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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Erelzi

International non-proprietary name: etanercept

Procedure No. EMEA/H/C/004192/0000

Note

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

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List of abbreviations

ADA	Antidrug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ANCOVA	Analysis of Covariance
ANOVA	Analysis of variance
AS	Ankylosing spondylitis
ATE	Averaged treatment effect
AUC	Area under the curve
BSA	Body surface area
BMI	Body mass index
CDC	Complement-dependent cytotoxicity
CI	Confidence Interval
Cmax	Maximum concentration
CHMP	Committee for Human Medicinal Products
CRP	C-reactive protein
hsCRP	High sensitivity CRP
CSR	Clinical study report
(e)CRF	(electronic) case record form
E_0	Baseline pharmacodynamic effect
EC_{50}	Effect compartment concentration at which 50% of the maximum effect occurs
ECG	Electrocardiogram
EMA	European Medicines Agency
E_{max}	Maximum pharmacodynamic effect
EU	European Union
FAS	Full analysis set
g	Gram
GCP	Good Clinical Practice
h	Hour
HAQ-DI	Health Assessment Questionnaire- Disability Index

ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IRT	interactive response technology
ITT	Intention-to-treat
JIA	Juvenile idiopathic arthritis
kg	Kilogram
MAA	Marketing Authorisation Application
mg	Milligram
MMRM	Mixed Model Repeated Measure
N	Number of Patients
Na	Not analysed
ns	Not specified
PASI	Psoriasis Area and Severity Index
PC	Placebo-controlled
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per-protocol set
RA	Rheumatoid arthritis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
sTNF	soluble Tumour Necrosis Factor
TEAE	Treatment-emergent adverse event
TNF	Tumour Necrosis Factor
TNFR	Tumour Necrosis Factor Receptor
tmTNF	membrane bound Tumour Necrosis Factor
VAS	Visual Analogue Scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sandoz GmbH submitted on 11 November 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Erelzi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Rheumatoid arthritis

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

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

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

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

Juvenile idiopathic arthritis

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

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

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

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

Psoriatic arthritis

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

Axial spondyloarthritis

Ankylosing spondylitis (AS)

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

Non-radiographic axial spondyloarthritis

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

Plaque psoriasis

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

Paediatric plaque psoriasis

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

The legal basis for this application refers to:

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

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 Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form:
  Enbrel, 10, 25 mg, powder for solvent for solution of injection
  Enbrel, 50 mg, solution for injection in pre-filled pen
  Enbrel, 25, 50 mg, solution for injection in pre-filled syringe
  Enbrel, 25 mg, powder for solution for injection
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 03-02-2000
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers:
  For 25 mg - EU/1/99/126/002-05
  For 50 mg - EU/1/99/126/013-22

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form:
  Enbrel, 10, 25 mg, powder for solvent for solution of injection
  Enbrel, 50 mg, solution for injection in pre-filled pen
  Enbrel, 25, 50 mg, solution for injection in pre-filled syringe
  Enbrel, 25 mg, powder for solution for injection
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 03-02-2000
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers:

For 25 mg - EU/1/99/126/002-05
For 50 mg - EU/1/99/126/013-22

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

- Product name, strength, pharmaceutical form:
  Enbrel, 10, 25 mg, powder for solvent for solution of injection
  Enbrel, 50 mg, solution for injection in pre-filled pen
  Enbrel, 25, 50 mg, solution for injection in pre-filled syringe
  Enbrel, 25 mg, powder for solution for injection
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 03-02-2000
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers:
  For 25 mg - EU/1/99/126/002-05
  For 50 mg - EU/1/99/126/013-22

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 indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 2 December 2010 and 17 February 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Outi Mäki-Ikola

- The application was received by the EMA on 11 November 2015.
- The procedure started on 4 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 22 February 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 February 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 3 March 2016.

- The PRAC Rapporteur's updated Assessment Report was circulated to all CHMP members on 16 March 2016.
- During the meeting on 1 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 December 2016.
- The following 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 triggered GCP inspection at 4 sites in Germany (sponsor site, CRO and two clinical investigator sites) was performed between 20 June and 26 August 2016. The outcome of the inspection carried out was issued on 14 October 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 January 2017.
- During the PRAC meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- The Rapporteurs circulated the Joint updated Assessment Report to all CHMP members on 16 February 2016.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 April 2017.
- During the meeting on 18-21 April 2017, 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 Erelzi on 21 April 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

This application concerns a centralised procedure for marketing authorisation of Erelzi, a biosimilar product to the European reference product Enbrel (EMA product number EMEA/H/C/000262). Enbrel is approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, and (juvenile) plaque psoriasis. Enbrel was first authorised in the European Union in 2000.

About the product

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The 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. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Type of Application and aspects on development

This is a MAA for Erelzi, a proposed biosimilar, submitted under Article 10(4) of Directive 2001/83/EC.

Erelzi is claimed to be a biosimilar product to the reference product Enbrel. In Europe Enbrel was approved via the centralised procedure on 03 February 2000 and is authorised for Pfizer Limited, UK.

Scientific advice

Non-clinical

In 2010 CHMP provided scientific advice on the non-clinical package. At that time the CHMP suggested some alternative approaches for the non-clinical in vivo studies proposed by the applicant. The Applicant performed and submitted a study in cynomolgus monkeys, justifying their choice with view on a global development and because etanercept was expected to have a lower immunogenic potential in this species (based on information in the Enbrel EPAR) compared to rodent models.

PK/PD

A cross-over design was considered feasible for the equivalence studies, as the half-life of etanercept is shorter than that of other TNFα antibodies. The lower drug clearance in patients with RA compared to healthy volunteers (0.066 vs. 0.11 l/h) may reflect differences in target binding. For this reason, it was advised to collect comparative PK and PD data for clearance-related parameters during a Phase III trial. This was followed by the Applicant in the psoriasis study.

The CHMP indicated that the general development approach of demonstrating pharmacokinetic equivalence in a single Phase I trial and therapeutic equivalence in a single Phase III trial seems acceptable, as long this would be adequately supported by quality and non-clinical data, and an EU-sourced Enbrel product was used as reference product. The CHMP recommendation to use EU Enbrel as a Reference product in the studies was adapted.

SAWP/CHMP advices, Clinical

The CHMP preferred rheumatoid arthritis (RA) to psoriasis as a model demonstrating equivalence, since patients with psoriasis may concern a more heterogeneous population, as a variety of prior treatments can be applied before the use of etanercept. Psoriasis may also be associated with a high inter-individual variability due to a more variable ‘load’ of target antigen than in RA, as there is more surface area in the skin than in the joints (Gottlieb 2007). The Applicant discussed the design of an equivalence study in RA in the follow-up advice of the SAWP/CHMP in 2011 (EMA/CHMP/SAWP/424696/2011). The final development plan, however, did not include a study in RA but in moderate-severe psoriasis instead. However, The CHMP’ recommendation to continue monitoring of safety and anti-drug antibodies (ADA) in a follow-up phase up to 12 months, was followed by the Applicant.

In several national scientific advices it was suggested to use the continuous PASI scale as the primary endpoint, as such an endpoint may be more sensitive to detect differences in efficacy than a dichotomous outcome of PASI75. In response, the Applicant included percentage change from baseline in the absolute PASI scores as key secondary endpoint. Furthermore, the proposed equivalence margin of the primary endpoint PASI75 of +/-18% was considered too broad by several agencies. The equivalence margin of the key secondary endpoint based on percentage change from baseline in PASI score was set to +/- 15%.

Furthermore, the Applicant sought scientific advice regarding cross-over of the study medications after 12 weeks in the follow-up study phase after 12 weeks, as supportive evidence for establishing exchangeability. This concept was disputed in some national scientific advices.

A GCP-inspection has been performed by the German Inspectorate for Study GP15-302 (EudraCT number: 2012-002011-26), on request of the EMA. Several critical findings were noted. The inspection was followed by a re-monitoring procedure by independent auditors, as aligned with the inspectorate. Based on Inspectors' recommendations and outcomes of the re-monitoring, no major critical issues regarding GCP compliance of the pivotal clinical trial of this application are remaining.

2.2. Quality aspects

2.2.1. Introduction

Erelzi (etanercept) has been developed as a similar medicinal product according to Article 10(4) of Directive 2001/83/EC. The reference medicinal product used throughout the development program is Enbrel, sourced from the European Union. The same therapeutic indications are proposed for Erelzi as granted for Enbrel in the EU.

The finished product is presented as a solution for injection in a pre-filled syringe (PFS) containing the active substance etanercept at a concentration of 50 mg/mL. The excipients are sodium citrate as buffer, sodium chloride as tonicity agent, sucrose and L-lysine as stabilizers and water for injection as diluent.

Two strengths of Erelzi finished product, 25 mg/0.5 mL and 50 mg/1.0 mL, have been developed based on the available presentations of the reference product Enbrel. Both strengths are solutions for injection in a pre-filled syringe (PFS) assembled with a Needle Safety Device (NSD). The 50 mg PFS is also available assembled in an Autoinjector (AI). The paediatric 10 mg strength approved for the reference medicinal product is not included in the marketing authorisation application for Erelzi.

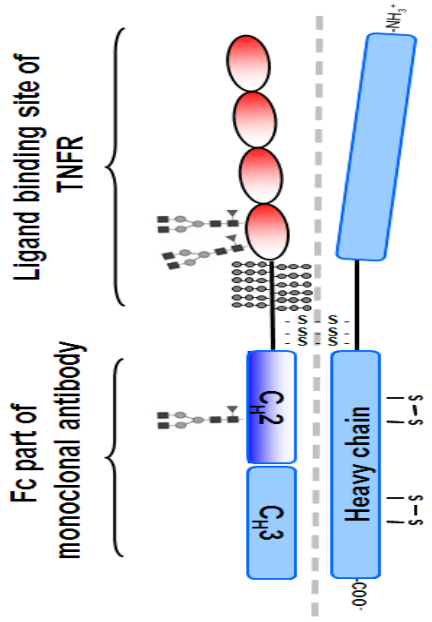
2.2.2. Active substance

General Information

Etanercept is a recombinant dimeric fusion protein consisting of two extracellular domains of the 75-kilodalton tumor necrosis factor receptor (TNFR) linked to the Fc (fragment, crystallisable) portion of an immunoglobulin G1 (IgG1) antibody (TNFR:Fc). Etanercept exerts its biological effect through binding and neutralisation of TNFα.

Erelzi is produced using the Chinese Hamster Ovary (CHO) cell expression system, contains 934 amino acids (homo-dimer: 467) and has an approximate molecular mass of 125 kDa as determined by mass spectroscopy. The apparent molecular size (determined by SDS-PAGE) is 150 kDa. Erelzi is glycosylated and contains 6 N-glycans and multiple O-glycans. These variants are sialylated as well. In addition, 29 disulfide bridges are present throughout the molecule.

Figure 1: Schematic representation of etanercept



Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The manufacture of the active substance takes place at Sandoz GmbH Schaftenau, Langkampfen, Austria. Appropriate GMP certificates have been provided.

A production batch is generated from a working cell bank (WCB) vial, upon cell expansion and protein production during the upstream process (fermentation) and the subsequent downstream process (purification).

Fermentation comprises the consecutive operations inoculum preparation, pre-stage cultivation, and main-stage cultivation. The purification includes primary separation followed by a combination of chromatography and filtration steps leading to the final active substance.

Control of materials

Erelzi is expressed from a CHO cell line. A classical two tiered cell bank system is established. The origin of the cell substrate, relevant information on the vector map, as well as the complete nucleotide sequence of the expression vector has been presented in the dossier. The cell banking system is conventional and established according to ICH Q5D. Specifications for the cell banks have been adequately presented.

Raw materials used for the Erelzi active substance manufacturing process are controlled by specifications that assure their identity, strength and purity. They are obtained from established suppliers together with a certificate of analysis. These materials either comply with pharmacopoeial monographs (USP, Ph. Eur.) or internal test procedures.

Control of critical steps and intermediates

Based on risk assessment and results from process characterisation studies, the PPs have been divided into critical-PPs (CPP), key-PPs (KPP) and non-key PPs (NKPP). For each PP, an acceptable range was defined through process characterisation and/or validation studies.

As for the PPs, also the IPCs are divided into critical, key and non-key process controls. CIPCs are defined by acceptance criteria or by action limits. If an acceptance criterion is not met, the batch will be rejected, while for action limits, an investigation will be conducted. The decision to release the batch is taken based on the results of the investigation. Key in-process controls (KIPCs) have associated action limits, while NKIPCS either have alert limits or no associated limits.

The Applicant submitted brief justifications for all critical steps/parameters/tests; and upon request, additional justification was provided. These cumulative justifications are based on extensive process characterisation studies and are considered acceptable.

Process validation

To ensure consistent product quality and to demonstrate robust process performance the manufacturing process at the intended commercial manufacturing scale was validated in accordance with GMP with a variety of experimental setups and targets. In addition, large scale validation was supported by small scale studies.

The validation batches have been manufactured within the defined ranges for process parameters and the output data presented demonstrate high batch to batch consistency both for the upstream cell culture process and for the downstream purification process. All acceptance criteria for the selected process controls provided were fulfilled. Furthermore, the active substance batch release data are comparable between batches and comply with the acceptance criteria.

Furthermore, the Applicant submitted data for impurity removal at full scale; hold time validation; limit of in vitro cell age; and column resin lifetime studies.

Manufacturing process development

As a key tool for developing the manufacturing process, for establishing the overall control strategy, as well as for justifying the characterisation and comparability program, the Applicant has performed criticality assessment of quality attributes based on a risk ranking approach. This criticality assessment is considered acceptable.

During development of Erelzi, the active substance has been manufactured using two main manufacturing processes; Phase I and Phase III processes. In addition, smaller changes have occurred within the main processes.

The Applicant has conducted extensive comparability exercises. Overall it is concluded, that comparability between batches produced throughout product development is demonstrated.

Characterisation

The Applicant has provided characterisation data on primary and higher order structures, molecular mass, charge, and heterogeneity with regard to glycosylation, AA-sequence, size and amino acid modifications. Furthermore, results from binding assays (TNF-α and Fc receptor) and in vitro bioassays (ADCC, CDC, inhibition of apoptosis, TNF-α and TNF-β neutralisation assays) have been presented.

For the characterisation of impurities, the Applicant has considered both process- and product-related impurities. Efficient removal of all process-related impurities has been demonstrated.

As part of the characterisation of potential product-related impurities, the Applicant has studied oxidation, deamidation, basic variants (by CEX and CZE), aggregation and degradation products (by SEC-UV, AUC, SEC-MALLS, non-reducing CE-SDS), N-glycans and sialic acids, glycation, and wrongly bridged disulphides.

Upon request, additional data and clarification was submitted regarding wrongly bridged disulphide variants (including the so called T7 peptide variant), which are major impurities. Submitted data suggest that these misfolded variants may refold to the active variant correctly. In addition, the applicant committed to submit a variation to implement an appropriate analytical method for the assessment of hydrophobic variants in the release and shelf-life specifications for active substance and finished product once optimized/developed and validated (see "Recommendation for future quality development).

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

Specification

The proposed DS release and shelf life specifications include control for pharmaceutical characteristics (colour of solution, pH and clarity), identity, purity, content, and potency. Overall, the test items included in the specifications are considered adequate and in line with relevant guidance.

Analytical methods

The analytical procedures, including the used controls, system suitability, and sample acceptance criteria, have been described. Compendial methods are sufficiently defined by their respective monograph. Furthermore, the Applicant has provided validation reports on non-compendial methods (e.g. bioactivity assay). In general, the validation reports are thorough and cover the relevant aspects.

Batch analysis

Batch analysis data of the active substance were provided. The results were within the specifications and confirm consistency of the manufacturing process.

Reference materials

The Applicant has provided a description of reference standards used throughout the development of Erelzi. For commercial manufacturing, working standards are used for routine analytical testing, while the in-house primary reference is only used for release and re-testing of working standards.

The reference standard is satisfactorily established and an appropriate protocol has been laid down to replace the reference standard or to qualify working standards as needed.

Stability

The proposed shelf life is 36 months at ≤ -60°C

The Applicant has provided long-term stability data from multiple commercial scale batches.

In addition, the Applicant performed studies at accelerated and stressed conditions.

Taken together, the proposed shelf life and associated conditions are acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Erelzi 25 mg/0.5 mL and 50 mg/1.0 mL solution for injection is a colourless to slightly yellowish solution comprising etanercept as active substance, sodium citrate as buffer, sodium chloride as tonicity agent, sucrose and L-lysine as stabilizers and water for injections as diluent. The pH is adjusted to 6.3 with sodium hydroxide and hydrochloric acid as required.

The finished product is supplied in pre-filled syringes (PFS) (clear glass barrel with fixed needle) closed with a plunger stopper and is intended for subcutaneous administration. The bulk PFS is combined with either an Autoinjector (AI) or a CE-marked Needle Safety Device with an add-on finger flange (NSD). Neither the NSD nor the AI is in direct contact with the finished product. The information provided for the container closure system is satisfactory.

During the development of Erelzi combined quality attribute ranges of US-licensed Enbrel and EU-authorized Enbrel were employed as Quality Target Product Profile (QTPP). Citrate buffer, Sucrose, NaCl and L-lysine was chosen as the most suitable Erelzi formulation, as it provided stability and PK parameters which were closer to the reference product than other investigated formulations. Compared to the reference product, phosphate and L-arginine were exchanged for citrate and L-lysine. The formulation process development has been presented in detail and is considered acceptable.

The manufacturing process development has been clearly described; the main differences between process A and process B (varied batch sizes) have been identified and analytical comparability between finished product produced with process A and process B has been demonstrated.

Manufacture of the product and process controls

Manufacturing formula was adequately provided. The batch size is calculated based on the quantity and protein content of etanercept in Erelzi DS solution.

A clear description of the Erelzi finished product manufacturing process has been provided including IPCs and maximum hold/standing times applied. Erelzi finished product is produced using standard manufacturing steps such as thawing of the active substance, dissolving of excipients, compounding, sterile filtration and aseptic filling into syringes. The evaluation and justification of PPs and IPCs has been presented. Process parameters and IPCs are specified and limits have been provided, where applicable. The description of the manufacturing process is appropriate.

Process Validation

Validation of Erelzi 25mg/0.5ml and 50mg/1.0ml solution for injection in pre-filled syringe was performed. Consecutive validation batches of bulk finished product solution were produced. In addition, appropriate hold time validation and media fills were performed. All analytical data complied well with requirements.

Product specification

The specifications include general tests (e.g. color, pH, clarity, extractable volume, appearance of container, osmolality), tests for identity, purity, content and potency.

The specification for the 25 mg and 50 mg presentations are analogous and differ only in parameters related to reduced content/fill volume, but not concentration.

Analytical methods

The Applicant has described the analytical procedures, including the used controls, system suitability and sample acceptance criteria. Most of the finished product release methods are identical to the active substance methods.

Batch analysis

Batch analysis data from several finished product batches were provided. The results were within the specifications and confirm consistency of the manufacturing process.

Stability of the product

The claimed shelf life is 30 months, when stored at 5 ± 3°C, followed by 28 days at 25 ± 2°C. This applies for both strengths and for both the AI and PFS with NSD.

A summary of the data provided to support the proposed shelf life is outlined in Table 1 below.

Table 1: Summary of conditions and available data

		Data available [months]	
Condition		**Erelzi 25 mg/0.5 mL**	**Erelzi 50 mg/1.0 mL**
5 ± 3°C	Long term storage	30	36
Condition A	Long term storage	30	36
25 ± 2°C/60 ± 5% RH	Accelerated	6	6
40 ± 2°C	Stress	1.5	1.5

Condition A is the intended condition to claim shelf-life. To this end samples were stored for several days at 25 ± 2°C/60 ± 5% RH, shaken and stored at 5 ± 3°C thereafter. The samples were additionally stored at 25 ± 2°C/60% ± 5% RH for a period of 28 days prior to every sampling point.

