26 March 2020
EMA/212524/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nepexto

International non-proprietary name: etanercept

Procedure No. EMEA/H/C/004711/0000

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

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
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
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
HMW	High Molecular Weight
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation
IGA	Investigator’s Global Assessment
IgG1	Immunoglobulin G1
ITT	Intention-to-treat
JIA	Juvenile idiopathic arthritis
Kel	Constant of elimination
kg	Kilogram
LMW	Low Molecular Weight
MAA	Marketing Authorisation Application
mg	Milligram
MI	Multiple imputation
mM	millimolar
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
N	Number of Patients
nAB	Neutralizing Antibodies
NRI	Non-response imputation
NSAIDs	Nonsteroidal anti-inflammatory drugs
PC	Placebo-controlled
PD	Pharmacodynamics
PFP	Pre-filled pen
PFS	Pre-filled syringe
PPS	Per-protocol set
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
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

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Lupin Healthcare UK Ltd submitted on 30 April 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Nepexto, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2016.

During the evaluation, the applicant was transferred from Lupin Healthcare UK Ltd to Mylan IRE Healthcare Limited.

The applicant applied for the following indications:

Rheumatoid arthritis

Nepexto 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.

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

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

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

Juvenile idiopathic arthritis

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

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

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

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

Psoriatic arthritis

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

Axial spondyloarthritis

Ankylosing spondylitis

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 legal basis for this application refers to:

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

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 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: 03-02-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers:
  For 25 mg- EU/1/99/126/013-014; 023-026
  For 50 mg - EU/1/99/126/016-021

Medicinal product authorised in the Union/Members State where the application is made or 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: 03-02-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers:
  For 25 mg – EU/1/99/126/013-014, EU/1/99/126/023-026
  For 50 mg – EU/1/99/126/016-021

Medicinal product which is or has been authorised in accordance with 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: 03-02-2000
- Marketing authorisation granted by:
  - Union
  - Union Marketing authorisation numbers:
    For 25 mg – EU/1/99/126/013-015,
    For 50 mg – EU/1/99/126/016-021

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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 because there is no authorised orphan medicinal product for a condition related to the proposed indications.

Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application.

Date	Reference	SAWP co-ordinators
20 November 2014	EMEA/H/SA/2891/1/2014/III	Dieter Deforce; Thomas Lang

The scientific advice pertained to quality, non-clinical and clinical aspects of the dossier.

- Considerations concerning the development plans for a prefilled syringe/prefilled pen;
- Physicochemical comparability to proposed reference medicinal product sourced from Japan and India;
- Manufacturing process scale-up;
- Comparative *in vitro* cell-based bioassays;
- In-vivo studies to support comparability demonstration;
- Design and comparator to be used in the Phase I studies in Japan and India;
- Assessment of immunogenicity;

- Overall adequacy of clinical development plan, including geographical location of studies.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	30 April 2018
The procedure started on	24 May 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 August 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	14 August 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	28 August 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 September 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2019
The following GMP an GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at two investigator sites in Ukraine and Japan between 14/08/2018 and 07/09/ 2018. The outcome of the inspection carried out was issued on: – A GCP inspection at the clinical site and at the bioanalytical laboratory, in Jordan and India between 25/08/2019 and 14/11 2019. The outcome of the inspection carried out was issued on:	3 November 2018 10 January 2020
– A GMP inspection at one manufacturer of the active substance and finished product site in India between 3 and 7 December 2018. The outcome of the inspection carried out was issued on:	29 July 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	6 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	29 May 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 June 2019
The Rapporteurs circulated the Joint Assessment Report on the	10 July 2019

responses to the List of Outstanding Issues to all CHMP members on	
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 July 2019
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	21 February 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	12 March 2020
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 Nepexto on	26 March 2020

2. Scientific discussion

2.1. Problem statement

About the product

Nepexto, containing the active substance etanercept, has been developed as a biosimilar to the reference medicinal product Enbrel (etanercept).

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.

The applicant applied for the full range of indications approved for the reference medicinal product Enbrel: treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PA), axial spondyloarthritis (AxSpA) (ankylosing spondylitis, non-radiographic AxSpA), plaque psoriasis and paediatric plaque psoriasis.

Nepexto 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 Nepexto. If an alternate dose is required, other etanercept products offering such an option should be used.

Type of Application and aspects on development

The marketing authorisation application (MAA) is submitted in accordance with Article 3(1) Indent 1 - Biotech medicinal product of Regulation (EC) No 726/2004. The proposal legal basis for this MAA is a similar biological application under Article 10(4) of Directive 2001/83/EC as amended.

Similarity is claimed to the reference medicinal product Enbrel which was authorised in the European Union (EU) on the 3rd of February 2000 thus having been marketed for over 10 years.

To demonstrate that the similar biological and reference products already authorised in the EU have similar profiles in terms of quality, safety and efficacy an extensive comparability exercise is required.

The development programme of Nepexto is based on the relevant CHMP guidelines, particularly the guideline on 'Similar Biological Medicinal Products', so-called over-arching guideline (CHMP/437/04 Rev. 1), the guideline on 'Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues' (CHMP/BWP/247713/2012) and 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).

Prior to initiation of the European Phase III programme, Scientific Advice (SA) was requested from the EMA in October 2014 and this advice was provided in November 2014 (EMA/CHMP/SAWP/693250/2014; Procedure EMEA/H/SA/2891/1/2014/III). During this SA procedure the clinical model of moderate to severe RA was confirmed as sensitive and suitable to demonstrate biosimilarity between the test and the reference medicinal product.

In line with the overarching guideline on similar biological medicinal products, extrapolation to other indications of the reference medicinal products could be acceptable, provided that biosimilarity has been demonstrated in one indication and with appropriate scientific justification.

GMP inspections

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.

GCP inspections

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 this 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 are of sufficient quality to be used for the evaluation of the MAA.

2.2. Quality aspects

2.2.1. Introduction

Nepexto 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.

2.2.2. Active Substance

General information

Etanercept 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.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Etanercept is recombinantly expressed by CHO cells. The active substance manufacturing process is a conventional process starting with generation of production batch from a working cell bank (WCB), upstream process includes cell expansion and target protein production. The subsequent downstream process includes purification through a series of chromatographic steps, virus inactivation and filtration steps leading to the active substance.

The process description has been thoroughly revised during the procedure and a satisfactory level of detail has been included.

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, the Applicant states NORs (normal operating ranges) and MORs (maximum operating ranges) within the PARs (proven acceptance ranges). 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 during the procedure. To demonstrate that the process validation batches still comply with the revised control strategy, the Applicant has submitted comparative tables on IPC, IPT (for the USP) and testing of quality attributes (for the down-stream process (DSP) intermediates) of the process validation (PV) batches versus "consistency batches" that were manufactured recently 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

Nepexto was developed as biosimilar to Enbrel. The process development, including several process versions, has been described. Changes during development includes 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 (see clinical section).

Characterisation

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

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.

Specification

The active substance specification contains parameters like identity, glycan content, biological activity, purity and impurities, endotoxin, content and bioburden. Other general tests like visual inspection, pH are also included in the specification.

Analytical methods

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 several 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. Newly 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.

Stability

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

The applicant has provided long term stability data from multiple development and commercial scale batches

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

All batches were stable at accelerated conditions.

The proposed shelf life and storage conditions are acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Nepexto 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. Nepexto 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).

Nepexto 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.

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 Nepexto 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 occur which might affect safety or quality of the finished product up to its end of shelf life.

The primary packaging is clear type I glass with 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.

