22 March 2018
EMA/223369/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Zessly

International non-proprietary name: infliximab

Procedure No. EMEA/H/C/004647/0000

Note

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

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List of abbreviations

%CV	Percent coefficient of variation
%RE	Percent relative error
Ab	Antibody
Abs	Absolute
ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC-SE	Analytical Ultracentrifugation-Sedimentation Equilibrium
BL	Baseline
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
CDC	Complement-Dependent Cytotoxicity
CGE	Capillary Gel Electrophoresis
CHO	Chinese Hamster Ovary
CI	Confidence Interval
C_{max}	Observed serum drug concentration prior to the end of infusion
C_{trough}	Observed pre-dose trough serum drug concentration
CPP	Critical Process Parameter
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
DA	Disease activity
DAS	Disease activity score
DAS28-CRP	Disease Activity Score-28; 4 components based on hs-CRP

DBP	Diastolic BP
DCT	Data collection tool
DIP	Distal interphalangeal
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic Acid
EBV	Epstein Barr Virus
ECG	Electrocardiogram
ECL	Electrochemiluminescent
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
EOT	End of treatment
ESI MS	Electrospray Ionisation Mass Spectrometry
ET	Early termination
EU	European Union
EULAR	European League Against Rheumatism
Fab domain	Fragment antigen binding domain
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
G0F	N-linked glycan with zero terminal galactose residue
G1F	N-linked glycan with one terminal galactose residue
HAQ-DI	Health Assessment Questionnaire -Disability Index
HBV	Hepatitis B virus
H chain / HC	Heavy chain
HILIC	Hydrophilic Interaction Liquid Chromatography
iCE	Imaged Capillary Electrophoresis
ICH	International Conference on Harmonisation
ID	Identification
IgG1	Immunoglobulin G 1
IP	Investigational product
IRR	Infusion-related reaction

ITT	Intent-to-Treat
IV	Intravenously administered
IWRS	Interactive web-based response system
LC	Liquid Chromatography
L chain / LC	Light chain
LD	Last dose
LLOQ	Lower limit of quantification
mAB	Monoclonal Antibody
MS	Mass Spectrometry
NAb	Neutralizing antibody
NC	Not calculated
NCI	National Cancer Institute
ND	Not done
NS	No sample
NSAID	Nonsteroidal anti-inflammatory drug
OBS	Observed data
PAAP	Patient's Assessment of Arthritis Pain
PD	Pharmacodynamic(s)
PE	Physical examination
PGA	Patient's Global Assessment of Arthritis
PGAA	Physician's Global Assessment of Arthritis
PIPD	Potentially important protocol deviation
PMDA	Pharmaceuticals and Medical Devices Agency
PK	Pharmacokinetic(s)
PP	Per-Protocol
PT	Preferred term
QC	Quality control
RA	Rheumatoid arthritis
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan

SD	Standard deviation
SDS-PAGE	Sodium Dodecyl Sulfate - Polyacrylamide Gel Electrophoresis
SE	Standard error
SE-HPLC	Size exclusion – High Performance Liquid Chromatography
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedure
SPR	Surface plasmon resonance
SW	Switch (of study drug)
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor-α
mTNF-α	Transmembrane TNF-α
TP1-3	Treatment Period 1-3
TX	Treatment administration (study dosing)
US	United States
USPI	US Prescribing Information
UV	Ultraviolet
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sandoz GmbH submitted on 21 April 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Zessly, 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

Zessly, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated.

Adult Crohn's disease

Zessly is indicated for:

- treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Paediatric Crohn's disease

Zessly is indicated for treatment of severe, active Crohn's disease, in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Ulcerative colitis

Zessly is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis

Zessly is indicated for treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

Ankylosing spondylitis

Zessly is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis

Zessly is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.

Zessly should be administered

- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated

Infliximab 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.