Batches were tested at appropriate time points in line with ICH Q5C. The tests are those described in the shelf life specification. It is noted and accepted that not all tests were performed at all time points.

The results of the photostability studies demonstrate that Erelzi finished product is light sensitive and should be protected from light. A statement is included in the SmPC that the product should be kept in the outer carton in order to protect from light.

The claimed shelf life of 30 months, when stored at 5 ± 3°C, followed by 28 days at 25 ± 2°C is sufficiently justified by the data provided and consequently acceptable.

2.2.4. Biosimilarity

In order to compare the physicochemical and biological characteristics of Erelzi and Enbrel, the Applicant has conducted a comprehensive comparability exercise. The study follows the general recommendations given in the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012).

For the head-to-head comparison, the Applicant has compared several batches of Erelzi and EU Enbrel as well as US-sourced Enbrel batches. Although the comparative studies demonstrate high similarity between EU- and US-sourced Enbrel batches, only the EU Enbrel batches are considered pivotal for the head-to-head analyses.

In order to establish comparability ranges, the Applicant has considered historical characterisation data collected from Enbrel batches. Based mainly on a quality attribute criticality assessment the quality attributes of

etanercept have been classified into different tiers. The risk assessment and tier classification was described in detail and was found acceptable.

The comparative characterisation studies include assessment of primary structure, higher order structure, molecular mass/size, charge, content, heterogeneity in glycosylation pattern (O-glycosylation N-glycosylation, glycation, sialic acids), heterogeneity in amino acid sequence (variability of the N- and C-terminus), size heterogeneity, heterogeneity with regard to amino acid modifications (deamidation and oxidation), charge heterogeneity, hydrophobicity, compendial methods, process related impurities, binding assays and *in* vitro bioassays. Orthogonal methods have been used, where possible. All methods have been fully developed and implemented.

For most quality attributes and characteristics, high similarity between Erelzi and EU Enbrel has been established. Primary and higher order structures do not display any significant differences. With regard to the variability of the N- and C-terminus, minor differences were observed, but these differences were shown to have no impact on safety or efficacy. Overall, protein deamidation and oxidation levels appear to be highly similar. In the head-to-head comparison, lower levels of aggregates and degradation product were seen for Erelzi compared to EU Enbrel, with corresponding higher SEC main peak purity. Similar results were also obtained using orthogonal analytical methods. From a clinical point of view, the lower level of aggregates and degradation products are, however, of no concern. In reverse phase chromatography, lower amounts of post-peak variants were detected in Erelzi. Upon request, further data and justification was submitted regarding these variants (see also characterisation section); this difference is acceptable from a biosimilarity point of view.

The level of free cysteines was slightly lower for Erelzi than for EU-authorized Enbrel. Low amounts of free SH-groups are preferable, as they indicate open disulfide bridges and hence a possible change in the higher order structure of the overall molecule. This difference is therefore acceptable.

For comparison of protein content the comparability criteria were fulfilled.

The charge variant profile of disialylated Erelzi and EU Enbrel has been compared using capillary zone electrophoresis (CZE) and capillary isoelectric focusing (cIEF). By CZE, slightly higher amounts of acidic variants and clearly lower amounts of basic variants have been observed in Erelzi compared to EU Enbrel. Upon request, the Applicant sufficiently demonstrated that these differences are due to clinically irrelevant variants.

In reverse phase chromatography of disialylated samples, lower amounts of post-peak variants were detected in Erelzi compared to EU Enbrel. Based on characterisation studies the post peak fraction mainly consists of inactive wrongly bridged disulfide variants as well as of size variants with low activity. As the TNF-α bioactivity are similar between Erelzi and EU Enbrel, the difference in post peak variants as detected by reverse phase chromatography can be considered to be clinically irrelevant.

Some degree of differences between Erelzi and Enbrel can be observed in 2D-DIGE electrophoresis. These differences are mostly seen for minor variants and are considered acceptable. The more abundant variants display high similarity.

In the comparison of the glycan profiles, the Applicant has considered both O-glycans and N-glycans. The qualitative comparison of O-glycans did not reveal any differences. For N-glycans, both quantitative and qualitative differences were seen. Considering that these differences have been present throughout the product development, it is unlikely that the differences would have a clinical impact. Quantitative differences in N-glycans were observed in the head-to-head analyses for non-fucosylated and alpha-galactosylated N-glycans, as well as for high mannose structures. In the case of non-fucosylated N-glycans, the Erelzi active substance batches were also outside the tolerance interval of the EU Enbrel range. A resulting lower mean ADCC activity

was observed for Erelzi compared to Enbrel. In order to exclude a relevant contribution of ADCC, the Applicant submitted appropriate data to justify the claim that neither Erelzi nor Enbrel were able to induce ADCC activity under more physiological conditions. CDC is also not expected to be involved in the mode of action for etanercept. Therefore, the small difference detected between Enbrel and Erelzi is considered clinically irrelevant.

High mannose species are present at lower levels in Erelzi compared to EU Enbrel. A thorough discussion on the possible clinical impact of the difference was provided by the Applicant, sufficiently justifying that this difference is not relevant.

In order to compare the mode of action characteristics of Erelzi and Enbrel, the Applicant has used two reporter gene assays for the neutralization of TNF-α and TNF-β, a cell-based TNF-α neutralization assay to characterise the inhibition of TNF-α-mediated apoptosis by etanercept, and measured TNF-α binding by surface plasmon resonance (SPR). Although a slight difference between Erelzi and Enbrel could be seen in the head-to-head analyses using the two reporter gene assays, the historical data summarised suggest similarity between Erelzi and Enbrel.

In the binding studies to C1q and Fc receptors (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa (F158 and V158), FcγRIIIb and FcRn), no differences were observed.

In addition to the analytical methods used in the extended comparative characterisation, the Applicant has also applied compendial methods for comparing characteristics of Erelzi and EU Enbrel. No significant differences were observed with regard to the colour of the solution, clarity, pH, extractable volume, osmolality, as well as for the amount of visible and subvisible particles present. Investigations into process-related impurities (DNA, Protein A, HCPs) did not reveal relevant differences between Erelzi and EU Enbrel.

Finally, comparative stability studies conducted under long-term storage conditions as well as under accelerated and stressed conditions provided evidence of similar degradation profiles of Erelzi and EU Enbrel.

The outcome of the physicochemical and biological comparability exercise between Erelzi and Enbrel is summarised in the tables below.

Table 2: Physico-chemical methods used to characterize and compare Erelzi and Enbrel

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Primary structure	Amino acid sequence	Reducing peptide mapping (MS)	Identical primary sequence[1)]
		Amino acid analysis	Ratios amino acids comparable[2)]
	Degradation product N-terminal heterogeneity	LC-MS	Erelzi has lower amounts of diketopiperazine except for one aged batch
	Disulfide bridging	Non-reducing peptide mapping	Identical disulfide bridging pattern
	Free cysteines	Ellman's assay, non-reducing peptide mapping	Slightly lower levels of free cysteins for Erelzi
Higher order structure	Secondary and tertiary structure	CD spectroscopy (NUV, FUV)	Comparable higher order structure
		DSC	Tm1 and Tm2 consistent to EU-authorized batches
		H/D exchange	Comparable higher order structure[3)]
		FT-IR	FT-IR profiles comparable between all batches
		1D-NMR	Overlay of spectra comparable[3)]
		X-ray crystallography	Identical higher order structure
Molecular Mass/Size	Molecular mass	MALDI-ToF; SEC-MALLS	Intact mass comparable
Charge	Charge/Size	2D-DIGE	Qualitative pattern comparable to EU-authorized batches. For minor variants quantitative differences detectable
Content	Content	UV/Vis spectroscopy	Equivalent content

[1)] Identity of the primary sequence was confirmed between Erelzi and US-licensed Enbrel only. This is considered justified since the primary sequence is unique for etanercept and was shown to be identical to the primary sequence presented in literature (Osslund T. D. et al 2007).
[2)] The comparison of amino acid ratios was performed between Erelzi and US-licensed Enbrel only. This is considered justified since the amino acid ratio is dependent on the primary sequence of the product which was shown to be identical to the primary sequence of etanercept (see above).
[3)] H/D exchange and 1D-NMR was performed for Erelzi and US-licensed Enbrel only which is considered justified since the higher order structure strongly depends on the primary structure which was shown to be identical the primary sequence of etanercept (see above). Furthermore, comparable higher order structure between Erelzi and EU-authorized Enbrel was shown by other analytical techniques like CD spectroscopy, FT-IR, DSC and X-ray crystallography.

Table 3: Physico-chemical characterization of heterogeneity and stability indicating degradation products

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
Glycosylation	O-Glycans	MALDI-ToF of released O-glycans (after sialidase digestion)	Identical qualitative O-glycan pattern
	Glycosylation site occupancy and site specific (e.g. Fc part) N-glycan analysis	Peptide mapping coupled to ESI-MS NP-HPLC	Qualitatively, Erelzi N-glycan pattern comparable except for additional two minor abundant N-glycans qG3/tG4 and bG1-N-F. Quantitatively, lower levels of non-fucosylated N-glycans detectable for Erelzi
	Glycation	Boronate affinity chromatography	Lower levels of glycated variants detectable for Erelzi
	Sialic Acids incl. NGNA (N-glycolylneuraminic acid)	Overall sialylation by AEX WAX of 2-AB labelled N-glycans RP-HPLC of DMB labelled sialic acids released from N- and O-glycans	Overall amounts of sialic acids comparable (e.g. by DMB labelling)
AA-sequence	Variability of N-terminus (– Leu, – Leu-Pro)	Reducing Peptide Mapping	Comparable N-terminal pattern; lower amounts of L1(3-34) (=N-terminus – Leu-Pro) for Erelzi
	Variability of C-terminus: – Lys, truncation to proline amide	Reducing Peptide Mapping	Comparable C-terminal pattern; lower amounts of lysine variants for Erelzi
Size	Aggregation	SEC/FFF-MALLS, AUC	Smaller amounts of oligomers for Erelzi
	Fragmentation	CE-SDS, SEC, SDS-PAGE	Slightly higher purity and lower amounts of high molecular weight variants for Erelzi
Charge	Charged variant profile	CZE, cIEF	Lower amounts of basic variants and higher amounts of acidic variants in Erelzi
Hydrophobic	Hydrophobic variants	RPC	Lower amounts of post-peak variants in Erelzi
Amino acid modifications	Oxidation	RP-HPLC, Peptide Mapping	Comparable amounts of oxidized variants
	Deamidation	Reducing Peptide Mapping	Comparable amounts of deamidated variants

Table 4: Binding assays and in-vitro bioassays

	Test	Method / cell line	Key findings
Binding assays	TNF-α binding assay	Surface plasmon resonance assay	Comparable potency
	FcγRIIIa (F158 and V158) binding assay	Surface plasmon resonance assay	Comparable K_D
	FcγRIIIb binding assay	Surface plasmon resonance assay	Comparable K_D
	FcγRIIa binding assay	Surface plasmon resonance assay	Comparable K_D
	FcγRIIb binding assay	Surface plasmon resonance assay	Comparable K_D
	FcγRIa binding assay	Surface plasmon resonance assay	Comparable K_D
	FcγRn binding assay	Surface plasmon resonance assay	Comparable K_D
	FcRn binding assay	Surface plasmon resonance assay	Comparable K_D
	C1q binding	C1q binding ELISA	Comparable binding
In-vitro bioassays	TNF-α neutralization reporter gene assay	Luciferase reporter gene assay	Comparable potency
	TNF-β neutralization reporter gene assay	Luciferase reporter gene assay	Comparable potency
	Apoptosis inhibition assay	Cell based apoptosis assay	Comparable inhibition
	ADCC assay	Cell based ADCC assay, ADCC surrogate assay	ADCC activity of Erelzi lower than ADCC activity of Enbrel[1)]
	CDC assay	Cell based CDC assay	Slightly outside the range for CDC activity

[1)] It has been established in previous comparability assessments that Erelzi shows a lower activity in assays quantifying ADCC activity than Enbrel. This difference is consistent with differences in N-glycosylation and is considered to have no adverse impact on patient safety and efficacy, as ADCC not considered a mode of action in indications for which EU-authorized Enbrel is currently licensed.

Table 5: Compendial methods and process related impurities

	Test	Key findings
Compendial methods	Color of solution	No relevant differences
	Clarity	No relevant differences
	pH	No relevant differences
	Extractavle volume	No relevant differences
	Visible particles	No relevant differences
	Subvisible particles	No relevant differences
	Osmolality	No relevant differences
Process related impurities	DNA	No relevant differences
	Protein A	No relevant differences
	HCPs	No relevant differences

In conclusion, an extensive analytical comparability exercise has been conducted and demonstrates that Erelzi is highly similar to the reference product Enbrel.

2.2.5. Adventitious agents

Erelzi is expressed in Chinese hamster ovary (CHO) cells. Multiple control elements are applied to ensure non-viral and viral safety of Erelzi active substance and finished product:

- Careful selection and control of the source and quality of the raw materials used in production
- Absence of primary human and animal-derived raw materials in the cell banks and in the manufacturing process
- Use of the well-characterized CHO parental cell line
- Characterization and testing for microbial contaminants, endogenous retrovirus-like particles known to be produced by the parental cell line and adventitious agents of the master cell bank (MCB), working cell bank (WCB) and extended cell bank (ECB)
- Testing for microbial contaminants, parental cell line-derived retrovirus-like particles and adventitious agents in bulk harvests (BH)
- The purification process for Erelzi comprises well-proven standard steps effective for virus removal, including chromatography steps as well as dedicated virus inactivation and virus removal steps
- Virus validation studies were conducted for various steps of the purification process to demonstrate inactivation/removal of xenotropic murine leukemia virus (MuLV) and several other model viruses according to ICH Q5A
- For release of active substance as well as finished product, testing for endotoxin and microbial purity/sterility is mandatory

Virus validation studies

The data sufficiently demonstrate that virus removal/inactivation is robust due to the presence of multiple orthogonal steps.

2.2.6. GMO

N/A

2.2.7. 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 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.

The applicant is recommended to implement an appropriate analytical method for the assessment of hydrophobic variants in the release and shelf-life specifications for active substance and finished product once optimized/developed and validated (See “Recommendation for future quality development”).

The extensive analytical comparability exercise conducted between Erelzi and the reference product Enbrel sufficiently demonstrates high similarity.

2.2.8. 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. Biosimilarity to the reference product Enbrel has been satisfactorily demonstrated at the quality level.

2.2.9. 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 points for investigation:

The applicant should submit a variation to implement an appropriate analytical method for the assessment of hydrophobic variants in the release and shelf-life specifications for active substance and finished product once optimized/developed and validated.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant performed and submitted a study in cynomolgus monkeys, justifying their choice with view on a global development and because etanercept was expected to have a lower immunogenic potential in this species compared to rodent models (based on information in the Enbrel EPAR). The study was conducted in accordance with GLP.

The following guidelines were applied:

- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1)
- Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6 (R1))
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005)
- Similar biologic medicinal products containing monoclonal antibodies: non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)

2.3.2. Pharmacology

Primary pharmacodynamic studies

Etanercept, the active pharmaceutical ingredient (API) of Erelzi and Enbrel, is a recombinant dimeric fusion protein consisting of two extracellular domains of the 75-kilodalton tumor necrosis factor receptor (TNFR) linked to the Fc (fragment, crystallizable) portion of an immunoglobulin G1 (IgG1) antibody (TNFR:Fc). Erelzi is produced using the Chinese Hamster Ovary (CHO) cell expression system.

Etanercept binds to and neutralizes the biological activity of TNFα and lymphotoxin alpha (LTα). By competitively inhibiting the binding of TNFα to cell surface receptors etanercept prevents the TNFα mediated signal transduction which requires the cross-linking of cell surface receptors.

In vitro assays comparing Enbrel/EU, Enbrel/US and Erelzi were conducted to investigate

- Binding and functional neutralization of TNFα and LTα in a reporter gene assay. The cell based TNFα neutralization assay covers the main function of Erelzi/Enbrel, i.e. the binding and neutralization of TNFα.
- Binding to TNFα using surface plasmon resonance (SPR).
- Binding to human Fc receptors (FcγRI, FcγRII, FcγRIII and neonatal Fc receptor (FcRn)) using surface plasmon resonance (SPR).
- Binding to C1q using an enzyme-linked immunosorbent assay (ELISA).
- TNFα neutralization in a cell based assay using the ability of etanercept to inhibit TNFα-mediated apoptosis.
- The ability of etanercept to initiate ADCC- and CDC-mediated depletion of transmembrane TNFα-expressing target cells using suitable cell-based assays.
- Binding to tmTNFα on stably tmTNF-transfected human cell lines.
- Caspase induction in tmTNF-transfected cell lines.

The in vitro bioassays and target and receptor binding assays performed to control and characterize Erelzi showed that Erelzi has the same in vitro target binding specificity to TNFα, LTα3 and LTα2β1 as Enbrel/EU and Enbrel/US, as well as similar functional neutralization of TNFα as Enbrel/EU and Enbrel/US in a reporter gene assay. The binding affinities to all tested Fc receptors (FcγRI, FcγRII, FcγRIII and FcRn) were similar between Erelzi, Enbrel/EU and Enbrel/US, the binding to human C1q was similar as was the ability to inhibit

TNFα-mediated apoptosis. Binding to tmTNF for EU or US Enbrel and Erelzi was slightly different, while this did not lead to caspase induction (as measure for apoptosis) in a cell-based assay. In contrast, binding of Remicade to tmTNF did lead to caspase induction, indicating suitability of this assay.

In contrast to Remicade, both EU or US Enbrel and Erelzi did not suppress cytokine release subsequent to binding of etanercept to tmTNF.

A twofold reduced ADCC and an increased CDC activity for Erelzi compared to Enbrel was shown.

Further nonclinical comparison of the PD effects of Erelzi and the reference medicinal product Enbrel/EU was performed in vivo upon single and repeated dosing in the human TNFα transgenic mouse model of polyarthritis (Tg197 strain). Erelzi and Enbrel/EU were compared at the intermediate and hence more sensitive dose level of 10 mg/kg after single and repeated (twice weekly for 2 or 4 weeks) i.p. administration to Tg197 mice. Additional vehicle buffer control (Erelzi formulation buffer) and positive control (Enbrel/EU at 30 mg/kg) groups were dosed twice weekly for 4 weeks. The primary endpoints for the PD response evaluation were the in life Tg197 arthritic pathology (morphological and functional changes on both ankle joints) and the histopathology of the underlying lesions in the synovium and the arthritic joints.

The results of study BMC248 (GP15-007) showed that Erelzi and Enbrel/EU were indistinguishable and both were statistically significantly better than the vehicle in inhibiting the in life Tg197 arthritic pathology and the underlying histopathology compared to the age-related aggravation of Tg197 pathology found in the vehicle buffer control group, the effects being most pronounced following twice weekly treatment for 4 weeks.

Secondary pharmacodynamic studies

No secondary PD studies are required for a biosimilar product developed in accordance with current EMA guidance Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

Safety pharmacology programme

No safety pharmacology studies are required for a biosimilar product. However, safety pharmacology parameters covering the cardiovascular system such as recording of electrocardiograms and blood pressure measurements were assessed in the repeat-dose monkey toxicity study (study 8240755 (GP15-003). Neither Erelzi nor Enbrel/EU showed any adverse effects in these safety pharmacology parameters.

Pharmacodynamic drug interactions

No PD drug interaction studies are required for a biosimilar product developed in accordance with current EMA guidance Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

2.3.3. Pharmacokinetics

The concentration of etanercept (either administered as Erelzi or Enbrel/EU) in serum from rabbits and monkeys was determined using an enzyme-linked immunosorbent assay. The assay was validated for the detection of etanercept in rabbit and monkey serum. The concentration of anti-etanercept antibodies in serum from monkeys was determined using an electrochemiluminescence bridging immunogenicity assay. The assay was

set up in a two-step approach, i.e. a screening assay was followed by a confirmatory assay in case of a positive result in the screening assay.