Manufacture of the product and process controls

The finished product manufacturing process solely consists of dispensing active substance lots, filtration and filling of the bulk solution into the syringes. In addition, the manufacturing processes are 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 Nepexto PFS and PFP of intended quality

Product specification

The specification for the finished product includes test parameters on identity, pharmaceutical properties, potency, content, purity and impurities, safety, syringe functionality and device testing.

The proposed PFS 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 components of the primary packaging are 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.

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.

Analytical methods

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 various scales of the finished product 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.

Stability of the product

The claimed finished product shelf-life is 2 years when stored in a refrigerator (2°C - 8°C). Appropriate stability studies have been initiated at the two manufacturing sites in line with the respective ICH requirements.

Stability data from PFS 50 mg/mL batches are available covering the proposed shelf life of 24 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 support PFP shelf life of 24 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 been presented, one of them only for 12 months. Nevertheless, a shelf life of 24 months may be 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 rather than in the fill volume.

Multiple batches of Nepexto 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. In order to comply with the requirements of ICH Q5C, additional commercial scale batches manufactured at the Lupin manufacturing site will be put on storage. Results of 12 months storage at recommended storage

conditions and 6 months at accelerated conditions are currently available from the ongoing stability studies. All results met the specification acceptance criteria. Since no significant difference in the stability results of the batches manufactured at the different sites has been observed so far, a shelf life of 24 months for the product manufactured at the Lupin site is considered acceptable as well.

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 suggests that Etanercept is susceptible to exposure to light, oxidizing agents, agitation and high temperature stress factors. Percentage impurities generated and rate of degradation is less for Lupin's in-house batches when compared to innovator from different geographies for all stress factors except for incubation at 45°C.

Temperature excursion studies have been 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.

The finished product shelf life is 2 years when stored in a refrigerator (2°C - 8°C). The finished product should not be frozen. The pre-filled syringes or pens should be kept in the outer carton in order to protect from light.

Nepexto may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Nepexto should be discarded if not used within four weeks of removal from refrigeration.

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.

GMO

N/A

Biosimilarity

Evaluation of biosimilarity was split into two parts and three campaigns.

"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 Company 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 Nepexto 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 Nepexto 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 characterization 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 Nepexto and Enbrel. Etanercept is almost fully processed to the C-1 variant missing lysine and this impacts the charge profile of Nepexto compared to Enbrel that has a small proportion of lysine-carrying variants. Nepexto 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 Nepexto. As regards the charge profile a lower number of basic variants is found for Nepexto 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 Nepexto 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 1: **Physico-chemical methods used to characterize and compare Nepexto and Enbrel**

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of the tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Several quality major objections have been raised during the procedure regarding GMP, biosimilarity reference standards, manufacturing process description and the control strategy which were appropriately resolved during the review.

Conformance with EU GMP requirements of the active substance and finished product manufacturing site at Lupin Limited (Biotech Division) was confirmed during the procedure by providing the respective GMP certificate, confirming compliance with EU GMP status.

The active substance manufacturing process description and control strategy has been thoroughly revised and adequately supplemented during the procedure.

Further information has been provided regarding the active substance manufacturing process consistency which was found acceptable.

Information on impurities and associated analytical methods was substantially complemented during the MAA procedure and is now satisfactory.

Procedures for qualification of reference standards were amended during the assessment all allow for appropriate control of the active substance and the finished product.

Active substance stability data was amended and clarified.

The data presented to support the biosimilarity claim was significantly amended. In conclusion, an extensive analytical comparability exercise has been conducted and demonstrates that Nepexto is highly similar to the reference product Enbrel.

Additionally, the Applicant is recommended to introduce the first two commercial scale batches of Nepexto finished product manufactured at Lupin, India manufacturing site into ICH compliant stability studies.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

To introduce the first two commercial scale batches of Nepexto finished product manufactured at Lupin, India manufacturing site into ICH compliant stability studies.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical programme for Nepexto (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 Nepexto alone.

Scientific advice regarding the product development program of Nepexto 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 2 **List of in vitro pharmacology studies performed for Nepexto**

Sr. No.	Title of Test
Binding and Neutralization Assays	
1.	TNF-α neutralization assay
2.	TNF-β neutralization 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 3 **List of in vivo preclinical studies performed for Nepexto**

No.	Study No	Title of the Study	Batch Number	GLP Status
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	GLP
2.	ABD-2994	Evaluation of Efficacy of Etanercept Biosimilar in an animal model of collagen induced Arthritis	Etanercept: ET/PR03/11 Enbrel: F17194	GLP
3.	457-1-05-1401	Single dose subcutaneous toxicity study of TNFR:Fc Fusion Protein (Etanercept) in Swiss Albino Mice	Etanercept: ETPR03/11	GLP
4.	457-1-05-1402	Single dose subcutaneous toxicity study of TNFR:Fc Fusion Protein (Etanercept) in Wistar Rats	Etanercept: ETPR03/11	GLP
5.	456-1-05-1403	Single dose intravenous toxicity study of TNFR:Fc Fusion Protein (Etanercept) in Swiss Albino Mice	Etanercept: ETPR03/11	GLP
6.	457-1-05-1404	Single dose intravenous toxicity study of TNFR:Fc Fusion Protein (Etanercept) in Wistar Rats	Etanercept: ETPR03/11	GLP

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	GLP
8.	423-1-02-1406	28-Day Repeated dose subcutaneous toxicity study of TNRF:Fc Fusion Protein (Etanercept) in New Zealand White Rabbits	Etanercept: ETPR03/11	GLP
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	GLP

2.3.2. Pharmacology

Primary pharmacodynamic studies

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 Nepexto 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 3.1 '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 Nepexto 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 Nepexto respectively Enbrel were applied daily for two weeks following arthritis induction by Bovine collagen type 2 in Freud's adjuvants.

Nepexto 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 Nepexto 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, Nepexto appeared to be slightly more potent (i.e. already effective at lower doses) than Enbrel.

Secondary pharmacodynamics, Safety pharmacology, Pharmacodynamic drug interactions studies

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

2.3.3. Pharmacokinetics

The pharmacokinetic profile of Nepexto 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 (Nepexto, 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).

Absorption

Study BIO-BN 011: Single dose mouse study

The 90% confidence interval of the ratio of the geometric mean of C_{max} and AUC between test (Test 1: Nepexto´s etanercept drug substance applied in the innovator formulation; Test 2: Nepexto´s etanercept drug substance applied in Nepexto´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 Nepexto´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 Nepexto 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 (Nepexto or Enbrel) were quantifiable in all animals dosed with 1, 5 and 15 mg/kg. Exposure values obtained for Nepexto and Enbrel (15 mg/kg) were similar on day 1 and were comparable for males and females. Median time to maximum etanercept concentration (t_{max}) 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 AUC_t, the increase showed about dose-proportionality, while C_{max}-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 neutralizing or not neutralizing. AUC_t and C_{max} on day 22 were higher for Nepexto drug substance than for Enbrel, which could possibly be related to a higher incidence of ADA in the Enbrel-treated animals (see also Section 2.3.4. Toxicology).

Distribution, Metabolism, Excretion, Pharmacokinetic drug interaction

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

2.3.4. Toxicology

Single dose toxicity

Four GLP-compliant single dose toxicity studies were conducted by both s.c. and i.v. administration of Nepexto 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. Nepexto doses of up to 500 mg/kg (mice), respectively 250 mg/kg (rats).

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 Nepexto doses of up to 500 mg/kg and (India-sourced) Enbrel (10 mg/kg), given s.c. once weekly. However, Nepexto 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 Nepexto 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 Nepexto 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.

Toxicokinetics: see section 2.3.3 'Absorption' of this assessment report.

Genotoxicity, Carcinogenicity, Reproductive and development toxicity

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

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 Nepexto 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.

