (etanercept) and Enbrel was evaluated *in vitro* in TNF binding and neutralisation assays and in Fc effector functional assays, related to the antibody part of the fusion protein (see Table above). The discussion concerning the results of these *in vitro* studies, which are considered paramount for the non-clinical biosimilar comparability exercise, is provided in section 3 'Quality aspects', subsection 'Biosimilarity' of this assessment report.

***In vivo* studies**

A comparative *in vivo* pharmacodynamic study was conducted to demonstrate similar anti-arthritic activity of YLB113 (etanercept) and Enbrel (sourced from India) in a mouse model of collagen-induced arthritis (study ABD-2994).

The anti-arthritic activity was evaluated by investigating arthritic score, paw swelling and joint histological damage and cartilage erosion. I.p. doses of 0.1, 1, 10 and 50 µg YLB113 (etanercept) respectively Enbrel were applied daily for two weeks following arthritis induction by Bovine collagen type 2 in Freud's adjuvants.

YLB113 (etanercept) showed a dose-dependent anti-arthritic activity (at doses ≥ approximately 0.2-fold the equivalent human 50 mg clinical dose, assuming a mouse body weight (BW) of 25 g, a mouse to human conversion factor of 12.3, and a human BW of 60 kg). Effects of YLB113 (etanercept) and Enbrel on arthritic score and paw swelling appeared to be comparable. However, with regard to histopathology scoring (joint inflammation, pannus formation, cartilage damage, bone resorption) and for residual anti arthritic activity three weeks after treatment termination, YLB113 (etanercept) appeared to be slightly more potent (i.e. already effective at lower doses) than Enbrel.

4.3.1.2. Secondary pharmacodynamics

In line with the current EU biosimilar guidelines no secondary pharmacodynamics studies have been provided by the applicant.

4.3.1.3. Safety pharmacology

In line with the current EU biosimilar guidelines no safety pharmacology studies have been provided by the applicant.

4.3.1.4. Pharmacodynamic drug interactions

In line with the current EU biosimilar guidelines no pharmacodynamic drug interactions studies have been provided by the applicant.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

Study BIO-BN 011: Single dose mouse study

The 90% confidence interval of the ratio of the geometric mean of Cmax and AUC between test (Test 1: YLB113 (etanercept)´s etanercept drug substance applied in the innovator formulation; Test 2: YLB113 (etanercept) ´s etanercept drug substance applied in YLB113 (etanercept)´s modified formulation) and reference (India-sourced Enbrel) was found to be within a range of 0.8 and 1.25, whereby formally establishing bioequivalence of YLB113 (etanercept)´s etanercept drug substance when applied in either formulation.

Study S48117: Etanercept drug substance: 4-week toxicity study in the Cynomolgus monkey by s.c. administration with a 2-week recovery period - toxicokinetic evaluation

The pharmacokinetic/toxicokinetic profile of YLB113 (etanercept) drug substance was assessed after s.c. administration to Cynomolgus monkeys twice a week for a period of 4 weeks at doses of 1, 5 or 15 mg/kg on day 1 and day 22 of the study. The toxicokinetic profile of Enbrel (Japan-sourced), administrated at 15 mg/kg, was assessed for comparison.

Serum etanercept levels (YLB113 (etanercept) or Enbrel) were quantifiable in all animals dosed with 1, 5 and 15 mg/kg. Exposure values obtained for YLB113 (etanercept) and Enbrel (15 mg/kg) were similar on day 1 and were comparable for males and females. Median time to maximum etanercept concentration (tmax) ranged from 24 to 36 hours in males and females at the different dose levels on day 1 and 22.

Serum etanercept levels increased with dose. For AUCt, the increase showed about dose proportionality, while Cmax-values for the 5 mg/kg dose were higher than theoretically expected.

Following repeated administration, a notable decrease of etanercept exposure was observed for most animals, especially those exposed to the low and intermediate dose, which appeared to be correlated with the formation of anti-drug antibodies (ADA) detected in most of these cases. It was not evaluated whether the induced ADA were neutralising or not neutralising. AUCt and Cmax on day 22 were higher for YLB113 (etanercept) drug substance than for Enbrel, which could possibly be related to a higher incidence of ADA in the Enbrel-treated animals (see also Section 4.4).

4.3.2.2. Distribution

In line with the current EU biosimilar guidelines, no studies have been provided by the applicant.

4.3.2.3. Metabolism

In line with the current EU biosimilar guidelines, no studies have been provided by the applicant.

4.3.2.4. Excretion

In line with the current EU biosimilar guidelines, no studies have been provided by the applicant.

4.3.2.5. Pharmacokinetic drug interactions

In line with the current EU biosimilar guidelines, no studies have been provided by the applicant.

4.3.2.6. Other pharmacokinetic studies

In line with the current EU biosimilar guidelines, no studies have been provided by the applicant.

4.4. Toxicology

4.4.1. Single-dose toxicity

Four GLP-compliant single dose toxicity studies were conducted by both s.c. and i.v. administration of YLB113 (etanercept) to mice and rats (according to the current EU biosimilar guidelines, such studies are not considered necessary for a biosimilar MAA). No noteworthy findings were observed for s.c. and i.v. YLB113 (etanercept) doses of up to 500 mg/kg (mice), respectively 250 mg/kg (rats).

4.4.2. Repeat-dose toxicity

Three GLP-compliant 4-week repeat dose toxicity studies with a two-week recovery period were conducted in mice, rabbits and Cynomolgus monkeys by s.c. administration, which is the intended way for clinical application

Study 418-1-02-1405: 28-Day Repeated dose s.c. toxicity study of TNRF: Fc Fusion Protein (Etanercept) in Swiss Albino Mice

No noteworthy systemic findings were observed for YLB113 (etanercept) doses of up to 500 mg/kg and (India sourced) Enbrel (10 mg/kg), given s.c. once weekly. However, YLB113 (etanercept) and Enbrel induced local granulocyte and mononuclear cells infiltration at the injection site, which appeared to be reversible during the 14-day recovery period.

Study423-1-02-1406: 28-Day Repeated dose s.c. toxicity study of TNRF: Fc Fusion Protein (Etanercept) in New Zealand White Rabbits

No noteworthy findings were observed for YLB113 (etanercept) doses of up to 25 mg/kg given s.c. once weekly.

Study S48117: Etanercept drug substance: 4-week toxicity study in Cynomolgus monkeys by s.c. administration with a 2-week recovery period

No toxicologically relevant systemic findings were observed with YLB113 (etanercept) doses of up to 15 mg/kg and with Enbrel (Japan-sourced) at a dose of 15 mg/kg, given s.c. twice a week. Histological findings at the injection sites (mononuclear cell foci with subcutaneous fibrosis and granulomatous inflammation) were of slight intensity and were present in all groups, including the control group.

4.4.3. Genotoxicity

In line with the current EU biosimilar guidelines, no genotoxicity studies have been provided by the applicant.

4.4.4. Carcinogenicity

In line with the current EU biosimilar guidelines, no carcinogenicity studies have been provided by the applicant.

4.4.5. Developmental and reproductive toxicity

In line with the current EU biosimilar guidelines, no developmental and reproductive toxicity studies have been provided by the applicant.

4.4.6. Toxicokinetics and exposure margins

Toxicokinetics: see section 4.3.2.1 'Absorption' of this assessment report.

4.4.7. Local tolerance

Local tolerance was investigated during the repeated dose toxicity studies in mice (Study No. 418-1 02-1405) and Cynomolgus monkeys (Study S48117).

- In the mouse study (with India-sourced Enbrel as comparator), a treatment-related local reaction of granulocyte and MNC infiltration was seen at the site of injection (subcutaneous tissue) in YLB113 (etanercept) and in Enbrel-treated groups which appeared to be reversible during the 14-day recovery period.

- In the Cynomolgus monkey study (with Japan-sourced Enbrel as comparator), histological findings at the injection sites (mononuclear cell foci with subcutaneous fibrosis and granulomatous inflammation) were of slight intensity and were present in all groups, including the control group.

4.4.8. Other toxicity studies

The immunogenicity of YLB113 (etanercept)´s etanercept drug substance and of (Japan-sourced) Enbrel was investigated in the 4-week repeated dose s.c. toxicity study in Cynomolgus monkeys (Study S48117; see section 4.3.2.1 'Absorption' and section 4.4.2 'Repeat Dose Toxicity' of this assessment report).

4.4.9. Ecotoxicity/environmental risk assessment

The applicant provided a justification for not submitting any environmental risk assessment studies based on the fact that etanercept is a protein and therefore unlikely to pose a significant risk to the environment which is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Fubelv, a duplicate of Nepexto, was developed to be a biosimilar product to the EU reference product Enbrel and, in accordance with the current EU biosimilar guidelines, the non-clinical evaluation was mainly comparative in nature and designed to detect differences in the pharmaco-toxicological response between YLB113 (etanercept) and the reference medicinal product (RMP) Enbrel.

The non-clinical programme comprised comparative *in vitro* TNF binding studies and Fc-related functional assays, comparative *in vivo* pharmacology, pharmacokinetics and toxicity studies and non-comparative toxicity studies conducted with YLB113 (etanercept) alone.

***In vitro* studies**: As clearly expressed in the EMA scientific advice given to the applicant, according to the current EMA biosimilar guidelines the assessment of *in vitro* differences in receptor binding and biological activity between YLB113 (etanercept)and the RMP Enbrel is considered paramount for providing non-clinical evidence for biosimilarity. The assessment of the data submitted for YLB113 (etanercept) concerning *in vitro* TNF binding and functional activity is provided in section 3.4.5 'Quality aspects', subsection 'Biosimilarity exercise' of this report.

***In vivo* studies**: According to the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 Rev 1), a stepwise approach is recommended. If the *in vitro* comparability exercise is considered satisfactory and no factors of concern are identified, *in vivo* animal studies may not be necessary.

A large amount of *in vivo* animal data has been submitted by the applicant for YLB113 (etanercept), both from comparative and non-comparative studies and with different RMPs:

• Studies comparing YLB113 (etanercept) to India-sourced Enbrel:

- an efficacy study in a mouse collagen-induced arthritis model

- a mouse single dose s.c. pharmacokinetic study

- a 4-week s.c. repeat dose toxicity study in mice

• A study comparing YLB113 (etanercept) to Japan-sourced Enbrel:

- A 4-week s.c. repeat dose toxicity in Cynomolgus monkeys, including toxicokinetic and immunogenicity assessment

• Additional non-comparative studies in mice, rats, and rabbits for evaluation of single and repeat dose toxicity of YLB113 (etanercept).

In the EMA scientific advice given to the applicant, it was pointed out, that the package of non-clinical *in vivo* studies provided for YLB113 (etanercept) is not considered necessary in the frame of a comparability exercise for a biosimilar as proposed in the current EU biosimilar guidelines.

It was explained by the applicant that the non-clinical *in vivo* studies had been requested by non-EU regulatory authorities and that they had already been completed when asking for scientific advice by the EMA. On the other hand, the fact that the applicant has not provided (i) pharmacodynamic studies on secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions, (ii) pharmacokinetic studies on distribution, metabolism, excretion and pharmacokinetic drug interactions and (iii) toxicity studies concerning genotoxicity, carcinogenicity and reproduction and development is in accordance with the recommendations given in the current EU biosimilar guidelines for a biosimilar MAA.

Besides these general comments on the necessity of *in vivo* studies as part of the non-clinical biosimilar comparability exercise, the following issues had been initially identified in context with the specific non-clinical *in vivo* studies submitted by the Applicant for YLB113 (etanercept) and have been resolved or been decided not to be followed further:

• TNFalpha-binding in different species: *In vivo* animal studies with YLB113 (etanercept) have been performed in different species. However, information concerning the potency of etanercept for TNFalpha-binding in the different species has not been provided.

• YLB113 (etanercept) batches used in the *in vivo* animal studies: Information to what extent the YLB113 (etanercept) batches used in the non-clinical *in vivo* studies are comparable to the batches used in the pivotal clinical studies has been asked for and has been provided by the applicant.

● Studies using India-sourced Enbrel as RMP: *In vivo* animal studies using India-sourced Enbrel can only be regarded as informative as India is not an ICH member. According to EMA's overarching biosimilar guideline (CHMP/437/04 Rev 1), a non-EEA sourced RMP 'will need to be authorised by a regulatory authority with similar scientific and regulatory standards as EMA (i.e. ICH countries)'. In this context, the potential clinical relevance of the difference observed in anti-arthritic activity (with regard to the evaluated histopathological parameters) between YLB113 (etanercept) and India-sourced Enbrel in the mouse model of collagen-induced arthritis cannot be reliably assessed.

● Study using Japan-sourced Enbrel as RMP: The applicant has provided adequate comparative data to support an acceptable analytical bridge between Japan-sourced Enbrel and EU-sourced Enbrel and to justify the use of Japan-sourced Enbrel as a comparator in the 4-week repeat dose toxicity study with a 2-week recovery period in Cynomolgus monkeys. However, interpretation of the toxicity study is hampered by the fact that similarity of initial process material with lower amount of misfolds and sialic acid used in the toxicity study to improved process material (used clinically) is not considered given (see section 3.4.5 'Quality aspects', subsection 'Biosimilarity' of this assessment report) and (small) differences with regard to PK, PD, and safety, including immunogenicity, cannot be excluded.

● Differences in anti-drug antibody formation: In the 4-week repeat dose toxicity study in Cynomolgus monkeys, following repeated application, exposure on day 22 to Japan-sourced Enbrel was lower than exposure to YLB113 (etanercept), which was considered to be related to an increased incidence of ADA formation in the Enbrel group. However, as outlined in the "Guideline on immunogenicity assessment of therapeutic proteins" (EMEA/CHMP/BMWP/14327/2006 Rev 1), the comparison of the ADA response to the biosimilar and the RMP in an animal model is not recommended as part of the biosimilar comparability exercise, due to the low predictive value for the immunogenic potential in humans (however, as in this case, may be needed to aid in the interpretation of the toxicokinetic data).

The applicant did not submit ERA studies with the appropriate justification in line with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

There were no new non-clinical data since the approval of Nepexto. In addition, the proposed text for SmPC section 4.6 and 5.3 of the SmPC is in line with that of the reference product.

4.5.2. Conclusions

Overall, the CHMP considers that the non-clinical data provided by the applicant is considered sufficient to support the approval of YLB113 (etanercept).

5. Clinical aspects

5.1. Introduction

The applicant carried out three phase I PK studies in healthy volunteers, one in India, one in Japan, and one in Jordan (conducted during clock-stop) to support the application in the EU. The latest PK study in Jordan (study ETA.50/334) was required since the two previously conducted studies could not be accepted as a proof of similarity between YLB113 (etanercept) and the Enbrel reference medicinal product.

In addition, the applicant performed a multi-national, double-blinded, phase III equivalence trial (YLB113-002) in patients with rheumatoid arthritis in Europe, India, Ukraine and Japan.

The above-mentioned clinical trials supporting the clinical development program are presented in Table 5.

5.1.1. Good Clinical Practice (GCP) aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

A routine GCP inspection was carried out at two clinical sites of the phase III study (YLB113-002) following a request from the CHMP, dated 28 June 2018, in connection with the evaluation of the MAA for Nepexto for which Fubelv is a duplicate application of. No critical findings were found but some major and minor findings were observed. The observations, which were considered to be in the responsibility of the investigator sites are sites specific and are unlikely to affect the validity of the data.

A triggered GCP inspection was carried out at the clinical and analytical sites of the phase I PK study (ETA.50/334) conducted during the clock-stop of the Nepexto application. The request was due to the pivotal nature of the study in order to verify the newly submitted PK data. The major findings observed at these two sites were considered system-related and could therefore potentially have an impact on the quality of all study data. It is overall concluded that overall reliability of the data is not affected despite the major findings that were made and the reported clinical and PK data of the study ETA.50/334 are considered to be of sufficient quality to be used for the evaluation of the application.

Furthermore, the applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

5.1.2. Tabular overview of clinical trials

Table 5: Tabular overview of clinical studies

CSR Report No./Phase PK Report No. Location of Report	Status Study Dates[1] No of Centres Study Location	Study Design	Primary Objectives	Dose and Regimen	Patient Population	Total Patients n per dosage YLB113 + Enbrel	Sex Mean Age
ETA.50/334 Phase I	Complete 12/2018-02/2019 1 centre, Jordan	DB, R, AC, CO, 2x single dose	PK and Safety	50 mg SC injection (2x single dose applications 28 days apart – cross-over) YLB113 vs Enbrel	Healthy male subjects	N=52	M 31.0
YLB113-001 Phase I	Complete 7/2014 – 10/2014 1 centre, Japan	DB, R, AC, CO, 2 x Single dose	PK and Safety	25 mg SC injection (2x single dose applications 28 days apart – cross-over) YLB113 vs Enbrel	Healthy male subjects	N = 60	M 28.1
LBC-14-155 Phase I	Complete 8/2014 – 11/2014 1 centre, India	OL, R, AC, CO, 2 x Single dose	PK and Safety	50 mg SC injection (2x single dose applications 28 to 35 days apart – cross-over) YLB113 vs Enbrel	Healthy male subjects	N = 58	M 26.3
YLB113-002 Phase III	Complete 07/2015-06/2017 120 centres in Europe, Ukraine, India, Japan	R, DB, AC	Equivalence to Enbrel	YLB113: 50 mg once a week for 24 weeks (Stage A), and additional 28 weeks (Stage B or Stage C), respectively Enbrel: 50 mg once a week for 24 weeks (Stage A), and additional 28 weeks (Stage B or Stage C), respectively	Patients with moderate to severe RA	N=528 (randomised) FAS/PP: N=263/239 (Nepexto); N=254/238 (Enbrel)	M: 114, F: 403 52.3 years

[1] Represents first patient enrolled to last patient last visit. Note: DB = double blind, OL = open-label, R = randomised, AC = active-controlled, CO = cross-over, PK = pharmacokinetics, SC = subcutaneous, M = male

5.2. Clinical pharmacology

5.2.1. Methods

Etanercept was measured by a validated ELISA assay.