In a pilot single dose subcutaneous pharmacokinetic study in rabbits the formulation containing citrate and lysine (designated as citrate/lysine containing formulation) instead of phosphate and arginine as used in the originator formulation showed pharmacokinetic values closest to those obtained with the Enbrel or Erelzi in Enbrel formulation.

The definitive subcutaneous pharmacokinetic comparability study in rabbits showed somewhat lower absolute total exposures (AUC values) of Erelzi compared to Enbrel/EU. The 90% CI for the dose-adjusted pharmacokinetic parameters Cmax, $AUC_{0\text{-}168h}$ and $AUC_{0\text{-}inf}$ fell entirely within the comparability margins 80-125%. Comparable bioavailability of Erelzi in the citrate/lysine containing formulation with Enbrel has been demonstrated in rabbits when administered subcutaneously at a nominal dose of 8 mg/kg.

Pharmacokinetics after repeated administration is described as toxicokinetic data in the next section.

2.3.4. Toxicology

Single dose toxicity

No dedicated single-dose toxicity studies were performed. Based on the results of the first dose in the repeated dose toxicity study 8240755 (GP15-003), no deaths or change in general conditions were noted within one day after subcutaneous (s.c.) administration of Erelzi and Enbrel/EU to cynomolgus monkeys at a dose level of 15 mg/kg.

Repeat dose toxicity

Nonclinical toxicology data are available from one repeat-dose toxicity study in cynomolgus monkey. Two groups of 3 animals/sex received Erelzi or Enbrel/EU at the dose level of 15 mg/kg/dose once every 3 days for 4 weeks (total of 10 treatments).

For both Erelzi and Enbrel/EU, no unscheduled mortality occurred during the study. There were no treatment-related effects on body weight, food consumption, ophthalmoscopy, ECG, heart rate, blood pressure, urinalysis and organ weights. The major findings in this study were local skin reactions at the injection sites characterized by rash, erythemas as well as inflammatory lesions for one and two males treated with Erelzi and Enbrel/EU, respectively.

Changes in clinical pathology in the Erelzi and Enbrel/EU-treated groups were generally mild and did not differ significantly from control groups. However, individual animals showed some notable changes. Red and white blood cell parameter changes were seen in the Erelzi-treated animal 5M and the Enbrel/EU-treated animals 7M and 8M. Prominent etanercept-induced rash and associated changes in red blood cell and other haematological parameters including neutropenia and thrombocytopenia correlate with findings of ADAs and reduced etanercept levels.

In the monkey study, serum etanercept levels initially moderately accumulate during the first week, but subsequently decrease, most likely due to the formation of anti-drug antibodies (ADA). A similar pattern was observed for both products.

In the comparative 4-week subcutaneous repeated dose toxicity study in cynomolgus monkeys (8240755 (GP15-003) immunogenicity was evaluated. In some monkeys of each administered group the development of anti-etanercept antibodies on Day 32 could be confirmed.

The toxicokinetic (TK) parameters for Erelzi following subcutaneous administration at 15 mg/kg on Days 1, 7 and 28 are presented below.

Table 6: TK evaluation results for GP2015 – Days 1, 7, 28

Occasion	Gender	Animal	$AUC_{0-\tau}$ (h*µg/mL)	C_{max} (µg/mL)	t_{max} (h)	$t_{1/2}$ (h)	RA_{AUC}	RA_{Cmax}
Day 1	Male	N	3	3	3	1	NA	NA
		Mean	4020	78.4	24.7	45.9	NA	NA
		SD	164	9.89	7.02	NC	NA	NA
		CV%	4.1	12.6	28.5	NC	NA	NA
	Female	N	3	3	3	3	NA	NA
		Mean	4390	83.9	22.0	59.4	NA	NA
		SD	1050	22.3	3.46	16.3	NA	NA
		CV%	23.9	26.6	15.7	27.5	NA	NA
Day 7	Male	N	3	3	3	2	3	3
		Mean	5570	98.9	18.0	55.8	1.38	1.27
		SD	690	8.16	10.4	NC	0.122	0.0753
		CV%	12.4	8.2	57.7	NC	8.8	5.9
	Female	N	3	3	3	2	3	3
		Mean	5610	95.9	22.7	66.1	1.33	1.20
		SD	223	13.5	10.1	NC	0.327	0.321
		CV%	4.0	14.0	44.4	NC	24.6	26.8
Day 28	Male	N	3	3	3	3	3	3
		Mean	2180	49.3	22.0	13.8	0.554	0.649
		SD	1950	39.7	3.46	2.76	0.515	0.577
		CV%	89.8	80.6	15.7	20.0	92.9	88.9
	Female	N	3	3	3	3	3	3
		Mean	987	27.1	24.0	7.93	0.260	0.370
		SD	653	14.6	0.00	2.65	0.235	0.294
		CV%	66.2	53.9	0.0	33.4	90.5	79.5

τ = 72 hours
NA = Not applicable
NC = Not Calculable

The toxicokinetic parameters for Enbrel following subcutaneous administration at 15 mg/kg on Days 1, 7 and 28 are presented below:

Table 7: TK evaluation results for Enbrel – Days 1, 7, 28

Occasion	Gender	Animal	$AUC_{0-\tau}$ (h*µg/mL)	C_{max} (µg/mL)	t_{max} (h)	$t_{1/2}$ (h)	RA_{AUC}	RA_{Cmax}
Day 1	Male	N	3	3	3	1	NA	NA
		Mean	4050	77.9	24.0	61.1	NA	NA
		SD	463	13.6	0.00	NC	NA	NA
		CV%	11.4	17.5	0.0	NC	NA	NA
	Female	N	3	3	3	1	NA	NA
		Mean	3230	62.2	29.3	50.4	NA	NA
		SD	275	5.76	4.62	NC	NA	NA
		CV%	8.5	9.3	15.7	NC	NA	NA
Day 7	Male	N	3	3	3	3	3	3
		Mean	6300	122	16.0	62.0	1.56	1.55
		SD	810	33.6	9.17	29.3	0.183	0.149
		CV%	12.9	27.5	57.3	47.3	11.7	9.6
	Female	N	3	3	3	3	3	3
		Mean	6200	109	24.0	83.2	1.93	1.77
		SD	71.2	6.39	0.00	26.6	0.162	0.234
		CV%	1.1	5.8	0.0	32.0	8.4	13.2
Day 28	Male	N	3	3	3	3	3	3
		Mean	2000	38.7	20.0	12.6	0.517	0.521
		SD	3100	55.8	6.93	8.22	0.805	0.759
		CV%	155.1	144.3	34.6	65.1	155.7	145.7
	Female	N	3	3	3	3	3	3
		Mean	1500	34.9	26.7	13.2	0.490	0.581
		SD	1240	22.0	4.62	6.82	0.447	0.412
		CV%	82.8	62.9	17.3	51.7	91.2	71.0

τ = 72 hours
NA = Not applicable
NC = Not calculable

The comparative systemic exposure of GP2015 relative to Enbrel (relative bioavailability; Frel) was assessed by comparing AUC0-τ and Cmax estimates between each treatment:

Table 8: Erelzi and Enbrel comparative exposure – Days 1, 7, 8

Occasion	Gender	F_{rel} $AUC_{0-\tau}$ (%)	F_{rel} C_{max} (%)
Day 1	Male	99.3	101
	Female	136	135
Day 7	Male	88.4	81.1
	Female	90.5	88.0
Day 28	Male	109	127
	Female	65.8	77.7

Genotoxicity

Genotoxicity studies are not required for a biosimilar product developed in accordance with the current EMA guidance Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

Carcinogenicity

Carcinogenicity studies are not required for a biosimilar product developed in accordance with the current EMA guidance Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

Reproduction Toxicity

Reproductive and developmental toxicity studies are not required for a biosimilar product developed in accordance with the current EMA guidance Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

Local Tolerance

No dedicated local tolerance studies were performed with Erelzi. However, local tolerance was assessed in the single-dose PK study in rabbits (study 26668 (GP15-006); as well as in the repeat-dose monkey toxicity study (study 8247055 (GP15-003).

Erelzi was well tolerated after a single bolus injection in rabbits. In monkeys, after repeated injections (once every 3 days), Erelzi and Enbrel/EU showed similar skin rashes, erythema, edema and inflammatory skin reactions at the injection sites. Overall, Erelzi and Enbrel/EU showed similar local tolerance.

Other toxicity studies

No further specific safety concerns, based on the nonclinical data provided and clinical use of the reference product, warrants additional animal studies with the proposed biosimilar Erelzi, in accordance with the current EMA guidance Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

2.3.5. Ecotoxicity / environmental risk assessment

Erelzi is a similar biological medicinal product to Enbrel (INN: etanercept). Etanercept, the active pharmaceutical ingredient of Enbrel and Erelzi, respectively, is a dimeric fusion protein consisting of two naturally occurring soluble 75 kDa TNFR linked to the Fc portion of an IgG1 antibody (TNFR:Fc). Etanercept in Erelzi is a protein produced from a CHO cell line using a CHO expression vector which was re-designed to allow expression of etanercept from one single gene encoding the same amino acid sequence as etanercept in the reference product Enbrel. As Enbrel, Erelzi is intended for subcutaneous injection.

According to the CHMP guideline "Environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr 2), in the case of products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient the ERA may consist of an adequate justification for the absence of specific study data. The proposed similar biological medicinal product

Erelzi is a recombinant protein and would be expected to react like a naturally occurring protein both *in vivo* and in the environment. No potential risk of the medicinal product to the environment has been identified and further ERA data are not required to accompany this marketing authorization application.

2.3.6. Discussion on non-clinical aspects

Biosimilarity is supported by the data on binding of soluble TNFα (sTNFα), and to human Fc receptors (FcγRI, FcγRII, FcγRIII and neonatal Fc receptor (FcRn)) using surface plasmon resonance (Biacore®), as well as binding to C1q using an enzyme-linked immunosorbent assay (ELISA).

A comparison of sTNFα and LTα neutralising capacity using a reporter gene assay suggested similar ranges of activity for Enbrel and Erelzi when all tested batches throughout development were considered.

Another TNFα neutralisation cell based assay using the ability of etanercept to inhibit TNFα-mediated apoptosis suggested similarity, but the data presented were very concise.

Binding of etanercept to transmembrane TNFα (tmTNFα) was evaluated in cell lines stably transfected with tmTNFα. A difference in binding for Enbrel and Erelzi was shown, apparently reflecting different levels of wrongly linked disulphide bridges. This difference was considered to be clinically not relevant due to rearrangement of disulphide bridges once the protein enters the body.

Binding of etanercept to tmTNFα did not lead to caspase induction (in contrast to Remicade), suggesting absence of functional activity through this pathway. Etanercept did not suppress cytokine release subsequent to binding of etanercept to tmTNF, further supporting the view that this mode of action does not contribute to etanercept's pharmacology.

With regard to the ADCC assay the Applicant showed that Erelzi is approximately half as potent as Enbrel in an assay with an NK effector cell line and transgenic target cells expressing a protease-resistant, constitutively membrane-associated form of transmembrane TNF-α. The Applicant argues that this difference is clinically not relevant in the arthritic and psoriatic indications. One of the arguments is that most clinical pharmacogenomics data on polymorphisms for Fc gamma IIIA receptor suggest no or a limited role for this receptor, which is pivotal in mediating ADCC.

Another argument presented is that the ADCC assay was developed to a very high level of sensitivity, in order to detect etanercept-mediated target cell depletion and provide a functional correlate of the observed differences in N glycosylation between Erelzi and Enbrel. The assay differs from the expected physiological environment in important aspects of the target cell population: the target cells employed in this assay express very high levels of a constitutively membrane-associated, protease-resistant pro-TNF-α, while putative endogenous target cell populations are expected to express lower levels of membrane-associated pro-TNF-α, which is subject to proteolytic shedding and therefore providing a less stable interaction platform between target and effector cells. Data obtained with U937 monocytes or primary human PBMC as target cells showed that in contrast to alemtuzumab, etanercept did not induce cell lysis at clinically relevant concentrations. Taken together, it has been sufficiently shown that the difference in ADCC observed in the highly sensitive transgenic target cells is not expected to translate into clinical differences.

A difference in CDC has been observed. In this case Erelzi seems to be more active than Enbrel in a CDC assay, while the binding (measured by ELISA) of C1q was similar for both products. However, there is currently no data to support the clinical relevance of CDC for etanercept's efficacy in the sought indications.

The limited pharmacokinetic data in rabbits and monkeys do not raise concerns. However, for a more reliable and meaningful evaluation of the PK characteristics of Erelzi human data will always prevail.

Changes in clinical pathology in the Erelzi and Enbrel/EU-treated groups were generally mild and did not differ significantly from control groups. However, individual animals showed some notable changes. These adverse effects are explained as an immunological response of animals when administered humanised therapeutic proteins. These reactions appear to be much more prominent than in the monkey studies described in the Enbrel EPAR. In the study submitted by the Applicant, these reactions were observed for both Enbrel and Erelzi treated monkeys. Injection site reactions occur frequently in humans after administration of etanercept, according to the SmPC for Enbrel (36% in RA, 13.6% in Psoriasis). In the pivotal clinical trial in Psoriasis performed by the Applicant, the incidence for Enbrel after 12 weeks of treatment was 14.2%, and 4.9% for Erelzi. Collectively, it can be concluded that the safety signals observed in the monkey study do not raise novel concerns and do not indicate differences between Enbrel and Erelzi.

There is inter-animal variability and consequently the sensitivity of the study to detect differences between both products is limited, especially when considering the low number of animals that are used in non-clinical studies with non-human primates. A study like this would not have been required when guidance provided in the relevant biosimilar guidelines is taken into consideration. However, the study was performed before these (revised) guidelines were issued. In summary, the limited toxicology data provided do not raise concerns.

In the comparative 4-week subcutaneous repeated dose toxicity study in cynomolgus monkeys (8240755 (GP15-003) immunogenicity was evaluated. In some monkeys of each administered group the development of anti-etanercept antibodies on Day 32 could be confirmed. Immunogenicity of humanised therapeutic proteins in animals is an expected reaction in animals when treated with these proteins and does not predict immunogenicity in humans. The ADA present in the monkey sera appeared to be completely cross-reactive with either Enbrel or Erelzi. This indicates there are no apparent differences in epitopes involved.

2.3.7. Conclusion on the non-clinical aspects

Comparable binding and activity of Erelzi and Enbrel has been shown for most parameters. Where differences were observed (ADCC), these have been properly addressed by the Applicant and it is not expected that these would translate into clinical differences. The non-clinical data support biosimilarity of Erelzi and Enbrel.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development program includes four PK studies (GP15-104, GP15-101, GP15-102 and GP15-103) involving 216 healthy volunteers and one comparative randomised double-blind efficacy and safety study (GP15-302) in 531 patients with chronic plaque-type psoriasis (Table 13). Pharmacodynamic studies have been integrated within the clinical efficacy and safety Study GP15-302.

GCP

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

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.

- Tabular overview of clinical studies

Table 9: Summary of the clinical development program of Erelzi

Study ID	N study centres	Design	Study Posology	Study Objective	Subjects by arm entered/completed	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
GP-15302	71 *	**Period 1:** randomised, parallel, double-blind, active-controlled **Period 2:** Week 13-30, parallel and cross-over [switching] arms (3:2 actual re-randomisation) **Extension Period:** Week 31-52, blinding maintained	**Period 1:** 50 mg SC twice weekly. **Period 2**: 50 mg SC once weekly **Period 3**: 50 mg SC once weekly	demonstrating equivalence of efficacy and to compare safety and immunogenicity of a biosimilar etanercept (Erelzi) and EU Enbrel	**Period 1:** Erelzi: 264/ 256 (97.0%) EU Enbrel: 267/ 255 (95.5%) **Period 2:** Erelzi: 150/ 143 (95.3) Enbrel: 151/ 146 (96.7) **Period 3:** ongoing	**Period 1:** Week 1-12 **Period 2:** Week 13-30 **Period 3:** Week 31-52	**Period 1:** M/ 62/38% Median age 41.0 years	Moderate-severe plaque psoriasis	PASI75 at Week 12 Equivalence acceptance margin: +/-18%
PK studies in healthy volunteers									
GP15-104 (PK-pivotal)	1	randomised, double-blind, 2-way cross-over	Single dose 50 mg s.c.	Determine PK and safety of Erelzi and EU/Enbrel.	Erelzi: 54/54 EU/ Enbrel: 54/54	Up to 3 months from screening to follow-up including 35 days washout between doses	Only Male Median age 32 years	Healthy volunteers	Cmax, $AUC_{0-tlast}$ and AUC_{0-inf}
GP15-103 (PK-supportive)	1	randomised, open-label, 2-way cross-over	Single dose 50 mg s.c	Determine PK and safety of Erelzi injection by autoinjector and pre-filled syringe	Erelzi: PFS 51/49 AI 51/50	Up to 3 months from screening to follow-up including 35 days washout	Only Male Median age 34 years	Healthy volunteers	Cmax, $AUC_{0-tlast}$ and AUC_{0-inf}
GP15-101 (PK-supportive)	1	randomised, double-blind, 2-way cross-over	Single	Determine PK and safety of	Erelzi: 54/51 EU/ Enbrel: 54/51		33/21	Healthy volunteers	

			dose 50 mg s.c	Erelzi and EU/Enbrel		ut between doses	Male/Female Median age 40 years		
GP15-102 PK-supportive)	1	randomised, double-blind, 2-way cross-over	Single dose 50 mg s.c	Determine PK and safety of Erelzi and US/ Enbrel	Erelzi: 57/54 US/ Enbrel: 57/54	Up to 3 months from screening to follow-up including 35 days washout between doses	42/15 Male/Female Median age 28	Healthy volunteers	Cmax, AUC_{0-t}
						Up to 3 months from screening to follow-up including 35 days washout between doses			Cmax, AUC_{0-t}

2.4.2. Pharmacokinetics

Four studies in healthy subjects and one sub-study in psoriasis patients (from the phase 3 study GP15-302) were submitted to support the pharmacokinetics part of the application.

Studies GP15-104 (pivotal) and GP15-101 (supportive) compared the PK profiles of Erelzi and Enbrel/EU in healthy volunteers using 50 mg pre-filled syringe (PFS).

Study GP15 -102 (supportive) compared the PK profiles of Erelzi and Enbrel/US in healthy volunteers using 50 mg PFS.

Study GP15-103 compared the pharmacokinetics of Erelzi in healthy volunteers administered by PFS and autoinjector (AI) presentations.

Study GP15-302 (supportive), wherein PK in a subset of psoriasis patients was investigated by determining the trough concentrations during steady-state.

Study GP15-101, was a single centre, randomized, double-blind, two-way crossover study with two treatment periods comparing a single-dose 50 mg sc injection of the test product Erelzi and reference product Enbrel/EU in healthy volunteers under fasting state. Comparable bioavailability was shown only for the Cmax (ratio 0.91 [0.82 – 1.01] but not for the AUC0- tlast (ratio 0.85 [0.78 – 0.93] and AUC0-inf (ratio 0.85 [0.78 – 0.92].