Other toxicity studies

The immunogenicity of Nepexto'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 2.3.3 'Absorption' and section 2.3.4 'Repeat Dose Toxicity' of this assessment report).

2.3.5. 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).

2.3.6. Discussion on non-clinical aspects

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 Nepexto and the 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 Nepexto 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 Nepexto and the RMP Enbrel is considered paramount for providing non-clinical evidence for biosimilarity. The assessment of the data submitted for Nepexto concerning *in vitro* TNF binding and functional activity is provided in section 3.1 'Quality aspects', subsection 'Biosimilarity' of this AR.

***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 step-wise 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 Nepexto, both from comparative and non-comparative studies and with different RMPs:

- Studies comparing Nepexto 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 Nepexto 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 Nepexto.

In the EMA scientific advice given to the Applicant, it was pointed out, that the package of non-clinical *in vivo* studies provided for Nepexto 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 Nepexto and have been resolved or been decided not to be followed further:

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

● Nepexto batches used in the *in vivo* animal studies: Information to what extent the Nepexto 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 Nepexto 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 3.1 '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 Nepexto, 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).

2.3.7. Conclusion on the non-clinical aspects

Taken together, the submitted non-clinical data (and here in particular the *in vitro* TNF binding and Fc effector functional assay data, see section 3.1 'Quality aspects', subsection 'Biosimilarity' of this assessment report) support the biosimilarity between Nepexto and Enbrel.

2.4. Clinical aspects

2.4.1. 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 Nepexto 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 programme are presented in table 4.

GCP

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. 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 this 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 MAA.

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.

Table 4: **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 Nepexto + 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) Nepexto 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) Nepexto 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) Nepexto 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	Nepexto: 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

2.4.2. 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 Nepexto versus Enbrel EU-source
- *Study YLB113-001 (informative study)*: single dose, PK and safety study conducted in Japan in healthy volunteers (n=60), comparing Nepexto 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 Nepexto 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 [1]. 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 Nepexto 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

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.

[1] 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

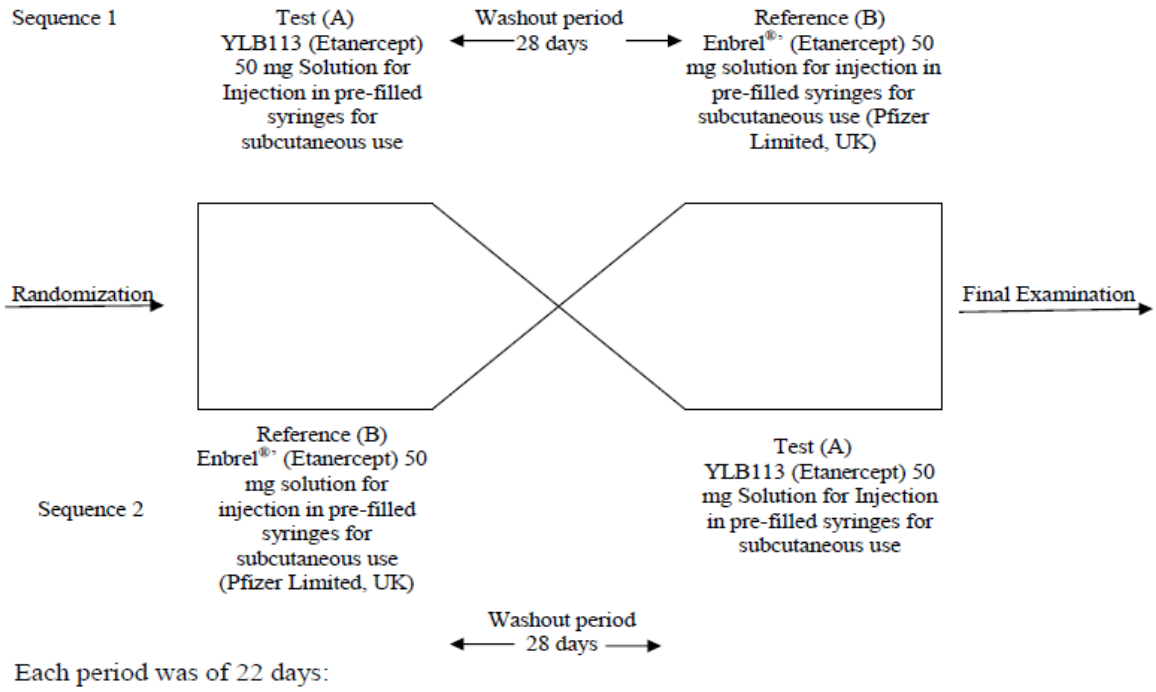


Figure 1 **Schematic chart of the study ETA.50/334 (crossover design)**

Objectives

The primary objective was to compare the relative bioavailability of etanercept between Nepexto 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 Nepexto 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 - Nepexto) 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.

Analytical method

Etanercept was measured by a validated ELISA assay.

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 C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$,and for the untransformed data of T_{max}, 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 C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ falls within the acceptance range of 80.00%-125.00%. Median was used upon reporting T_{max} values unlike all other parameters where mean was used.

Results

The results of study ETA.50/334 are presented in Figure 2, Table 5, Table 6 and Table 7.

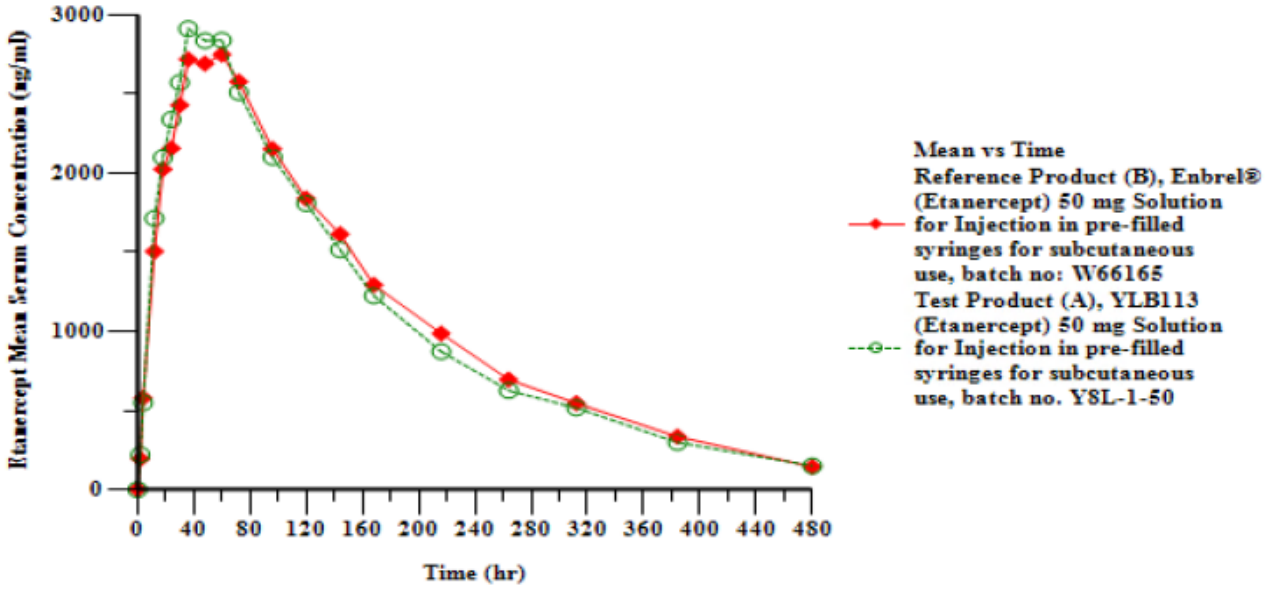


Figure 2 **Mean 480-hour profiles serum concentrations of Nepexto versus Enbrel**

Table 5 **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),	**Reference Product (median± SD,**

	(Min-Max)	(Min-Max))
T max (hr)	48.00 ± 17.645 (18.00 – 96.00)	48.00 ± 19.706 (18.00 – 120.00)

Table 6 **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 7).