5.2.2. Pharmacokinetics

Three phases I PK studies in healthy volunteers were conducted to support the PK clinical programme:

- Study ETA.50/334 (main study): single dose, PK and safety study conducted in Jordan in healthy volunteers (n=52) comparing YLB113 (etanercept) versus Enbrel EU-source
- Study YLB113-001 (informative study): single dose, PK and safety study conducted in Japan in healthy volunteers (n=60), comparing YLB113 (etanercept) versus Enbrel Japan-sourced, previously designed as the pivotal PK study
- Study LBC-14-155 (informative study): single dose, PK and safety study conducted in India in health volunteers (n=58) comparing YLB113 (etanercept) versus Enbrel India-sourced, presented for information and not supportive of the present MAA

Studies YLB113-001 and LBC-14-155 were performed using material from the manufacturing process which contains lower amounts of misfolded forms and sialic acids per molecule of etanercept as compared to the proposed commercial process. Thus, the product used in these phase I studies cannot be considered representative of the proposed commercial product

Furthermore, study LBC-14-155 was conducted at the contract research organisation (CRO) which was inspected by Austrian and Dutch authorities in February 2016. The inspections identified several concerns at the company's sites regarding misrepresentation of study data and deficiencies in documentation and data handling. This triggered an Article 31 of Directive 2001/83/EC referral procedure which concluded that data from studies conducted at the sites between June 2012 and June 2016 are unreliable and cannot be accepted as a basis for MA in the EU[2]. Since Study LBC-14-155 was conducted during that time frame, the results cannot be taken into a consideration in this application.

The study ETA.50/334 was conducted during the clock-stop after the two previously conducted PK studies (YLB113-001, LBC-14-155) could not be accepted as a proof of similarity between YLB113 (etanercept) and Enbrel. Study ETA.50/334 is considered as the main PK study in the context of the present MAA.

Study ETA.50/334 (main study)

This was an open label, randomised, two-period, two-treatment, two-sequence, crossover, balanced, single dose comparative PK study.

The study was conducted during the clock-stop period of the evaluation.

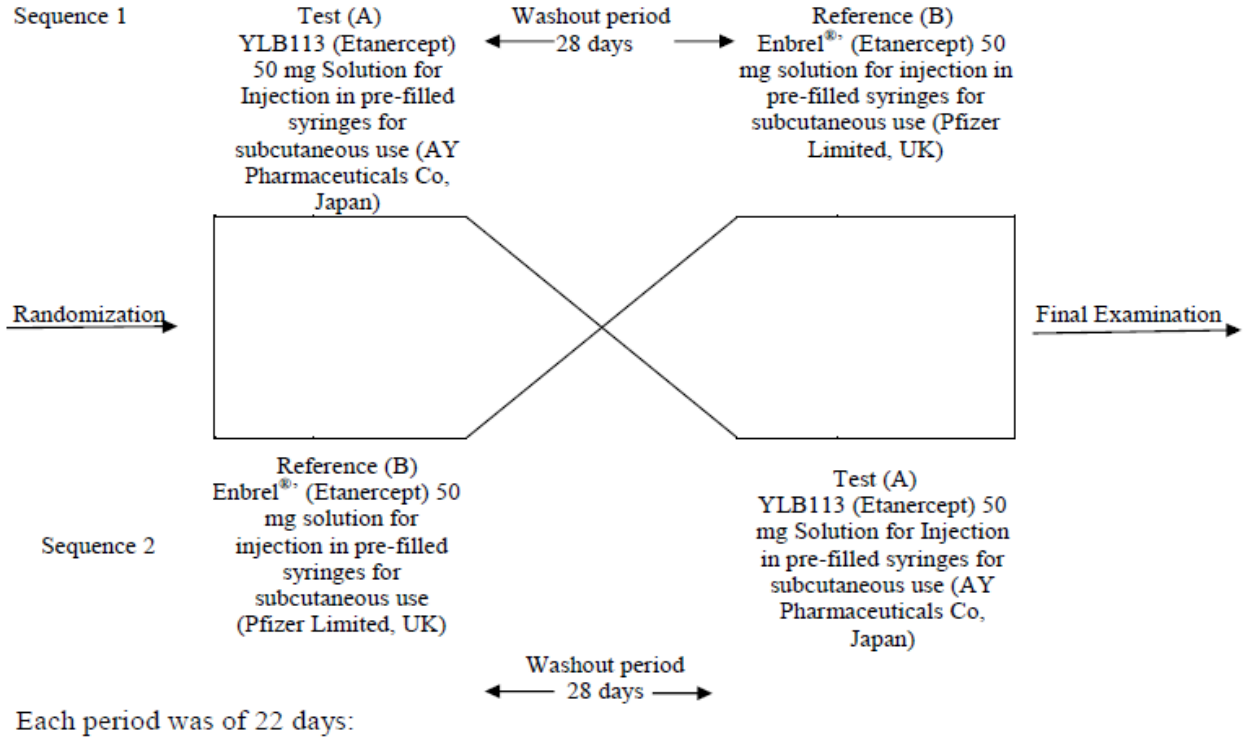
The test product is declared to represent current manufacturing and therefore to be representative for the to-be commercialised finished product. EU-sourced Enbrel reference product was used.

Design

[2] Article 31 referral. EMA recommends suspension of medicines due to unreliable studies from Micro Therapeutic Research Labs.(EMA/188204/2017) https://www.ema.europa.eu/en/documents/referral/micro-therapeutic-research-article-31-referral-ema-recommends-suspension-medicines-due-unreliable_en.pdf

The study design is presented in Figure 1. The study duration was approximately 50 days and started on admission day of period I and ended by giving the last blood sample in period II. Washout period was 28 days between doses.

Figure 1: Schematic chart of the study ETA.50/334 (crossover design)



Objectives

The primary objective was to compare the relative bioavailability of etanercept between YLB113 (etanercept) 50 mg solution and the reference product Enbrel 50 mg solution for injection in pre-filled syringes for subcutaneous use.

The secondary objective was to evaluate and compare the overall safety, tolerability and local tolerance of YLB113 (etanercept) 50 mg solution and Enbrel 50 mg solution for injection in pre-filled syringes for subcutaneous use.

Study population

The subjects were 51 healthy adult male subjects from Jordan population, 18 to 50 (inclusive) years old.

Treatment

Single dose (1 mL) of either test product (A - YLB113 (etanercept)) or reference product (B- EU sourced Enbrel) solution for injection in pre-filled syringes for subcutaneous use was administered to the subjects slowly by subcutaneous route in the abdomen (except for the 5 cm area right around the navel) as per the randomisation schedule in a supine posture.

Pharmacokinetic and statistical evaluation

ANOVA analysis (testing the sequence, subjects 'nested within sequence, product and period effect) using 5 % significance level was done for log-transformed and untransformed data for Cmax, AUC0-t, and AUC0-∞,and for the untransformed data of Tmax, AUC_%Extrap_obs, t1/2, Kel, Vd & Cl. Pharmacokinetic equivalence of the test product (A) with reference product (B) for Etanercept was

demonstrated if: The 90% confidence interval of the ratio of the geometric least squares mean for ln-transformed pharmacokinetic parameters Cmax, AUC0-t, and AUC0-∞ falls within the acceptance range of 80.00%-125.00%. Median was used upon reporting Tmax values unlike all other parameters where mean was used.

Results

The results of study ETA.50/334 are presented in Figure 2,Table 6, Table 7 and Table 8.

Figure 2: Mean 480-hour profiles serum concentrations of YLB113 (etanercept) versus Enbrel

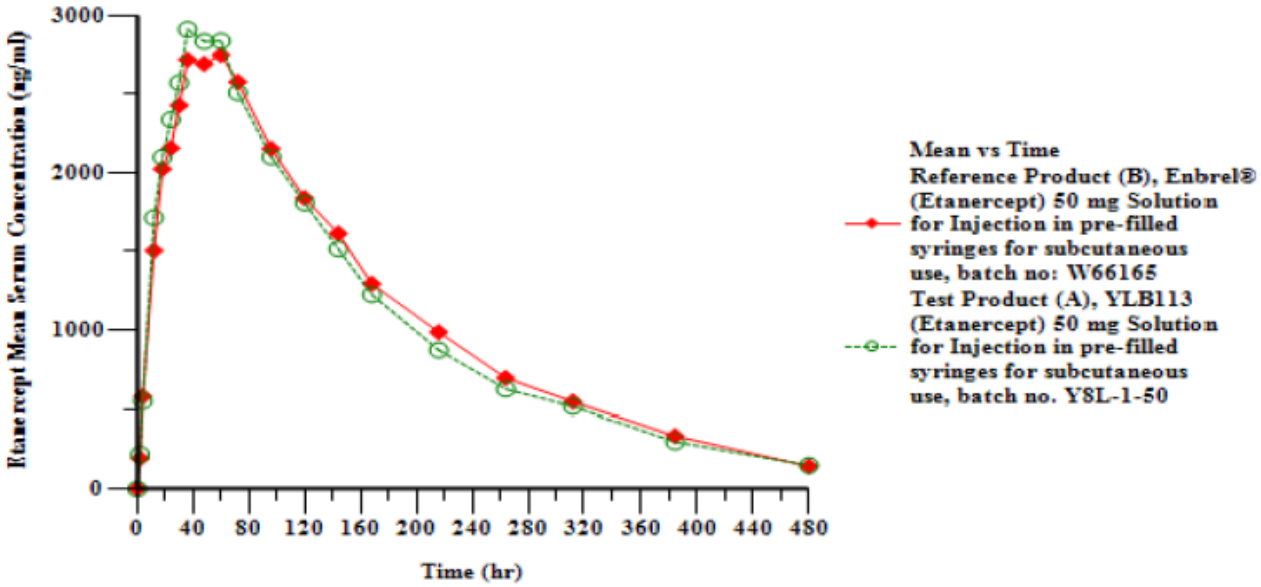


Table 6: Summary of Etanercept PK parameters (all subjects)

Pharmacokinetic Parameter	**Test Product (mean ± SD) N=43**	**Reference Product (mean ± SD) N=43**
C max (ng /ml)	3273.694 ± 1565.0337	3151.320 ± 1261.6810
AUC 0-t (ng*hr/ml)	508301.685 ± 205307.8081	521664.665 ± 188285.1017
A UC 0-∞ (ng*hr/ml)	531129.085 ± 215602.8685	548684.557 ± 200975.4062
T half (hr)	94.20 ± 11.671	94.55 ± 19.215
K elimination (hr-1)	0.0075 ± 0.00094	0.0077 ± 0.00200
AUC_%Extrap_obs,	4.46 ± 1.771	4.84 ± 2.184
Vd (ml)	15037.37 ± 7078.677	13705.60 ± 4755.415
Cl (ml/hr)	113.63 ± 59.402	104.87 ± 43.504
	Test Product (median ± SD), (Min-Max)	**Reference Product (median± SD, (Min-Max))**
T max (hr)	48.00 ± 17.645	48.00 ± 19.706

	(18.00 – 96.00)	(18.00 – 120.00)

Table 7: Statistical comparisons of Etanercept Pharmacokinetic Parameters

Primary PK Parameter	Intra-subject Variability CV	Geometric Means		Ratio (%)	90% Confidence Intervals of the Ratio		Power
		Test A (N=43)	Reference B (N=43)		Lower	Upper	
Cmax (ng /ml)	24.376	2873.880	2884.390	99.64	91.31	108.72	99.021
AUC 0-t (ng*hr/ml)	20.455	463705.430	487979.400	95.03	88.29	102.27	98.716
AUC 0-∞ (ng*hr/ml)	19.994	485443.450	512892.180	94.65	88.08	101.70	98.702

Due to potential carry-over effects in period II indicated by a pre-administration blood concentration potentially higher than 5% Cmax in 5 subjects, a revised PK analysis was provided by the applicant excluding these subjects (Table 8).

The acceptance criteria of 90% confidence intervals for Cmax and AUC are well within the 80-125% acceptance range. Therefore, the exclusion of these subjects does not change the overall conclusion on bioequivalence.

Table 8: Statistical comparison of Etanercept PK parameters (excl. 5 patients with pre-administration blood concentration potentially higher than 5% Cmax)

Primary PK Parameter	Intra-subject Variability CV	Geometric Means		Ratio (%)	90% Confidence Intervals of the Ratio		Power
		Test	Reference		Lower	Upper	
Cmax (ng/mL)	24.116	3258.30	3220.42	101.176	92.228	110.993	97.954
AUC0-t (ng*hr/mL)	20.460	510826.48	530882.39	96.222	88.924	104.119	98.782
AUC 0-∞ (ng*hr/mL)	20.270	532627.63	557399.22	95.556	88.372	103.324	98.384

Study YLB113-001 (informative study)

This Japanese study was a double-blind, randomised, two-way crossover trial to investigate the safety and bioavailability of YLB113 (etanercept) compared to Enbrel administered as a single subcutaneous dose of a buffered aqueous solution formulation (25 mg) in healthy male subjects compared to the same dose of the reference product.

The study was initiated in 60 healthy male adult subjects. Etanercept was administered in the abdomen. There was a 28 day of washout period between administrations.

The results are presented for information and cannot support similarity assessment for the MAA.

Results

The results are shown on Figure 3, Table 9 and Table 10.

Figure 3: Mean 480-hour profiles of Serum Concentration of YLB113 (etanercept) versus Enbrel of Study YLB113-001

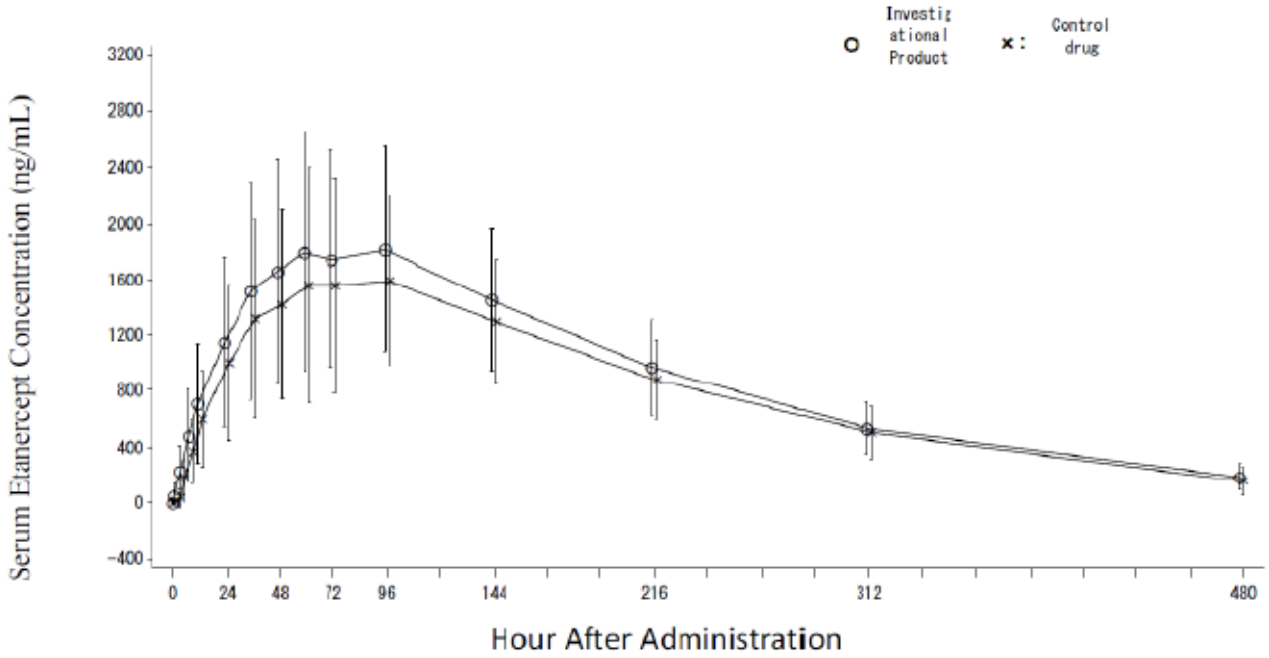


Table 9: Summary of Pharmacokinetic Parameters in Serum Etanercept Concentration

Treatment Group	Parameter		N	Mean	SD	Min	Median	Max
Investigational Product	Cmax	[ng/mL]	58	1966.5	856.1	541	1745.0	3740
	AUCt	[hr*ng/mL]	58	431280.3	163922.9	137856	393351.5	807110
	AUCinf	[hr*ng/mL]	57	468987.5	173889.9	172941	422363.3	883564
	tmax	[hr]	58	83.0	29.8	36	84	216
	t1/2	[hr]	57	115.14	21.78	71.8	115.93	215.0
	Kel	[1/hr]	57	0.006211	0.001103	0.00322	0.005979	0.00965
	Vd	[mg/ng/mL]	57	0.010283	0.004893	0.00463	0.009847	0.02905
	CL/F	[mg/(hr*ng/mL)]	57	0.00006224	0.00002729	0.0000283	0.00005912	0.0001445
Control Drug	Cmax	[ng/mL]	58	1742.2	864.6	400	1610.0	5710
	AUCt	[hr*ng/mL]	58	380838.5	142768.1	94560	353095.5	853037
	AUCinf	[hr*ng/mL]	57	424374.2	143984.4	203828	387678.2	920247
	tmax	[hr]	58	81.1	20.3	36	96	144
	t1/2	[hr]	57	114.83	18.29	48.7	114.78	147.4
	Kel	[1/hr]	57	0.006234	0.001377	0.00470	0.006039	0.01424
	Vd	[mg/ng/mL]	57	0.010793	0.003821	0.00477	0.010470	0.02251
	CL/F	[mg/(hr*ng/mL)]	57	0.00006528	0.00002071	0.0000272	0.00006466	0.0001231

Table 10: Equivalence Testing Analysis Results

Item	Cmax	AUCt
Logarithmic conversion average difference	1.13	1.12
90% confidence Interval	log(1.04)~ log(1.22)	log(1.03)~ log(1.21)

For both primary PK parameters AUCt and Cmax, values were significantly higher for the test product as compared to the reference (ratios AUCt 1.12 [1.03-1.21], Cmax 1.13 [1.04-1.22]). However, compliance with the pre-defined 80-125% acceptance criteria for the 90% CI was shown. In terms of elimination half live, very similar values for both products were calculated (t1/2: test 115.14 hrs, reference 114.83 hrs).