The pivotal study GP15-104, has a similar study design and methodology as study GP15-101. The results are summarized below:

Table 10: Pharmacokinetic parameters for etanercept (n=54, Study GP15-104)

(arithmetic mean ± SD, Tmax median, range)

Treatment	**$AUC_{0\text{-}tlast}$** ng/ml/h	**$AUC_{0\text{-}\infty}$** ng/ml/h	**C_{max}** ng/ml	**T_{max}** h
Test (Erelzi)	645121 ± 185459	693379 ± 194732	3567 ± 1296	58.3 (23.0 – 121.2)
Reference (EU/Enbrel)	696065 ± 167636	764190 ± 183338	3399 ± 1035	59.9 (24.2 – 119.9)
***Ratio (90% CI)**	92% (88 - 95)	90% (87 - 94)	103% (98- 109)	

$AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-}tlast}$ area under the plasma concentration-time curve from time zero to last quantifiable timepoint
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
***Ratio** uses geometric means

The 90% CI of the ratio of the geometric means of the primary PK parameters Cmax, AUC0-tlast and AUC0-∞ of etanercept between the two products are within the pre-specified range of 0.80 -1.25 for bioequivalence. A statistical testing using the nominal dose was also performed and the same results were shown. However, the upper limits of the 90%CI for AUC exclude 1.0. Similar results were observed in Study GP15-101.

The supportive study GP15-103 comparing a single-dose 50 mg sc injection of Erelzi delivered via pre-filled syringe (PFS) and autoinjector (AI) in healthy volunteers under fasting condition was a single center, randomized, open-label, 2-way crossover study with 2 treatment Periods. The primary objective of the study was to show bioequivalence when Erelzi is administered by an AI or PFS. Other PK analyses, among others, included repeat primary endpoint analysis by weight category. Subjects were stratified at randomization by body weight categories (low: 50 -79.9 kg; medium: 80 - 99.9 kg; high: 100 - 140 kg). The ANCOVA model was used and subject weight was included in the model as a covariate. The results are summarized below:

Table 11: Pharmacokinetic parameters for etanercept (n=48, Study GP15-103)

(arithmetic mean ± SD, Tmax median, range)

Treatment	$AUC_{0\text{-tlast}}$ ng/ml/h	$AUC_{0\text{-}\infty}$ ng/ml/h	C_{max} ng/ml	T_{max} h
PFS	724790 ± 253278	783762 ± 269383	3987 ± 1616	60.0 (36.0– 170.0)
Autoinjector	719129 ± 230742	779142 ± 238019	3922 ± 1471	60.0 (24.0 – 120.2)
***Ratio (90% CI)**	101% (95 - 107)	101% (96 - 107)	101% (94- 108)	

$AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-tlast}}$ area under the plasma concentration-time curve from time zero to last quantifiable timepoint

C_{max} maximum plasma concentration
T_{max} time for maximum concentration
***Ratio** uses geometric means

Comparable PK was demonstrated between the two delivery devices as the 90% CI of the ratio of the geometric means of the primary PK parameters are within the pre-specified range of 0.80 -1.25.

In addition, in the multi-dose study performed in a subset of 147 out of 531 psoriasis patients in the pivotal efficacy and safety study (GP15-302), trough levels were comparable between Erelzi and Enbrel/EU. Steady–state levels were already achieved at week 2 in line with the half-life of 70-100h of etanercept.

A waiver is made to the reference product's dossier regarding establishing ADME (absorption, distribution, metabolism and excretion) of etanercept and PK studies in special populations (e.g elderly, renal patients). This is acceptable for a biosimilar drug.

2.4.3. Pharmacodynamics

Mechanism of action

Etanercept is a well-known TNFα inhibitor. TNFα is an inflammatory mediator which is over expressed in several auto-immune-disorders like rheumatoid arthritis and psoriasis. Etanercept's postulated mechanism of action concerns competitive inhibition of the binding of TNFα to the soluble TNF receptors (TNFR), which are involved in different types of arthritis and psoriasis. Etanercept, however, has low affinity to membrane bound TNFR, which are thought to be involved in inflammatory bowel disorders.

Primary and Secondary pharmacology

Pharmacodynamic (PD) effects of Erelzi in comparison with EU Enbrel were evaluated in the pivotal Phase III Study GP15-302 in patients with chronic plaque psoriasis up to 12 weeks of treatment. High-sensitivity C-reactive protein (hsCRP) serum concentration was measured as a PD marker of inflammation in this study. No formal equivalence exercises were performed.

The hsCRP levels were moderately increased at baseline in the study population. Less than 50% had a high hsCRP level > 10 mg/L at baseline. At week 4, roughly similar hsCRP levels were observed in the Erelzi and EU-Enbrel arms, which remained stable until week 12. See Figure 2 and Table 12 below.

Figure 2: Mean hsCRP concentration versus time by treatment

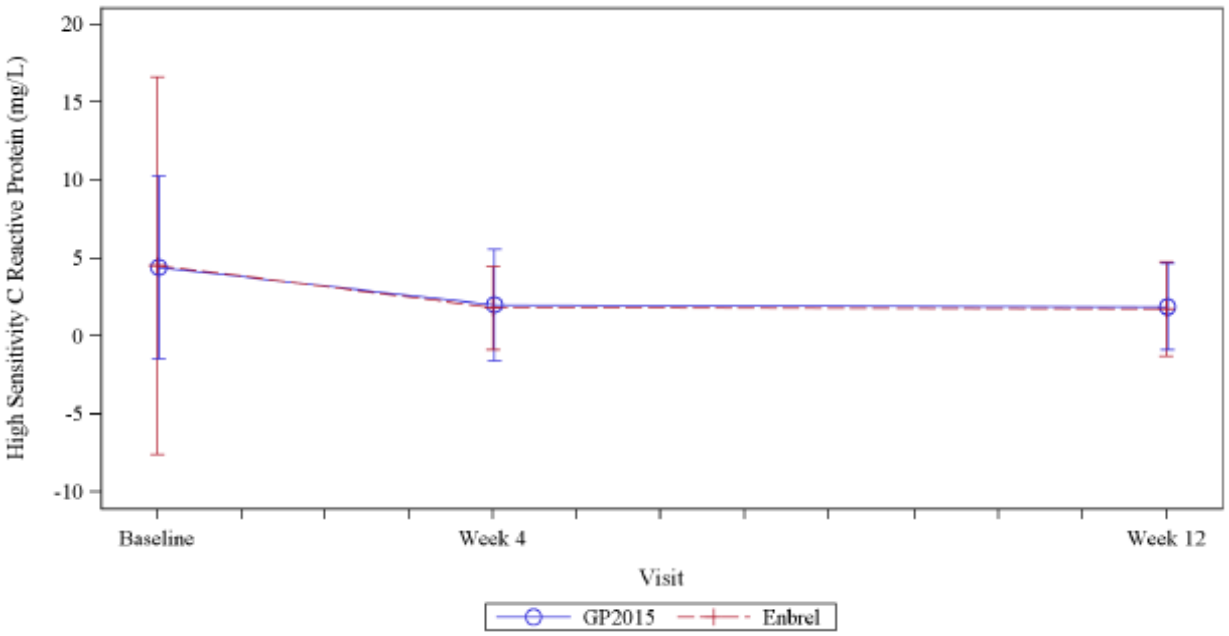


Table 12: Proportion of patients with high hsCRP concentration and mean hsCRP concentration

Parameter	GP2015 N=264	Enbrel/EU N=267
Proportion of patients with high hsCRP levels[1], n (%)		
Baseline	42.4%	31.8%
Week 4	17.4%	13.5%
Week 12	17.8%	14.2%
hsCRP concentration (mg/L)		
Baseline (mean±SD)	4.390±5.8540	4.529±12.0969
Week 4 (mean±SD)	1.993±3.5787	1.810±2.6836
Week 12 (mean±SD)	1.889±2.7920	1.747±3.0309

SD=standard deviation; hsCRP=high sensitivity C-reactive protein
[1]High hsCRP value was defined as >10 mg/L after having been initially reduced to <10 mg/L

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Four studies in healthy subjects and one sub-study in psoriasis patients (from the phase 3 study GP15-302) were submitted to support the pharmacokinetics part of the application: Studies GP15-104 (pivotal) and GP15-101 (supportive) compared the PK profiles of Erelzi and Enbrel/EU in healthy volunteers using 50 mg

pre-filled syringe (PFS). Comparable PK was not formally shown in study GP15-101 and was repeated as study GP15-104.

Study GP15 -102 (supportive) compared the PK profiles of Erelzi and Enbrel/US in healthy volunteers using 50 mg PFS. This study is considered less relevant to the current application as this was a study comparing the proposed product with Enbrel/US.

The number and type of studies submitted to show comparable PK are adequate for a biosimilar application in line with EMA *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).*

In study GP15-101, comparable PK was shown only for the Cmax but not for the AUC0- tlast and AUC0-inf. In the Statistical Analysis Plan, it was pre-defined that an analysis using adjusted dose (actual dose received by subject) can be performed in case comparable PK using nominal dose is not shown. When the primary analysis was repeated using actual dose administered (calculated from the pre-/post-injection PFS weight difference) and added as a covariate in the ANOVA model, the lower limit for AUC0-tlast achieved the required limit of 0.80 (i.e. 0.8037). AUC0- inf was not part of the primary analysis. A post hoc analysis including operator as a fixed effect was also performed and also showed comparable PK between the two treatments. The Applicant decided to repeat the study based on the scientific advices given by PEI (Germany) and FIMEA (FI).

The repeated study, which is presented as pivotal study GP15-104, has a similar study design and methodology as study GP15-101. However, there were some differences: among others, study site is different, subjects included only males while males and females were included in the 1st study, the drugs in the 2 periods of each subject were administered by the same operator while in the first study this was not the case and the analytical method used is the revalidated ELISA while the original validated ELISA was used in the first study. Both studies used the ANOVA model but the primary parameters were normalized by protein content injected in this repeated study.

The 90% CI of the ratio of the geometric means of the primary PK parameters Cmax, AUC0-tlast and AUC0-∞ of etanercept between the two products are within the pre-specified range of 0.80 -1.25 for bioequivalence. However, the upper limits of the 90%CI for AUC exclude 1.0, indicating a lower exposure of Erelzi compared to that of Enbrel/EU. Similar results were observed in Study GP15-101.

It was adequately justified that the estimated lower exposure (i.e that the 90% CI for AUC did not include 1 and AUC was statistically significant lower for Erelzi than for Enbrel) does not preclude biosimilarity. The results of the pivotal pharmacokinetic study showing 90%CI for AUC within the required range of 0.80-1.25, however with exclusion of 1, but with similar tmax and t1/2, suggest comparable clearance. The similarity in clearance indicates the absence of intrinsic differences between the test and reference product. This is further supported by the observed similar plasma exposure in patients upon multiple dosing treatment with etanercept in the clinical study GP15-302.

The study further showed that etanercept exposure decreases with increasing body weight. This observation had a clinical impact as in the pivotal efficacy and safety study (GP15-302) the proportion of patients with a PASI 75 response rate was lower for patients weighing ≥ 90 kg (62.2-63.6%) compared to patients weighing <90kg (81.2-84.2%) (see Clinical Efficacy part). Similar efficacy results have been obtained for Enbrel (see EPAR Enbrel 2006).

Analytical methods

The assays used for etanercept measurements have some limitations, especially the one that was validated for the early studies. As that PK data was only supportive the main focus of assessment was in the pivotal PK study

GP15-104 and its validation. Overall, the assay is more robust and the validation appears properly done. Concerning the question on reliability of the method near higher assay range, the applicant has recognized the variability near the upper and lower detection limit of the assay range and therefore only the linear range of the method is used, thus ensuring integrity of all results. The applicant has also provided additional data concerning possible ADA interference and according to the results there is equal ADA interference between Erelzi and Enbrel. Furthermore, the dilutions used in the sample analysis lower the ADA levels below 1ng/ml, which in the presence of higher drug concentrations does not impact the PK data.

For the ADA measurements a three-step approach has been used, involving a screening assay (MSD bridging assay), a confirmatory assay (inhibition of the screening signal) and an ELISA-based assay to detect neutralizing antibodies

However, the approach to use several positive controls even if justified by the company, raised questions about the impact of these different positive controls on the relative immunogenicity results. The Applicant has provided further characterisation data for the positive controls used in ADA measurements and assay validations. However, due to the chosen different scales between the Ab results and high concentration ranges it is difficult to interpret the actual differences between positive controls analysed. It is recognised that the discrepancies do not affect the screening assay results, where the cut-off value is based on human serum, not on positive controls and that a low positive control is used in all analysis settings ensuring proper sensitivity of each measurement. Furthermore, considering that Erelzi and Enbrel seem to behave in a similar manner in the binding assay, the issue of characterisation and use of positive controls is considered resolved. However, for any future application for Erelzi containing immunogenicity assessment, the Applicant was advised to ensure that for each assay validation and corresponding sample analysis the same, properly characterised positive control Ab is used.

The drug tolerance data from the validation report ba13019 suggested that the ADA assay would not be equally sensitive for both Erelzi and Enbrel. It was clarified that this is due to the differences in assay settings and the variability of the assay near the cut-point. In addition, binding data is provided demonstrating equal performance of the assay with both analytes. Thus, the concern of the different sensitivities of the ADA method is considered resolved.

Pharmacodynamics

Serum hsCRP was measured, as a PD marker of efficacy in the clinical equivalence Study GP15-302, in patients with plaque psoriasis. Though not formally tested, the data roughly indicate similarity in PD response between Erelzi and Enbrel. However, the PD data should be interpreted with caution and considered as supportive evidence only, since hsCRP is not a specific biomarker and infections may also induce a hsCRP response. Moreover, only a minority of the study population had increased hsCRP levels at baseline, and these percentages were not equally distributed over study arms.

The hsCRP data provided some supportive evidence regarding therapeutic equivalence. Although some methodological shortcomings were noted, no additional PD studies are warranted, as there is no specific or validated biomarker available.

2.4.5. Conclusions on clinical pharmacology

From a clinical pharmacology point of view, Erelzi has shown to be similar to Enbrel.

The remaining issues on clinical, bioanalytical methods and their validation are considered resolved. However, the CHMP recommended that for any future application for Erelzi containing immunogenicity assessment the

MAH should ensure that for each assay validation and corresponding sample analysis the same, properly characterised positive control Ab is used.

2.5. Clinical efficacy

2.5.1. Dose response studies

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

2.5.2. Main study

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

Methods

Study Participants

Main inclusion criteria were: age ≥ 18 years, diagnosis of active, but clinically stable, chronic (i.e. ≥ 6 months) plaque-type psoriasis involving at least 10 percent of the body surface area (BSA), corresponding to a minimal PASI score of 10 (indicating moderate-to-severe psoriasis). Patients who were candidates for systemic therapy were eligible, with Investigator's General Assessment score of ≥3, previously received at least one phototherapy or systemic therapy for psoriasis, or candidate to receive such therapy in the opinion of the investigator.

The main exclusion criteria were: other types of chronic psoriasis than plaques psoriasis, active inflammatory diseases other than psoriasis, (increased risk of) central or peripheral nervous system demyelinating disorders, history of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system, plans for administration of live vaccines during the study period or live vaccination within 6 weeks prior to baseline, unwillingness to limit UV light exposure during the course of the study, a total white blood cell count < 3500/µL, or neutrophils < 2000/µL or platelets< 125000/µL or hemoglobin < 10.0 g/dL at screening, or the use of prohibited treatments (Table 13).

Table 13: Prohibited treatments

Prohibited treatments[1,2]	Washout period
Washout period relative to randomization	
Etanercept	No prior use allowed
TNF antagonists (investigational or approved), e.g. adalimumab, infliximab	6 months
Biological immunomodulating agents other than above, e.g. alefacept, briakinumab, ustekinumab, abatacept, anakinra	6 months
Other systemic immunomodulating treatments (e.g., methotrexate, cyclosporine A, corticosteroids[3])	4 weeks
Cyclophosphamide	6 months
Leflunomide	8 weeks (unless a cholestyramine wash-out has been performed)
Other systemic psoriasis treatments(e.g., retinoids, fumarates)	4 weeks
Photochemotherapy (e.g., PUVA)	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks
Topical treatment that is likely to impact signs and symptoms of psoriasis (e.g., vitamin D analogues, pimecrolimus, retinoids, salicyl vaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids	2 weeks
Live vaccinations	6 weeks
Prohibited regimen of topical corticosteroids:	
Topical corticosteroids with higher than moderate potency on any body location	2 weeks
Topical corticosteroids with mild to moderate potency on any body location other than the face, scalp and/or genitoanal area	2 weeks
Topical corticosteroids with mild to moderate potency on the face, scalp and/or genitoanal area	1 day
Washout period relative to screening	
Any investigational treatment (other than those mentioned above) or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)

PUVA=psoralen ultra violet between 320 and 400 nanometers; TNF=tumor necrosis factor; UVA=ultra violet between 320 and 400 nanometers; UVB=ultra violet B.
[1] If the prohibited treatment was used during the study for any indication, the patient had to discontinue use of the prohibited treatment if he/she wished to continue in the study.
[2] In case of undue safety risk for the patient, the patient had to discontinue study treatment at the discretion of the investigator. If the patient received a live vaccination during the study, the patient had to discontinue study treatment.
[3] Inhalative corticosteroids with only a topical effect (e.g., to treat asthma) were not considered "systemic immunomodulating treatments" and were therefore acceptable as co-medication.

Treatments

Treatment period 1 (Week 1-12)

Patients were randomized to receive 50 mg subcutaneous injections of either Erelzi or Enbrel twice weekly.

Treatment period 2 (Week 13-30)

In treatment period 2, etanercept doses were lowered from 50 mg twice a week to 50 mg once a week, aligned with the SmPC posology for maintenance treatment of Enbrel. Subjects were either assigned to continue their

initially assigned treatment from treatment Period 1, or were assigned to the switching treatment arms, in a 3: 2 ratio.

Extension Period (Week 31-52)

The allocated treatment regime of the extension period was allowed to be continued for an additional 22 weeks during the extension period.

Concomitant treatment

Permitted concomitant treatments included emollients without pharmacologically active ingredients, and analgesic treatments.

All permitted prior concomitant treatments had to be on a stable dose for at least 4 weeks before the first study drug administration. Dose adjustments of these treatments were to be avoided during the study. Patients were advised to limit exposure to UV light (including sunbathing and/or use of UV tanning devices) during the study to avoid possible effects on psoriasis.

Objectives

Primary objective:

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

Secondary objectives:

- To compare the efficacy and safety of Erelzi and Enbrel in patients with moderate to severe chronic plaque-type psoriasis for several other outcomes, including the PASI score over time and Investigator's Global Assessment (IGA)
- To compare the effects of Erelzi and Enbrel on health-related quality of life in patients with moderate to severe chronic plaque-type psoriasis

Outcomes/endpoints

Primary efficacy variable was the PASI 75 response rate (i.e. proportion of patients showing at least a 75% improvement in PASI) after the first 12 weeks of treatment (Treatment Period 1).

Key secondary endpoint was relative percentage of change from baseline in the PASI score at Week 12.

Secondary endpoints in treatment period 1 and 2 included PASI 50, 75, and 90 response rates, investigator's global assessment (IGA), and several health-related quality of life scores. IGA ranges from 0 (= clear skin) up to 4 (=severe lesions).

In patients with concurrent psoriatic arthritis, HAQ-DI, a functional score was assessed.

Sample size

In literature PASI 75 responder rates at 12 weeks of study treatment were 49% for etanercept and 3-4% for placebo (Leonardi et al. 2003; Papp et al. 2005). Hence, the observed treatment effect size of Enbrel was 45-46%. Therapeutic equivalence was concluded if the exact 95% confidence interval for the difference in the PASI 75 rates would be completely contained within the interval [−18%; 18%]. Based on the above described

assumptions, a sample size of approximately 546 patients (to maintain 464 evaluable patients with an assumed drop-out and major protocol deviation rate of 15%) would provide a power of 90% to show equivalence between Erelzi and Enbrel, assuming an expected difference of 3%.

Randomisation

Treatment period 1

At day 1 of treatment period 1, eligible patients were randomized in a 1:1 ratio to either Erelzi or Enbrel treatment. Randomization of treatment period 1 was stratified by body weight (i.e. <90 kg versus ≥ 90 kg) and prior therapy. The strata for prior therapy were defined as: a) no prior systemic therapy, b) any prior systemic therapy including biologic immune-modulating agents except for a TNF-alpha antagonist, or c), prior treatment with a TNF-alpha antagonist other than etanercept.