Psoriasis

Zessly is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, 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: Remicade, 100 mg, Powder for concentrate for solution for infusion
- Marketing authorisation holder: Janssen Biologics B.V., NL
- Date of authorisation: 13-08-1999
- Marketing authorisation granted by:
  - Community
- Marketing authorisation number: EU/1/99/116/001-005

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

- Product name, strength, pharmaceutical form: Remicade, 100 mg, Powder for concentrate for solution for infusion
- Marketing authorisation holder: Janssen Biologics B.V., NL
- Date of authorisation: 13-08-1999
- Marketing authorisation granted by:
  - Community

  Marketing authorisation number: EU/1/99/116/001-005

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Remicade, 100 mg, Powder for concentrate for solution for infusion
- Marketing authorisation holder: Janssen Biologics B.V., NL
- Date of authorisation: 13-08-1999
- Marketing authorisation granted by:
  - Community
- Marketing authorisation number(s): EU/1/99/116/001-005

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 15 November 2012, 25 July 2013, 19 December 2013, 24 July 2014 and 17 December 2015. The Scientific Advices 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: Nithyanandan Nagercoil Co-Rapporteur: Svein Rune Andersen

- The application was received by the EMA on 21 April 2017.
- The procedure started on 18 May 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 August 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 4 August 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 16 August 2017.
- During the meeting on 14 September 2017, 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 19 December 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 January 2018.
- During the PRAC meeting on 8 February 2018, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 February 2018, 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 26 February 2018.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 March 2018.
- During the meeting on 22 March 2018, 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 Zessly on 22 March 2018.

2. Scientific discussion

2.1. Problem statement

Tumour necrosis factor-alpha (TNF-α) plays an important pathogenic role in multiple inflammatory diseases. Inhibition of the TNF receptor-ligand interaction by TNF antagonist therapy results in down regulation of mediators of the inflammatory cascade and is associated with clinical improvement of inflammatory diseases such as Rheumatoid Arthritis, Psoriasis, and Inflammatory Bowel Disease among others.

Zessly has been developed as a similar biological medicinal product, with the TNF-α inhibitor Remicade (infliximab) as the reference medicinal product.

About the product

Zessly contains the active substance infliximab. Infliximab is a recombinant chimeric IgG1 kappa monoclonal antibody (mAb) composed of complementarity-determining regions derived from mouse anti-human TNF-α mAB and framework, and constant regions derived from human Immunoglobulin G 1 (IgG1). Zessly is produced using a recombinant Chinese Hamster Ovary cell culture process and is capable of binding to human TNF in a dose-dependent manner and neutralizing its effects.

Zessly finished product is supplied as a sterile, white lyophilised powder for concentrate for solution for infusion. Zessly is presented as a vial containing 100 mg infliximab, to be administered via intravenous infusion, at the same dose as Remicade.

The proposed clinical use of Zessly is identical to that of the reference medicinal product, Remicade. Zessly is proposed for the treatment of adult patients with Rheumatoid arthritis, Crohn's disease, Ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis; and the treatment of paediatric patients with Crohn's disease and Ulcerative colitis.

Type of Application and aspects on development

This Marketing Authorisation Application is an abridged application for a similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC as amended by Directive 2004/27/EC.

Zessly was developed as a similar biological medicinal product to Remicade. The European reference medicinal product is Remicade 100 mg powder for concentrate for solution for infusion, MA numbers EU/1/99/116/001-005, MA holder Janssen Biologics B.V., NL, authorised 13 August 1999.

The applicant received Scientific Advice from the CHMP as outlined below:

Interactions with competent authorities	**Topics mainly discussed**	**Date of final letter**
EMA – Initial scientific advice EMEA/H/SAWP/2440/1/2012/III	Sufficiency of the analytical and functional characterization program and the nonclinical *in vivo* study program; Design of clinical PK study GP11-101 and confirmatory efficacy and safety study GP11-301, including alternative clinical approaches (PK study or efficacy/safety study in Crohn's disease, if study in rheumatoid arthritis is insufficient or not deemed acceptable)	15 November 2012
FDA and EMA - Parallel qualification advice EMEA/H/SAB/036/1/Q/2013	Novel modelling approaches for clinical comparative studies of biologic therapies in rheumatoid arthritis with the intent of defining sensitive endpoints as applied to biosimilarity assessment.	25 July 2013
CHMP/EMA – First Follow-Up Scientific Advice procedure EMEA/H/SA/2440/1/FU/1/2013/II	Design of confirmatory efficacy and safety study in rheumatoid arthritis patients (study GP11-301): enrolment criteria, concomitant medication, dose escalation, primary endpoint,	19 December 2013

	deduction of equivalence margin, safety and immunogenicity assessments.	
CHMP/EMA – Second Follow-Up Scientific Advice procedure EMEA/H/SA/2440/1/FU/2/2014/III	Sufficiency of strategy to show analytical and functional similarity, including statistical tools for assessment of quality attributes; Sufficiency of the *in vivo* nonclinical program; Results of PK study GP11-101 and consequent acceptability to start efficacy/safety study	24 July 2014
CHMP/EMA – Third Follow-Up Scientific Advice procedure: EMEA/H/SA/2440/1/FU/3/2015/II	Extrapolation rationale; Efficacy/safety study GP11-301: asymmetric equivalence margin, missing data handling for ACR20 and DAS28	17 December 2015