The acceptance criteria of 90% confidence intervals for C_{max} 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 7 **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 Nepexto 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 8 and Table 9.

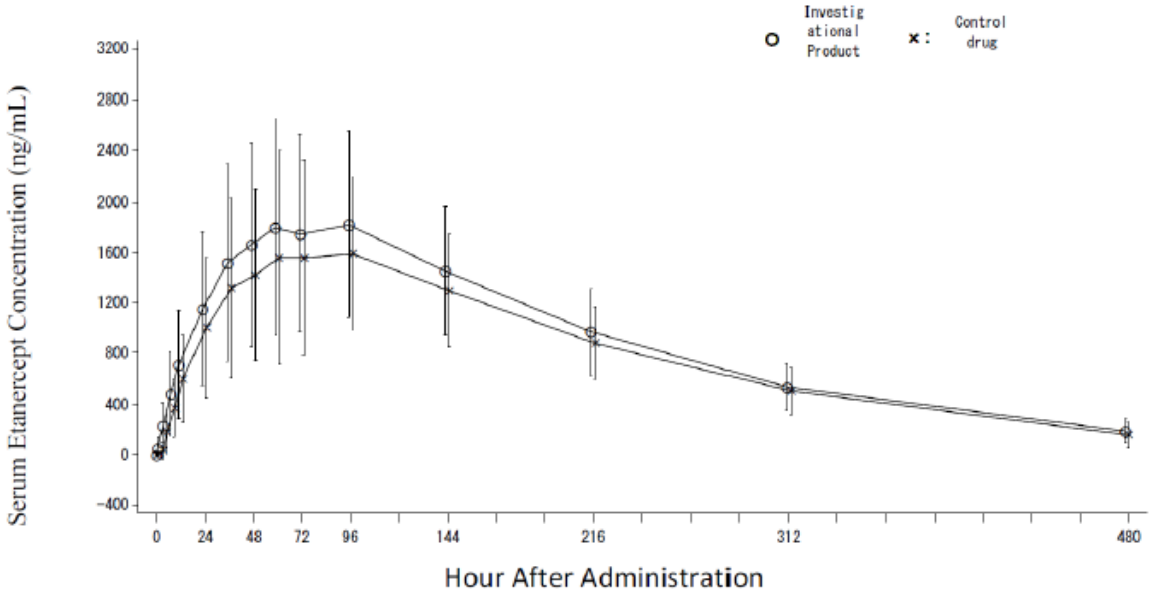


Figure 3 **Mean 480-hour profiles of Serum Concentration of Nepexto versus Enbrel of Study YLB113-001**

Table 8 **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 9 **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 AUC_t and C_{max}, values were significantly higher for the test product as compared to the reference (ratios AUC_t 1.12 [1.03-1.21], C_{max} 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 ($t_{1/2}$: 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 C_{max}. These subjects were excluded.

The results are presented for information only.

Results

The results are presented in Figure 4, Table 10, Table 11 and Table 12.

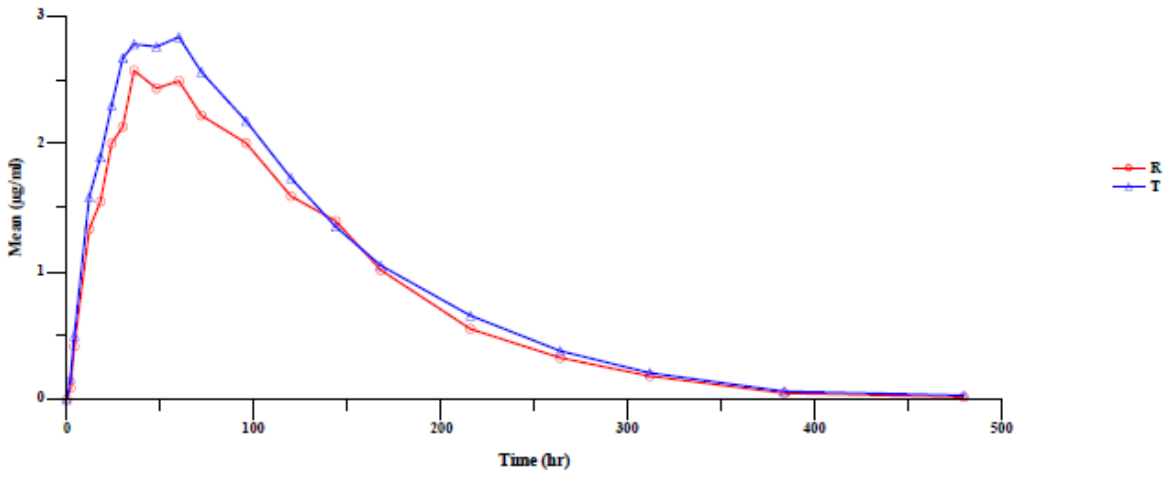


Figure 4 **Linear plot of mean serum concentrations versus time of Etanercept for Test (T) and Reference (R) product in 38 healthy, adult, human male subjects under standard breakfast conditions**

Table 10 **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	856.7924	44.27	376.5 1336
AUCo- (µg*br/mL)	38	443.7 6499	190.42438	160.2815	416.9200	943.4838	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	181.1248	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 2 subjects (in period-I) and 2 subjects (in period-II) were found more than 5% of their individual Cmax for Etanercept, hence excluded from PK and Statistical analysis.

Table 11 **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 2 subjects (in period I) and 2 subjects (in period II) were found more than 5% of their individual Cmax for Etanercept hence excluded from PK and Statistical analysis.

Table 12 **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	
Cmax (µg/mL)	30.42	0.9382	0.4332	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
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 AUC_{0-480}, AUC_{inf} and C_{max} 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 (C_{max} 105.27 [93.80-118.15], AUC_{0-480} 108.80 [98.73-119.90], AUC_{inf} 107.79 [98.41-118.08]). In this case, however, the difference between the test and the reference product was not significant.

2.4.3. 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 Nepexto, 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 2.4.1.), levels of TNF-α were measured to determine comparative effect of Nepexto 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.

2.4.4. Discussion on clinical pharmacology

Study (ETA 50/334), conducted in Jordan during the clock-stop of this application, was considered pivotal for the comparative PK evaluation between Nepexto 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 Nepexto 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 Nepexto 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 C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ falling within the acceptance range of 80.00%-125.00%, showed bioequivalence between Nepexto and Etanercept.

Five study subjects were excluded from the statistical analysis in the comparison between Nepexto 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 (C_{max} 101.18 [92.23-110.99], AUC_{0-t} 96.22 [88.92-104.12], $AUC_{0-\infty}$ 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 Nepexto 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[1],. The referral concluded that bioequivalence studies in which bioanalysis was carried at the 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 Nepexto.

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 Nepexto. 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.

2.4.5. Conclusions on clinical pharmacology

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

2.5. Clinical efficacy

2.5.1. Dose response studies

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

The proposed dosing regimens for Nepexto are identical to those approved for Enbrel.

2.5.2. Main study

Study YLB113-002

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

Methods

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 Nepexto (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 Nepexto 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 Nepexto 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.