Treatment period 2

Patients who achieved a PASI 50 response, were re-randomized to one of four treatment arms (i.e. 2 continued treatment arms, 2 switching treatment arms) of treatment period 2, in a 3:2 ratio between continuous treatment and switching. Re-randomization for treatment period 2 was not stratified for body weight or prior therapy

Blinding (masking)

The study was double blinded.

Statistical methods

Primary analyses

For the analysis of PASI 75, covariate-adjusted difference in response rates and corresponding 95% CI for the difference were calculated, using a logistic regression model. The following terms were included as factors in the model: treatment group, body-weight category (<90 kg or ≥ 90 kg), and prior use of systemic therapy. Therapeutic equivalence in terms of PASI75 will be concluded if the 95% confidence interval for the difference in the PASI75 rates is completely contained within the interval (−18%; 18%). Missing values were imputed with non-response values regardless of the reason for the missing data. The primary analysis set consisted of the per-protocol population (PPS). In the full analysis set (FAS), all randomized patients were analyzed according to the treatment assigned to at randomization.

Key secondary endpoint

A mixed model repeated measures (MMRM) analysis was performed with respect to the percentage change from baseline in the PASI score up to week 12. Treatment group (Erelzi/Enbrel), visit, body-weight category (<90 kg, or ≥90 kg) and prior systemic therapy were fitted as factors and baseline score for the PASI as continuous covariate. For this outcome, the equivalence criterion was predefined as -15%; 15%.

The ATE (average treatment effect) is defined as the average of percent change from baseline in PASI scores at weeks 2, 4, 8 and 12. This parameter is the weighted average (weights based on the time intervals between two consecutive visits in weeks) of the relative response to treatment. This outcome was designed to incorporate gradual change per visit -instead of change over a 12 weeks period as for the other key secondary outcome %change in PASI from baseline (as described above).

Secondary endpoints

Only frequencies and descriptive statistics were applied.

Results

Participant flow

In Table 14 and 15, the number of study patients at randomisation and at the end of study and reasons for dropout are presented. The overall, drop-out rates were low. Most common reasons for premature study discontinuation during study period 1 and 2 were adverse events and subject decision.

Table 14: Subjects flow in Treatment Period 1

	Treatment period 1 (n=531)	
	Erelzi	**Enbrel**
n-randomised	264	267
n-completed	256	255
n-discontinued	8	12
Reasons for discontinuation		
Adverse events	4	3
Death	0	1
Lost to follow-up	1	0
Non-compliance with study treatment	0	1
Physician decision	0	1
Protocol deviation	1	0
Patient decision	2	5
Injection site reaction	0	1
Study terminated by sponsor	0	0
Lack of efficacy	0	0

Table 15: Subjects flow in Treatment Period 2

	Treatment period 2 (n= 497)		
	Continued Erelzi	**Continued Enbrel**	**Pooled switched treatment**
n-randomised	150	151	196
n-completed	143	142	187
n-discontinued	7	9	9
Reasons for discontinuation			
Adverse events	1	2	4
Death	0	0	0
Lost to follow-up	0	0	0
Non-compliance with study treatment	0	0	0
Physician decision	1	0	0
Protocol deviation	0	1	0
Patient decision	3	4	2
Injection site reaction	0	0	0
Study terminated by sponsor#	1	2	2
Lack of efficacy	1	0	1

#A total of 5 patients (1.0%) were discontinued in Ukraine as the war situation resulted in closure of the study site.

Recruitment

Overall, 71 study centres enrolled patients in Bulgaria, Czech Republic, Estonia, Germany, Hungary, Poland, Romania, Russia, Slovakia, South Africa, United Kingdom and Ukraine.

Study period: First patient first visit: 24-Jun-2013; Last patient completed TP2: 29-Oct-2014 (data cut-off date for Week 30 analyses); Study completion date: 30-Mar-2015 (Last patient last visit Week 52).

Data from the Extension Period (EP – Week 30-52) are only mentioned in the next sections in case of relevance to the discussion.

Conduct of the study

Treatment period 1

Overall, 75.7% of randomized patients had at least one protocol deviation. A total of 34 patients (6.4%) were determined to have major protocol deviations during treatment period 1 and the proportion of patients with major protocol deviations was balanced between the Erelzi (6.8%) and Enbrel (6.0%) groups, with the most common being violations of visit windows (13 patients, 2.4% total), violation of inclusion and exclusion criteria (12 patients, 2.2% total) and use of prohibited medication (8 patients, 1.5%).

Treatment period 2

38.4% of patients had at least one protocol deviation. 5.6% of protocol deviations were major. The proportion of patients with major protocol deviations was lower in the continued Erelzi (4.0%) group than in the continued Enbrel (8.6%) group. The most common deviations were use of prohibited medication (8 patients, 1.6% total) and violations of exclusion criteria (7 patients, 1.4% total). The proportion of patients with major protocol deviations was generally similar between the pooled continued groups and the pooled switched groups (6.3% vs. 4.6%).

Treatment compliance

During treatment period 1, 86.7% of Erelzi-treated patients and 86.5% of the Enbrel-treated patients missed none of the study treatment doses. More than 4 doses of study treatment were missed by 2.7% of Erelzi-treated and 4.5% of Enbrel-treated patients in this period.

In treatment period 2, 90.9% of patients missed none of the study treatment doses. More than 4 doses of study treatment were missed by 4.6% of patients. Results were comparable for the different treatment groups.

Inappropriate stratification

Discrepancies with respect to stratification according to prior systemic treatment (i.e. no prior systemic therapy, any prior systemic therapy including biologic immunomodulating agents but no prior treatment with a tumour necrosis factor (TNF) antagonist, and prior treatment with a TNF antagonist) were discovered between the interactive response technology system and the applicant's clinical database. It was decided to use the strata as recorded in the clinical database. Individual patient's data were reviewed and –if necessary- re-stratified.

57 Patients were re-stratified:

-54 patients from 'prior systemic treatment' to 'no prior systemic treatment'

-3 patients from 'no prior systemic treatment' to 'prior systemic treatment'

Baseline data

Baseline data of Treatment Period 1 are presented in Table 16.

Table 16: Baseline data

	Treatment Period 1 (n=531)		**Baseline values of subjects who entered Treatment Period 2 (N=497)**
	Erelzi	Enbrel	*Pooled data*
n	264	267	*497*
Age, mean (sd)	42.1 (12.3)	42.7 (12.9)	*42.4 (12.5)*
Age, range	18 - 78	19 – 75	*18 - 78*
Male	59.5%	64.4%	*62.2%*
Weight, mean (sd)	86.3 (21.1)	85.9 (18.7)	*86.9 (20.1)*
Weight group			
< 90 kg	60.6%	60.3%	*58.6%*
≥ 90 kg	39.4%	39.7%	*41.4%*
BMI (kg/m2), median	27.7	28.2	*28.2*
Years diagnosed with plaque-type psoriasis, mean (sd)	17.6 (11.3)	17.8 (11.9)	*17.4 (11.5)*
Psoriatic arthritis	20.5%	19.9%	*19.5%*
Prior systemic therapy	40.9%	38.6%	39.7%
Prior systemic therapy with TNF antagonist	1.1%	0.7%	*1.0%*
IGA of psoriasis			
Mild	0	0.4%	*0*
Moderate	72.3%	69.7%	*70.4%*
Severe	27.7%	30.0%	*29.6%*
PASI score, mean (sd)	22.5 (8.9)	22.5 (9.5)	*22.6 (9.2)*
BSA affected, mean (sd)	30.5 (13.8)	30.9 (14.8)	*30.7 (14.3)*

Numbers analysed

The study enrolled 531 patients. A total of 774 patients were screened at 71 study centres and 531 patients were randomized 1:1 to receive one of the treatments during TP1; 264 and 267 patients in the Erelzi group and Enbrel groups, respectively. The majority (511 patients, 96.2%) of randomized patients completed TP1. A total of 497 patients were re-assigned to TP2 at Week 12. At the end of TP2, a total of 467 patients continued into the EP.

Treatment Period 1

All 531 randomized patients were included in the FAS on the basis of the intent-to-treat principle, and all of these patients received at least 1 dose of study drug and were thus included in the Safety analysis set. Three of the 34 patients with major protocol deviations were discontinued during TP1; 31 of the 511 patients who completed TP1 were excluded from the PPS due to major protocol deviations. Therefore, the PPS comprised 480 patients.

All patients provided data for ADA assessment at baseline and were included in the Immunogenicity set. 147 patients finally contributed to the PK set after 2 patients in the Erelzi group and 1 patient in the Enbrel group were excluded to incompliant administration (i.e. missed doses) of study drug.

Table 17: Analysis sets (TP1)

Disposition/Reason	GP2015 N=264 n (%)	Enbrel N=267 n (%)	Total N=531 n (%)
Screened			774
Randomized	264 (100.0)	267 (100.0)	531 (100.0)
FAS[1]	264 (100.0)	267 (100.0)	531 (100.0)
PPS[2]	239 (90.5)	241 (90.3)	480 (90.4)
Safety[3]	264 (100.0)	267 (100.0)	531 (100.0)
Immunogenicity set	264 (100.0)	267 (100.0)	531 (100.0)
PK set	72 (27.3)	75 (28.1)	147 (27.7)

FAS=full analysis set; PK=pharmacokinetics; PPS=per-protocol set; TP=treatment period; [1] Comprised of all randomized patients to whom study treatment was assigned. [2] Patients completed 12 weeks without any major protocol deviation. [3] Included all patients who took at least 1 dose of study treatment during the treatment period. Percentages are based on the number of patients within the treatment groups in the FAS (N). Source: Table 14.1-2.1

Treatment Period 2

All 497 re-assigned patients in the FAS received at least 1 dose of study drug and were thus included in the Safety analysis set. The PPS comprised 446 (89.7%) patients, after a total of 51 patients were excluded; 28 patients due to major protocol deviations and another 23 patients who discontinued during TP2. While a total of 25 patients discontinued in TP2; 2 patients discontinued due to lack of efficacy and so were still included in the PPS as non-responders, consistent with the definition of the TP2 PPS. All patients in the TP2 FAS were included in the TP2 Immunogenicity set.

Table 18: Analysis patient sets (all re-assigned patients in TP2)

Disposition/Reason	Continued GP2015 N=150 n (%)	Continued Enbrel N=151 n (%)
Re-assigned	150 (100)	151 (100)
TP2 FAS[1]	150 (100)	151 (100)
TP2 PPS[2]	138 (92.0)	129 (85.4)
TP2 Safety[3]	150 (100)	151 (100)
TP2 Immunogenicity set	150 (100)	151 (100)

FAS=full analysis set; PPS=per-protocol set; TP=treatment period [1] Comprised of all re-assigned patients who took at least 1 dose of study treatment during TP2. [2] Patients completed 30 weeks without any major protocol deviation. [3] Included all patients who took at least 1 dose of study treatment during TP2. Percentages are based on the number of patients within the treatment groups in the TP2 FAS (N). Source: Table 14.1-2.2

Outcomes and estimation

Primary endpoint

Table 19: Response rates

PASI 75 response	N	n	Adjusted response rate (%)	Adjusted response rate difference (GP2015-Enbrel/EU)	95%CI (%)
PPS					
GP2015	239	176	73.4		
Enbrel/EU	241	182	75.7	−2.3	[−9.85; 5.30]
FAS					
GP2015	264	186	70.4		
Enbrel/EU	267	191	71.6	−1.2	[−8.77; 6.45]

CI=confidence interval; FAS=full analysis set; N=total number of patients with evaluable data within each treatment group; n=number of patients achieving PASI 75 response; PASI=psoriasis area and severity index; PPS=per-protocol set.
The adjusted response rates for the treatment groups were derived from the logistic regression analysis including treatment, body weight categories and prior systemic therapy in the model; the 95% CI for the rates difference is derived based on the normal approximation.

Key secondary outcome

Table 20: Statistical analysis of % changes from baseline in PASI score up to 12 weeks of treatment (TP1 PPS)

Endpoint	Erelzi N=239	Enbrel N=241	LS means difference (Erelzi – Enbrel (%)	95% CI for LS means difference (%)
% change from baseline in PASI score (MMRM approach)	−56.11	−55.48	-0.64	-3.474, 2.204
ATE of % change from baseline in PASI score (ANCOVA approach)	−52.99	−52.11	-0.88	-3.610, 1.845

ANCOVA=analysis of covariance; ATE=averaged treatment effect; BW=body weight; CI=confidence interval; LS=least squares; MMRM=mixed-model repeated measures; N=number of patients within each treatment group; PASI=psoriasis area and severity index; TP1 PPS=treatment period 1 per-protocol set.
% change from baseline in PASI score is analyzed by employing a mixed effects repeated measures model with treatment, visit, treatment-by-visit interaction, BW strata and prior systemic therapy as fixed factors and baseline PASI score as covariate. An unstructured covariance matrix is used to model the within-patient variance-covariance matrix.
The ATE of % change from baseline in PASI score is analyzed by employing an ANCOVA model with treatment, BW strata and prior systemic therapy as fixed effects and baseline PASI score as covariate. ATE is the weighted average of (weights based on the time intervals between two consecutive visits in days) the percent change from baseline in PASI scores at Weeks 2, 4, 8 and 12.

Secondary endpoints

Absolute PASI scores and changes in PASI score from baseline (referred to as “diff”) up to 12 weeks of treatment are presented in Table 21.

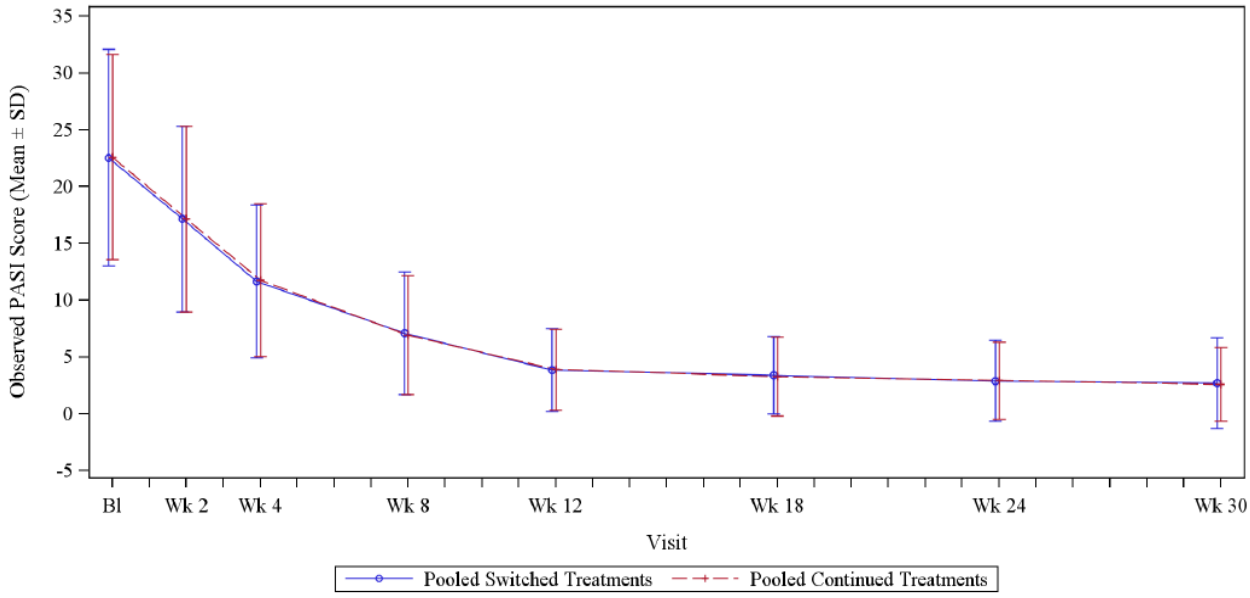
Table 21: Mean, SD of absolute PASI scores and change from baseline in treatment period 1 (FAS)

	Erelzi	Enbrel
n	264	267
PASI scores		
Baseline	22.52 (SD 8.93)	22.51 (SD 9.52)
Week 2	17.22 SD 8.147 (diff: -5.3)	17.02 SD 8.044 (diff: -5.5)
Week 4	11.51 SD 6.730 (diff: -11.0	12.05 SD 6.748 (diff: -10.5
Week 8	6.91 SD 5.624 (diff: -15.6)	7.23 SD 5.230 (diff: -15.3)
Week 12	3.99 SD 4.217 (diff: -18.5)	4.09 SD 3.762 (diff: -18.4)

Diff=difference from mean baseline score

Mean PASI scores for the pooled continued and switched treatment groups (as re-randomized at Week 12) are presented in Figure 3.

Figure 3: Mean PASI scores versus time in treatment period 1 and 2 (PPS TP2).



Proportion of IGA responders

The proportion of Investigator's Global Assessment responders (IGA score of 0 or 1) for treatment period 1 and 2 are presented in Table 18. Responder rates increased with time for both Erelzi and Enbrel, and tended to stabilize beyond 12 weeks.

Table 22: Proportion of IGA responders with time (FAS)

	Treatment period 1 (n=531)		Treatment period 2 (n= 497)			
	Erelzi	Enbrel	Continued Erelzi	Continued Enbrel	Switched Erelzi**	Switched Enbrel***
n	264	267	150	151	100	96
Week 2*	0	2.3%	0	3.3%	0	1.0%
Week 4*	11.4%	9.2%	9.3%	10.6%	13.0%	8.3%
Week 8*	36.4%	24.8%	35.3%	25.2%	38.0%	24.0%
Week 12*	58.2%	55.3%	60.0%	55.6%	57.0%	58.3%
Week 18	Na	Na	61.2%	61.7%	57.6%	58.5%
Week 24	Na	Na	63.6%	64.2%	65.3%	64.5%
Week 30	Na	Na	64.8%	68.8%	67.7%	65.9%

*Treatment period 1
** Switched to treatment sequence Enbrel>Erelzi>Enbrel in treatment period 2
*** Switched to treatment sequence Erelzi>Enbrel>Erelzi in treatment period 2

Secondary arthritis outcomes

The HAQ-DI assessment was performed in a total of 107 patients (20.2%) with a medical history of psoriatic arthritis.

At baseline, HAQ-DI scores were similar Erelzi and Enbrel groups (0.9 in both groups, Table 23). Mean changes in HAQ-DI scores declined to similar extent for Erelzi and Enbrel groups from baseline.

Table 23: Mean changes from Baseline of HAQ-DI scores (FAS)

	Treatment period 1		Treatment period 2	
	Erelzi (n=264)	Enbrel (n=267)	Continued Erelzi (n=150)	Continued Enbrel (n=151)
Baseline value	**0.9**	**0.9**	**0.8**	**1.0**
Week 2	-0.2	-0.2	-0.1	-0.2
Week 4	-0.2	-0.2	-0.1	-0.2
Week 8	-0.3	-0.2	-0.3	-0.3
Week 12	-0.3	-0.3	-0.3	-0.4
Week 18	Na	Na	-0.3	-0.5
Week 24	Na	Na	-0.3	-0.4
Week 30	Na	Na	-0.3	-0.4

The HAQ-DI also includes a 100 mm VAS pain score. At baseline, mean VAS of pain scores were roughly similar between the Erelzi and Enbrel groups (49.5 (SD 26.85) vs. 43.6 (SD 24.15)). The mean VAS scores of pain were similar between the Erelzi and Enbrel groups at Week 12 (31.6 (26.45) vs. 30.2 (SD 24.66) at Week 12, FAS population). No formal statistics for group comparisons were performed.

Ancillary analyses

Subgroup analyses were performed for stratification factors body weight (cut-off value 90 kg), the presence of prior systemic therapy, and region.