Study LBC-14-155 (informative study)

This was an open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover, comparative pharmacokinetics-pharmacodynamics study of etanercept 50 mg solution for injection for subcutaneous injection manufactured by Lupin Limited, India and Enbrel (Etanercept 50 mg) Solution for Injection for subcutaneous injection manufactured by John Wyeth and Brother Ltd.

The study was initiated in 58 healthy male adult subjects. Indian sourced Enbrel reference product was used. The study is considered as informative only.

Of 58 enrolled subjects, 16 subjects were absent for subsequent period, missed consecutive blood draws or were withdrawn due to adverse event (AE).

A minimum washout period between two dosing periods of 28 days was observed. This is acceptable given an expected elimination half-life of about 70 hours. However, in 4 subjects pre-dose levels were above 5% of the individual Cmax. These subjects were excluded.

The results are presented for information only.

Results

The results are presented in Figure 4, Table 11, Table 12 and Table 13.

Figure 4: Linear plot of mean serum concentrations versus time of Etanercept for Test (T) and Reference (R) product in 38 healthy, adult, human male subjects under standard breakfast conditions

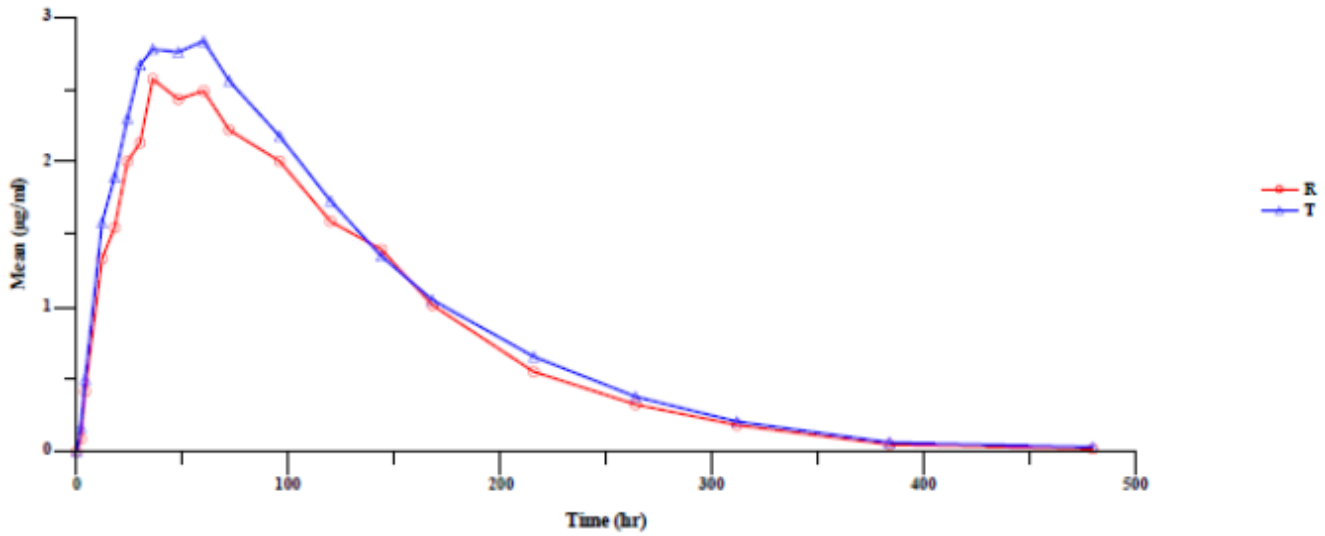


Table 11: Descriptive Statistics of Pharmacokinetic Parameters of Test (T) Formulation for Etanercept

PK parameters (Units)	*N	Mean	SD	Min	Median	Max	CV%	Geometric Mean
Tmax(hr)	38	55.105	15.957	18.0 0	60.00	96 .00	28.96	52.406
Cmax (µg/mL)	38	3.25598	1.85279	0.9872	2.6689	9.1778	56.90	2.84490
AUC0-t, (µg * hr/mL)	38	415.33 616	183.88147	132.8674	389.9291	856.792 4	44.27	376.5 1336
AUCo- (µg*br/mL)	38	443.7 6499	190.42438	160.2815	416.9200	943.483 8	42.91	405.29927
Kel (hr-1)	38	0.01065	0.00402	0.0038	0.0099	0.0237	37.74	0.00998
T1/2 (hr)	38	74.13924	28.77544	9 2473	70 0271	181.124 8	38.81	69.43873
Vd/F (L)	38	1 3.67750	6.60299	4.5583	12.5208	39.46 04	48. 28	12.35863
CI/F (mL/min)/kg	38	0.13575	0.06300	0.0530	0.1199	0.3120	46.41	0.12337

N-Number of Observations

*Pre-dose concentration of subject no. 19 & 22 (in period-I) and 03 & 25 (in period-II) were found more than 5% of their individual Cmax for Etanercept, hence excluded from PK and Statistical analysis.

Table 12: Descriptive Statistics of Pharmacokinetic Parameters of Reference (R) Formulation for Etanercept

PK parameter (Units)	*N	Mean	SD	Min	Median	Max	CV%	Geometric Mean
Tmax (hr)	38	50.054	23.227	24.00	4 2.04	144 .00	46.40	46.293
Cmax µg*hr/mL	38	2.90435	1.01777	0.8130	2.9571	5.1852	35.04	2.71562
AUCo-t (µg*hr/mL)	38	372.58306	141.50516	129.2515	342.9931	715.2455	37 .98	347.75322
AUCo-∞ (µg*hr/mL)	38	401.21988	144.37577	154.255 1	374.3827	767.0 008	35.98	377.82324

Ke1(hr-1)	38	0.010 90	0.00372	0.0060	0.0100	0.0244	34.12	0.0104
T1/2 (hr)	38	69 06426	18.24246	28.4395	69.1869	115.0572	26 .41	66.49723
Vd/F (L)	38	13.8 3831	6.60852	6.0342	12.7653	42.7866	47.76	12.69578
Cl/F (mL/min)/kg	38	0.14058	0.05148	0.0652	0.1336	0.3241	36.62	0.13234

N-Number of Observations

* Pre-dose concentration of subjects no. 19 & 22 (in period I) and 03 & 25 (in period II) were found more than 5% of their individual Cmax for Etanercept hence excluded from PK and Statistical analysis.

Table 13: The summary statistics of log transformed primary pharmacokinetic parameters for Etanercept

Parameter	***N**		**Geometric Least Square Means**		**Ratio T/R (%)**	**90% CI**	**p-value**		
	T	**R**	**T**	**R**			**Formulation**	**Period**	**Sequence**
Cmax (µg/mL)	38	38	2.8551	2.7122	105.27	93.80-118.15	0.0716	0.0930	0.5992
AUC0-t (µg*hr/ mL)	38	38	377.7927	347.2201	108.80	98.73-119.90	0.1700	0.0543	0.6081
AUCo-∞ (µg*hr/ mL)	38	38	406.7595	377.3529	107.79	98.41-118.08	0.1429	0 0441	0.5314

Parameter	**ISCV (%)**	**Power**	**P-Value** **Group Effect**	T - Test Product - Etanercept 50 mg Solution for Injection for Subcutaneous Injection Manufactured by Lupin Limited, India R - Reference Product - Enbrel (Etanercept 50 mg) Solution for Injection for Subcutaneous Injection Manufactured by John Wyeth and Brother Ltd., UK N - Number of Observations Note: For group effect the obtained p-value is statistically not significant at 0.05 level of sig1uficance. *Pre-dose concentration of 2 subjects (in period-I) and 2 subjects (in period-II) were found more than 5% of their individual Cmax for Etanercept, hence excluded
Cmax (µg/mL)	30.42	0.9382	0.4332	
AUC0-t (µg*hr/ mL)	25 .44	0.9825	0.4960	
AUCo-∞ (µg*hr/ mL)	23 .82	0.9903	0.4537	

Equivalence was reached with regard to the primary PK endpoints AUC0-480, AUCinf and Cmax since the 90% CIs for the respective GMRs were within the predefined equivalence margins of 80-125%. As in the Japanese PK study, point estimates were > 1 (Cmax 105.27 [93.80-118.15], AUC0-480 108.80 [98.73-119.90], AUCinf 107.79 [98.41-118.08]). In this case, however, the difference between the test and the reference product was not significant.

5.2.3. Pharmacodynamics

Etanercept is a recombinant human tumour necrosis factor receptor p75Fc fusion protein. It interferes with the soluble TNF α by mimicking the inhibitory effects of naturally occurring soluble TNF receptors that deactivate TNF-α and therefore down-regulate immune responses. Etanercept acts as a decoy receptor for TNF-α, reducing TNF-α effects and hence represents a competitive TNF-α inhibitor.

In accordance with EU guidance (EMEA/CHMP/BMWP/ 42832/2005; EMA/CHMP/BMWP/403543/2010), clinical evidence for comparability/similarity can be demonstrated by pharmacodynamics (PD) surrogate endpoints or clinical evidence. In case of YLB113 (etanercept), clinical evidence for similarity was aimed to be demonstrated by clinical rather than PD endpoints. The applicant did not submit clinical studies on the PD of etanercept. This is acceptable.

In the bioequivalence study LBC-14-155, that is informative for the purpose of MA due the limitations explained in introduction (Section 5.1), levels of TNF-α were measured to determine comparative effect of YLB113 (etanercept) and Enbrel on inhibition of TNF-α in an *in-vitro* test system as measured by recovery of TNF-α.

The TNF-α concentration in healthy subjects was too low to demonstrate an additional drop achieved by etanercept. To circumvent the problem and to demonstrate a PD effect of etanercept, a fixed predetermined concentration of TNF-α was added into the sample containing etanercept. The *in vitro* neutralisation of TNF-α is demonstrated by a drop in the TNF-α concentration. The measurement of depletion of artificially added TNF-α in human serum samples was based on an *in-vitro* assay using human serum as a matrix.

Prior to etanercept administration (Time 0.00 hrs) and after addition of the fixed TNF-α amount, the TNF-α concentrations were around 14 ng/ml. Measurable TNF-α concentrations in the samples declined very rapidly after etanercept administration to about 10 ng/ml at 12 hrs post-dosing. This value was maintained throughout the rest of the sampling period at 480 hrs. Consistent results were observed for the test and reference product. Due to the artificial character of the *in vitro* test setting and to the limitations pertaining to this study, these results cannot be interpreted to draw conclusions on biosimilarity between the test and reference product.

5.2.4. Overall discussion and conclusions on clinical pharmacology

5.2.4.1. Discussion

Study (ETA 50/334), conducted in Jordan during the clock-stop of this application, was considered pivotal for the comparative PK evaluation between YLB113 (etanercept) and Enbrel.

At the CHMP request, a GCP inspection was carried out at the clinical and analytical sites of the study. The request was due to the pivotal nature of the study in order to verify the newly submitted PK data. The major findings observed at these two sites were considered system-related and could therefore potentially have an impact on the quality of all study data. It is concluded that overall reliability of the data is not affected despite the major findings that were made and the reported clinical and PK data of the inspected trial ETA.50/334 are considered to be of sufficient quality to be used for the evaluation of the MAA.

The study was a single dose, PK and safety study conducted in Jordan in healthy volunteers (n=52) comparing YLB113 (etanercept) versus Enbrel EU-sourced.

Healthy subjects are considered an adequate, most homogenous, population when conducting a comparative PK study in the context of a biosimilar MAA. The analytical method is considered validated in line with the relevant guidelines.

Design, selected dose and sample size were considered adequate to evaluate PK-bioequivalence between YLB113 (etanercept) and Enbrel. The test product was representative of the to-be commercialised finished product.

The results of the primary endpoints, i.e. 90%CI for the ratio on Cmax, AUC0-t, and AUC0-∞ falling within the acceptance range of 80.00%-125.00%, showed bioequivalence between YLB113 (etanercept) and Etanercept.

Five study subjects were excluded from the statistical analysis in the comparison between YLB113 (etanercept) and EU sourced Enbrel due to carry-over effect. This exclusion did not have a relevant impact on the outcome of the study, point estimators remained close to 1 with 90% confidence

intervals contained within the 80-125% acceptance range (Cmax 101.18 [92.23-110.99], AUC0-t 96.22 [88.92-104.12], AUC0-∞ 95.56 [88.37-103.32]).

Two other phase I studies (LBC-14-155 and YLB113-001) were initially carried out to demonstrate biosimilarity between YLB113 (etanercept) and Enbrel. In each study compliance with the 80-125% acceptance criteria could formally be shown for the primary PK parameters. However, these results could not be accepted as proof of biosimilarity due to the following reasons.

Both studies used material from the active substance manufacturing process with lower amount of misfolds and sialic acid which is not representative of the intended commercialised product.

Study LBC-14-155 was conducted at a CRO inspected in an Article 31 referral. The referral concluded that bioequivalence studies in which bioanalysis was carried at this CRO in the time span between June 2012 and June 2016 cannot be accepted to support MAAs. Since Study LBC-14-155 was conducted in 2014, the results could not be taken into account in support of the MAA for YLB113 (etanercept).

In Study YLB113-001, more than 50% of subjects in period II of the study had to be excluded due to potential carry-over effect. Reliable bioequivalence evaluation after exclusion of more than half of subjects is therefore questionable by CHMP. PK data obtained from study YLB113-001 were therefore not accepted by CHMP as proof for bioequivalence between the test and the reference product.

No PK data were generated throughout the phase III in patients with RA. Hence, no multiple dose data are available for YLB113 (etanercept). Similarity between the test and reference product in terms of attainment of steady state conditions and associated peak and trough levels after multiple dose administration cannot be evaluated.

There were no new clinical data since the approval of Nepexto. In addition, the proposed text for SmPC section 4.2, 4.5 and 5.2 of the SmPC is in line with that of the reference product.

5.2.4.2. Conclusions

The similarity of the PK profiles between YLB113 (etanercept) and Enbrel was demonstrated based on the results obtained from the most recently conducted BE study ETA.50/334.

5.3. Clinical efficacy

5.3.1. Dose response studies

No dose-response studies were performed, which is acceptable for a biosimilar product.

The proposed dosing regimens for YLB113 (etanercept) are identical to those approved for Enbrel.

5.3.2. Main study

5.3.2.1. Study YLB113-002

Study YLB113-002 was a multicentre, double-blind, randomised, parallel-group comparative study to assess the efficacy, safety, and immunogenicity of YLB113 (etanercept) and Enbrel for the treatment of rheumatoid arthritis (RA).

Study Participants

The selection of the patient population followed the current treatment guidelines for the treatment of patients with moderate to severe RA. Patients had to fulfil several inclusion criteria to get the appropriate treatment in the frame of the study.

Main inclusion criteria

Patients between 18 and 75 years old, diagnosed with RA according to the 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria for RA and capable of providing written informed consent to participate in the study were enrolled in the study. Patients had to have ⩾ 6 tender joints and ⩾ 6 swollen joints (based on the Swollen Joint Count [SJC] using 66 joints and Tender Joint Count [TJC] using 68 joints) and DAS28 score ⩾ 3.2 and should have been treated with MTX for at least 3 months at an optimum dose (6 - 25 mg/week, not exceeding the local approved dose) that has remained stable for at least 6 weeks prior to screening.

Main exclusion criteria

1. Patients previously treated with any other biologic response modifiers for any autoimmune indication (including but not limited to tocilizumab, adalimumab, anakinra, abatacept, infliximab, rituximab, golimumab, etanercept, certolizumab, and tofacitinib);
2. Patients who had been taking any of the following concomitant medications, within the timeframe specified:
   - systemic/intra-articular corticosteroids above levels equivalent to 10 mg/day of prednisolone daily, 2 weeks prior to screening;
   - any live or attenuated vaccines within 4 weeks of screening;
   - alkylating agents within 6 months prior to screening only if being received for conditions other than cancer or multiple sclerosis;
   - non-steroidal anti-inflammatory drugs (NSAIDs) not on a stable dose within 2 weeks prior to screening;
3. Patients with active tuberculosis (TB), prior history of unsuccessfully treated TB, latent TB, or those who were at risk of developing TB and subjects who were not negative for TB tests;
4. Patients which had any of the following conditions:
   - other rheumatic diseases, autoimmune disease, connective tissue disease, or immune deficiencies;
   - active or prior history of malignancies within 5 years prior to Screening
   - active or prior history of clinically significant or uncontrolled respiratory, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic (including demyelinating disorders), metabolic, pulmonary, cardiovascular disease, or a history of any autoimmune disease or psychiatric illness;
   - history of congestive heart failure (New York Heart association criteria Class III/ IV)
   - serious systemic infections (positive serological test for hepatitis B or hepatitis C or had a known history of infection)

Treatments

Design / duration

The biosimilar YLB113 (etanercept), manufactured in Japan, was tested against EU-sourced Enbrel as

active comparator for therapeutic equivalence in the clinical model of RA.

The maximum duration of the study for each subject was up to 56 weeks, including treatment period of 52 weeks and follow-up period of 4 weeks or until the time of discontinuation from the study.

According to the subject disposition scheme, 497 subjects completed Stage A (247 patients in YLB113 (etanercept) group and 250 patients in Enbrel group). These were distributed to either proceed to Stage B (n=471) or Stage C (n=18).

Stage A

The first 24-weeks of this study was stage A. Eligible subjects were enrolled in stage A and randomly assigned to receive YLB113 (etanercept) 50 mg or Enbrel 50 mg once a week as a subcutaneous injection for 24 weeks (on a background of stable dose of MTX). The first dose was administered on Day 1 (Week 0).

After completion of Stage A, subjects could have continued either in stage B (same treatments as stage A) or stage C (crossover of treatments of stage A). Stage C ran in parallel to stage B and included those subjects who were eligible as per the eligibility criteria for stage C. Both the stage B and stage C were double-blind.