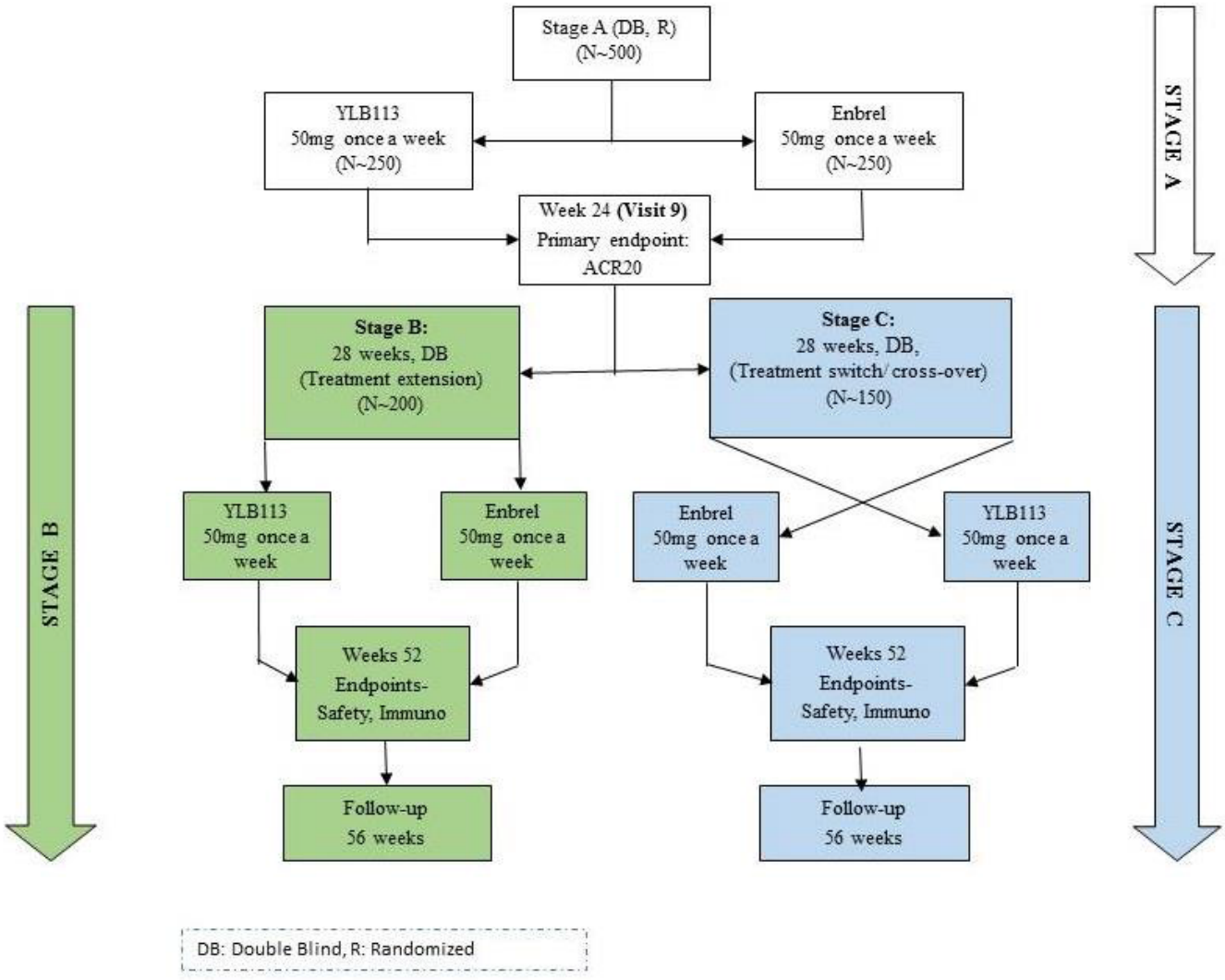
Stage B

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 (Nepexto 50 mg 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 Nepexto and Enbrel.

Stage C

All subjects who demonstrated reduction in their baseline DAS28 score by ≥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 Nepexto to Enbrel and Enbrel to Nepexto) 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).

The study design is presented in *Figure 5.*



*YLB113 is the development code for Nepexto

Figure 5 Schematic of study design

Objectives

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 13.

Table 13 **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[2]	24 weeks	59	71%	30	27%	45%
Combe et al[3]	24 weeks	100	74%	50	28%	46%
Keystone et al[4]	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 Nepexto 50 mg or Enbrel ("EU 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 Randomized 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

[2] 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.
[3] 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.
[4] 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.

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).

Results

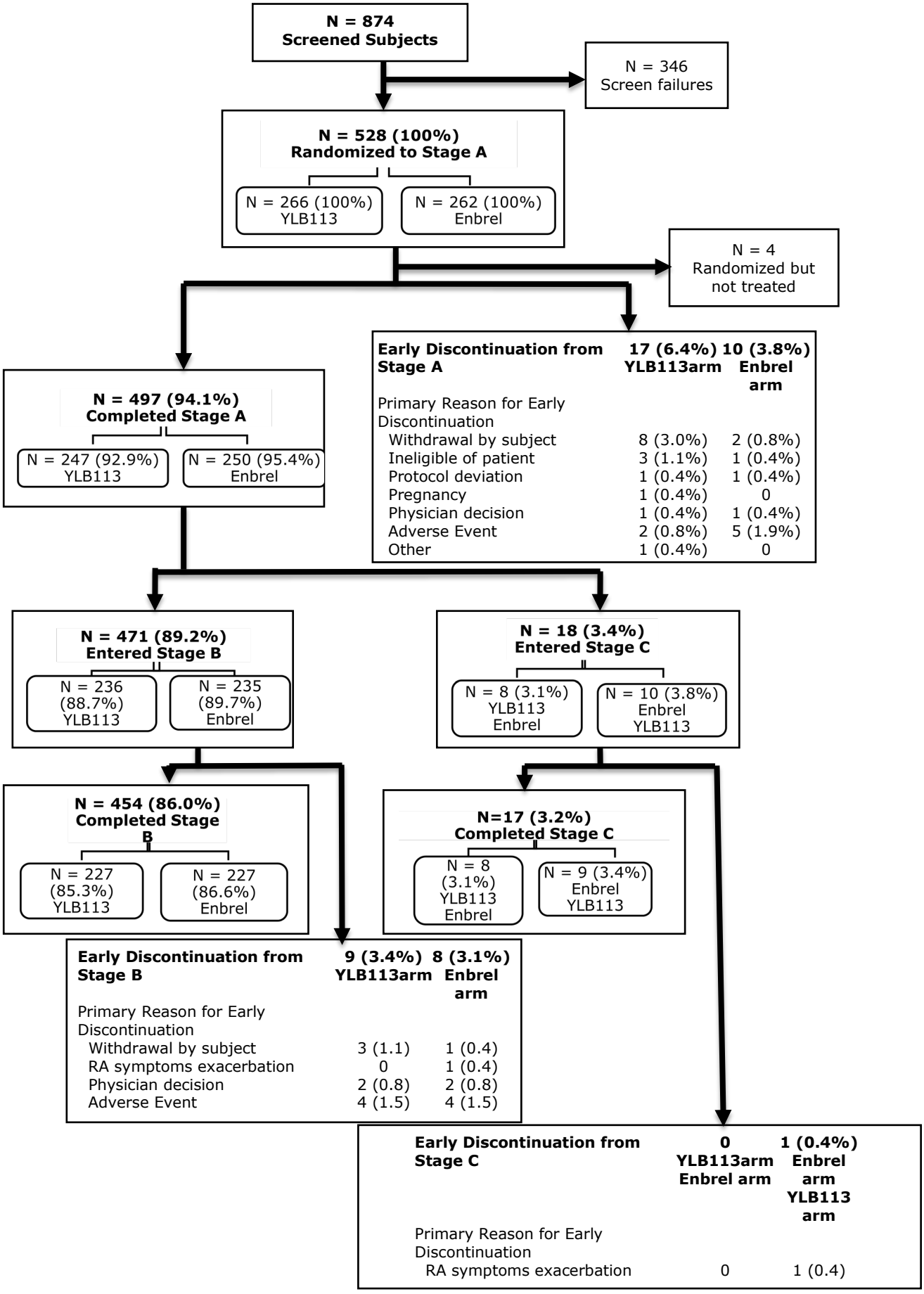
Participant flow

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: Nepexto 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; Nepexto n=2). Two subjects in the Enbrel arm discontinued due to administration site reactions and another two for rash / urticaria. No subject in the Nepexto 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**



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 Nepexto 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 14.