In the per protocol set, the proportion of patients achieving PASI 75 at week 12 was comparable between the no prior systemic therapy subgroup (71.6% and 73.4% in the Erelzi and Enbrel groups, respectively) and any prior

systemic therapy subgroup (77.3% and 81.1% in the Erelzi and Enbrel groups, respectively). Difference in the PASI 75 responder rates for Erelzi and Enbrel were −1.8% (95% CI: −11.13%; 7.52%) and −3.7% (95% CI: −16.58%; 9.16%) for no prior systemic therapy and prior systemic therapy subgroups, respectively. However, as there were errors noted in the assignment to prior systemic therapy, re-analyses were requested (please see below).

The proportion of patients achieving PASI 75 at week 12 was numerically higher in the < 90 kg subgroup (81.2% and 84.2% in the Erelzi and Enbrel groups, respectively) than in the ≥ 90 kg subgroup (62.2% and 63.6% in the Erelzi and Enbrel groups, respectively). However, results of the body weight category subgroup analyses were consistent with the total primary efficacy results, with a difference (Erelzi − Enbrel) in the PASI 75 rates of −3.1% (95% CI: −11.89%; 5.72%) and −1.4% (95% CI: −14.83%; 12.02%) for < 90 kg and ≥ 90 kg subgroups, respectively.

No regional differences were observed.

Post-hoc analyses

Post-hoc sensitivity analyses of the primary endpoint PASI75 were performed to evaluate the impact of errors in the assignment of subjects with or without prior systemic psoriasis therapy. In these analyses, the stratification factor was deleted from the statistical model. This was considered to be a conservative approach reflecting a worst-case scenario, since exclusion of the factor could no longer reduce variability of the patient population. The results were consistent with the primary analysis, demonstrating a difference in the adjusted response rates of -2.2 with the limits of the 95% confidence interval being [-9.82, 5.37] (for comparison: the respective results of the primary analysis were -2.3 [-9.85, 5.30]).

An additional sensitivity/subgroup analysis (Table 20) was requested, excluding the 82 subjects with potential erroneous stratification based on prior systemic psoriasis treatment (in a way that only prior systemic psoriasis treatment used 6 months before inclusion were taken into account, whereas this should include any time before randomisation). Since the Interactive Response Technology system used for stratification did not allow any correction afterwards, sensitivity analyses were performed excluding all the 82 subjects from the affected sites. The predefined similarity criteria were still met for primary and key secondary PASI endpoints, indicating robustness of the outcomes

See Table 24 below.

Table 24: Overview on sensitivity analysis excluding 82 patients concerned by potential erroneous stratification based on prior psoriasis treatments

Analysis Endpoint	N GP2015/ Enbrel	Adjusted Response Rate (%) GP2015/Enbrel	Main (PPS) and supportive (FAS) analysis: mean difference (%) and 95% CI
Sensitivity analysis excluding 82 patients			
Primary: PASI 75 response at Week 12	PPS: 204/202 FAS: 225/224	PPS: 74.1/75.2 FAS: 70.9/70.7	PPS: −1.1 [−9.33, 7.08] FAS: 0.2 [−8.06, 8.52]
Secondary: Percentage change from baseline in PASI score up to 12 weeks (MMRM)	PPS: 204/202 FAS: 225/223	PPS: -55.83/-55.35 FAS: -55.45/-54.07	PPS: −0.48 [−3.505, 2.548] FAS: −1.38 [−4.359, 1.602]
Secondary: Analysis of averaged treatment effect of percent PASI change (ANCOVA)	PPS: 204/202 FAS: 225/223	PPS: -52.96/-52.23 FAS: -52.21/-49.96	PPS: −0.73 [−3.641, 2.175] FAS: −2.25 [−5.295, 0.802]
Efficacy results based on the original analysis sets defined in the final Statistical Analysis Plan			
Primary: PASI 75 response at Week 12	PPS: 239/241 FAS: 264/267	PPS: 73.4/75.7 FAS: 70.4/71.6	PPS: −2.3 [−9.85, 5.30] FAS: −1.2 [−8.77, 6.45]
Secondary: Percentage change from baseline in PASI score up to 12 weeks (MMRM)	PPS: 239/241 FAS: 264/266	PPS: -56.11/-55.48 FAS: -55.96/-54.36	PPS: −0.64 [−3.474, 2.204] FAS: −1.59 [−4.367, 1.178]
Secondary: Analysis of averaged treatment effect of percent PASI change (ANCOVA)	PPS: 239/241 FAS: 264/266	PPS: -52.99/-52.11 FAS: -52.30/-50.16	PPS: −0.88 [−3.610, 1.845] FAS: −2.14 [−4.966, 0.686]

ANCOVA=analysis of covariance; CI=confidence intervals; FAS=full analysis set; MMRM=mixed-model repeated measures; PASI=psoriasis area and severity index; PPS=per-protocol set

Switching data

The proportion of patients achieving PASI 50, PASI 75, and PASI 90 were overall similar between the pooled continued and pooled switched treatment groups. The PASI 75 and PASI 90 response rates were overall steady over time from Week 12 up to Week 30 for all groups, i.e. switched groups or continuous treatment groups. The results of the analysis on the FAS were similar to those in the PPS. See Table 25 below.

Neither was there a difference in switchers from Enbrel and switchers from Erelzi, with mean % change from baseline of -88.287 in the switched Erelzi group and -88.517 in the switched Enbrel group at Week 30 (at the end of TP2; PPS), and of -85.574 in the switched Erelzi group and -88.527 in the switched Enbrel group at Week 52 (at the end of the Extension Period).

Table 25: Proportions of patients with PASI 50, PASI 75, and PASI 90 response rate for pooled treatment groups by visit (TP2 PPS)

Visit	Endpoint	Treatment group	N	n	Adjusted response rate (%)	Adjusted response rate difference (%) (pooled switched – pooled continued)	95% CI (%)
Week 12	PASI 50	Pooled continued	267	267	NE	NE	NE
		Pooled switched	179	179	NE		
	PASI 75	Pooled continued	267	204	76.3	-1.8	-9.78, 6.13
		Pooled switched	179	133	74.5		
	PASI 90	Pooled continued	267	94	35.1	3.5	-5.52, 12.57
		Pooled switched	179	69	38.7		
Week 18	PASI 50	Pooled continued	267	262	98.2	-0.6	-3.30, 2.18
		Pooled switched	179	175	97.6		
	PASI 75	Pooled continued	267	220	82.4	-3.6	-11.04, 3.88
		Pooled switched	179	141	78.8		
	PASI 90	Pooled continued	267	124	46.4	-1.6	-10.98, 7.75
		Pooled switched	179	80	44.8		
Week 24	PASI 50	Pooled continued	267	260	97.4	-0.8	-4.09, 2.43
		Pooled switched	179	173	96.6		
	PASI 75	Pooled continued	267	224	83.9	1.5	-5.29, 8.22
		Pooled switched	179	153	85.4		
	PASI 90	Pooled continued	267	155	58.0	-5.5	-14.85, 3.82
		Pooled switched	179	94	52.5		
Week 30	PASI 50	Pooled continued	267	260	97.4	-0.3	-3.35, 2.84
		Pooled switched	179	174	97.2		

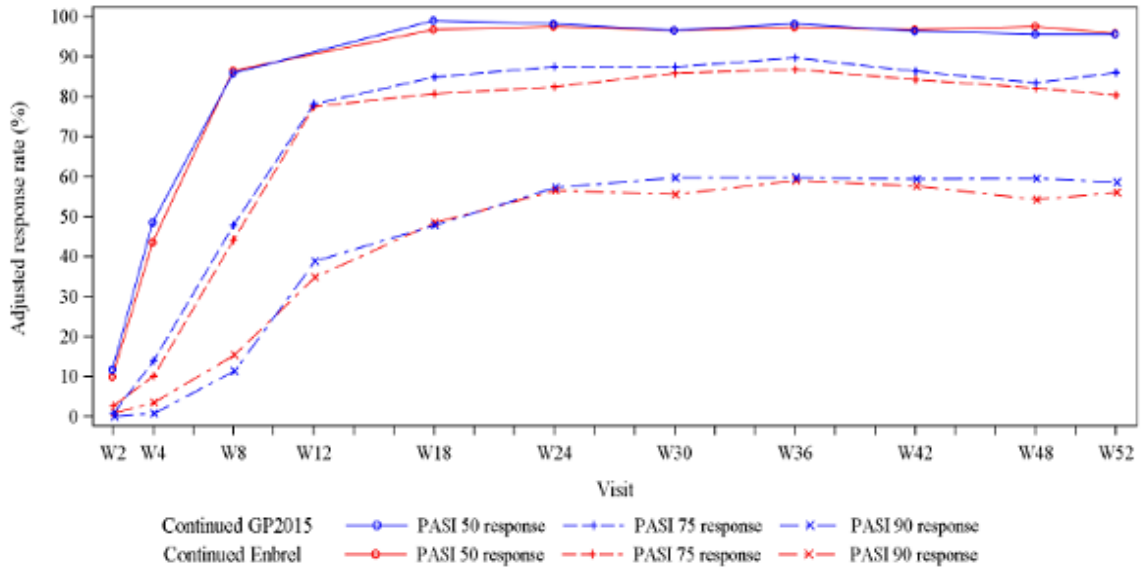
Visit	Endpoint	Treatment group	N	n	Adjusted response rate (%)	Adjusted response rate difference (%) (pooled switched – pooled continued)	95% CI (%)
	PASI 75	Pooled continued	267	231	86.6	-0.7	-7.18, 5.80
		Pooled switched	179	154	85.9		
	PASI 90	Pooled continued	267	158	59.2	-0.5	-9.82, 8.72
		Pooled switched	179	105	58.6		

CI = confidence interval; N=number of patients with evaluable data within each treatment group; n=number of patients achieving PASI 50, 75, or 90 responses; PASI = psoriasis area and severity index; PPS = per-protocol set; TP=treatment period Source: Table 14.2-2.2.3.1

Long-term extension phase (Week 52)

No dissimilarity in trend was observed for Erelzi versus the reference product Enbrel in the extension phase till 52 weeks. See figure 4 on the PASI response below.

Figure 4: Plot for adjusted response rate (%) for PASI 50, PASI 75 and PASI 90 by visit and continued treatment group from baseline to week 52 (OA PPS)



OA PPS=overall analysis per-protocol set; PASI=psoriasis area and severity index.

Summary of main study

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

Table 26: Summary of efficacy for study GP15-302

Title: A 52-week randomized, double-blind, multicenter study to demonstrate equivalent efficacy and to compare safety and immunogenicity of a biosimilar etanercept (Erelzi) and Enbrel in patients with moderate to severe chronic plaque-type psoriasis (EGALITY)			
Study identifier: GP15-302			
Design	TP 1: Randomized, double-blind, parallel-group TP 2: Randomized, double-blind, re-assignment continuous or cross-over groups (actual re-randomization 3:2) Extension phase: continuation treatment assignment from TP2, blinding maintained		
	Duration TP 1: Duration TP 2: Duration of Extension phase:	Week 1-12 Week 13-30 Week 31-52	
Hypothesis	Therapeutic equivalence		
Treatments groups	Erelzi	50mg s.c. twice weekly (Week1-12) 50 mg s.c. once weekly (Week12-52)	
	Enbrel	50mg s.c. twice weekly (Week1-12) 50 mg s.c. once weekly (Week12-52)	
Endpoints and definitions	Primary endpoint	PASI75 responder rate at week 12	
	Key Secondary endpoint	Relative % change from baseline in the PASI score at week 12	
Database lock	Study data are collected from 24 June 2013 until all patients had completed the Week 52 visit on 30 March 2015		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Per Protocol set (PPS), week 12		
Descriptive statistics of primary and key secondary endpoints	Treatment group	Erelzi	Enbrel
	FAS (randomized) PPS	264 239	267 241
	PASI75 responders PPS	73.4%	75.7%
	%change from baseline in PASI scores (mean*) PPS	-56.11%	-55,48%
Effect estimate per comparison	Comparison groups	Erelzi versus EU Enbrel	Pre-specified equivalence limits (%)
Primary endpoint	difference in response rates PPS	-2.3	
	95%CI of the difference in response rates	PPS: -9.85; 5.30	-18;18 Equivalence criterion is met
Key secondary	mean difference PPS	−0.64	
	95%CI of the mean difference (MMRM) PPS	−3.47; 2.20	-15;15 Equivalence criterion is met
Notes:	Equivalence criteria were also met for secondary analyses in the FAS population for primary and key secondary endpoints		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable for a biosimilar product.

Supportive studies

None were conducted.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Choice of the disease model

The choice of psoriasis as a model to evaluate therapeutic equivalence to the reference product product Enbrel (EU-authorised) is considered adequate. As demonstrated in the trial and known from historical data, psoriasis lesions are sensitive to change by the treatment with etanercept, and the response is specifically related to TNF-inhibition by etanercept. Moreover, the lesions can be scored independently by investigators, with limited inter-rater variability.

In the CHMP scientific advice, concerns were expressed whether psoriasis may be a less suitable model, since a high variability is to be expected regarding prior treatments and disease severity (i.e. TNF-expression). Patients were stratified for prior treatments (systemic or not), and a wash-out for different prior treatments was included in the protocol. Sensitivity analyses did not indicate a significant effect of prior systemic psoriasis treatment status, further supporting the choice of psoriasis as a model to evaluate equivalence.

Design of the study

The active comparator (Enbrel from EU source) is considered adequate. No placebo was included. However, assay sensitivity could be considered established, since it is unlikely that an improvement of more than 50% from baseline would be achieved without treatment. Placebo response was reported to be very low in comparable study populations with moderate-severe psoriasis from other trials.

Baseline characteristics were comparable between Erelzi and Enbrel assignments, and over the two study periods. The pooled analysis showed that the pattern of background and disease related characteristics were similar between treatment-continued and switching groups in Treatment Period 2.

The main part of the equivalence trial has duration of 12 weeks. This is considered optimal to establish therapeutic equivalence, since the main response is achieved shortly after treatment initiation.

After 12 weeks, a part of the population (~40%) was re-assigned to the switching arms in Treatment Period 2, where subjects switched between Enbrel or Erelzi every 6 weeks. The data demonstrated maintenance of efficacy under switching. However, these data should be interpreted with caution, as only a portion of the study population switched etanercept treatment after 12 weeks, and carry-over effects are not excluded. These data are considered as supportive evidence for establishing equivalence in efficacy.

Choice of the primary endpoint

The primary endpoint (PASI75 responder rates) may not be considered optimal for establishing biosimilarity, because responder rates may be less sensitive to detect differences between a biosimilar and its reference product, if any exists. However, the PASI75 is supported by mean changes from baseline of the absolute PASI score, early after initiating treatment of 6-12 weeks, which is considered a sensitive period to detect differences –as compared to steady state.

Choice of the equivalence acceptance margin

Based on treatment effect sizes from historical data, a margin of +/- 18% was pre-defined for the PASI75 response rates. A margin of +/-15% was predefined for the key secondary outcome of mean percentage change from baseline (BL) in PASI scores. From a clinical perspective, the equivalence margins are considered too wide and not sufficiently justified, as these may include a relevant difference in effect size. Although the acceptance criteria are considered too broad, no questions were raised on this issue, as the actual 95% Confidence Intervals of these outcomes fell between smaller ranges (<10%).

GCP Inspection

A GCP inspection has been performed for the pivotal Phase III trial GP15-302 by the German Inspectorate (Federal Institute for Vaccines and Biomedicines - Paul Ehrlich Institut), on request of the EMA on Day 120.

The main reason of the CHMP for requesting a GCP inspection were discrepancies noted between the interactive response technology (IRT) system and the sponsor's clinical database regarding prior systemic psoriasis treatment, resulting in a significant number of subjects being wrongly stratified. The Inspectors concluded that the deletion of prior data of systemic psoriasis treatment (by an erroneous correction of a CRA) from IRT, which was a main trigger for requesting Inspection, could be reasonably explained. Root-cause analyses were performed, resulting in preventive actions of better coordination and communication between Sponsor and CRO for future studies.

The Inspector also noted that underreporting of AEs, and their treatment relatedness, could not be excluded. Criticalities were noted regarding the GCP monitoring system, particular regarding Source Data Verification (SDV).

Therefore, and aligned with the Inspectorate, a re-monitoring of 10 sites was performed by independent auditors, with the focus on Source Data Verification of the reported adverse events. The report of this re-monitoring exercise was finished in 22 December 2016. Data files of 104 subjects were re-monitored. In total, 12 TEAEs from 104 subjects were detected *de novo* based on source data verification, of which 7 were Injection Site Reactions for Enbrel. Investigators declared that they did not include the AEs in the CRF, as they considered the issues minor, self-limiting or not treatment-related.

On Request of the CHMP, a 'worst-case scenario' extrapolation to the whole study population was performed, assuming similar underreporting rate that was observed in the subset of re-monitored cases for the total study population. No relevant changes in the incidence rates of patients with Adverse Events were predicted. A higher incidence of ISR was noted for Enbrel than for Erelzi in both the post-hoc estimates as the original data (see details under Clinical Safety section of this report).

Moreover, re-inspection was targeted to Source Data Verification of Adverse Events and establishment of the stratification factor. The selection of independent CRAs was done in consultation with the Inspectors.

Efficacy outcomes (PASI-scores) were not considered affected at Source Data Verification.

It was not clear amongst investigators and CRAs, and also statisticians, how the stratification factor "prior systemic psoriasis treatment' should be defined according to the protocol. Erroneously, this was wrongly

interpreted by CRA's that this would only refer to systemic therapies of the last 6 months before entering the trial, instead of an unlimited period before the trial. The correct definition was that any prior use of systemic psoriasis therapy, disregarding how long before entering the study, should lead to a positive identification. In contrast, for all other pharmacological treatments, including topical psoriasis treatment, only data were to be recorded for a period of 6 months before entering the study, possible leading to misinterpretations that a 6 month period would also account for the systemic psoriasis therapy. It was difficult to establish how many sites/subjects were affected by this misspecification.

In the pivotal clinical trial, multiple misspecifications were noted regarding stratification based on prior use of systemic psoriasis treatment. Source Data Verification at re-monitoring indicated that misspecification of the stratification factor was random for either treatment, and the Inspectors concluded that the divergence could be reasonably explained. Conservative sensitivity analyses excluding all subjects that may have been misspecified indicated that this stratification factor had no impact on final conclusions regarding equivalence of the primary and key secondary clinical outcomes. Also, literature was provided that this factor was not relevant for the response to other TNF-inhibitors. Since the sensitivity analyses revealed that there was no impact of this stratification factor, this issue could be considered resolved.

GCP compliance is ultimately considered sufficiently guaranteed for the pivotal trial GP15-302, for the following reasons: During the study, on average 11.8 on-site monitoring visits took place per site. Blinding was not affected. Overall, the rate and nature of Adverse Events is similar as reported earlier for Enbrel. The AEs that were not included in the CRF could be traced down in the end. Re-estimating of the AE rates did not show major discrepancies from the originally reported data. More injection site reactions (ISR) were reported for Enbrel than for Erelzi, however, the totality of data (quality, pre-clinical) shows similarity. Moreover, similar rates of ISRs were reported before for Enbrel in psoriasis trials.

Efficacy data and additional analyses

Therapeutic equivalence

For the primary endpoint PASI75 at Week 12, the 95% CI of the difference between Erelzi and Enbrel was -9.85, 5.30, and the a priori defined criterion of therapeutic equivalence (i.e. -18, 18%) was met. Also for the key secondary endpoint mean percentage change form baseline in PASI scores at Week 12, the acceptance criterion of -15,15% was met (95% CI of the difference : −3.47, 2.20).

Robustness of the primary and key secondary outcome was demonstrated in secondary analyses in the FAS population. The conclusion from these primary analyses were also supported by the other secondary outcomes like IGA responders, PASI 50 and PASI 90 responders, and QOL scores, all indicating a high level of equivalence between Erelzi and Enbrel.