2.2. Quality aspects

2.2.1. Introduction

Zessly (infliximab), has been developed as a similar biological medicinal product, with Remicade as the reference medicinal product. The biosimilar development was initially carried out by Pfizer. Sandoz acquired the rights for seeking marketing authorization and commercialization of Zessly in the European Economic Area (EEA). Approved comparator products are referred to by regional source, i.e. EU-authorized Remicade (referred to as Remicade-EU in tables and figures) and US-licensed Remicade (referred to as Remicade-US in tables and figures).

The finished product is presented as a powder for concentrate for solution for infusion containing 100 mg of infliximab as active substance.

Other ingredients are: disodium succinate hexahydrate, succinic acid, sucrose and polysorbate 80.
The product is available in a type 1 glass vial with rubber stopper and aluminium crimp protected by a plastic cap.

2.2.2. Active Substance

General Information

Infliximab is a recombinant chimeric IgG1 kappa monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human TNF-α mAB and framework, and constant regions derived from human IgG1. Zessly is produced by a recombinant Chinese Hamster Ovary (CHO) cell culture process and is capable of binding to human TNF in a dose dependent manner and neutralizing its effects.

Zessly has two identical heavy (H) chains and two identical light (L) chains, covalently linked with four inter-chain disulfide bonds. The N-linked glycosylation consensus sequence in the CH2 region is essentially fully occupied with asialo, core-fucosylated, complex-type biantennary N-linked glycans with zero and one terminal galactose residues, abbreviated as G0F and G1F, respectively. C-terminal lysine is observed at minor

levels in the mature, secreted form of Zessly, presumably due to incomplete intracellular processing by CHO cellular proteases. The penultimate glycine residue is the predominant H chain C-terminus in Zessly.

Manufacture, characterisation and process controls

Manufacturing process and process controls

Zessly active substance is manufactured by Boehringer Ingelheim Pharma GmbH & Co KG, Germany. The manufacturing process for the active substance uses a recombinant CHO cell line that contains the deoxyribonucleic acid (DNA) encoding the sequence for infliximab and is grown in suspension culture using chemically-defined, animal-derived component-free media. Cells from a vial of the working cell bank (WCB) are thawed, and the culture is progressively expanded until the production bioreactor is inoculated. Conditioned medium containing the active substance is generated in the production bioreactor, with maximum cultivation time established by LIVCA. A description and corresponding acceptance criteria for handling of cell cultures to the next step in the culture expansion process including the production bioreactor and the precise ending of the production step have been provided. The criticality of these process parameters has also been evaluated. The production bioreactor culture is harvested, followed by clarification by centrifugation and depth filtration to remove cells and debris.

Information has been provided for control of the inoculum cultures during the expansion phase, to ensure that the maximum generation number is not exceeded during a production run and this has been sufficiently represented by the validation studies.

After the harvest step, the active substance is purified using a series of chromatography and filtration steps and a virus inactivation step. Excipients are added to achieve the final formulation of the active substance, followed by final filtration.

Information on the column sizes, buffer volumes and acceptable flow rates have been given for the purification process.

Control of materials

Details of the various solutions and media used in the manufacturing process are described. No animal-derived materials or excipients are used in the establishment of the MCB, WCB, active substance or finished product manufacturing. Both compendial and non-compendial raw materials are used during production of Zessly. The water for injections (WFI) meets Ph. Eur. requirements. Information and testing for raw materials is given.

The host cell line used in Zessly manufacturing is a CHO cell line. The host MCB was tested extensively to confirm the absence of adventitious contaminants. Gene and vector construction have been described and are satisfactory. Development of the production cell line, including cloning and expansion, are detailed. The amino acid sequence of Zessly was confirmed with 100% sequence coverage.

Details of generation of the MCB in accordance with ICH Q5D guidelines and GMP requirements have been provided. Clonality of the cell line was confirmed in the MCB. Details of testing for the MCB (in line with ICH Q5A, ICH Q5D and Ph. Eur. where appropriate) are given, including purity and viability testing, identity testing for the cell line, microbiological safety tests and virus safety tests (*in vitro* and *in vivo* assays), which were satisfactory.