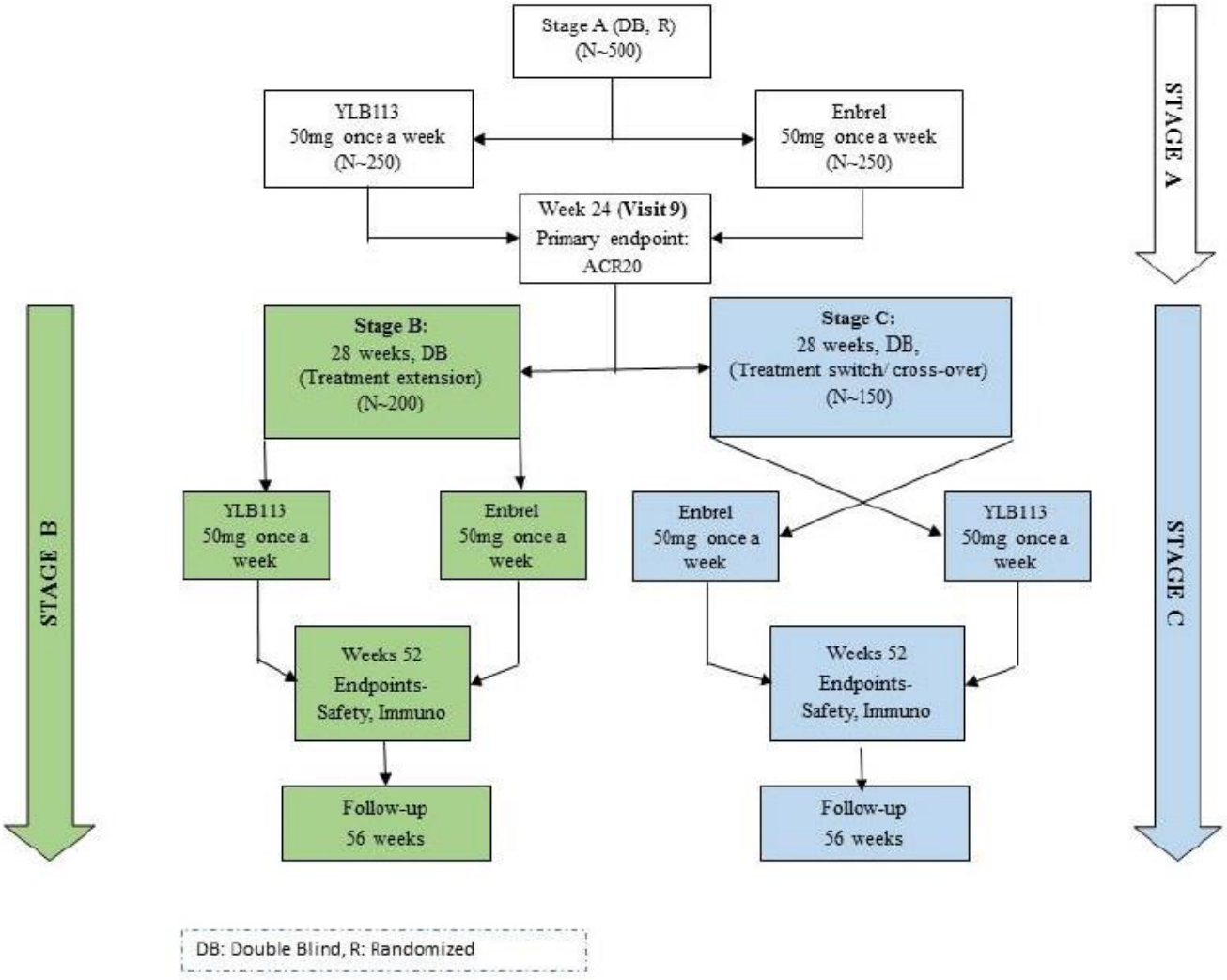
Stage B

All subjects who completed evaluations for Week 24 in stage A and were willing to continue in stage B, and tolerated the study medications administered in stage A with no serious adverse events (SAEs), or unresolved Grade 3 or higher AEs related to study medication were eligible to enter stage B. The subjects were administered the same drug as in stage A (YLB113 (etanercept) or Enbrel 50 mg) once a week as a subcutaneous injection for 28 weeks in this multicentre, comparative study. The objective of stage B was to compare long-term safety, and immunogenicity of YLB113 (etanercept) and Enbrel.

Stage C

All subjects who demonstrated reduction in their baseline DAS28 score by $\geqslant$0.6 at Week 12 and/or Week 24 and completed the 24-week period of stage A, and tolerated the study medications administered in stage A with no SAEs or unresolved Grade 3 or higher AEs related to study medication were eligible to enter stage C. Eligible subjects crossed over to the other treatment arm (from YLB113 (etanercept) to Enbrel and Enbrel to YLB113 (etanercept)) and received subcutaneous injections once a week for 28 weeks. However, the subjects whose DAS28 score had either not improved or those who were more inclined to participate in Stage B (in spite of DAS28 improvement), continued in stage B. Stage C was not conducted in Japan but done in Europe and India as an amendment to the original protocol (Protocol Version 2.1).

Figure 5: Schematic of study design



*YLB113 is the development code for etanercept test product

5.3.2.1.1. Objectives and estimands

Outcomes/endpoints

The primary efficacy endpoint was ACR20 response rate at Week 24 of dosing in the Full Analysis Set (FAS) (The proportion of subjects who achieved an ACR20 response at Week 24 of treatment compared with that prior to treatment [Baseline]). Subjects were considered to have achieved an ACR20 improvement if compared to Baseline (Day 1), they achieved a:

- 20% decrease in Swollen Joint Count (SJC),
- 20% decrease in Tender Joint Count (TJC) and
- 20% improvement in 3 of the following 5 measures:
  - Subject assessment of pain (visual analog scale [VAS]).
  - Subject global assessment of disease activity (VAS).
  - Physician global assessment of disease activity (VAS).

- C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR).
- Health Assessment Questionnaire Disability Index (HAQ-DI).

The secondary efficacy endpoints were:

- ACR20 response rate at Weeks 4, 8, and 12 of dosing;
- ACR50 response rate at Weeks 4, 8, 12, and 24 of dosing;
- ACR70 response rate at Weeks 4, 8, 12, and 24 of dosing;
- An improvement in the DAS28 response at Weeks 4, 8, 12, and 24 of dosing.

DAS28 Scores

The DAS28 score was calculated using results from a 28-joint subset of the 66/68 SJC/TJC. The DAS28 is a composite score (ranging from 0 to 9.4) calculated using the results of the 28-joint subset of the 66/68 SJC/TJC, CRP levels (mg/L) or ESR levels (mm/hr), and the subject's global assessment of diseases activity (0 to 100 scale).

For each patient the acute phase reactant (CRP or ESR) to be used throughout the study (for that specific patient) was recorded on the CRF at Screening. For patients for whom the CRP acute phase reactant was identified at screening, only CRP was used throughout the trial in the definition of ACR20 (as well as in the definitions of ACR50 and ACR70).

Sample size

Assuming 70% response rate (ACR20) to treatment with Etanercept and MTX with an equivalence margin of 15% at a statistical significance level of 5% and a power of 80%, a sample size of 392 (196 per treatment) was assumed to be required for equivalence testing. Approximately 500 patients were planned to be randomised for this study in consideration of dropouts and deviations. For determination of the equivalence margin, a meta-analysis of relevant studies was done as shown in Table 14.

Table 14: ACR20 Responses in Relevant Enbrel Studies used for Equivalence Margin Estimation

Study	**Time measurement**	**Enbrel**		**Placebo**		**Absolute difference Enbrel-Placebo (%)**
		N	**% Response**	**N**	**% Response**	
Weinblatt et al[3]	24 weeks	59	71%	30	27%	45%
Combe et al[4]	24 weeks	100	74%	50	28%	46%
Keystone et al[5]	8 weeks	192	49%	29	17%	32%

Randomisation

A total of 517 subjects (recruitment 50.3% Japan, 43.5% Europe, 6.2% India) with moderate to severe RA were randomised in a 1:1 ratio to receive either YLB113 (etanercept) 50 mg or Enbrel ("EU

[3] Weinblatt ME, Kremer JM, Bankhurst AD. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999 Jan 28;340(4):253-9.
[4] B Combe, C Codreanu, U Fiocco. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006 Oct; 65(10): 1357–1362.
[5] Keystone EC, Schiff MH, Kremer JM. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2004 Feb;50(2):353-63.

sourced") once weekly for 52 weeks by subcutaneous injection. Treatment arm allocation was done by a central automatic system. Randomisation to treatment arms was stratified by age, disease activity and region.

Blinding (masking)

This was a double-blind trial. After the last subject completed the Week 24 visit (stage A), the study was unblinded for analysis of efficacy, safety and immunogenicity endpoints. All investigators and all patients were to remain blinded until the database was locked for Parts B and C.

Statistical methods

Analysis sets

The Full Analysis Set (FAS) included all subjects in the All Subjects Randomised Set (RND) set, who received at least one dose of study medication, regardless of actual treatment received. Randomised assignment to treatment groups was used for analysis.

The Per Protocol Set (PPS) included all subjects in the RND set who received at least one dose of study medication, had all efficacy measures necessary to calculate the primary efficacy endpoint (ACR20) at Week 24 and complied with the requirements of the protocol / had no major protocol deviations. The primary efficacy analysis was the proportion of patients who achieve an ACR20 response at Week 24 compared to baseline and was primarily based on the full analysis set (FAS).

Statistical analysis and missing data handling

The primary analysis was conducted applying binomial regression (using identity link function). Missing ACR20 data were imputed using a combination of non-responder imputation (NRI) and multiple imputation (MI) methods. The primary analysis was defined for FAS, however, in parallel, results were reported for the PP population. Equivalence was based upon the 95 % (2-sided) CI for the difference in ACR20 response rates at week 24. If the 95 % CI is fully contained within equivalence range of -15 % to 15 %, equivalence is established.

The primary analysis chosen is considered unusual for the analysis of a response endpoint (binary regression with identity link function allows estimation of proportions outside the 0% to 100% limits). Therefore, several sensitivity analyses (log-binomial regression, Cochran-Mantel-Haenzel test, and logistic regression) were provided (also applying different missing data handling).

5.3.2.1.2. Results

Participant flow

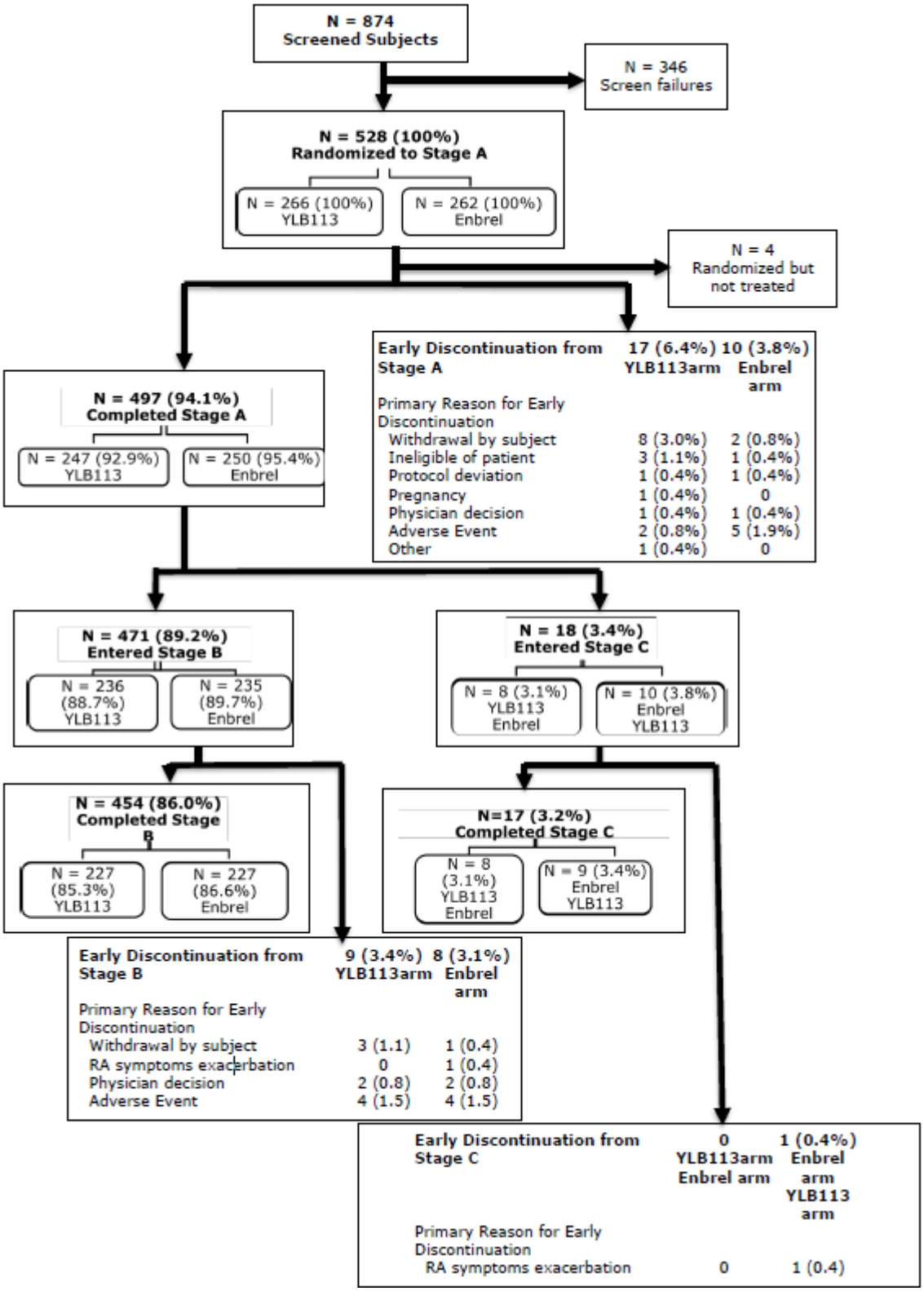
Of the 528 subjects randomised before week 24, 497 completed stage A. These were distributed to either proceed to Stage B (n=471) or Stage C (n=18).

Overall, early discontinuation was low during Stage A in both arms (Stage A completion: YLB113 (etanercept) 92.9%, Enbrel 95.4%). Primary reason for early discontinuation was withdrawal by subject, these were more often related to AE in the Enbrel arm (Enbrel n=5; YLB113 (etanercept) n=2). Two subjects in the Enbrel arm discontinued due to administration site reactions and another two for rash / urticaria. No subject in the YLB113 (etanercept) arm discontinued for AEs related to administration site reactions.

Subjects were given the choice after finalisation of Stage A to pursue either in Stage B or in parallel Stage C. However, entering Stage C was subject to fulfilling some criteria: Apart from good tolerability / absence of SAE subjects had to present with a minimum treatment success (improvement in DAS28

score ⩾0.6 at week 12 and/or week 24) to be eligible for entering the "switching arm" Stage C. Irrespective of fulfilling these criteria subjects could independently decide not to proceed to switching medication (Stage C), but to remain on the treatment that they have already received during Stage A and enter Stage B for the remainder of the study. Only a very small number of subjects entered Stage C. Seven patients were excluded from the FAS/SAF due concerns of data integrity and GCP compliance. The applicant provided the results of the study by including these 7 subjects. The re-analysis of the primary efficacy endpoint including the seven subjects did not relevantly change the conclusions. The efficacy results are presented for the 517 subjects (excluding the 7 subjects).

Figure 6: Disposition of subjects in study YLB113-002



Recruitment

Study YLB113-002 was conducted from July 2015 to June 2017 in 101 centres across Europe (Spain, Czech Republic, Hungary, Latvia, Bulgaria, Romania), Ukraine, India and Japan.

Conduct of the study

With Protocol Amendment Version 2.0 (Dated 26 May 2016), the study objective was changed to include an additional objective for assessing the sustainability of efficacy of Enbrel and YLB113 (etanercept) after crossing over the treatments. For this purpose, stage C was added, which, however, was not to be conducted in Japan.

Protocol Amendment Version 2.1 was implemented in all regions, except that stage C was not to be conducted in Japan. The target enrolled patient number since the competitive recruitment made it unlikely that the target number in each region would be as planned. The number of enrolled patients in Japan, EU and India was expected to be 500 with a competitive recruitment aiming to recruit approximately half the patients in Japan and half in Europe and India.

Baseline data

Demographic characteristics

The population of study YLB113-002 stage A (median age 54 years, 77.9% female) is considered representative for the general RA population. Age, gender and body mass index (BMI) of recruited subjects were similar across the arms. Due to high study completion rates the same applies to Stage B. Stage C was conducted in European sites only.

A summary of key demographic characteristics (age, gender, region etc.) is presented in Table 15.

Table 15: Demographic characteristics (Safety Analysis Set) – Stage A

Characteristic (unit)	Category	Statistics	YLB113 50 mg (N=263)	Enbrel 50 mg (N=254)	Total (N=517)
Age (years)		n (missing)	263 (0)	254 (0)	517 (0)
		Median	53.0	54.0	54.0
		Minimum	22	18	18
		Maximum	75	74	75
Sex	Male	n (%)	63 (24.0)	51 (20.1)	114 (22.1)
	Female	n (%)	200 (76.0)	203 (79.9)	403 (77.9)
Body Mass Index (kg/m^2)		n (missing)	263 (0)	254 (0)	517 (0)
		Mean	24.8	25.0	24.9
		SD	5.24	5.14	5.19
Country	Spain	n (%)	11 (4.2)	14 (5.5)	25 (4.8)
	Bulgaria	n (%)	25 (9.5)	22 (8.7)	47 (9.1)
	Czech Republic	n (%)	20 (7.6)	25 (9.8)	45 (8.7)
	Hungary	n (%)	37 (14.1)	27 (10.6)	64 (12.4)
	Romania	n (%)	1 (0.4)	0	1 (0.2)
	Latvia	n (%)	7 (2.7)	8 (3.1)	15 (2.9)
	Ukraine	n (%)	15 (5.7)	13 (5.1)	28 (5.4)
Region	Japan	n (%)	131 (49.8)	129 (50.8)	260 (50.3)
	India	n (%)	16 (6.1)	16 (6.3)	32 (6.2)
	Europe	n (%)	116 (44.1)	109 (42.9)	225 (43.5)

Baseline disease characteristics

Baseline characteristics were overall comparable across the treatment arms. The CRP was selected as acute phase reactant for 191 (36.9%) subjects and erythrocyte sedimentation rate (ESR) for 326 (63.1%) subjects. The mean (±SD) baseline composite DAS28 score of investigator chosen patient specific acute phase reactant was 5.763 (±1.078): 5.756 (±1.111) in YLB113 (etanercept) arm and 5.771 (±1.045) in Enbrel arm.