The PASI 75 responder rates were overall lower for patients weighing ≥90 kg (62.2-63.6% for Erelzi and Enbrel, respectively), compared to patients weighing <90kg (81.2-84.2%). An effect of weight on the PK and clinical response has been reported previously for the reference product Enbrel (see EPAR Enbrel 2006). However, according to the SmPC of Enbrel, marketed since 2000, no specific dose adjustments are required for patients with increased body weight. The same approach should then be applied for the biosimilar product.

Post-hoc analyses were performed to evaluate the impact of erroneous assignment as having no prior systemic therapy. There was no relevant impact on the outcomes of primary and key secondary endpoints.

Data on PASI 75 and IGA responses by individual switched groups, up to Week 52, do not indicate any loss of efficacy.

Extrapolation to other indications

A single study in psoriasis 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 characterized 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 psoriatic plaques. 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 psoriasis model. Equivalence has been convincingly shown for primary endpoint PASI75 and secondary sensitive endpoints like mean percentage change from baseline in PASI scores, within small therapeutic margins. Maintenance of efficacy was established for both treatments till the end of the study at 52 weeks, also after switching.

As discussed above, a number of subjects were wrongly assigned to the “no prior systemic psoriasis treatment” stratum. Conservative sensitivity analyses, ignoring this stratification factor or excluding all possible affected patients, did not show any relevant impact of the stratification factor on the primary and key secondary outcomes. Therefore, efficacy outcomes are accepted, despite the uncertainties regarding the stratification factors. When additional source-data-verification was carried out, no relevant differences were found for PASI scores, indicating that efficacy outcomes were not significantly affected by GCP-violations. CAPAs (Corrective & Preventive Action Programs) will be implemented for future studies. Based on the analytical, non-clinical and clinical similarity of Erelzi to Enbrel extrapolation to the other indications of the reference product is accepted.

2.6. Clinical safety

Patient exposure

Safety data for Erelzi are available from four pharmacokinetic studies in healthy volunteers (GP15-101, GP15-102, GP15-103, and GP15-104) and one confirmatory clinical efficacy and safety study in psoriasis (GP15-302).

Exposure in healthy volunteers

In the PK studies, 216 healthy volunteers were exposed to a single dose of Erelzi. In total, 192 Healthy volunteers were exposed to either Enbrel from the US market (n=54) or EU market (n= 138).

Treatment period 1 of Study GP15-302

In total, 264 psoriasis patients were exposed to Erelzi and 267 patients to Enbrel in Treatment Period 1. Mean duration of exposure to Erelzi and Enbrel was similar (80.6 (SD 9.7) versus 79.2 (SD 11.6) days).

Treatment period 2 of Study GP15-302

Hundred-fifty and 151 patients were exposed to Erelzi and Enbrel during Treatment Period 2, respectively. Mean duration of exposure to Erelzi and Enbrel was similar (117.1 (SD 15.4) versus 117.5 (SD 15.0) days).

Extension period of Study GP15-302

In the Extension Period (Week 31 to Week 52), 465 patients continued the study treatments (continued group: 280 patients; pooled switched group: 185 patients).

Adverse events

Phase I studies: Occurrence of adverse events in healthy volunteers was similar between Erelzi treated subjects and Enbrel treated subjects. None of them were serious.

Study GP15-302:

37.5% of the psoriasis patients treated with Erelzi and 36.0% of patients treated with Enbrel experienced at least one treatment-emergent adverse event in Treatment Period 1 of the study (BL-Week12). In the Erelzi treatment group, 1.5% of patients experienced serious adverse events compared to 1.1% of patients in the Enbrel treatment group. Similar proportions of patients discontinued the study due to treatment-emergent adverse events (1.9% and 1.5% in the Erelzi and Enbrel group respectively).

Most commonly affected system organ classes were infections and infestations (primarily nasopharyngitis), skin and subcutaneous tissue disorders (primarily dermatitis allergic and pruritus), gastrointestinal disorders (primarily abdominal pain upper, diarrhoea, and toothache) and musculoskeletal and connective tissue disorders (primarily arthralgia and back pain).

Table 27: Treatment emergent adverse events during Treatment Period 1

System organ class Preferred term	GP2015 N=264 n (%)	Enbrel N=267 n (%)	Total N=531 n (%)
Number of patients with at least one TEAE	99 (37.5)	96 (36.0)	195 (36.7)
Infections and infestations	49 (18.6)	45 (16.9)	94 (17.7)
Nasopharyngitis	17 (6.4)	13 (4.9)	30 (5.6)
Pharyngitis	3 (1.1)	7 (2.6)	10 (1.9)
Upper respiratory tract infection	5 (1.9)	4 (1.5)	9 (1.7)
Viral upper respiratory tract infection	3 (1.1)	4 (1.5)	7 (1.3)
Respiratory tract infection viral	4 (1.5)	2 (0.7)	6 (1.1)
Urinary tract infection	2 (0.8)	3 (1.1)	5 (0.9)
Cystitis	3 (1.1)	1 (0.4)	4 (0.8)
Acute tonsillitis	0	3 (1.1)	3 (0.6)
Bronchitis	2 (0.8)	1 (0.4)	3 (0.6)
Oral herpes	1 (0.4)	2 (0.7)	3 (0.6)
Skin and subcutaneous tissue disorders	17 (6.4)	11 (4.1)	28 (5.3)
Dermatitis allergic	3 (1.1)	1 (0.4)	4 (0.8)
Pruritus	1 (0.4)	3 (1.1)	4 (0.8)
Dermatitis contact	2 (0.8)	1 (0.4)	3 (0.6)
Dermatitis psoriasiform	1 (0.4)	2 (0.7)	3 (0.6)
Pruritus generalized	1 (0.4)	2 (0.7)	3 (0.6)
Gastrointestinal disorders	10 (3.8)	17 (6.4)	27 (5.1)
Abdominal pain upper	1 (0.4)	3 (1.1)	4 (0.8)
Diarrhea	2 (0.8)	2 (0.7)	4 (0.8)
Toothache	2 (0.8)	2 (0.7)	4 (0.8)
Vomiting	1 (0.4)	2 (0.7)	3 (0.6)
Musculoskeletal and connective tissue disorders	11 (4.2)	15 (5.6)	26 (4.9)
Arthralgia	1 (0.4)	7 (2.6)	8 (1.5)
Back pain	3 (1.1)	3 (1.1)	6 (1.1)
Osteoarthritis	1 (0.4)	2 (0.7)	3 (0.6)
Investigations[1]	15 (5.7)	7 (2.6)	22 (4.1)
Alanine aminotransferase increased	4 (1.5)	2 (0.7)	6 (1.1)
Aspartate aminotransferase increased	4 (1.5)	1 (0.4)	5 (0.9)
Blood pressure increased	4 (1.5)	1 (0.4)	5 (0.9)
Weight increased	3 (1.1)	3 (1.1)	6 (1.1)
Nervous system disorders	11 (4.2)	9 (3.4)	20 (3.8)
Headache	4 (1.5)	2 (0.7)	6 (1.1)
Paraesthesia	0	3 (1.1)	3 (0.6)
Somnolence	3 (1.1)	0	3 (0.6)
Respiratory, thoracic and mediastinal disorders	8 (3.0)	6 (2.2)	14 (2.6)

Oropharyngeal pain	1 (0.4)	2 (0.7)	3 (0.6)
Tonsillar hypertrophy	1 (0.4)	2 (0.7)	3 (0.6)
Metabolism and nutrition disorders	7 (2.7)	6 (2.2)	13 (2.4)
Hyperuricaemia	2 (0.8)	1 (0.4)	3 (0.6)
Vascular disorders	4 (1.5)	6 (2.2)	10 (1.9)
Hypertension	2 (0.8)	4 (1.5)	6 (1.1)
General disorders and administration site conditions	5 (1.9)	3 (1.1)	8 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.9)	1 (0.4)	6 (1.1)
Injury, poisoning and procedural complications	3 (1.1)	2 (0.7)	5 (0.9)
Renal and urinary disorders	2 (0.8)	3 (1.1)	5 (0.9)
Hematuria	2 (0.8)	1 (0.4)	3 (0.6)
Psychiatric disorders	2 (0.8)	2 (0.7)	4 (0.8)
Reproductive system and breast disorders	3 (1.1)	1 (0.4)	4 (0.8)
Eye disorders	1 (0.4)	2 (0.7)	3 (0.6)
Hepatobiliary disorders	1 (0.4)	2 (0.7)	3 (0.6)

Abbreviations: TEAE= treatment-emergent adverse event

Post-hoc analyses following re-inspection

As explained above, a re-monitoring of 10 sites was performed by independent auditors, with the focus on Source Data Verification of the reported adverse events. Twelve additional AEs were found that were not included in the Case Report Forms, and final dossier. None of them were serious. Two of them were worsening of psoriatic arthritis (both GP2015), one viral infection (Enbrel), one mild thrombocytopenia (GP2015), and one lipoma of the salivary gland (Enbrel). Seven AEs from 5 subjects were classified as non-serious Injection Site Reactions (ISR), all for Enbrel study arm. Investigators declared that they did not include the AEs in the CRF, as they considered the issues minor, self-limiting or not-related. According to the Investigator who noted 'worsening of psoriatric arthritis' in the Source Documents of two patients, these cases were already present before inclusion in the trial, and therefore not included in the CRF.

On request of the CHMP, a "worst case scenario" extrapolation was performed, assuming a similar underreporting rate for the whole study population that was observed in the subset of re-monitored cases. This was performed for incidence rates of subjects with any AEs by treatment arm in Period 1see Table 24 below), as well as for the number of total events. Considering the 10 patients with newly identified AEs, 2 patients out of these 10 did not have any documented AE in the clinical database. The new AEs of these 2 patients were ISRs which occurred in the Enbrel arm in TP1. Therefore, the underreporting rate was 2 out of 104 patients, which results in a rate of 0.019. Applying the 0.019 underreporting rate to all 531 patients, the extrapolated incidence increases by less than 2 % for TP1, as well as for the total study.

Based on the 12 findings in 104 patients during re-monitoring, assuming 12/104 is the additional event rate per patient, then applying this rate to all the patients in the whole study, the expected number of events would be 61 additional AEs for the whole study which represent ~5% of the already reported 1175 AEs (938 non-ISR AEs plus 237 ISRs).

In summary, when applying these worst case scenarios, there was no change in the overall clinical conclusions on safety of the study.

Table 28: Estimated impact on AE (including ISR) incidence in TP1 by treatment arm

Treatment arm	Incidence of AEs as reported in the clinical database n (%)	Incidence of AEs after re-monitoring n (%)	Extrapolated incidence of AEs n (%)
GP2015 (N=264)	103 (39.0)	103 (39.0)	103 (39.0)
Enbrel (N=267)	111 (41.6)	113 (42.3)	122 (45.7)
Total (N=531)	214 (40.3)	216 (40.7)	224 (42.2)

Table 29: Estimated impact of extrapolation on events for TP1 by treatment arm.

Treatment arm	AEs	Number of previously documented AEs	Number of extrapolated AEs	Number of total AEs after extrapolation	Increase in AEs
GP2015 (N=264)	PsA worsening ISR thrombocytopenia	211	14	**225**	**6.6%**
Enbrel (N=267)	ISR (5 ISRs in 4 patients)	312	28	**340**	**9.0%**

Long-term Safety

The combined analysis population included those patients who were not re-assigned at Week 12, but were assigned to receive Enbrel (n=171) or Erelzi (n=164) for 52 weeks from baseline. The number of patients with at least 1 TEAE was comparable between the continued Erelzi group (98 [59.8%] patients reporting 307 TEAEs) and the continued Enbrel/EU group (98 [57.3%] patients reporting 281 TEAEs). The incidence of SAEs was similar between the continued Erelzi and continued Enbrel groups (4.3% vs. 4.1%). Similar proportions of patients discontinued the study due to TEAEs in the continued Erelzi group (6.7%) and in the continued Enbrel group (4.7%). Regarding AEs of interest, there were no relevant differences of injection site reactions (Erelzi: 8.5%, Enbrel 15.8%) and infections (Erelzi: 36.0%, Enbrel 32.2%) till Week 52.

Table 30: TEAEs regardless of study drug relationship by system organ class and preferred term (1% of greater total incidence in either SOC or PT) for continued treatment groups from baseline to week 52 (OA Safety set)

System organ class Preferred term	Continued GP2015 N=164 n (%)	Continued Enbrel N=171 n (%)
Number of patients with at least one TEAE	98 (59.8)	98 (57.3)
Infections and infestations	59 (36.0)	55 (32.2)
Nasopharyngitis	20 (12.2)	17 (9.9)
Pharyngitis	7 (4.3)	10 (5.8)
Tonsillitis	5 (3.0)	1 (0.6)
Viral upper respiratory tract infection	5 (3.0)	6 (3.5)
Upper respiratory tract infection	4 (2.4)	5 (2.9)
Bronchitis	4 (2.4)	3 (1.8)
Respiratory tract infection viral	4 (2.4)	2 (1.2)
Cystitis	3 (1.8)	1 (0.6)
Viral infection	3 (1.8)	2 (1.2)
Influenza	2 (1.2)	3 (1.8)
Urinary tract infection	2 (1.2)	3 (1.8)
Rhinitis	2 (1.2)	4 (2.3)
Musculoskeletal and connective tissue disorders	20 (12.2)	21 (12.3)
Back pain	7 (4.3)	3 (1.8)
Arthralgia	5 (3.0)	7 (4.1)
Spinal pain	2 (1.2)	2 (1.2)
Investigations	19 (11.6)	15 (8.8)
Alanine aminotransferase increased	6 (3.7)	2 (1.2)
Gamma-glutamyl transferase increased	6 (3.7)	0
Aspartate aminotransferase increased	5 (3.0)	1 (0.6)
Blood uric acid increased	3 (1.8)	2 (1.2)
Weight increased	2 (1.2)	4 (2.3)

Blood pressure increased	2 (1.2)	2 (1.2)
Skin and subcutaneous tissue disorders	16 (9.8)	18 (10.5)
Dermatitis allergic	3 (1.8)	1 (0.6)
Pruritus	2 (1.2)	4 (2.3)
Psoriasis	0	5 (2.9)
Gastrointestinal disorders	15 (9.1)	17 (9.9)
Diarrhea	4 (2.4)	2 (1.2)
Abdominal pain upper	3 (1.8)	3 (1.8)
Gastritis	0	4 (2.3)
Nervous system disorders	11 (6.7)	12 (7.0)
Headache	3 (1.8)	8 (4.7)
Respiratory, thoracic and mediastinal disorders	11 (6.7)	10 (5.8)
Cough	3 (1.8)	2 (1.2)
Oropharyngeal pain	3 (1.8)	2 (1.2)
Blood and lymphatic system disorders	8 (4.9)	0
Lympadenopathy	4 (2.4)	0
Vascular disorders	7 (4.3)	10 (5.8)
Hypertension	5 (3.0)	7 (4.1)
Injury, poisoning and procedural complications	6 (3.7)	7 (4.1)
Psychiatric disorders	6 (3.7)	4 (2.3)
Metabolism and nutrition disorders	5 (3.0)	7 (4.1)
General disorders and administration site conditions	5 (3.0)	5 (2.9)
Fatigue	1 (0.6)	3 (1.8)
Reproductive system and breast disorders	5 (3.0)	3 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (3.0)	1 (0.6)
Cardiac disorders	4 (2.4)	5 (2.9)
Immune system disorders	4 (2.4)	2 (1.2)
Renal and urinary disorders	4 (2.4)	2 (1.2)
Hematuria	3 (1.8)	1 (0.6)
Hepatobiliary disorders	2 (1.2)	4 (2.3)

AE=adverse event; MedDRA=medical dictionary for regulatory activities; N=number of patients; n (%)=number of patients (percentage) with adverse events; OA=overall analysis; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
SOCs and PTs with events occurring with an incidence greater than 1% in total in the OA safety set are presented and sorted by descending order of frequency within SOC and PT in the GP2015 column. AE terms are coded using MedDRA version 17.0.

Regarding the adverse events of special interest, neoplasms were reported more frequently in patients treated with GP2015 compared to those treated with Enbrel (6 versus 1).

Most were benign (two cases of naevus (both GP2015), one lipoma (GP2015), one case of tubular-villous adenoma of the colon with low grade dysplasia), and two cases of skin papilloma (one for GP2015, one for Enbrel). There is no apparent relationship between the occurrence of this benign neoplasm and the use of etanercept.

One of them, in the GP2015 assignment group, was malignant (a malignant melanoma in situ). However, causality cannot be considered, because the melanoma (reported after receipt of the histological diagnosis) had been excised prior to start of study treatment.

Overall, infection rate is similar. Fungal infections were slightly more frequently for Erelzi (4 cases) than Enbrel (none).

Injection site reactions were more common for Enbrel than for Erelzi (Week 52, Erelzi: 8.5%, Enbrel 15.8%). On general, these were of mild severity, not leading to an increased drop-out rate.

Investigations ALT/AST and GGT were more frequently reported as AEs for Erelzi than or Enbrel. However, when looking at systematically monitoring of liver function test, no imbalance was observed (see subsection 'Laboratory findings' below).

The safety profile in switching subgroups (after week 12), was similar to patients who continued the same treatment from baseline on.

Serious adverse event / deaths / other significant events

Occurrence of death, serious adverse events, and premature study discontinuation because of treatment-emergent adverse events during treatment period 1 and 2 is presented in Table 31.

One patient died of cardiopulmonary failure while on Enbrel treatment in treatment period 1. The death was considered as not related to study treatment.

Table 31: Deaths, serious adverse events, and study discontinuations.

	Treatment period 1		**Treatment period 2**		
	Erelzi	**Enbrel**	**Continued Erelzi**	**Continued Enbrel**	**Pooled switched Erelzi and Enbrel**
n	264	267	150	151	196
Death	0	0.4%	0	0	0
Serious adverse events	1.5%	1.1%	0.7%	1.3%	3.1%
Discontinued due to treatment-emergent adverse events	1.9%	1.5%	0.7%	1.3%	3.1%

Immunological events

Anti-drug antibodies (ADA)

In the Healthy Volunteers PK studies, a total of 3 subjects had confirmed binding anti-drug antibodies (ADAs) at the follow-up visit (Day 65) with titers near the detection limit. All 3 subjects were in the treatment sequence of Erelzi/EU-Enbrel (with Enbrel in Period 2), and none of the ADAs were neutralizing. The binding ADA positive results were considered not clinically meaningful due to the very low titers and no other safety issues were identified.

In Study GP15-302, there were no ADA-positive samples detected in the Erelzi group up to Week 52.

In contrast, 5 of the 267 patients in the TP1 Enbrel group (1.9%) had a confirmed positive binding ADA result, all within the first 4 weeks of treatment. Additionally, one subject in the switched Enbrel group, who had undergone the last switch from Enbrel to Erelzi at Week 24, had a confirmed positive binding ADA result at Week 36. For all patients, the obtained titer values were low and transient, and none of the ADAs had neutralizing capacity.

Laboratory findings

No meaningful changes over time or differences between treatment groups were observed for haematology and chemistry outcomes including Liver Function Tests, which were routinely monitored throughout the studies. The most frequently reported laboratory abnormality was ALT increment (< 3 x Upper Limit Normality), which was equally distributed over the treatments (Erelzi: 3.7% and Enbrel 4.1% in the extension period).

Safety in special populations

Not applicable for a biosimilar product.

Safety related to drug-drug interactions and other interactions

In the clinical development of Erelzi drug interactions have not been systematically investigated by the applicant. The identified and potential interactions of the reference product Enbrel/EU with other medicinal products also apply to Erelzi.

Discontinuation due to adverse events

Overall occurrence of treatment-emergent adverse events leading to study discontinuation was low and comparable in the Erelzi and Enbrel treatment groups.