A working cell bank was established from the MCB. The purity of the Zessly WCB cells was confirmed, with no detectable adventitious microbial or viral agents introduced into the WCB.

The MCB and WCB have been assigned a shelf life from the date of retesting.

The proposed age for the limit of *in vitro* cell age (LIVCA) for the Zessly cell line and production process has been justified. The Zessly end-of-production LIVCA cells were tested for purity and shown to be free of viral and bacterial contamination. End-of-production cells demonstrated genotypic consistency compared with MCB and WCB. Phenotypic characteristics also demonstrated stability across process validation batches and clinical batches.

Control of critical steps and intermediates

For the control of the Zessly active substance manufacturing process, Critical Process Parameters (CPP), non-CPP, Critical Material Attributes and in-process tests have been defined for each step in the process. The criticality is associated with the impact on the defined critical quality attribute (CQA) of the Zessly. CQAs for Zessly are given and are satisfactory. Process controls have been defined and are based on development experience and risk assessments, which are sufficiently detailed in the submission. Results from these assessments and studies were used in the determination of appropriate process parameter and material attribute process validation (PV) control limits and process performance and product quality PV acceptance criteria. The control strategy is satisfactory.

Process validation

The active substance manufacturing process has been validated. All release results met acceptance criteria and the proposed commercial specifications. Consistency of each of the unit operations was demonstrated in the validation studies. Validation of the purification process has been conducted to confirm that each of the chromatography and filtration steps show consistent product yield and reduce the impurity content to an acceptably low level in the active substance. The impurities include e.g. host cell proteins (HCP), DNA or elemental impurities. All impurities were cleared with an acceptable safety margin, based on worst-case assumptions.

In-process pool hold times were validated to demonstrate biochemical stability of Zessly over defined periods of time. The hold study confirmed that no significant changes were observed. Sanitary processing of the process equipment and product intermediates used in the manufacturing of Zessly was demonstrated.

Shipping qualification has been provided for frozen active substance.

Manufacturing process development

No changes were made in the manufacturing scale during process development. Process performance was evaluated during several large-scale manufacturing campaigns. All clinical and process validation batches were manufactured at the commercial site and scale (Boehringer Ingelheim, Biberach, Germany). Throughout process development, the purification process has remained largely unchanged. The formulation of active substance was the same throughout process development. Comparability was demonstrated between the development / clinical batches and process validation batches.

The production bioreactor was evaluated in design of experiments (DOE). Process control ranges were determined based on characterisation studies for the production bioreactor and harvest steps. For the downstream process, risk evaluation was performed to determine the focus for the process characterization studies.

Characterisation

Extensive characterisation of Zessly included primary structure, post-translational modifications, charge and size heterogeneity, higher order structure and biological activity. The results demonstrate that Zessly has the expected structure and functional properties.

Primary structure analysis confirmed the expected amino acid sequence. Disulfide bonds with the correct linkages were identified.

The site of N-glycosylation was confirmed with G0F and G1F as the major N-linked glycans. Additional minor and trace-level N-linked glycans were identified. The relative abundances of the respective glycopeptides are consistent with the glycan mapping results.

Low levels of oxidation, deamidation and succinimide intermediate formation were detected.

Charge heterogeneity was investigated, with a main pI value of approximately 7.6. Additional peaks represent additional isoforms, the acidic variants and basic variants. Characterisation of the isolated main peak showed the predominant charge isoform corresponds to the 4-chain antibody with both H chains missing C-terminal lysine, and one H chain containing G0F and the other H chain containing either G0F or G1F N-linked glycans.

Higher order structure was characterised using several analytical methods. The level of high molecular mass species (HMMS) including aggregates was analysed showing a predominant peak consistent with the monomer molecular mass, low levels of HMMS and trace levels of low molecular mass species (LMMS).

Zessly is designed to bind to soluble TNF (sTNF) and membrane-bound TNF (mTNF) targets, resulting in a blockade of TNF effects. Functional cell-based assays and binding assays were developed to characterize Zessly. Biological activity was assessed by inhibition of sTNF-induced apoptosis in a cell based apoptosis assay. Inhibition occurs in a dose-dependent manner with activity compared to reference material. The FcγRIIIa reporter gene assay (RGA) was used to assess infliximab-induced FcγIIIa activation and signalling event. An FcRn binding assay was developed and applied to assess the binding to the FcRn receptor.

Forced deamidation studies, photodegradation studies and thermal degradation studies were also carried out as part of the characterisation.

Levels of process-related impurities were tested during manufacture of full scale batches and satisfactory clearance was shown.