Majority of subjects were having ACR global functional status of Class II (353 [68.3%]), followed by Class III (86 [16.6%]), and Class I (78 [15.1%]). The average dose of MTX at Baseline was 11.37 mg and 11.82 mg in YLB113 (etanercept) and Enbrel arms, respectively, which was within the allowable range specified in inclusion criteria.

Overall, the recruited patient population of study YLB113-002 is considered adequate.

The baseline disease characteristics are summarised in Table 16.

Table 16: Baseline disease characteristics (Safety Analysis Set) – Stage A

Characteristic (unit)	Category	Statistics	YLB113 50mg (N=263)	Enbrel 50mg (N=254)	Total (N=517)
Tender joint counts (TJC) at Baseline	68 Total Score	n	263	253	516
		(missing)	263 (0)	253 (1)	516 (1)
		Mean	18.1	18.9	18.5
		SD	10.02	10.38	10.20
	28 Total Score	n	263	253	516
		(missing)	263 (0)	253 (1)	516 (1)
		Mean	12.7	12.6	12.7
		SD	6.36	6.06	6.21
Swollen joint counts (SJC) at Baseline	66 Total Score	n	263	253	516
		(missing)	263 (0)	253 (1)	516 (1)
		Mean	13.3	14.2	13.7
		SD	7.07	7.17	7.12
	28 Total Score	n	263	253	516
		(missing)	263 (0)	253 (1)	516 (1)
		Mean	10.3	10.5	10.4
		SD	4.92	4.93	4.92
Patient assessment of pain (VAS) at Baseline		n	262	253	515
		(missing)	262 (1)	253 (1)	515 (2)
		Mean	60.6	63.1	61.8
		SD	22.26	21.76	22.03
Patient global assessment of disease activity (Visual Analog Scale) at Baseline		n	263	253	516
		(missing)	263 (0)	253 (1)	516 (1)
		Mean	61.3	63.4	62.4
		SD	21.47	21.60	21.54
Physician global assessment of disease activity (Visual Analog Scale) at Baseline		n	263	253	516
		(missing)	263 (0)	253 (1)	516 (1)
		Mean	59.8	60.6	60.2
		SD	19.13	19.71	19.40
Health Assessment Questionnaire(HAQ) at Baseline		n	263	253	516
		(missing)	263 (0)	253 (1)	516 (1)
		Mean	1.06	1.13	1.09
		SD	0.712	0.685	0.699
Acute Phase Reactant selected for patient in calculating for ACR20 and DAS28	CRP	n (%)	102 (38.8)	89 (35.0)	191 (36.9)
	ESR	n (%)	161 (61.2)	165 (65.0)	326 (63.1)

Characteristic (unit)	Category	Statistics	YLB113 50mg (N=263)	Enbrel 50mg (N=254)	Total (N=517)
Disease Activity (DAS28) score at Baseline based on investigator chosen patient specific Acute Phase reactant		n			
		(missing)	261 (2)	252 (2)	513 (4)
		Mean	5.756	5.771	5.763
		SD	1.1112	1.0448	1.0781
Disease Activity (DAS28) score at Baseline based on patient-specific Acute Phase reactant	DAS28-CRP	n			
		(missing)	100 (2)	88 (1)	188 (3)
		Mean	5.191	5.237	5.213
		SD	1.0013	0.9222	0.9628
	DAS28-ESR	n			
		(missing)	161 (0)	164 (1)	325 (1)
		Mean	6.108	6.057	6.082
		SD	1.0306	0.9955	1.0118
Erythrocyte Sedimentation Rate(ESR) results (mm/hr)		n			
		(missing)	161 (102)	164 (90)	325 (192)
		Mean	35.5	32.8	34.2
		SD	21.45	20.60	21.04
C-reactive protein (CRP) (mg/dl)		n			
		(missing)	258 (5)	249 (5)	507 (10)
		Mean	1.299	1.015	1.159
		SD	2.0762	1.4559	1.8024
ACR Global Functional Status of RA	Class I	n (%)	38 (14.4)	40 (15.7)	78 (15.1)
	Class II	n (%)	180 (68.4)	173 (68.1)	353 (68.3)
	Class III	n (%)	45 (17.1)	41 (16.1)	86 (16.6)
	Class IV	n (%)	0	0	0
MTX dose at Baseline		n			
		(missing)	239 (24)	233 (21)	472 (45)
		Mean	11.37	11.82	11.59
		SD	3.967	4.021	3.996
Rheumatoid Factor	+ve	n (%)	188 (71.5)	174 (68.5)	362 (70.0)
	-ve	n (%)	73 (27.8)	79 (31.1)	152 (29.4)
Anti-CCP	+ve	n (%)	197 (74.9)	182 (71.7)	379 (73.3)
	-ve	n (%)	64 (24.3)	68 (26.8)	132 (25.5)

ACR= American College of Rheumatology; ACR20=20% improvement according to American College of Rheumatology criteria; CRP = C-reactive protein; DAS28 = Disease Activity Score using 28 tender and swollen joint counts; IQR = Interquartile Range calculated as 3rd Quartile (75%) – 1st Quartile (25%); MTX=Methotrexate; N = all subjects assigned to the population set; n = number of subjects; RA= Rheumatoid Arthritis; SD= Standard Deviation; VAS = visual analog scale.

Numbers analysed

The analysis set for Stage A is summarized in Table 17.

Table 17: Data set analyses (all subjects enrolled set) – Stage A

Analysis Datasets	All (N=874) n (%)
Screened	874 (100)
Screen failure	346 (39.6)
All Subjects Randomized Set	528 (60.4)
Full Analysis Set (Intention to treat)*	517 (59.2)
Safety Analysis Set*	517 (59.2)
Per Protocol Set	477 (54.6)

Analysis Datasets	All (N=874) n (%)

N = all subjects assigned to the population set; n = number of subjects; % = percentage of subjects calculated relative to the total number of subjects in the analysis set.
*Does not include subjects who were randomized but not treated (n=4) and those with lack of data integrity and GCP compliance (n=7).

Outcomes and estimation

Primary efficacy endpoint

The primary endpoint is the proportion of patients with an ACR20 response at Week 24. As specified in Statistical Analysis Plan, the primary analysis population is the full analysis set (FAS). For the primary analysis, missing ACR20 data were imputed using a combination of non-responder imputation (NRI) and multiple imputation (MI) methods.

Table 18: Primary Efficacy: Estimate and Confidence Intervals for Differences in ACR20 Response Rate at Week 24 (NRI+MI) (Full Analysis Set)

			Difference in proportions (YLB113 50 mg – Enbrel 50 mg, %)	
Treatment Arm	N	Proportion	Estimate	95% Confidence Interval
YLB113 50 mg	26381.2		-5.6	(-11.6, 0.5)
Enbrel 50 mg	25486.8			

The adjusted proportions of subjects with ACR20 response in each treatment group at Week 24 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 Week 24 (E (response to treatment at Week 24) = treatment + Baseline DAS28 stratum + Age + Region). The 95% confidence interval for the estimated difference in proportions is produced using the binomial 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. One subject has Day 1 pre-treatment missing components and thus, the baseline value is imputed using multiple imputation.

The model estimate portion (NRI + MI) of subjects achieving ACR20 response was high in both arms, slightly higher for Enbrel (86.8%) as compared to the test medication (81.2%). The 95% CIs for the difference in portions (-5.6 [-11.6, 0.5]) were within the ±15% equivalence acceptance margin.

The results obtained for the per protocol set (PPS) are more favourable than those found for the FAS. Equally, the difference in results (per treatment arm) between the two datasets is in the same order of magnitude (around 3-5% higher response rates in PPS as compared to FAS).

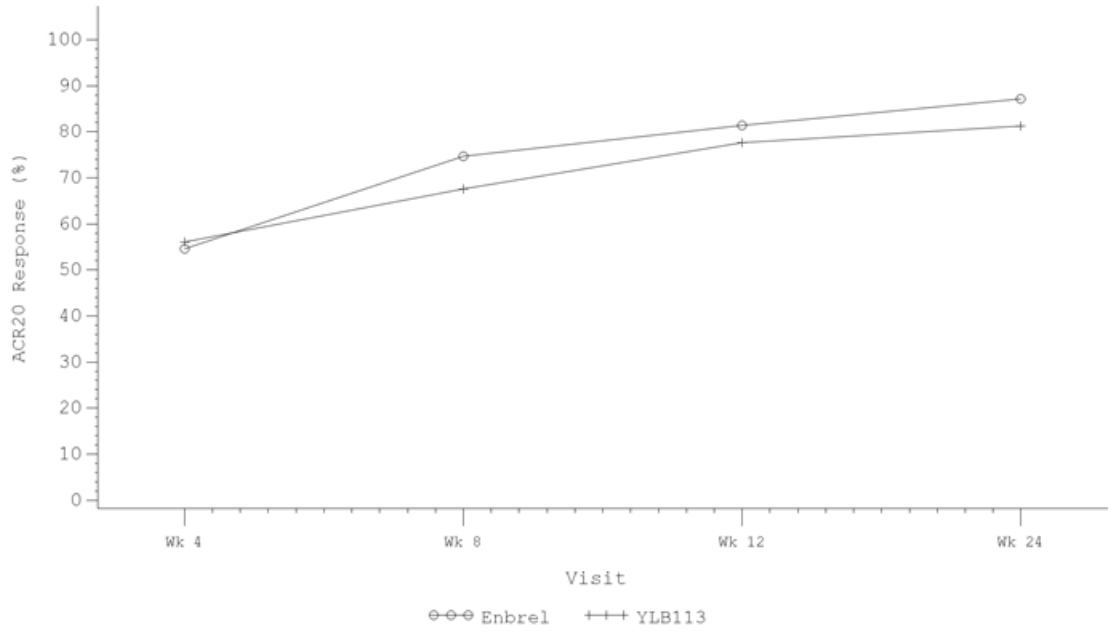
Table 19: Primary Efficacy: Sensitivity Analysis: Estimate and Confidence Intervals for Differences in ACR20 Response Rate at Week 24 (NRI) (Per Protocol Set)

			Difference in proportions (YLB113 50 mg – Enbrel 50 mg, %)	
Treatment Arm	N	Proportion	Estimate	95% Confidence Interval
YLB113 50 mg	23986.0		-4.6	(-10.1, 0.8)
Enbrel 50 mg	23890.6			

The adjusted proportions of subjects with ACR20 response in each treatment group at Week 24 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 Week 24 (E (response to treatment at Week 24) = treatment + Baseline DAS28 stratum + Age + Region) The 95% confidence interval for the estimated difference in proportions is produced using the binomial regression model. Missing data have been imputed according to NRI. 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.

In line with the results already observed for the FAS, the 95% CIs for the model estimate difference (NRI) in portions of ACR20 response are within the ±15% acceptance range for equivalence (-4.6 [-10.1, 0.8]). As could be expected for the PP population, response rates are higher as compared to the FAS (YLB113: 86.0 vs 81.2; Enbrel 90.6 vs 86.8).

Figure 7: ACR20 Response Over Time (Full Analysis Set)



The time course of ACR20 response rates were very similar between the YLB113 (etanercept) and the Enbrel treatment arm from the first efficacy assessment at week 4 until the end of Stage A after 24 weeks. In both treatment arms response rates are above 50% at the earliest assessment time point and are maintained slightly increasing until the end of Stage A.

Sensitivity analyses for the primary endpoint

Additional sensitivity analyses were provided for the primary endpoint (see Table 20) and overall support results of the primary analysis.

Table 20: Additional sensitivity analyses

Analysis Set	Statistical analysis	Treatment	N	Proportion	Adjusted risk difference	95% confidence interval
FAS	Cochran-Mantel-Haenzel test (NIR+MI)	YLB113	263	81.2	-4.6	(-10.9, 1.7)
		Enbrel	254	86.8		
	Cochran-Mantel-Haenzel test (MI)	YLB113	263	86.2	-2.5	(-8.2, 3.3)
		Enbrel	254	89.6		
	Log-binomial regression (NIR+MI)	YLB113	263	81.2	-6.6	(-13.8, 0.5)
		Enbrel	254	86.8		

	Log-binomial regression (MI)	YLB113	263	86.2	-3.9	(-10.2, 2.4)
		Enbrel	254	89.6		
	Statistical analysis	**Treatment**	**N**	**Proportion**	**Adjusted odds ratio**	**95% confidence interval**
	Logistic regression (NIR+MI)	YLB113	263	81.2	0.7	(0.2, 1.2)
		Enbrel	254	86.8		
	Logistic regression (MI)	YLB113	263	86.2	0.8	(0.2, 1.3)
		Enbrel	254	89.6		
PP	**Statistical analysis**	**Treatment**	**N**	**Proportion**	**Adjusted risk difference**	**95% confidence interval**
	Binomial regression	YLB113	239	86.0	-4.6	(-10.1, 0.8)
		Enbrel	238	90.6		
	Cochran-Mantel-Haenzel test	YLB113	239	86.0	-3.2	(-9.0, 2.6))
		Enbrel	238	90.6		
	Log-binomial regression	YLB113	239	86.0	-5.3	(-11.4, 0.8)
		Enbrel	238	90.6		
	Statistical analysis	**Treatment**	**N**	**Proportion**	**Adjusted odds ratio**	**95% confidence interval**
		YLB113	239	86.0	0.7	(0.4, 1.2)
		Enbrel	238	90.6		

Secondary endpoints

ACR20 at early time points

At early time points (week 4, 8, 12) equivalent efficacy in terms of ACR20 response was observed between the test product and Enbrel. In both treatment arms response rates increase with time (week 4: 55.8-53.9; week 8: 67.5-74.0; week 12: 77.5-81.0). At all-time points, the 95% CIs for the model estimate in response rates is within the ±15% acceptance range. The same applies to the results for the PP population.

Table 21: Secondary efficacy: Estimate and Confidence Intervals for Differences in ACR20 Response Rate by Visit (Week) (NRI+MI) (FAS)

				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	263	55.8	1.9	(-6.3, 10.2)
	Enbrel 50 mg	254	53.9		
Day 57 (Week 8)	YLB113 50 mg	263	67.5	-6.5	(-14.2, 1.2)
	Enbrel 50 mg	254	74.0		
Day 85 (Week 12)	YLB113 50 mg	263	77.5	-3.5	(-10.0, 3.1)
	Enbrel 50 mg	254	81.0		

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 binomial 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 120305 has Day 1 pre-treatment missing components and thus, the baseline value is imputed using multiple imputation.

ACR50

ACR50 response rates are lower in both treatment arms (as compared to ACR20). However, the portions of subjects achieving a 50% improvement in ACR are increasing over the 24-week Stage A treatment period. Apart from the assessment time point at 24 weeks, the 95% CIs for the estimate of portion difference between the arms are within the ±15% acceptance margin. Study YLB113-002 was not powered for ACR50 response rate comparison at single early time points. Very similar results were obtained for the PP population.

Table 22: Secondary efficacy: Estimate and Confidence Intervals for Differences in ACR50 Response Rate by Visit (Week) (NRI+MI) (FAS)

				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	263	19.9	-2.5	(-9.6, 4.7)
	Enbrel 50 mg	254	22.4		
Day 57 (Week 8)	YLB113 50 mg	263	38.0	-1.3	(-9.5, 6.8)
	Enbrel 50 mg	254	39.3		
Day 85 (Week 12)*	YLB113 50 mg	263	48.6	1.0	(-7.4, 9.5)
	Enbrel 50 mg	254	47.5		
Day 169 (Week 24)	YLB113 50 mg	263	56.3	-10.7	(-18.9, -2.6)
	Enbrel 50 mg	254	67.1		

The adjusted proportions of subjects with ACR50 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 binomial regression model.
Missing data have been imputed according to NRI and/or MI. N = number of subjects in the analysis set with ACR50 results non-missing.
For subject 120305 has Day 1 pre-treatment missing components and thus, the baseline value is imputed using multiple imputation.
* Estimates of proportions, the difference in proportions and confidence intervals are produced using binomial regression model with observed data as in-between imputation variance is zero.

ACR70

In terms of the ACR70 response rates, both for the FAS and the PP population the 95% CIs for the model estimates on portion differences were within the ±15% acceptance margin at early assessment time points of Stage A.

Table 23: Secondary efficacy: Estimate and Confidence Intervals for Differences in ACR70 Response Rate by Visit (Week) (NRI+MI) (FAS)

				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	263	8.7	2.3	(-1.4, 6.1)
	Enbrel 50 mg	254	6.3		
Day 57 (Week 8)*	YLB113 50 mg	263	15.3	0.9	(-5.0, 6.9)
	Enbrel 50 mg	254	14.3		
Day 85 (Week 12)*	YLB113 50 mg	263	25.6	-0.7	(-8.1, 6.7)
	Enbrel 50 mg	254	26.2		
Day 169 (Week 24)	YLB113 50 mg	263	35.1	0.0	(-8.0, 8.0)
	Enbrel 50 mg	254	35.0		

The adjusted proportions of subjects with ACR70 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 binomial regression model. Missing data have been imputed according to NRI and/or MI. N = number of subjects in the analysis set with ACR70 results non-missing. A subject had Day 1 pre-treatment missing components and thus, the baseline value is imputed using multiple imputation.

Due to less responders from India, Europe was pooled with India to get reliable estimates. * Estimates of proportions, the difference in proportions

DAS28 Response at Week 4, 8, 12 and 24 of Dosing

The secondary efficacy parameter, DAS28 response rate at Week 4, 8, 12, and 24 of dosing in FAS population was summarised using the LS mean (95% CI) change from baseline for both treatment arms.