Table 32 Treatment-emergent adverse events leading to study drug discontinuation in treatment period 1

System organ class Preferred term	GP2015 N=264 n (%)	Enbrel/EU N=267 n (%)
Number of patients with at least one TEAE	5 (1.9)	4 (1.5)
Gastrointestinal disorders	1 (0.4)	1 (0.4)
Abdominal distension	1 (0.4)	0
Colitis ulcerative[1]	0	1 (0.4)
Investigations	2 (0.8)	1 (0.4)
Alanine aminotransferase	0	1 (0.4)
Transaminases increased[2]	1 (0.4)	0
White blood cell count decreased[3]	1 (0.4)	0
Cardiac disorders	0	1 (0.4)
Cardiopulmonary failure[4]	0	1 (0.4)
Hepatobiliary disorders	0	1 (0.4)
Drug-induced liver injury[4]	0	1 (0.4)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	1 (0.4)	0
Malignant melanoma in situ[4]	1 (0.4)	0
Skin and subcutaneous tissue disorders	1 (0.4)	0
Pustular psoriasis	1 (0.4)	0

n (%)=number of subjects (percentage) with adverse events; N=number of subjects studied;

Table 33: Treatment-emergent adverse events leading to study drug discontinuation in treatment period 2

System organ class Preferred term	Continued GP2015 N=150 n (%)	Continued Enbrel/EU N=151 n (%)
Number of patients with at least 1 TEAE	1 (0.7)	2 (1.3)
Skin and subcutaneous tissue disorders	0	1 (0.7)
Psoriasis[1]	0	1 (0.7)
Blood and lymphatic system disorders	1 (0.7)	0
Thrombocytopenia	1 (0.7)	0
Immune system disorders	0	1 (0.7)
Hypersensitivity	0	1 (0.7)

Post marketing experience

At the time of the submission, Erelzi had not yet been approved or marketed in any country worldwide.

2.6.1. Discussion on clinical safety

Etanercept has been widely used in clinical practice for about 15 years, with a well characterised safety profile. The main safety issues are characterised by the immunosuppressive action of etanercept. Erelzi has been developed as a proposed similar biological medicinal product (biosimilar) to Enbrel.

The overall proportions, nature and severity of adverse events can be considered similar between Erelzi and Enbrel.

The fact that no ADA formation at all was observed for Erelzi, and the rate of local skin reactions was considerably lower for Erelzi than for Enbrel, might indicate that Erelzi may be 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. Notably, etanercept is also reported to have low immunogenicity has seen in several other studies in the literature. Thus, these findings are within expectations.

Re-monitoring and Source Data Verification in a large subset (104 out of total study population of 531 subjects) revealed that a small number of AEs were not included in the CRF and final dossier. Although it is expected that all AEs from the source documents would be included in the CRF, a selection was made by some Investigators. Though such a selection is not preferred, this was accepted, as the data were traceable, and the incidence of non-reporting in the CRF was low and balanced.

2.6.2. Conclusions on the clinical safety

Immunogenicity is low and transient for Enbrel and Erelzi in the Phase I studies. No ADAs were found for GP2015 in the Phase III trial, whereas a few transient ADAs were reported for comparator Enbrel (EU source). This difference regarding immunogenicity in the Phase III trial is not considered clinically meaningful.

The number and nature of adverse events were generally comparable between Erelzi and Enbrel.

Erelzi has comparable safety to Enbrel.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks – all indications	Malignancy (including lymphoma and leukemia)
	Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection)
	Lupus-like reactions
	Sarcoidosis and/or granulomas
	Injection site reactions
	Allergic reactions
	Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome)
	Systemic vasculitis (including ANCA positive vasculitis)
	Macrophage activation syndrome
	Central demyelinating disorders

Summary of safety concerns	
	Peripheral demyelinating events (CIDP and GBS)
	Aplastic anemia and pancytopenia
	Interstitial lung disease (including pulmonary fibrosis and pneumonitis)
	Autoimmune hepatitis
	Liver events in patients with viral hepatitis (including hepatitis B virus reactivation)
Important identified risks – specific indications	Change in morphology and/or severity of psoriasis in adult and pediatric populations
	Worsening of CHF in adult subjects
	Inflammatory bowel disease in JIA subjects
Important potential risks – all indications	Autoimmune renal disease
	Pemphigus/pemphigoid
	Amyotrophic lateral sclerosis
	Myasthenia gravis
	Encephalitis/leukoencephalomyelitis
	Progressive multifocal leukoencephalopathy
	Liver failure
	Hepatic cirrhosis and fibrosis
	Severe hypertensive reactions
	Adverse pregnancy outcomes
	Potential for male infertility
	Weight Gain
	Potential for medication errors (pre-filled pen)
Important potential risks – specific indications	Impaired growth and development in juvenile subjects
	Acute ischemic CV events in adult subjects
Missing information	Use in hepatic and renal impaired subjects
	Use in different ethnic origins
	Use in pregnant women

Pharmacovigilance plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final** **Reports (planned or actual)**
RABBIT (GER): Rheumatoid Arthritis Observation of Biologic Therapy Category 3	Evaluation of long-term safety and effectiveness of tumor necrosis factor (TNF)-inhibitor therapies in the treatment of rheumatoid arthritis (RA). Data for TNF–inhibitor therapies in the treatment of RA patients will be compared to a cohort of RA patients who are treated with non-biologic DMARDs.	Monitoring of all safety concerns described in RMP, including malignancy, serious and opportunistic infections, central demyelinating disorders, aplastic anaemia or, pancytopenia, worsening of congestive heart failure, acute ischemic cardio vascular events; use in pregnant woman	Planned (Start at time of drug availability in country following EMA approval)	Final report planned within 6-12 months after study completion. Summary reports provided to the MAH every 6 months.
ARTIS (SWE): Anti-rheumatic Therapies in Sweden Category 3	Evaluation of long-term safety and effectiveness associated with TNF-inhibitor therapies in the treatment of rheumatoid arthritis. The risk of selected AEs in RA, juvenile idiopathic arthritis, and other rheumatic disese patients treated with etanercept will be evaluated.	Monitoring of all safety concerns described in RMP, including malignancy, serious and opportunistic infections, central demyelinating disorders, aplastic anaemia or, pancytopenia, worsening of congestive heart failure, acute ischemic cardio vascular events; use in pregnant woman	Planned (Start at time of drug availability in country following EMA approval)	Summary reports provided to MAH every 6 months. An interim analysis is planned to be provided at 3 years after study start and and final planned within 6-12 months after study completion.

BSRBR (UK): British Society for Rheumatology Biologics Register – rheumatoid arthritis Category 3	Register is designed as national prospective study obtaining data from routine clinical practice and whose objective is to evaluate long-term safety from the use of these agents in routine practice.	Monitoring of all safety concerns described in RMP, including malignancy, serious and opportunistic infections, central demyelinating disorders, aplastic anaemia or, pancytopenia, worsening of congestive heart failure, acute ischemic cardio vascular events; use in pregnant woman	Planned (Start at time of drug availability in country following EMA approval)	Summary reports provided to the MAH every 6 months. Final report planned within 6-12 months after study completion
BADBIR (UK): British Association of Dermatologists Biologic Interventions Register (BADBIR, UK) Category 3	Assessment of long-term safety of biological treatments for psoriasis	Long-term safety of biologic treatments for psoriasis	Planned (Start at time of drug availability in country following EMA approval)	Summary reports provided to the MAH every 6 months. Final report planned within 6-12 months after study completion.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Malignancy (including lymphoma and leukemia)	Guidance is given in SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None
Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, and parasitic infection)	Guidance is given in SmPC sections 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, 4.6 Fertility, pregnancy and lactation and 4.8 Undesirable effects.	Patient alert cards are provided to Erelzi prescribing physicians for distribution to patients receiving Erelzi. This card provides important safety information for patients, including information relating to infections.

Lupus-like reactions	Guidance is given in SmPC section 4.8 Undesirable effects.	None
Sarcoidosis and/or granulomas	Guidance is given in SmPC section 4.8 Undesirable effects.	None
Injection site reactions	Guidance is given in SmPC section 4.8 Undesirable effects.	None
Allergic reactions	Guidance is given in SmPC sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None
Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome)	Guidance is given in SmPC section 4.8 Undesirable effects.	None
Systemic vasculitis (including ANCA positive vasculitis)	Guidance is given in SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None
Macrophage activation syndrome	Guidance is given SmPC section 4.8 Undesirable effects.	None
Central demyelinating disorders	Guidance is given in SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None
Peripheral demyelinating events (CIDP and GBS)	Guidance is given in SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None
Aplastic anemia and pancytopenia	Guidance is given in SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None
Interstitial lung disease (including pulmonary fibrosis and pneumonitis)	Guidance is given in SmPC section 4.8 Undesirable effects.	None
Autoimmune hepatitis	Guidance is given in SmPC section 4.8 Undesirable effects.	None

Liver events in patients with viral hepatitis (including hepatitis B virus reactivation)	Guidance is given in SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None
Change in morphology and/or severity of psoriasis in adult and pediatric populations	Guidance is given in SmPC section 4.8 Undesirable effects.	None
Worsening of CHF in adult subjects	Guidance is given in SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	Patient alert cards are provided to Erelzi prescribing physicians for distribution to patients receiving Erelzi. This card provides important safety information for patients, including information relating to congestive heart failure.
Inflammatory bowel disease in JIA subjects	Guidance is given in SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None
Autoimmune renal disease	Currently available data do not support the need for risk minimization.	None
Pemphigus/pemphigoid	Currently available data do not support the need for risk minimization.	None
Amyotrophic lateral sclerosis	Currently available data do not support the need for risk minimization.	None
Myasthenia gravis	Currently available data do not support the need for risk minimization.	None
Encephalitis/leukoencephalomyelitis	Currently available data do not support the need for risk minimization.	None
Progressive multifocal leukoencephalopathy	Currently available data do not support the need for risk minimization.	None
Liver failure	Currently available data do not support the need for risk minimization.	None

Hepatic cirrhosis and fibrosis	Currently available data do not support the need for risk minimization.	None
Severe hypertensive reactions	Currently available data do not support the need for risk minimization.	None
Adverse pregnancy outcomes	Guidance is given in SmPC section 4.6 Fertility, pregnancy and lactation.	None
Potential for male infertility	Guidance is given in SmPC section 4.6 Fertility, pregnancy and lactation.	None
Weight Gain	Currently available data do not support the need for risk minimization.	None
Potential for medication errors (pre-filled pen)	Clear instructions in package leaflet	Educational materials for health care professionals and care givers Needle-free demonstration device
Impaired growth and development in juvenile subjects	Currently available data do not support the need for risk minimization.	None
Acute ischemic CV events in adult subjects	Currently available data do not support the need for risk minimization.	None
Use in hepatic and renal impaired subjects	Guidance is given in SmPC sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use	None
Use in different ethnic origins	Currently available data do not support the need for risk minimization.	None
Use in pregnant women	Guidance is given in SmPC section 4.6 Fertility, pregnancy and lactation.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 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.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Enbrel. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Quick Response (QR) code

A request to include a QR code in the package leaflet and the outer carton for the purpose of providing instructions for use has been submitted by the applicant and has been found acceptable.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Erelzi (etanercept) is included in the additional monitoring list as a new biological.

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. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Erelzi is a biosimilar product of the reference product Enbrel and is approved for the same indications including, treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, and (juvenile) plaque psoriasis.

3.1.2. Main clinical studies

One confirmatory, parallel randomised double-blinded trial was performed to demonstrate equivalence regarding efficacy and safety between the biosimilar etanercept product Erelzi and the reference product Enbrel from EU source, in 531 patients with moderate-severe plaque psoriasis.

3.2. Favourable effects

From the quality perspective

Sufficient information has been provided on the manufacturing and control of Erelzi. It was demonstrated that when operating within the established input ranges for process parameters, a high quality medicinal product fulfilling its predetermined specifications can be reproducibly manufactured. The changes introduced into the manufacturing process during product development have been described in detail and their potential impact on product quality has been adequately addressed.

Comprehensive physicochemical and biological comparability studies using state-of-the art analytical methods have been carried out in order to demonstrate biosimilarity on the quality level between Erelzi and the reference medicinal product, Enbrel. The comparability studies address the primary, secondary and tertiary structures, post-translational modifications, purity/impurity profile, biological activity, as well as the degradation profile. The differences observed with regard to N- and C-terminal variants, size variants, as well as the minor qualitative differences in N-glycans, have been properly discussed and are considered to have no impact on the clinical performance of etanercept.

From a non-clinical perspective, it is considered that similarity between Erelzi and the reference product Enbrel was shown with regard to:

- the binding affinity to relevant receptors/ligands like TNF-alfa and Fc-receptors
- neutralisation of TNF-alfa and LT-alfa in reporter gene assays (RGA) and in an apoptosis assay
- Similar in vivo functionality in a rabbit arthritis model
- Similar pharmacokinetic behaviour
- Similar toxicity profile

From a clinical pharmacokinetics perspective, comparable PK has been adequately demonstrated in the repeat BE study. The primary PK parameters Cmax, AUC0-tlast and AUC0-∞ of etanercept between the two products are within the pre-specified criteria of 90% CI range of 0.80 -1.25 for bioequivalence (90% CI of the difference: AUC0-tlast: 88-95%, AUC0-∞: 87-94%, Cmax 98-109%). Equivalence is further supported by Ctrough data from the confirmatory study in psoriasis patients.

In the Phase III trial GP15-302, equivalence regarding efficacy between the biosimilar etanercept product Erelzi and the reference product Enbrel, was shown for the primary endpoint PASI75 responder rates at Week 12, which was well within the predefined margins of equivalence of -18% to +18% in the per protocol analysis (mean difference-2.3, 95% CI -9.85%, 5.30%). Similar results were obtained in the full analysis set, including all randomised subjects. Also for the –more sensitive- key secondary outcome, the percentage of change from baseline in PASI scores up to 12 weeks of treatment the equivalence criteria of +/- 15% were met (difference of the means -0.64, 95% CI -3.47, 2.20). The primary and key secondary outcomes were further supported by other secondary outcomes like Physician's Global Assessment, PASI50 and PASI90, and Quality of Life outcomes.

Maintenance of efficacy was shown up the 52 weeks for continuous treatment of Erelzi and Enbrel from baseline, as well as in the switching groups.

3.3. Uncertainties and limitations about favourable effects

There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance (see section 3.7. Benefit-risk assessment and discussion).

3.4. Unfavourable effects

The overall rate of adverse events was similar for Erelzi and Enbrel throughout the study (At week 12: 37.5% for Erelzi and 36.0% for Enbrel). No unexpected adverse events that were not already known for Enbrel were observed.

The main adverse events were infections, which were all rated as non-serious. Overall, the rate of infections was similar between Erelzi and Enbrel (about 17-19%) up to Week 52.

Injection Sites Reactions were more common for Enbrel (14.2%) than for Erelzi (4.9%) (TP1). None of them were serious.

The rates of ADA formation were low and transient for Enbrel (less than 2%). No ADAs were detected for continued Erelzi treatment in the Phase III trial.

3.5. Uncertainties and limitations about unfavourable effects

There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance (see section 3.7. Benefit-risk assessment and discussion).

3.6. Effects Table

Table 38 - Effects Table for Erelzi for the treatment of moderate to severe plaque-type psoriasis (TP1 – baseline to Week 12; final database lock: 30-July-2015.

Effect	Short Description	Unit	Erelzi treatment	Enbrel	Uncertainties/ Strength of evidence	References
Favourable Effects						
PASI75	PASI 75 response at week 12, primary endpoint	%	73.4	75.7	Difference in response rates (per protocol): -2.3 (95% CI -9.85; 5.30) Equivalence margins of -18% and +18% were met.	(1)
PASI	% change from baseline at week 12	%	-56.1	-55.8	LS Mean difference: -0.64, 95% CI -3.47, 2.20 Equivalence margins of -15% and +15% were met.	(1)
Unfavourable Effects (TP1)						
Infections		%	18.6	16.9	No serious infections were reported	(1)
ADA	Anti-drug antibodies (Week 12)	%	0	1.9%	ADAs were non-neutralizing and often transient. Differences are not considered clinically	(1)

Effect	Short Description	Unit	Erelzi treatment	Enbrel	Uncertainties / Strength of evidence	References
					meaningful	
Injection Site Reactions		%	4.9	14.2	None of these were serious	(1)

Abbreviations: ADA= anti-drug antibody, CI: confidence interval, LS= least square, PASI: psoriasis area and severity index
Notes: (1) Study GP15-302

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For a biosimilar, the benefit-risk balance is derived from the reference product, provided that the totality of evidence collected from the quality, non-clinical, and clinical data package supports the biosimilarity of both products.

With regard to analytical similarity, high similarity is demonstrated in several respects.

Comparable binding and activity of Erelzi and Enbrel has been shown for most parameters. Where differences were observed (ADCC), these have been appropriately addressed and it is not expected that these would translate into clinical differences. The non-clinical data supports biosimilarity of Erelzi and Enbrel.

From the clinical pharmacokinetics point of view, comparable bioavailability was not formally shown using nominal doses in the first study (Study GP15-101) comparing Erelzi and EU/Enbrel. However, in the Study Analytical Plan, it was pre-defined that an analysis using adjusted dose (actual dose received by subject) can be performed in case comparable bioavailability using nominal dose is not shown. When the primary analysis was repeated using actual dose administered (calculated from the pre-/post-injection PFS weight difference) and added as a covariate in the ANOVA model, the lower limit for $AUC_{0\text{-tlast}}$ achieved the required limit of 0.80 (i.e. 0.8037). Using the same study design, in the repeated study (GP15-104), the primary PK parameters C_{max}, $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-}\infty}$ of etanercept between the two products are within the required 90% CI range of 0.80 -1.25. However, the upper limits of the 90%CI for AUC exclude 1.0, indicating a lower exposure of Erelzi compared to that of Enbrel/EU.

It was adequately justified that the estimated lower exposure (i.e that the 90% CI for AUC did not include 1 and AUC was statistically significant lower for Erelzi than for Enbrel) does not preclude biosimilarity. The results of the pivotal pharmacokinetic study showing 90%CI for AUC within the required range of 0.80-1.25, however with exclusion of 1, but with similar tmax and t1/2, suggest comparable clearance. The similarity in clearance indicates the absence of intrinsic differences between the test and reference product. This is further supported by the observed similar plasma exposure in patients upon multiple dosing treatment with etanercept in the clinical study GP15-302.

Regarding clinical efficacy, therapeutic equivalence was evaluated in plaque psoriasis, which is considered a sensitive model to demonstrate equivalence. Altogether, it is concluded that therapeutic equivalence has been shown in the psoriasis model.

3.7.2. Balance of benefits and risks

The B-R balance is considered positive. Similarity has been adequately shown based on the totality of data from Quality, non-clinical and clinical perspective.

3.8. Conclusions

The overall B/R of Erelzi is positive.

4. Recommendations

Outcome

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

Rheumatoid arthritis

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

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

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

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

Juvenile idiopathic arthritis

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

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

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

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

Psoriatic arthritis

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

Axial spondyloarthritis

Ankylosing spondylitis (AS)

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

Non-radiographic axial spondyloarthritis

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

Plaque psoriasis

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

Paediatric plaque psoriasis

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

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

Prior to launch of Erelzi in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Erelzi is marketed, all healthcare professionals who are expected to prescribe Erelzi have access to the following educational package:

- **Educational materials** for healthcare professionals and patients to address the risk of medication errors and 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 Erelzi is not for use in children and adolescents weighing less than 62.5kg
    - Instructional materials to share with patients (i.e. Instructions for use provided in the Patient Leaflet)
- **The patient alert card** shall contain the following key messages:
    - A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Erelzi
    - That treatment with Erelzi may increase the potential risks of: opportunistic infections and tuberculosis (TB) and congestive heart failure (CHF)
    - Signs or symptoms of the safety concern and when to seek attention from a HCP
    - Contact details of the Erelzi prescriber
    - The importance to record the brand name and batch number

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

Not applicable.