Table 14 **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)

N = all subjects assigned to the population set; n = number of subjects; SD= Standard Deviation; IQR = Interquartile Range calculated as 3rd Quartile (75%) – 1st Quartile (25%); % = percentage of subjects calculated relative to the total number of subjects in the analysis set.

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 Nepexto 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 Nepexto 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 15.

Table 15 **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 (missing) Mean SD	263 (0) 18.1 10.02	253 (1) 18.9 10.38	516 (1) 18.5 10.20
	28 Total Score	n (missing) Mean SD	263 (0) 12.7 6.36	253 (1) 12.6 6.06	516 (1) 12.7 6.21
Swollen joint counts (SJC) at Baseline	66 Total Score	n (missing) Mean SD	263 (0) 13.3 7.07	253 (1) 14.2 7.17	516 (1) 13.7 7.12
	28 Total Score	n (missing) Mean SD	263 (0) 10.3 4.92	253 (1) 10.5 4.93	516 (1) 10.4 4.92
Patient assessment of pain (VAS) at Baseline		n (missing) Mean SD	262 (1) 60.6 22.26	253 (1) 63.1 21.76	515 (2) 61.8 22.03
Patient global assessment of disease activity (Visual Analog Scale) at Baseline		n (missing) Mean SD	263 (0) 61.3 21.47	253 (1) 63.4 21.60	516 (1) 62.4 21.54
Physician global assessment of disease activity (Visual Analog Scale) at Baseline		n (missing) Mean SD	263 (0) 59.8 19.13	253 (1) 60.6 19.71	516 (1) 60.2 19.40
Health Assessment Questionnaire(HAQ) at Baseline		n (missing) Mean SD	263 (0) 1.06 0.712	253 (1) 1.13 0.685	516 (1) 1.09 0.699
Acute Phase Reactant selected for patient in calculating for ACR20 and DAS28	CRP ESR	n (%) n (%)	102 (38.8) 161 (61.2)	89 (35.0) 165 (65.0)	191 (36.9) 326 (63.1)
Disease Activity (DAS28) score at Baseline based on investigator chosen patient specific Acute Phase reactant		n (missing) Mean SD	261 (2) 5.756 1.1112	252 (2) 5.771 1.0448	513 (4) 5.763 1.0781
Disease Activity (DAS28) score at Baseline based on patient-specific Acute Phase reactant	DAS28-CRP	n (missing) Mean SD	100 (2) 5.191 1.0013	88 (1) 5.237 0.9222	188 (3) 5.213 0.9628
	DAS28-ESR	n (missing) Mean SD	161 (0) 6.108 1.0306	164 (1) 6.057 0.9955	325 (1) 6.082 1.0118
Erythrocyte Sedimentation Rate(ESR) results (mm/hr)		n (missing)	161 (102)	164 (90)	325 (192)

Characteristic (unit)	Category	Statistics	YLB113 50mg (N=263)	Enbrel 50mg (N=254)	Total (N=517)
		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 16.

Table 16 **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)

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 17 **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	263	81.2	-5.6	(-11.6, 0.5)
Enbrel 50 mg	254	86.8		

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).

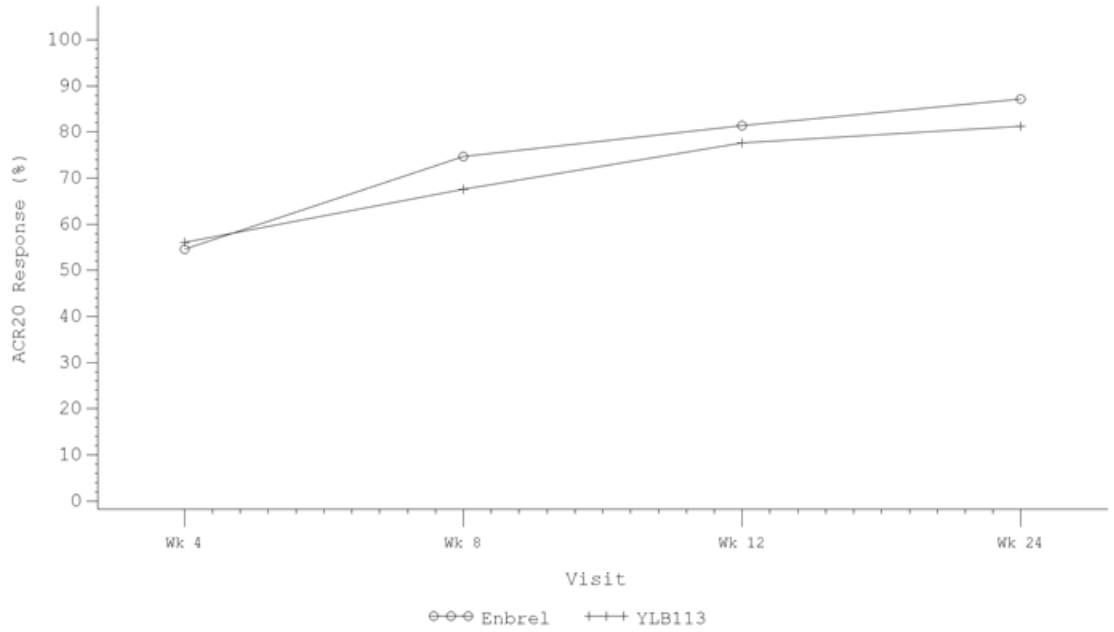
Table 18 **Primary Efficacy: Sensitivity Analysis: Estimate and Confidence Intervals for Differences in ACR20 Response Rate at Week 24 (NRI) (Per Protocol Set)**

			Difference in proportions (YLB113 50 mg – Enbrel 50 mg, %)	
Treatment Arm	**N**	**Proportion**	**Estimate**	**95% Confidence Interval**
YLB113 50 mg	239	86.0	-4.6	(-10.1, 0.8)
Enbrel 50 mg	238	90.6		

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 Nepexto (YLB113) 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 19) and overall support results of the primary analysis.

Table 19 **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		
		YLB113	239	86.0	-3.2	(-9.0, 2.6))

	Cochran-Mantel-Haenzel test	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 20 **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.
One subject had 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 21 **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 one subject 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 22 **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 23 **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)		
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 24.

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

			Mean Change from Baseline		Treatment Difference (YLB113 50 mg – Enbrel 50 mg)	
DAS28-Acute phase reactant		**N**	**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 Nepexto and 35% of patients receiving Enbrel or DAS28-ESR: in 61.2% in the Nepexto 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 25 **Summary of Efficacy for trial YLB113-002**

Title: A Comparative Study to Assess the Efficacy, Safety and Immunogenicity of Nepexto 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 Nepexto 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	Nepexto (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	Nepexto	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	Nepexto vs Enbrel
		Point estimate	-5.6
		95% CI	-11.6; 0.5
		Test	-15% < CI < +15%**
	ACR20 at wk 24 (%) (**PPS; NRI**)	Comparison groups	Nepexto 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	Nepexto 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	Nepexto 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	Nepexto 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	Nepexto 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		

2.5.3. Discussion on clinical efficacy

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 Nepexto 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 Nepexto (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. 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 Nepexto 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 Nepexto 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.