Table 24: Secondary efficacy: ANCOVA Model for DAS28 (MI) by Visit (Week) (FAS)

			Mean Change from Baseline		Treatment Difference (YLB113 50 mg – Enbrel 50 mg)	
Visit (Week)	Treatment Arm	N	LS Mean	95% CI	LS Mean	95% CI
Day 29 (Week 4)	YLB113 50 mg	263	-1.36	(-1.539, -1.183)	0.03	(-0.137, 0.204)
	Enbrel 50 mg	254	-1.39	(-1.577, -1.213)		
Day 57 (Week 8)	YLB113 50 mg	263	-1.69	(-1.883, -1.505)	0.00	(-0.179, 0.185)
	Enbrel 50 mg	254	-1.70	(-1.889, -1.504)		

Visit (Week)	Treatment Arm	N	Mean Change from Baseline		Treatment Difference (YLB113 50 mg – Enbrel 50 mg)	
			LS Mean	95% CI	LS Mean	95% CI
Day 85 (Week 12)	YLB113 50 mg	263	-1.94	(-2.138, -1.736)	0.03	(-0.166, 0.219)
	Enbrel 50 mg	254	-1.96	(-2.168, -1.759)		
Day 169 (Week 24)	YLB113 50 mg	263	-2.43	(-2.616, -2.239)	0.05	(-0.129, 0.228)
	Enbrel 50 mg	254	-2.48	(-2.668, -2.286)		

Missing data have been imputed according to multiple imputation (MI).
N = mean number of subjects in the analysis set with DAS28 (ESR or CRP) results computable across the multiply imputed datasets.
LS = Least Squares
DAS28 (where the acute phase reactant (CRP or ESR) mean change from Baseline (Week 0: Day 1) to Week X = overall mean + treatment group + Baseline DAS28 + age + region + random error

Baseline values for DAS28-ESR and DAS28-CRP were between 5.2 and 6.1 across arms, hence, reflecting "very active" disease activity. The decrease in the DAS28 score was already -1.36 to -1.39 at the earliest assessment time point. Over the entire duration of Stage A DAS28 score improvements were clinically meaningful and very similar between the arms.

The statistical analysis of change in DAS28 from Baseline at Week 24 by DAS28-acute phase reactants is shown Table 25.

Table 25: Secondary efficacy: ANCOVA Model for DAS28 at Week 24 (FAS)

DAS28-Acute phase reactant		N	Mean Change from Baseline		Treatment Difference (YLB113 50 mg – Enbrel 50 mg)	
			LS Mean	95% CI	LS Mean	95% CI
DAS28-CRP	YLB113 50 mg	102	-2.18	(-2.531, -1.820)	0.07	(-0.216, 0.365)
	Enbrel 50 mg	89	-2.25	(-2.609, -1.892)		
DAS28-ESR	YLB113 50 mg	161	-2.63	(-2.852, -2.412)	-0.01	(-0.230, 0.214)
	Enbrel 50 mg	165	-2.62	(-2.846, -2.403)		

N = mean number of subjects in the analysis set with DAS28 (ESR or CRP respectively).
LS = Least Squares
DAS28-ESR mean change from Baseline (Week 0: Day 1) to Week 24 = overall mean + treatment group + Baseline DAS28-ESR + age + region + random error (both DAS-ESR)
DAS28-CRP mean change from Baseline (Week 0: Day 1) to Week 24 = overall mean + treatment group + Baseline DAS28-CRP + age + region + random error (both DAS-CRP)

The DAS28 was calculated using specific formula depending on whether CRP or ESR was used for that particular patient (DAS28-CRP: in 38.8% of patients receiving YLB113 (etanercept) and 35% of patients receiving Enbrel or DAS28-ESR: in 61.2% in the YLB113 (etanercept) arm and 65% in the Enbrel arm).

Similar improvements in DAS28-CRP and DAS28-ESR scores were achieved between the arms.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26: Summary of Efficacy for trial YLB113-002

Title: A Comparative Study to Assess the Efficacy, Safety and Immunogenicity of YLB113 (etanercept) and Enbrel for the Treatment of Rheumatoid Arthritis			
Study identifier	YLB113-002		
Design	Pivotal ph.III study YLB113-002 was a randomised, double-blind, parallel group clinical equivalence study in 101 centers in Japan, India and 7 European countries (BG, ES, CZ, HU, RO, LV, Ukraine). A total of n=517 subjects (recruitment 50.3% Japan, 43.5% Europe, 6.2% India) with moderate to severe RA were randomised in a 1:1 ratio to receive either YLB113 (etanercept) 50 mg or Enbrel ("EU sourced") once weekly for 52 weeks by sc injection. Randomisation to treatment arms was stratified by age, disease activity and region as described above.		
	Duration of main phase:		After 28-day screening subjects were randomised to 24 weeks db main treatment for primary efficacy assessment Stage A; After unblinding for analysis of efficacy, safety and immunogenicity, subjects proceed to either Stage B (28 weeks db receiving the same treatment as during Stage A) or Stage C (28 weeks db switching the medication previously received during Stage A). Stage C was not conducted in Japan and was offered only to those subjects achieving minimum treatment success (>0.6 DAS28) at either week 12 or 24 of Stage A and not presenting with SAE.
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		4 weeks safety follow-up (week 53-56)
Hypothesis	Equivalence in terms of ACR20 response rate Equivalence of efficacy was assessed in the FAS (and PP population) and was based upon the 95% (2-sided) CIs for the difference in percentage of patients achieving an ACR20 response at wk 24 compared to baseline (Day 1) with an equivalence margin of ±15%		
Treatments groups	YLB113 (etanercept, manufactured in Japan)		50mg s.c., once weekly, 52 weeks, 266 subjects randomised
	Enbrel (manufactured by Pfizer)		50mg s.c., once weekly, 52 weeks, 266 subjects randomised
Endpoints and definitions	Primary endpoint	ACR20 at 24 weeks (end of Stage A)	The American College of Rheumatology (ACR) 20% response criterion is a multi-dimensional endpoint. To meet ACR20 response criteria, a patient must have at least 20% improvement from baseline (Day 1) in the all of following ACR Core Set values: - 20% decrease in SJC - 20% decrease in TJC - 20% improvement in at least 3 of the following 5 measures: - Patient assessment of pain (VAS) - Patient global assessment of disease activity (VAS) - Physician global assessment of disease activity (VAS) - Acute phase reactant as measured by CRP or ESR - HAQ-DI

	Secondary endpoints	ACR50; ACR70; ACR responses at early time points; DAS28 score	ACR20/50/70 rate at wk 4, 8, and 12 of dosing. An improvement in the DAS28 response at wk 4, 8, 12, and 24 of dosing. The DAS28 score was calculated using results from a 28-joint subset of the 66/68 SJC/TJC. The DAS28 is a composite score (ranging from 0 to 9.4) calculated using the results of the 28-joint subset of the 66/68 SJC/TJC, CRP levels (mg/L) or ESR levels (mm/hr), and the subject's global assessment of disease activity (0 to 100 scale).
	Safety endpoints	AE; Clinical parameters (lab, ECG, vital signs); Immunogenicity	Incidence of anti-drug antibodies (ADA) at wk 4,8,12,24,36,44,52

Results and Analysis

Analysis description	**Primary / Secondary Analysis**		
Analysis population and time point description	The primary analysis population is the FAS. Binomial regression (using identity link function) was used and missing ACR20 data were imputed using a combination of non-responder imputation (NRI) and multiple imputation (MI) methods. In parallel, results are reported for the PP population. Equivalence was based upon the 95 % (2-sided) CI for the difference in ACR20 response rates at wk 24. If the 95 % CI is fully contained within equivalence range of -15 % to 15 %, equivalence is established.		
Descriptive statistics and estimate variability	Treatment group	YLB113 (etanercept)	Enbrel
	Number of subject (FAS total 517)*	FAS: 263 PPS: 239	FAS: 254 PPS: 238
	ACR20 at wk 24 (%) (**FAS; NRI+MI**)	81.2	86.8
	ACR20 at wk 24 (%) (**PPS; NRI**))	86.0	90.6
	ACR50 at wk 24 (%) (FAS; NRI+MI)	56.3	67.1
	ACR70 at wk 24 (%) (FAS; NRI+MI)	35.1	35.0
	DAS28-CRP at wk 24 ANCOVA Model (FAS)	-2.18 (n=102)	-2.25 (n=89)
	DAS28-ESR at wk 24 ANCOVA Model (FAS)	-2.63 (n=161)	-2.62 (n=165)
Effect estimate per comparison	ACR20 at wk 24 (%) (**FAS; NRI+MI**)	Comparison groups	YLB113 (etanercept) vs Enbrel
		Point estimate	-5.6
		95% CI	-11.6; 0.5
		Test	-15% < CI < +15%**

	ACR20 at wk 24 (%) (**PPS; NRI**)	Comparison groups	YLB113 (etanercept) vs Enbrel
		Point estimate	-4.6
		95% CI	-10.1; 0.8
		Test	-15% < CI < +15%
	Secondary endpoint ACR50 at wk 24 (%) (FAS; NRI+MI)	Comparison groups	YLB113 (etanercept) vs Enbrel
		Point estimate	-10.7
		95% CI	-18.9; -2.6
		Test	Outside equivalence margin***
	Secondary endpoint ACR70 at wk 24 (%) (FAS; NRI+MI)	Comparison groups	YLB113 (etanercept) vs Enbrel
		Point estimate	0.0
		95% CI	-8.0; 8.0
		Test	-15% < CI < +15%
	Secondary endpoint DAS28-CRP at wk 24 ANCOVA Model (FAS)	Comparison groups	YLB113 (etanercept) vs Enbrel
		Treatment difference LS mean	0.07
		95% CI	-0.216; 0.365
		Test	-0.216<0.07<0.365
	Secondary endpoint DAS28-ESR at wk 24 ANCOVA Model (FAS)	Comparison groups	YLB113 (etanercept) vs Enbrel
		Treatment difference LS mean	-0.01
		95%	-0.230; 0.214
		Test	-0.230<-0.01<0.214
Notes	*Data presentation for FAS based on n=517. According to the Disposition of subjects tree, n=528 were randomised to treatment. Further clarification is requested for n=4 subjects not receiving any treatment and n=7 subjects with GCP violations ** equivalence margin of 95% CIs within ±15% was defined along previous etanercept biosimilar MAAs. *** 95% CIs of point estimates for ACR50 response rates at wk 4 (-2.5 [-9.6, 4.7]), wk 8 (-1.3 [-9.5, 6.8]) and wk 12 (1.0 [-7.4, 9.5]) were within the equivalence margin; presentation of secondary endpoints in study YLB113-002 is exploratory		

5.3.3. Overall discussion and conclusions on clinical efficacy

5.3.3.1. Discussion

Design and conduct of clinical studies

Study design

The pivotal phase III study (YLB113-002) was a multicentre, double-blind, randomised, parallel-group comparative study to assess the efficacy, safety, and immunogenicity of YLB113 (etanercept) and Enbrel for the treatment of rheumatoid arthritis (RA). A total of 517 subjects (22.1% male, 77.9% female; recruitment 50.3% Japan, 43.5% Europe, 6.2% India) were randomised and included in the FAS in a 1:1 ratio to receive either YLB113 (etanercept), manufactured in Japan, 50 mg or Enbrel ("EU sourced") once weekly for 52 weeks by subcutaneous injection. Randomisation to treatment arms was

stratified by age, disease activity and region. The RA severity of included subjects was adequately reflected by their baseline disease characteristics.

The choice of the clinical model of moderate to severe RA patients not adequately controlled with methotrexate is in line with the scientific advice given to the applicant in 2014 (EMA/CHMP/SAWP/693250/2014) and in accordance with CHMP guidance (CPMP/EWP/556/95 Rev.2). This clinical model is considered sufficiently sensitive to enable the detection of differences between the biosimilar candidate and the originator, as among the approved therapeutic indications of Enbrel, RA has been the most thoroughly studied. In addition, there are validated and reasonably sensitive methods to study the disease activity of RA which would therefore allow for the detection of any possible differences between the compared products.

The general design of the study, the dosing regimen, the duration of the treatment (24 weeks Stage A, 28 weeks safety / immunogenicity assessment, 4 weeks follow-up) are in line with EMA guideline recommendations on clinical investigation of medicinal products for the treatment of RA (CPMP/EWP/556/95 Rev.2) and are therefore acceptable by CHMP.

The switching data obtained from stage C are considered supportive evidence for exchangeability as the study was not powered for the switching analysis.

Study endpoints

ACR20 response rate at week 24 as primary efficacy endpoint is representative of the clinical status in RA and is therefore acceptable by CHMP. As a multidimensional endpoint, the ACR response rate combines measuring objective clinical signs and symptoms (SJC, TJC, CRP or ESR), subjective measuring of the most debilitating key symptom pain [VAS] and subjective / objective global assessment of disease activity. Thus, a wide range of RA clinical features is covered by the ACR response rate.

Secondary endpoints like e.g. responder rates at earlier time points than 24 weeks (e.g. after 12 weeks) and responder rates for improvements greater than 20% (ACR50, ACR70) in addition to the continuous endpoint DAS28 scores etc. were also assessed. Thereby, the choice of the secondary endpoints including DAS28 scores, continuous endpoint, is considered adequate by CHMP.

For each patient, the acute phase reactant (CRP or ESR) to be used throughout the study (for that specific patient) was recorded on the CRF at screening. For patients for whom the CRP acute phase reactant was identified at screening, only CRP was used throughout the trial in the definition of ACR20 (as well as in the definitions of ACR50 and ACR70). The decision to follow up a patient either for CRP or ESR for the remainder of the study (as ACR and DAS component) was within the responsibility of the investigator according to the preference of each rheumatology centre. The approach is agreed by CHMP.

Equivalence margin

The sample size was calculated assuming 70% response rate (ACR20) to treatment with Etanercept and MTX with an equivalence margin of 15% at a statistical significance level of 5% and a power of 80%. The equivalence margin was defined based on a meta-analysis of three historical Enbrel studies.

The random-effects meta-analysis of these 3 studies estimated a risk difference of 40.4% with a 95% CI of (31%, 50%). To preserve at least 50% of the effect of Enbrel over and above placebo, an equivalence limit of 15% was used for the primary analysis. This is considered adequate by CHMP.

GCP inspection

A routine GCP inspection was carried out at two clinical sites of the phase III study (YLB113-002) following a request from the CHMP, dated 28 June 2018, in connection with the evaluation of the MAA

for Nepexto procedure for which Fubelv is a duplicate of. No critical findings were found but some major and minor findings were observed. The observations, which were considered to be in the responsibility of the investigator sites are sites specific and are unlikely to affect the validity of the data. Overall, no violations to GCP compliance were detected that would question validity of data obtained from the pivotal study YLB113-002.

Efficacy data and additional analyses

Therapeutic equivalence

The pivotal trial has demonstrated comparable efficacy of YLB113 (etanercept) and the reference product Enbrel in terms of proportion of ACR20 responders at week 24.

The model estimate portion (NRI + MI) of subjects achieving ACR20 response was high in both arms, slightly higher for Enbrel (86.8%) as compared to the test medication (81.2%). The 95% CIs for the difference in portions (-5.6 [-11.6, 0.5]) were within the ±15% equivalence acceptance margin.

Response rates for ACR20 at week 24 observed in study YLB113-002 are in the same order of magnitude (however, about 5-10% higher) as observed in preceding etanercept biosimilar MAAs for which the RA treatment setting was chosen to demonstrate equivalence.

For the primary analysis, missing ACR20 data were imputed using a combination of non-responder imputation (NRI) and multiple imputation (MI) methods. Additional sensitivity analyses were provided for the primary endpoint and support the results of the primary analysis.

In line with results obtained for the primary endpoint, similar efficacy outcomes between the arms were also observed for secondary endpoints. The time course of ACR20 response rates was similar between the YLB113 (etanercept) and the Enbrel treatment arm from the first efficacy assessment at week 4 till the end of stage A after 24 weeks. In both treatment arms, response rates are above 50% at the earliest assessment time point and are maintained and slightly increasing for the remainder of stage A. At each early time points (week 4, 8. 12) the 95% CIs for the model estimate in response rates were within the ±15% acceptance range.

Broken down to the single ACR parameters (SWJ, TJC, Pain, Patient Global Assessment of Disease Activity, Physician Global Assessment of Disease Activity, Health Assessment Questionnaire, ESR and CRP as acute phase reactants), the summarised percent changes in ACR-N were similar between the treatment arms.

Extrapolation to other indications

A single study in RA was performed. According to the EMA guidelines on biosimilarity, extrapolation to other indications may be accepted based on the total package of quality, pre-clinical, PK and clinical evidence. Extrapolation to other authorised indications of Enbrel is considered justified, since all conditions for which Enbrel is approved are characterised by increased levels of TNFα as prominent inflammatory mediator forming the necessary elements in the chain of pathophysiological events. Elevated levels of TNFα are found in the serum and synovium in the diverse arthritis indications and in RA. Etanercept is a competitive inhibitor of TNFα-binding to its cell surface receptors and thereby inhibits the biological activity of TNFα.

The proposed text for SmPC section 4.1 and 5.1 of the SmPC is in line with that of the reference product.

5.3.3.2. Conclusions on the clinical efficacy

Equivalence regarding efficacy has been shown in a RA model. The results obtained for the primary efficacy endpoint (ACR20 response rate at week 24) and secondary efficacy measures (ACR20 at earlier time points, ACR50/70 response rates, and continuous DAS28 scores) show therapeutic equivalence between YLB113 (etanercept) and the reference product Enbrel within the ±15% (for the 95% 2-sided CIs) equivalence margin.

Based on the analytical, non-clinical and clinical similarity of Nepexto to Enbrel, extrapolation to the other indications of the reference product is accepted by CHMP.

5.4. Clinical safety

Please refer to the table of studies in section 5.1.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

Safety data for YLB113 (etanercept) are available from three phase I PK study in healthy volunteers (YLB113-001, LBC14-155, ETA.50/334) and one pivotal phase III (YLB113-002) efficacy and safety trial in RA patients. Overall, over 690 subjects/patients have been exposed to etanercept, as single (n=169) or multiple (n=524) doses.

5.4.2. Patient exposure

Exposure in healthy volunteers:

In the (cross-over) PK studies, 169 healthy male volunteers were exposed to a single dose of YLB113 (etanercept). In the Japanese phase I study YLB113-001, a single dose of 25 mg was used in 60 subjects whereas in the supportive Indian phase I study LBC14-155, a single dose of 50 mg was administered to 58 subjects. In the pivotal Jordanian phase I study ETA.50/334, a single dose of 50 mg was used in 51 subjects.

Exposure in patients with moderate to severe RA:

In the pivotal study YB113-002, a dose of 50 mg was administered once a week together with MTX.