2.5.4. 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 equivalence between Nepexto 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.

2.6. Clinical safety

Safety data for Nepexto 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.

Patient exposure

Exposure in healthy volunteers:

In the (cross-over) PK studies, 169 healthy male volunteers were exposed to a single dose of Nepexto. 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 Nepexto and n = 260 for Enbrel).

Treatment period A (first 24 weeks of treatment, efficacy and safety) was completed by 248 (93.9%) of the Nepexto 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 Nepexto 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 Nepexto patients and 8 Enbrel patients, of whom 9 (90%) and 8 (100%) completed the 52-week treatment.

Adverse events

Phase 1 trials in healthy volunteers:

Study YLB113-001

In this study, a total of 10.2% of subjects in the Nepexto 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 Nepexto 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 Nepexto (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 Nepexto 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 Nepexto and Enbrel.

Phase 3 Study in RA patients:

YLB113-002 – Stage A

In the Nepexto 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 Nepexto group, 65.4% vs 55.3%. Of all patients with reported TEAEs, the majority of the events were mild (33.7% for Nepexto and 37.3% for Enbrel) to moderate (18.6% for Nepexto and 26.2% for Enbrel).

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

Table 26 **Overview of adverse events – Stage A**

Adverse Event category	**Nepexto** 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 27).

Table 27 **Overview TEAEs >5% by SOC - Stage A**

TEAE by System Organ Class	**Nepexto**		**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 Nepexto 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 Nepexto and Enbrel, respectively.

YLB113-002 – Stage B and C

For Stage B, 52.5% of the patients in the Nepexto 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 Nepexto 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 Nepexto 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 28 **Overview of Adverse Events - Stage B/C**

	Stage B		**Stage C**	
Adverse Event Category	**Nepexto**	**Enbrel**	Enbrel/ **Nepexto**	Nepexto**/ 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 29 **Overview TEAEs by SOC - Stage B/C**

TEAE by System Organ Class	**Stage B**				**Stage C**			
	Nepexto		**Enbrel**		Enbrel/ **Nepexto**		Nepexto/ **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			
	Nepexto		**Enbrel**		Enbrel/ **Nepexto**		Nepexto/ **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 Nepexto 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 Nepexto showed a similar AE profile as Enbrel. No new safety signal was derived from the presented data.

Serious adverse event/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 Nepexto 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 Nepexto 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 Nepexto 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 Nepexto 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 (Nepexto 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.

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 Nepexto 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 Nepexto 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 Nepexto group.

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 Nepexto 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 Nepexto 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.

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 Nepexto and 46.8% for Enbrel in Europe compared to 80.9% for Nepexto and 84.5% for Enbrel in Japan.

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

Discontinuation due to adverse events

Stage A

Two patients in the Nepexto group and 5 patients in the Enbrel group experienced AEs leading to discontinuation of study drug. Two patients in the Nepexto 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 Nepexto group and 4 cases in the Enbrel group led to study drug discontinuation. There were 2 SAEs in the Nepexto 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 Nepexto and Enbrel groups.

2.6.1. Discussion on clinical safety

The active substance etanercept has been widely used in clinical practice for approximately 15 years with a well-known safety profile. The main safety issues are related to the immunosuppressive properties of etanercept.

The pharmacology of Nepexto 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 Nepexto and Enbrel in these studies.

In the pivotal study YB113-002, a dose of 50 mg/mL of Nepexto 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 Nepexto (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 Nepexto 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 (Nepexto 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 Nepexto 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 Nepexto. 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 Nepexto 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 Nepexto 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 Nepexto 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 Nepexto and Enbrel groups.

The safety profile as reflected by nature and severity of detected adverse events indicates similarity between Nepexto and Enbrel.

The lower ADA formation and lower rate of local skin reactions reported for Nepexto compared to Enbrel suggest that Nepexto 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.

2.6.2. Conclusions on the clinical safety

The safety profile of Nepexto and Enbrel appear to be similar. The incidence and severity of reported TEAEs in the submitted trials are in accordance with the known safety profile of etanercept. The submitted safety data support the biosimilarity.

2.7. Risk Management Plan

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Malignancy (including lymphoma and leukemia)	Routine risk minimisation measures: SmPC section 4.8 PL section 2 and 4 Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up form for Malignancy, Mycosis fungoides and Lymphoma* Additional pharmacovigilance activities: *German Biologics Register – Rheumatoid Arthritis (RABBIT)*
Serious infections (including opportunistic infections, tuberculosis, Legionella, Listeria and parasitic infections)	Routine risk minimisation measure: SmPC sections 4.3, 4.4 and 4.8 PL section 2 and 4 Legal status: prescription only medicine Additional risk minimisation measure: *Patient alert card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Lupus-like reactions	Routine risk minimisation measure: SmPC section 4.8 PL section 4 Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Sarcoidosis and/ or granulomas	Routine risk minimisation measure:	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.8 PL section 4 Legal status: prescription only medicine Additional risk minimisation measure: None	reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Allergic reactions	Routine risk minimisation measure: *SmPC section 4.3, 4.4 and 4.8* *PL section 2 and 4* Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Severe cutaneous adverse reactions, including toxic epidermal necrolysis [TEN] and Stevens-Johnson Syndrome [SJS]	Routine risk minimisation measure: SmPC section 4.8 PL section 4 Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Systemic vasculitis, including anti-neutrophil cytoplasmic antibodies [ANCA] positive vasculitis	Routine risk minimisation measure: SmPC sections 4.8 PL section 4 Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Macrophage activation syndrome	Routine risk minimisation measure: SmPC section 4.8 PL section 4 Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Central demyelinating disorders	Routine risk minimisation measure: SmPC section 4.4 and 4.8 PL section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: prescription only medicine Additional risk minimisation measure: None	*AE follow-up form for Demyelination* Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Peripheral demyelinating events (Chronic inflammatory demyelinating polyneuropathy [CIDP] and Guillain-Barré syndrome [GBS])	Routine risk minimisation measure: SmPC section 4.4 and 4.8 PL section 2 and 4 Legal status: prescription only medicine Additional risk minimisation measure: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up form for Guillain-Barré Syndrome* Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Aplastic anaemia and pancytopenia	Routine risk minimisation measure: SmPC section 4.4 and 4.8 PL section 2 and 4 Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Interstitial lung disease (including pulmonary fibrosis and pneumonitis)	Routine risk minimisation measure: SmPC section 4.8 PL section 4 Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Autoimmune hepatitis	Routine risk minimisation measure: SmPC section 4.8 PL section 4 Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Liver events in patients with viral hepatitis (including hepatitis B virus [HBV] reactivation)	Routine risk minimisation measure: SmPC section 4.4 and 4.8 PL section 2 and 4 Legal status: prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	medicine Additional risk minimisation measure: None	 Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Change in morphology and/or severity of psoriasis in adult and pediatric populations	Routine risk minimisation measure: SmPC section 4.8 PL section 4 Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Congestive heart failure [CHF] in adult subjects	Routine risk minimisation measure: SmPC section 4.4 PL section 2 Legal status: prescription only medicine Additional risk minimisation measure: *Patient alert card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Inflammatory bowel disease in Juvenile idiopathic arthritis [JIA] subjects	Routine risk minimisation measure: SmPC section 4.4 and section 4.8 PL section 2 Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up form for Juvenile idiopathic arthritis subtype* Additional pharmacovigilance activities: None
Autoimmune renal disease	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Pemphigus/ pemphigoid	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		German Biologics Register - Rheumatoid Arthritis (RABBIT)
Amyotrophic lateral sclerosis [ALS]	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up form for ALS* Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Myasthenia gravis	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Encephalitis/ leukoencephalomyelitis	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Progressive multifocal leukoencephalopathy [PML]	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up form for PML* Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Liver failure	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Hepatic cirrhosis and fibrosis	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Severe hypertensive reactions	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Adverse pregnancy outcomes	Routine risk minimisation measure: SmPC section 4.6 PL section 2 Legal status: prescription only medicine Additional risk minimisation measure: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up form for Adverse events in pregnancy* Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*
Potential for medication errors (pre-filled pen)	Routine risk minimisation measure: *Clear Package insert instructions for use of the pre-filled pen* *PL section 7* Legal status: prescription only medicine Additional risk minimisation measure: *Educational guide for healthcare professionals and patients*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Potential for male infertility	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Weight gain	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		None
Impaired growth and development of juvenile subjects	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Acute ischaemic cardiovascular [CV] events in adult subjects	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: *German Biologics Register - Rheumatoid Arthritis (RABBIT)*

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports 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.