The safety population included all randomised patients who had received at least one dose of trial medication (n= 264 for YLB113 (etanercept) and n = 260 for Enbrel).

Treatment period A (first 24 weeks of treatment, efficacy and safety) was completed by 248 (93.9%) of the YLB113 (etanercept) patients and by 248 (95.4%) of the Enbrel patients. The total exposure for a single patient was 24 doses equivalent to 24 weeks of treatment.

Treatment period B (long-term safety over 52 weeks and immunogenicity) was completed by 226 (95.8%) of the YLB113 (etanercept) patients and by 229 (97.4%) of the Enbrel patients. The total exposure for a single patient was 52 doses equivalent to 52 weeks of treatment.

Treatment period C (cross-over treatment) was entered by additional 10 YLB113 (etanercept) patients and 8 Enbrel patients, of whom 9 (90%) and 8 (100%) completed the 52-week treatment.

5.4.3. Adverse events

Phase 1 trials in healthy volunteers:

Study YLB113-001

In this study, a total of 10.2% of subjects in the YLB113 (etanercept) group experienced an adverse event (AE) compared to 20% in the Enbrel group. Most of the AEs were mild to moderate and all were known from Enbrel. Infections and infestations were seen at a higher frequency in the Enbrel group compared to YLB113 (etanercept) group (6.7% vs 0%).

Study LBC14-155

A total of 14 AEs was seen of which 3 AEs occurred during the study and 11 during post study evaluation. All were mild or moderate, unexpected and unlikely related to the investigational product.

Study ETA.50/334

Fifty-one (51) subjects were dosed in period I whereas 43 subjects were dosed in period II. A total of 47 subjects received YLB113 (etanercept) [treatment A] and 47 subjects received EU-sourced Enbrel [treatment B]. During the study, 53 adverse events were reported in 24 of the study subjects (47.06 %). At least one TEAE was experienced by 14 subjects (out of 47 subjects, 29.79%) after administration of YLB113 (etanercept) and by 16 subjects (out of 47 subjects, 34.04%) after administration of reference product, Enbrel. None of these AEs was serious and there were no AEs that resulted in any subject's death, or the occurrence of any other significant event.

Conclusion

In the three studies, the safety profile was similar between both products. No deaths or serious adverse events (SAEs) were reported. There were no clinically significant differences in the occurrence of AEs in healthy volunteers between YLB113 (etanercept) and Enbrel.

Phase 3 Study in RA patients:

YLB113-002 – Stage A

In the YLB113 (etanercept) group, 22.0% of the patients reported an AE related to the study drug whereas 35.8% of patients reported the respective drug-related AEs in the Enbrel group.

Treatment emergent adverse events (TEAE) as reported in this study Stage A were significantly higher in the Enbrel group compared to the YLB113 (etanercept) group, 65.4% vs 55.3%. Of all patients with reported TEAEs, the majority of the events were mild (33.7% for YLB113 (etanercept) and 37.3% for Enbrel) to moderate (18.6% for YLB113 (etanercept) and 26.2% for Enbrel).

In total, 3.0% of the patients in the YLB113 (etanercept) group and 1.9% of the patients in the Enbrel group showed a severe outcome of their TEAE.

Table 27: Overview of adverse events – Stage A

Adverse Event category	**YLB113 (etanercept)** n (%)	**Enbrel** n (%)
	264	260
TEAEs	146 (55.3)	170 (65.4)
TEAES related to drug	58 (22.0)	93 (35.8)
Serious TEAEs	8 (3.0)	4 (1.5)
Serious TEAEs related to drug	4 (1.5)	1 (0.4)
AEs leading to premature study discontinuation	2 (0.8)	5 (1.9)
AEs leading to death	0	0

n: number of patients with at least 1 AE in the category

In Stage A, the most frequently reported TEAEs belonged to the System Organ Class (SOC) infections and infestations and administration site conditions (Table 28).

Table 28: Overview TEAEs >5% by SOC - Stage A

TEAE by System Organ Class	**YLB113 (etanercept)**		**Enbrel**	
	n (%)	# Events	n (%)	# Events
	264		260	
Infections and infestations	63 (23.9)	81	72 (27.7)	92
General disorders and admin site conditions	29 (11.0)	79	80 (30.8)	466
Gastrointestinal disorders	25 (9.5)	31	27 (10.4)	39
Injury, poisoning and procedural complications	17 (6.4)	20	16 (6.2)	18
Musculoskeletal and connective tissue disorders	21 (8.0)	25	27 (10.4)	40
Respiratory, thoracic and mediastinal disorders	17 (6.4)	19	12 (4.6)	14
Skin and subcutaneous tissue disorders	20 (7.6)	26	22 (8.5)	31
Nervous system disorders	7 (2.7)	8	17 (6.5)	28

n: number of patients with at least 1 AE in the category

The main TEAE by preferred term (PT) reported for infections and infestations was nasopharyngitis including 11.4% of the patients in the YLB113 (etanercept) group and 10.0% in the Enbrel group. For general disorders and administration site conditions, the main AEs were injection site erythema and injection site reaction, 1.9% vs 9.6%, and 3.8% vs 13.5% for YLB113 (etanercept) and Enbrel, respectively.

YLB113-002 – Stage B and C

For Stage B, 52.5% of the patients in the YLB113 (etanercept) group reported at least one TEAE, whereas the respective percentage was 62.1% in the Enbrel group. This is similar to Stage A Drug related AEs were reported for 11.9% in the YLB113 (etanercept) group compared to 26.4% in the Enbrel group.

Most TEAEs assessed as related or possibly related to study medication were mild in severity and resolved. The most frequently reported TEAE considered related to trial medication classified by SOC was general disorders and administration site conditions, and infections and infestations.

In Stage C, 3 patients experienced a TEAE in both groups, 1 patient in the YLB113 (etanercept) compared to 2 patients in the Enbrel group with a TEAE possibly related to the study drug.

Most TEAEs assessed as related or possibly related to study medication were mild in severity and resolved. The most frequently reported TEAE considered related to study medication by SOC was general disorders and administration site conditions observed in 12.5% subjects in the Enbrel arm.

Table 29: Overview of Adverse Events - Stage B/C

	Stage B		**Stage C**	
Adverse Event Category	**YLB113 (etanercept)**	**Enbrel**	Enbrel/ **YLB113 (etanercept)**	YLB113 (etanercept)/ **Enbrel**
	n (%)	n (%)	n (%)	n (%)
	236	235	10	8
TEAEs	124 (52.5)	146 (62.1)	3 (30.0)	3 (37.5)
TEAEs related to drug	28 (11.9)	62 (26.4)	1 (10.0)	2 (25.0)
Serious TEAEs	8 (3.4)	5 (2.1)	0	0
Serious TEAEs related to drug	4 (1.7)	1 (0.4)	0	0
AEs leading to premature study discontinuation	4 (1.7)	4 (1.7)	0	0
AEs leading to death	0	0	0	0

Table 30: Overview TEAEs by SOC - Stage B/C

TEAE by System Organ Class	**Stage B**				**Stage C**			
	YLB113 (etanercept)		**Enbrel**		Enbrel/ **YLB113 (etanercept)**		YLB113 (etanercept)/ **Enbrel**	
	n (%)	# Events	n (%)	# Events	n (%)	# Events	n (%)	# Events
Total number of patients	236		235		10		8	
Infections and infestations	60 (25.4)	76	81 (34.9)	119	2 (20)	2	0	0
Gastrointestinal disorders	14 (5.9)	17	18 (7.7)	23	0	0	0	0

TEAE by System Organ Class	Stage B				Stage C			
	YLB113 (etanercept)		**Enbrel**		Enbrel/ **YLB113 (etanercept)**		YLB113 (etanercept)/ **Enbrel**	
	n (%)	# Events	n (%)	# Events	n (%)	# Events	n (%)	# Events
Injury, poisoning and procedural complications	9 (3.8)	11	17 (7.2)	17	0	0	0	0
Musculoskeletal and connective tissue disorders	17 (7.2)	19	21 (8.9)	27	0	0	1 (12.5)	1
Respiratory, thoracic and mediastinal disorders	11 (4.7)	11	12 (5.1)	12	0	0	0	0
Blood and lymphatic system disorders	5(2.1)	6	5 (2.1)	6	1 (10)	1	1 (12.5)	2
General disorders and admin site conditions	15 (6.4)	29	34 (14.5)	201	0	0	1 (12.5)	16

n: number of patients with at least 1 AE in the category

Similar to Stage A, in Stage B the main AE by PT reported for infections and infestations was nasopharyngitis in 14.8% of the patients in the YLB113 (etanercept) group and 18.7% in the Enbrel group. Injection site reactions occurred also more often in the Enbrel group (1,3 vs 7.2%).

In both groups of Stage C, there was one patient with blood and lymphatic system disorder (neutropenia, neutropenia and leukopenia).

Overall, the data suggest that YLB113 (etanercept) showed a similar AE profile as Enbrel. No new safety signal was derived from the presented data.

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Phase 1 trials in healthy volunteers:

None related to study drug.

Phase 3 Study in RA patients:

Stage A

The percentage of number of SAEs reported in the YLB113 (etanercept) group was 3.0% compared to 1.5 % of the SAEs reported in the Enbrel group. No clinically meaningful differences were observed in the SAEs between groups in Stage A.

In the YLB113 (etanercept) group, 4 patients (1.5%) have been reported with a serious TEAE related to the study drug compared to 1 patient (0.4%) in the Enbrel group. These were one urinary tract infection, 3 cases of pneumonia (one in the Enbrel group) and Still's disease adult onset. All patients recovered.

There was no AE reported leading to death.

Stage B

The proportion of patients reporting a SAE was 3.4% in the YLB113 (etanercept) group compared to 2.1 % in the Enbrel group in Stage B. No clinically meaningful differences were observed in the SAEs between groups in Stage B.

In the YLB113 (etanercept) group, 4 patients (1.7%) were reported with a serious TEAE which was related to the study drug compared to 1 patient (0.4%) in the Enbrel group. These were one interstitial lung disease, one pneumoniae, rhinitis, sinusitis, pleural cyst (YLB113 (etanercept) group) and one Herpes zoster (Enbrel group). All patients recovered.

There was no AE reported leading to death.

Stage C

No SAEs, premature study discontinuation or death were reported.

In summary, the occurrence of SAEs was low (<5%) and no clinically meaningful differences were observed in the SAEs between the treatment groups in the different treatment periods.

5.4.5. Discontinuation due to adverse events

Stage A

Two patients in the YLB113 (etanercept) group and 5 patients in the Enbrel group experienced AEs leading to discontinuation of study drug. Two patients in the YLB113 (etanercept) group experienced a SAE with a severe grade leading to the discontinuation of the administration of the study drug (Still's disease adult onset - possibly related, Lobular breast carcinoma in situ - unlikely related). In the Enbrel group all AEs leading to discontinuation were non-serious and of mild to moderate intensity.

Stage B

Four cases in the YLB113 (etanercept) group and 4 cases in the Enbrel group led to study drug discontinuation. There were 2 SAEs in the YLB113 (etanercept) group (Interstitial lung disease – possibly related, Pancreatic carcinoma with metastasis – unlikely related) that led to study drug discontinuation and 2 SAEs in the Enbrel group (Renal abscess and uterine cancer – both not related).

Stage C - No discontinuation of study medication was reported.

In summary, the overall occurrence of treatment-emergent adverse events leading to study discontinuation was low and comparable in the YLB113 (etanercept) and Enbrel groups.

5.4.6. Safety in special populations

The safety profile for special populations has been described for the originator Enbrel and does not have to be established for the biosimilar candidate if similarity can be shown in a sensitive study population.

The phase III trial YLB113-002 was performed in Europe, Japan, Ukraine and India. Of note, the percentage of patients with at least one TEAE were 30.2% for YLB113 (etanercept) and 46.8% for Enbrel in Europe compared to 80.9% for YLB113 (etanercept) and 84.5% for Enbrel in Japan.

The frequency of TEAEs were comparable between males and females in the phase III trial YLB113-002.

5.4.7. Immunological events

Immunological events

During the Phase 1 trial YLB113-001, no ADA were detected. No detection of antibodies was performed in the Phase 1 trial LBC-14-155.

During the pivotal efficacy trial YLB113-002 in patients with RA, samples for detection of anti-drug antibodies (ADA) were taken at baseline and at week 4, 8, 12, 24, 36, 44 and 52. Immunogenicity was assessed using a validated and highly sensitive MDS electro-chemiluminescence (ECL) method. Neutralising ADAs (nAB) were evaluated for samples testing positive in the confirmatory ADA assay.

At week 24, 2 patients in the YLB113 (etanercept) group showed positive ADAs, but no neutralising anti-Etanercept antibody. In the Enbrel group, 2 cases with a neutralising potential out of 21 positive ADAs were detected.

As regards to the long-term immunogenicity outcome, in Stage B and C of the study, no ADAs were detected in the YLB113 (etanercept) group, while 3 patients in the Enbrel group had positive ADAs (without neutralising potential) in Stage B and 1 in Stage C.

In summary, occurrence of ADAs was low and transient and without neutralising capacity in the YLB113 (etanercept) group.

5.4.8. Laboratory findings

Laboratory values were assessed by the Investigator and abnormalities considered to be clinically significant were reported as AEs. There were 29 patients in the YLB113 (etanercept) group for whom an alteration in at least one laboratory value has been reported compared to 21 patients with at least one TEAEs based on a laboratory value in the Enbrel group.

Fifteen patients of the YLB113 (etanercept) group were reported with increased liver enzyme values including Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), cholesterol and triglyceride parameters, mostly of mild grade. One severe and one moderate graded events were reported as unlikely related to the study drug. In the Enbrel group, 17 patients have been reported with increased liver enzymes, one severe and 8 moderate. In one case, the causality was judged as related to the study drug intake. To treat these events, the MTX dose was decreased or temporarily stopped as such an increase in liver enzymes is well described for MTX as cDMARD to treat patients with RA.

Besides increase in liver enzymes, alterations in haematological laboratory values have been described in both treatment groups, recovering in most of the cases. None of the described alterations in laboratory values were reported as AESI.

No clinically important treatment group difference was noted in the mean change from baseline for any haematology, biochemistry and urine analysis parameter.

No drug-related clinically relevant abnormalities were observed regarding clinical laboratory evaluation, vital signs and physical examination.

5.4.9. Overall discussion and conclusions on clinical safety

5.4.9.1. Discussion

The active substance etanercept has been widely used in clinical practice with a well-known safety profile. The main safety issues are related to the immunosuppressive properties of etanercept.

The pharmacology of YLB113 (etanercept) has been investigated in three phase I clinical studies (YLB113-001, LBC-14-155 and ETA.50/334), comparing its pharmacokinetics and safety after single subcutaneous application with the reference product Enbrel. As the single dose administration of these trials does not reflect the clinical situation of multiple dose administration, the impact of the derived safety data is considered limited by CHMP. Furthermore, an accurate attribution of AEs to either treatment is uncertain in a cross-over design. Overall, the safety profile was similar between YLB113 (etanercept) and Enbrel in these studies.

In the pivotal study YB113-002, a dose of 50 mg/mL of YLB113 (etanercept) was administered once a week together with MTX in patients with moderate to severe RA. The SAF population included those patients who received 1 or more doses of YLB113 (etanercept) (n = 264) or Enbrel (n = 260) as study medication. Overall, the extent of exposure is considered similar between treatment groups.

Treatment emergent adverse events (TEAE) in stage A were higher in the Enbrel group compared to YLB113 (etanercept) group (65.4% vs 55.3%), also those related to study drug were higher in the Enbrel group (35.8 vs 22.0%). The majority of TEAEs was mild or moderate in severity in both treatment groups. The results in stage B were similar.

For both treatment groups in stage A, TEAEs were reported most frequently for the SOC Infections and infestations (YLB113 (etanercept) 23.9% vs Enbrel 27.7%) and General disorders and administration site conditions (11% vs 30.8). The most commonly reported PTs for infections and infestations were nasopharyngitis (11.4% vs 10.0%), injection site erythema (1.9% vs 9.6%) and injection site reaction (3.8% vs 13.5%). Similar results were obtained in Stage B.

The relatively lower incidence of injection site reactions with YLB113 (etanercept) compared to Enbrel is in alignment with results of other biosimilar trials. No apparent correlation between ADA and injection site reactions could be demonstrated. A plausible immunological explanation may not pertain to ADA but to latex allergy/hypersensitivity reactions. Enbrel is available in the form of vials, pre-filled syringes and auto-injectors. The needle cover of the prefilled syringe as well as the needle cover within the cap of the auto-injector contain dry natural rubber, which is a derivative of latex. The applicant considers that the lower injection site reactions can be explained by the absence of latex from needle shield of YLB113 (etanercept). The explanation is agreed by CHMP.

Some differences in the TEAES profile between the three Phase I and the Phase III studies were observed, which might be attributed to a different potential for developing or reporting AEs among the studied populations (ethnicity). Participants in each Phase I study were of ethnic homogeneity (Japanese, Indian or Jordanian) while YB113-002 was conducted in Japan, India, Ukraine and Europe. The percentage of patients with at least one TEAE was much lower in Europe (30.2% for YLB113 (etanercept) and 46.8% for Enbrel) than in Japan (80.9% and 84.5%). The applicant outlined several possible reasons for the higher reporting of AEs in the Japanese population. Ethnic differences may be explained by lower body weight compared to European RA patients. There is evidence that on an average, Japanese patients report generally more adverse events than patients from Europe and especially in rheumatoid arthritis clinical trials. The issue was not further pursued since the observations are comparable between YLB113 (etanercept) and the reference product Enbrel.

The frequency of TEAEs were comparable between males and females in the Phase III trial YLB113-002.

No SAEs related to study drug were reported for the Phase I trials. In study YLB113-002, overall, SAEs were observed by 3.0% of the patients in the YLB113 (etanercept) group and 1.5% in the Enbrel group of which drug related SAEs were reported respectively by 1.5 and 0.4% of the patients. It is therefore considered by CHMP there are no clinically meaningful differences in the SAEs between the treatment groups in the different treatment periods.

No clinically important treatment group difference was noted in the mean change from baseline for any hematology, biochemistry and urine analysis parameter and no drug-related clinically relevant abnormalities were observed regarding clinical laboratory evaluation, vital signs and physical examination.