2.9. Product information

2.9.1. 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.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nepexto (etanercept) is included in the

additional monitoring list as a new biological product.

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Nepexto (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 Nepexto are identical to those of the reference product Enbrel.

Nepexto 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 Nepexto 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 Nepexto. 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 between Nepexto and the reference product Enbrel at quality level two biosimilarity studies were conducted; one was conducted during the developmental stage of Nepexto and one was conducted after Nepexto was available from the commercial manufacturing process. A varying number of Nepexto active substance and finished product batches were used in both studies.

To increase representativeness of the commercial process and verify independence of Nepexto batches used an additional (third) biosimilarity study was conducted with up to 11 active substance batches of the post-process validation stage.

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 Nepexto 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 Nepexto 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 Nepexto versus Enbrel EU-source
- **Study YLB113-002:** a multicentre, double-blind, randomised, parallel-group comparative study to assess the efficacy, safety, and immunogenicity of Nepexto 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 Nepexto versus Enbrel and could not be accepted as a proof of similarity between Nepexto 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 procedure[1] 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.

3.2. Results supporting biosimilarity

Quality

With respect to primary, secondary and higher order structure, comparability of Nepexto with the reference product Enbrel EU has been confirmed. Similar purity was demonstrated with respect to oxidised and deamidated variants; a lower level of N- and C-terminal variants was observed for Nepexto.

Analytical similarity of Enbrel sourced from EU and Japan was established and further supported with additional lots of Enbrel from Japan.

Non clinical

In the comparative *in vitro* studies, including the evaluation of TNF receptor related biological activities and Fc related binding characteristics, similarity between Nepexto 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 Nepexto product to be commercialised and EU-sourced Enbrel as reference product.

The results showed that the primary PK parameters AUC_{0-t} and C_{max} fall within the acceptance range of 80.00%-125.00% (90%CI). Point estimators were close to 1 and 90% CIs include 100% (ratios AUC_t 96.22 [88.92-104.12], C_{max} 101.18 [92.23-110.99]). The study met the bioequivalence criteria and support 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 Nepexto 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 (Nepexto: 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 Nepexto 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 Nepexto and Enbrel with a lower incidence of ADAs and local skin reactions for Nepexto 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.

3.3. Uncertainties and limitations about biosimilarity

Quality & non-clinical

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

Clinical

Out of the three single dose phase I PK studies submitted by the applicant to demonstrate biosimilarity between Nepexto and the reference product 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 2.4.2.).

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 2.4.2.).

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 C_{max} of the respective subject was > 1500 ng/mL, since pre-administration concentrations must not exceed 5% of individual C_{max}. Actual C_{max} 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 the test product.

3.4. Discussion on biosimilarity

With a new comparability study based on up to eleven batches of Nepexto, a representative data pool is available for similarity assessment with the reference product and the initially raised major objection on the analytical biosimilarity claim is resolved.

Results obtained from the new biosimilarity study confirmed results obtained from the previous biosimilarity studies that had limited representativeness.

Differences in the N-glycosylation profile further exist while differences in the site occupancy profile of O-glycans turned out to be method-related and thus structurally irrelevant. The differences in N-glycan profile affect the ADCC. Several biological assays were performed with a representative number of batches (TNF-α and TNF- α neutralisation assay, apoptosis bioassay, ADCC, CDC). The methods used to investigate the product related variants aggregates, HMW species and LMW species (SE-HPLC) as well as misfolded species and degradants (HI-HPLC) were improved and therefore results reflect a similar or slightly better purity profile of Nepexto.

A lower level of C-terminal variants with lysine affected the charge profile; however, this is of no concern for the functionality of the molecule.

The claim of analytical biosimilarity is supported based on the results of the additional comparability study performed with a representative number of batches and using suitable analytical methods.

In addition, clinical PK data obtained from the pivotal study ETA 50/334 demonstrate similarity between the test Nepexto and the reference Enbrel product, based on point estimators for etanercept exposure after SD administration of 50 mg solution for injection in PFS (C_{max} 101.18 [92.23-110.99], AUC_{0-t} 96.22 [88.92-104.12], $AUC_{0-\infty}$ 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 test and reference product.

3.5. Extrapolation of safety and efficacy

The number and nature of adverse events were generally comparable between Nepexto and Enbrel with a lower incidence of local skin reactions for Nepexto indicating possibly a lower immunogenic potential. This, however, is not regarded to have an impact on the assessment of biosimilarity since reduced immunogenicity is not considered a risk from a clinical perspective, and the small difference did not have a clinical impact.

The clinical model of moderate to severe RA was chosen to demonstrate similar efficacy between the test and the reference medicinal product. Moderate to severe RA was confirmed as a sensitive and suitable clinical setting in the preceding scientific advice procedure and in line with applicable Guidelines. In view of reported baseline data in terms of Swollen Joint Count, Tender Joint Count, DAS28 Score and acute phase reactants (ESR, CRP) the chosen patient population is considered representative of the intended population and suitable for the efficacy comparison between the test and reference product.

According to the overarching guideline on similar biological medicinal products, extrapolation to other indications of the reference medicinal product could be acceptable, provided that biosimilarity has been demonstrated in one indication. 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.

Based on the available data, the extrapolation of efficacy and safety profile of Enbrel in RA patients to other indications is considered acceptable.

3.6. Additional considerations

Not applicable

3.7. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nepexto is favourable in the following indications:

Rheumatoid arthritis

Nepexto 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.

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

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

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

Juvenile idiopathic arthritis

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

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

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

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

Psoriatic arthritis

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

Axial spondyloarthritis

Ankylosing spondylitis

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 following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

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.

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

Risk Management Plan (RMP)

The 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.

Additional risk minimisation measures

1. Prior to launch in each Member State, the MAH shall agree the final educational material with the competent authority in that Member State, consisting of information provided to all healthcare professionals expected to prescribe the product on the correct and safe use of the pre-filled pen/pre-filled syringes and to inform them that the product is not for use in children and adolescents who weigh less than 62.5 kg, and a Patient Alert Card which is to be given to patients using Nepexto.
2. The healthcare professional's educational material should contain the following key elements:
    - Teaching guide to facilitate training of the patients in the safe use of the pre-filled pen
    - A needle-free demonstration device
    - Material to remind healthcare professionals that Nepexto is not for use in children and adolescents who weigh less than 62.5 kg
    - Instructional materials to share with patients.
3. The Patient Alert Card should contain the following key elements for patients treated with Nepexto:
    - The risk of opportunistic infections and tuberculosis (TB)
    - The risk of Congestive Heart Failure (CHF)
    - Nepexto is not for use in children and adolescents who weigh less than 62.5 kg.