The overall occurrence of TEAEs leading to study discontinuation was comparable in the YLB113 (etanercept) and Enbrel groups.

The safety profile as reflected by nature and severity of detected adverse events indicates similarity between YLB113 (etanercept) and Enbrel.

The lower ADA formation and lower rate of local skin reactions reported for YLB113 (etanercept) compared to Enbrel suggest that YLB113 (etanercept) is less immunogenic than Enbrel. Reduced immunogenicity on itself is not considered a risk from a clinical perspective, and the small difference did not have a clinical impact and as such did not preclude biosimilarity. These findings were also reported for other biosimilar products to Enbrel.

The incidence and severity of reported TEAEs in the submitted trials did not suggest any major safety concerns. The profile of the adverse reactions are known as indicated in the SmPC of Enbrel and its subsequent recovery was confirmed.

The proposed text for SmPC sections 4.3, 4.4, 4.6, 4.7, 4.8 and 4.9 of the SmPC is in line with that of the reference product. In addition, the risk of congestive heart failure in adult subjects has been removed from the patient card in Annex II.D, in alignment with the reference product.

5.4.9.1.1. Overall assessment of available safety data

There were no major differences in safety profiles of YLB113 (etanercept), and Enbrel observed in the conducted clinical studies. Moreover, there were no new AE reported. Therefore, based on the submitted data it can be concluded that safety profiles of YLB113 (etanercept) and Enbrel are similar and support the biosimilarity.

5.4.9.2. Conclusions on clinical safety

Based on the provided data, no unexpected safety concerns were detected across the clinical studies. The observed safety findings correspond to the know safety profile of the reference medicinal product. Therefore, YLB113 (etanercept) and Enbrel can be considered biosimilar with respect to safety.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 31: Summary of safety concerns in the proposed RMP

Important Identified Risks	• Malignancy (including lymphoma and leukemia) • Serious and opportunistic infections (including tuberculosis, Legionella, Listeria and parasitic infections) • Demyelinating disorders
Important Potential Risks	• Encephalitis/ leukoencephalomyelitis • Progressive multifocal leukoencephalopathy [PML] • Impaired growth and development of juvenile subjects
Missing Information	• None

6.1.2. Discussion on proposed safety specification

The proposed safety concerns for this biosimilar product are the same as for the reference product Enbrel (RMP version 7.9, date of final sign off: 12 June 2025). This is agreed. No additional safety concerns other than those reported for Enbrel were identified during the development of this biosimilar.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

The routine pharmacovigilance measures proposed in the RMP can be summarised as follows:

- Reporting of adverse reactions, including important information such as the MAH and batch number
- Administration of Etanercept in hospital settings and, if not, collection of relevant information on supply.
- Batch number contained in the SmPC
- Expert evaluation of adverse reaction reports.
- Programmes for the detection and evaluation of new signals.
- The pharmacovigilance plan also includes a discussion on clinical settings of product use and how this may impact on routine product name and batch recording.
- There are questionnaires for monitoring adverse reactions in Annex 4 of the RMP.

The applicant did not propose any additional pharmacovigilance activities.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

The proposed routine pharmacovigilance activities are aligned with the reference product Enbrel. The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product. The PRAC also considers that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

6.2.2.2. Additional pharmacovigilance activities

The applicant proposed to not include patients treated with Fubelv in the German Biologics RABBIT registry (as for Nepexto), as this medicinal product will only be marketed in France, making a study from said registry unfeasible. This is considered acceptable by PRAC; no additional pharmacovigilance activities are thus required for Fubelv.

6.3. Plans for post-authorisation efficacy studies

None.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 32: Planned routine risk minimisation measures

Safety Concern	Routine Risk Minimisation Activities
1. Malignancy (including lymphoma and leukaemia).	Routine risk communication: SmPC sections 4.4 and *4.8* PL sections 2 and *4* Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine

2. Serious and opportunistic infections (including tuberculosis, Legionella, Listeria and parasitic infections)	Routine risk communication: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.3 and 4.4 PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
3. Demyelinating disorders	Routine risk communication: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 PL: section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
4.Encephalitis/ leukoencephalomyelitis	Routine risk communication: None proposed. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None. Legal status: prescription only medicine
5. Progressive multifocal leukoencephalopathy [PML]	Routine risk communication: None proposed. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None. Legal status: prescription only medicine

6. Impaired growth and development of juvenile subjects	Routine risk communication: None proposed. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None. Legal status: prescription only medicine

In addition, the applicant has proposed the following additional risk minimisation measures:

In line with the reference biologics Enbrel (etanercept), this medicine has additional risk minimisation measures i.e. "Patient card" for the important identified risk of Serious infections. The aim is to educate patients and prescribers about important safety information associated with the use of Fubelv such as serious infections (including opportunistic infections, TB, Legionella, Listeria, parasitic infection).

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The routine risk minimisation measures have been aligned to the reference medicinal product (Enbrel) and are considered adequate.

The PRAC having considered the data submitted was of the opinion that:

In line with the reference product, the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

6.4.2.2. Additional risk minimisation measures

The additional risk minimisation measures proposed by the applicant are in line with the reference product (Enbrel) and consist of a patient reminder card concerning the risk of serious infections. The PRAC considers that the proposed additional risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The PRAC consider that the risk management plan version 0.2 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

☒ The CHMP rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

☒The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

8. Product information

The product information is in line with the reference product.

8.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: The applicant confirmed that with the exception of differences based on scientific grounds, no deviations from the Enbrel reference medicinal product's package leaflet have been introduced. This is acceptable by CHMP.

8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fubelv (etanercept) is included in the additional monitoring list since it is a biological product that is authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Biosimilarity assessment

9.1. Comparability exercise and indications claimed

YLB113 (etanercept) was developed as a biosimilar to the reference medicinal product Enbrel (etanercept).

The applicant applied for the same therapeutic indications as for Enbrel: moderate to severe rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis (non-radiographic axial spondyloarthritis), plaque psoriasis and paediatric plaque psoriasis.

The indications (and where appropriate: posology instructions) and route of administration (subcutaneous use) proposed for YLB113 (etanercept) are identical to those of the reference product Enbrel.

YLB113 (etanercept) is available as 25 mg pre-filled syringe, 50 mg pre-filled syringe and 50 mg in pre-filled pen. Thus, it is not possible to administer YLB113 (etanercept) to paediatric patients that require less than a full 25 mg or 50 mg dose. Paediatric patients who require a dose other than a full 25 mg or 50 mg should not receive YLB113 (etanercept). If an alternate dose is required, other etanercept products offering such an option should be used.

The claim of biosimilarity is based on analytical, non-clinical and clinical data.

Quality

To establish biosimilarity of YLB113 (etanercept) to EU Enbrel on the quality level, a comprehensive analytical comparability exercise, split into two Parts and three Campaigns, was performed comparing YLB113 (etanercept) to EU Enbrel and Enbrel Japan. A sufficiently large sample size and independent batches of active substance that were not pooled were included in the analytical similarity studies.

Non-clinical data

The non-clinical programme comprised comparative *in vitro* binding studies and functional assays, comparative in vivo pharmacology, pharmacokinetics and toxicity studies and non-comparative toxicity studies conducted with YLB113 (etanercept) alone.

The large amount of *in vivo* animal data submitted, both from comparative and non-comparative studies and with different reference medicinal products was not required in the frame a comparability exercise for an EU biosimilar as per scientific advice given (EMA/CHMP/SAWP/693250/2014) and EMA guideline (EMEA/CHMP/BMWP/42832/2005 Rev1). Since the studies had already been conducted at the request of non-EU regulatory authorities, they were submitted as supportive information.

The *in vivo* pharmacology study was examined in a mouse model of collagen induced arthritis. The PK profile of YLB113 (etanercept) was investigated and compared with Enbrel in one single dose comparative pharmacokinetic study in Swiss albino mice and in a 4-week repeat dose toxicity and toxicokinetic study in Cynomolgus monkeys. The studies conducted mouse model of collagen induced arthritis and in Swiss albino mice were only considered as a supportive study for the EU MAA as the comparator Enbrel used in was sourced from India, not an ICH country, therefore not meeting the requirements of the Guideline on similar medicinal products (CHMP/437/04 Rev 1).

Clinical data

Demonstration of clinical equivalence is based on:

- **Study ETA.50/334**: single dose, PK and safety study conducted in Jordan in healthy volunteers (n=52) comparing YLB113 (etanercept) versus Enbrel EU-source
- **Study YLB113-002**: a multicentre, double-blind, randomised, parallel-group comparative study to assess the efficacy, safety, and immunogenicity of YLB113 (etanercept) and Enbrel for the treatment of rheumatoid arthritis (RA). In 2014, scientific advice was provided to the applicant (EMA/CHMP/SAWP/693250/2014) and the clinical model of moderate to severe RA was confirmed as sensitive and suitable to demonstrate biosimilarity between the test and reference medicinal product, Enbrel. The overall design and conduct of the study is in line with relevant EMA guidelines (CHMP/437/04 Rev.1; CPMP/EWP/556/95 Rev.2; EMEA/CHMP/BMWP/42832/2005).

Two other single dose phase I PK-safety studies, one in India (LBC-14-155), one in Japan (YLB113-001), were conducted in healthy volunteers comparing YLB113 (etanercept) versus Enbrel and could not be accepted as a proof of similarity between YLB113 (etanercept) and Enbrel since these studies were performed using material from the manufacturing process containing lower amounts of misfolded forms and sialic acids per molecule etanercept as compared the material to be commercialised. Thus, the product used in these phase I studies cannot be considered representative of the proposed commercial product. In addition, study LBC-14-155 was conducted at the contract research organisation (CRO) whereas an Article 31 of Directive 2001/83/EC referral procedure1 concluded that data from studies conducted at the sites between June 2012 and June 2016 are unreliable and cannot be accepted as a basis for MA in the EU. Since Study LBC-14-155 was conducted during that time frame, the results cannot be taken into a consideration in this application.

9.2. Results supporting biosimilarity

Quality

Similarity evaluation was conducted during various developmental stages of the active substance and finished product and included for comparison of reference product (Enbrel) from EU, Japan and India. Some basic structural elucidation studies were completed and evaluated. Inherent structural quality attributes related to the protein backbone (such as amino acid sequence, disulfide bonding, secondary, tertiary and higher order structure) are comparable between YLB113 (etanercept) and Enbrel. Differences exist in the glycosylation profiles (N- and O-glycans). The potential impact of the differences in glycosylation has addressed in the various biological assays demonstrating that the structural differences observed for glycan structures do not have any impact on functional parameters including potency.

Differences are observed in N- and C-terminal heterogeneity of YLB113 (etanercept) and Enbrel. Etanercept is almost fully processed to the C-1 variant missing lysine and this impacts the charge profile of YLB113 (etanercept) compared to Enbrel that has a small proportion of lysine-carrying variants. YLB113 (etanercept) also has lower amounts of N-terminal variants (N-1, N-2). Similarity can be concluded on this attribute as no impact is expected from variability in N- and C-termini for etanercept. This is confirmed by similarity studies.

Comparable or lower amounts of oxidized methionines, deamidated asparagines, of aggregates or misfolded forms are found for YLB113 (etanercept). As regards the charge profile a lower number of basic variants is found for YLB113 (etanercept) consequential to the almost fully processed C-terminal variant without lysine. This has been concluded to have no impact on the molecular function of

etanercept.

A small study of similarity of finished product related attributes (protein content, extinction coefficient, subvisible particles) was conducted and did not result in any remarkable difference between YLB113 (etanercept) and Enbrel.

Non-clinical

In the comparative *in vitro* studies, including the evaluation of TNF receptor related biological activities and Fc related binding characteristics, similarity between YLB113 (etanercept) and Enbrel was demonstrated. Similar efficacy, safety and pharmacokinetics profiles were seen in a 4-week repeat dose toxicity and toxicokinetic study in Cynomolgus monkeys between the test and the reference product.

Clinical Pharmacokinetics

The phase I study ETA.50/334 was conducted at the clinical site using a test product batch that is representative of YLB113 (etanercept) product to be commercialised and EU-sourced Enbrel as reference product.

The results showed that the primary PK parameters AUC0-t and Cmax fall within the acceptance range of 80.00%-125.00% (90%CI). Point estimators were close to 1 and 90% CIs include 100% (ratios AUCt 96.22 [88.92-104.12], Cmax 101.18 [92.23-110.99]). The study met the bioequivalence criteria and therefore supports biosimilarity.

Efficacy

Comparative efficacy data were obtained from the phase III study YLB113-002, designed as a randomised double-blind parallel group study to demonstrate equivalence in efficacy and safety between the biosimilar test product YLB113 (etanercept) and the Enbrel reference in patients with moderate to severe RA when co-administered with MTX (6 to 25 mg/week). The RA severity of included subjects was adequately reflected by their baseline disease characteristics. Study discontinuation was low. More than 96% (497/517) of randomised subjects completed stage A. Only minor disparities were observed for subjects discontinuing during stage A (YLB113 (etanercept): n=17 [6.4%], Enbrel: n=10 [3.8%]).

In terms of the ACR20 primary endpoint, the model estimate portion (NRI + MI) of subjects achieving ACR20 response was high in both arms, slightly higher for Enbrel (86.8%) as compared to the test medication (81.2%). However, the 95% CIs for the difference in portions (-5.6 [-11.6, 0.5]) were within the pre-specified ±15% equivalence acceptance margin.

In line with results obtained for the primary endpoint, similar efficacy outcomes between the arms were also observed for secondary endpoints. The time course of ACR20 response rates was very similar between the YLB113 (etanercept) and the Enbrel treatment arm from the first efficacy assessment at week 4 until the end of stage A after 24 weeks. In both treatment arms response rates are above 50% at the earliest assessment time point and are maintained and slightly increasing for the remainder of stage A. At each early time points (week 4, 8. 12) the 95% CIs for the model estimate in response rates were within the ±15% acceptance range.

Broken down to the single ACR parameters (SWJ, TJC, Pain, Patient Global Assessment of Disease Activity, Physician Global Assessment of Disease Activity, Health Assessment Questionnaire, ESR and CRP as acute phase reactants), the summarised percent changes in ACR-N were similar between treatment arms.

Overall, the results obtained for the primary efficacy endpoint (ACR20 response rate at week 24) and secondary efficacy measures (ACR20 at earlier time points, ACR50/70 response rates, and continuous

DAS28 scores) point to equivalence between the test and the reference product within the ±15% (for the 95% 2-sided CIs) equivalence margin.

Clinical safety

The number and nature of adverse events were generally comparable between YLB113 (etanercept) and Enbrel with a lower incidence of ADAs and local skin reactions for YLB113 (etanercept) indicating possibly a lower immunogenic potential. This, however, does not preclude a conclusion of biosimilarity since reduced

immunogenicity is not considered a risk from a clinical perspective, and the small difference did not have a clinical impact.

9.3. Uncertainties and limitations about biosimilarity

Quality

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity of YLB113 (etanercept) and Enbrel.

Non-clinical

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity of YLB113 (etanercept) and Enbrel.

Clinical

Out of the three single dose phase I PK studies submitted by the applicant to demonstrate biosimilarity between YLB113 (etanercept) and Enbrel, only one study (ETA.50/334) could be accepted as proof of biosimilarity.

The study YLB113-001 initially designated as the pivotal PK study did not allow reliable conclusion of biosimilarity due to objections relating to carry-over effects in combination with concerns regarding the representativeness of the test product used during PK study programme for the product intended to be marketed (see section 5.2.2).

The study LBC-14-155 was conducted at a CRO part of an article 31 referral which concluded that data from studies conducted at this CRO between June 2012 and June 2016 are unreliable and cannot be accepted as a basis for MA in the EU. Since study LBC-14-155 was conducted during that time frame, the results cannot be taken into a consideration in this application (see section 5.2.2).

Due to the shortcomings in the two PK studies described above, the applicant conducted a third PK study during the clock stop period.

In this study, as for in study YLB113-001, relevant pre-administration etanercept dose levels were observed in five subjects before the start of period II. Given the 75 ng/mL LLoQ, individual plasma profiles are eligible for statistical analysis if the Cmax of the respective subject was > 1500 ng/mL, since pre-administration concentrations must not exceed 5% of individual Cmax. Actual Cmax values for five subjects were so low that a LLoQ of 75 ng/mL could not be accepted for

these subjects as carry over effects cannot be excluded. A revised PK analysis was submitted excluding the respective subjects. Exclusion of the five subjects did not have a relevant impact on the outcome of the study, point estimators remained close to 1 with 90% confidence intervals contained within the 80-125% acceptance range.

Upon request by CHMP, a triggered GCP inspection was conducted at the clinical and analytical sites of study ETA.50/334 to verify the newly submitted PK data. The major findings observed at these two sites were considered system-related and could therefore potentially have an impact on the quality of all study data. However, the inspections at both sites concluded that overall reliability of the data is not affected despite the major findings that were made.

The above uncertainties and limitations have been addressed by the newly PK study and the findings of the GCP inspection.

There are no remaining uncertainties and limitations concerning the safety profile of YLB113 (etanercept).

9.4. Discussion on biosimilarity

Quality

From a quality point of view, biosimilarity has been demonstrated in the comprehensive analytical study.

Non-clinical

Similarity of YLB113 (etanercept) to the reference product Enbrel (EU) has been shown in a satisfactory manner.

Clinical

In addition, clinical PK data obtained from the pivotal study ETA 50/334 demonstrate similarity between the test YLB113 (etanercept) and the reference Enbrel product, based on point estimators for etanercept exposure after SD administration of 50 mg solution for injection in PFS (Cmax 101.18 [92.23-110.99], AUC0-t 96.22 [88.92-104.12], AUC0-∞ 95.56 [88.37-103.32]). Efficacy and safety data obtained from phase III trial YLB113-002 in patients with moderate to severe RA demonstrated biosimilarity between the YLB113 (etanercept) and Enbrel.

9.5. Extrapolation of safety and efficacy

The available data support the extrapolation of efficacy and safety profile of YLB113 (etanercept) in RA patients to other indications approved for Enbrel.

9.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, YLB113 (etanercept) is considered biosimilar to Enbrel. Therefore, a benefit/risk balance comparable to the reference product can be concluded.