Specification

The drug substance specification includes test methods for appearance (clarity, coloration), pH, protein concentration, glycan profile, charge heterogeneity, identity, purity, product-related impurities, sterility, endotoxins, and biological activity.

Analytical methods

The proposed specification for Zessly has been provided with information on the analytical methods used for release and shelf life. Product-specific, non-compendial methods, have been used for assessing the protein concentration, glycan profile, charge heterogeneity, identity, purity, product-related impurities, and biological

activity. Some of the limits should be reviewed and revised based on further batch data (see "Recommendations for future quality development").

Compendial methods are used to determine appearance (clarity, coloration), pH, bioburden and endotoxin levels.

Summary validation reports for non-compendial methods were provided.

The purpose of the cell based potency assay is to measure the *in vitro* functional activity. The assay is based on the inhibition of tumor necrosis factor alpha (TNFα)-induced cell apoptosis by Zessly in a cell line that expresses TNFα receptors. The number of apoptotic cells in a population is proportional to the caspase-3 and caspase-7 activities. The functional activity of Zessly test samples is determined by comparison to Zessly reference material.

Batch analysis

Batch data was provided for several Zessly active substance batches manufactured at the commercial scale at Biberach site and used for non-clinical studies, clinical studies, stability and process validation studies. Batch analysis showed consistent production of active substance and all results were within the acceptance criteria.

The initial strategy for setting the specification limits for release and shelf life of active substance was not accepted. Upon request, the specification limit strategy has been revised and the limits have been tightened. The specification limits are considered acceptable, however the Applicant should commit to re-evaluate some of the specifications once further experience has been gained (see "Recommendations for future quality development").

Reference Standards or Materials

The existing Primary Reference Material and Working Reference Material have been suitably manufactured and characterised for their purpose. A protocol for qualification of future working reference materials has been described, listing the methods to be used.

All future working reference material lots will be calibrated against the primary reference material and the potency (by cell-based bioassay) with be monitored on a regular basis, to ensure that long-term drift or shift in relative potency of the released commercial materials is unlikely.

Container closure system

The information on the active substance container closure systems has been supplied. A review of available safety data of elemental impurities has been conducted in accordance with the ICH Guideline for Elemental Impurities Q3D. Compatibility with the active substance has been assessed.

Stability

Active substance stability has been demonstrated under long term conditions at the recommended conditions using clinical batches of active substance manufactured at the proposed commercial scale and site. The stability studies monitored the biological activity, protein concentration, purity, identity, appearance and general quality attributes, including stability-indicating methods.

Stability data obtained from accelerated storage temperature condition are also given in support of the shelf life claim and to support temporary excursions. In addition, active substance batches were stored at thermal stress conditions.

A temperature cycling study was included. All data remained within the commercial acceptance criteria and no trends were noted in the active substance exposed to freeze/thaw cycles.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is presented as a powder for concentrate for solution for infusion. It is supplied in a glass vial sealed with a stopper and an aluminium crimp protected by a plastic cap. The finished product contains no preservatives and is intended for single use.

After reconstitution with 10mL sterile water for injections, the concentration of the finished product is 10 mg/mL. The formula contains succinate buffer, sucrose and polysorbate 80. The reconstituted product is further diluted with sterile 0.9% sodium chloride for administration by intravenous infusion.

Comparative information on the reference product is provided. The reference product, Remicade, is supplied as a 100mg lyophilisate in a 20 mL vial, and its excipients are listed as sucrose, polysorbate 80, monobasic sodium phosphate and dibasic sodium phosphate. There is a difference in the buffering system between Zessly and Remicade, but not in the theoretical strength of the reconstituted active substance, nor the nature of the stabilizer or the surfactant.

Pharmaceutical Development

Critical quality attributes for Zessly have been identified. The attributes are as expected for a lyophilized monoclonal antibody. Data indicate that although the succinate buffering system selected is different from that of the reference medicinal product (phosphate), the formulation could be expected to provide adequate stability of the active substance. In the freeze-dried finished product vial, the formulation could be expected to provide adequate stability during storage when protected from light. The choice and concentration of excipients has been adequately justified from a safety and efficacy perspective.

Process development has included a combination of small-scale studies with univariate and multivariate process parameter assessments, and commercial scale verifications. CPPs and non-CPPs are given.

Container closure integrity is controlled.

Data from assessment of robustness to process excursions have been provided and indicate that the formulated finished product is tolerant to the in-process conditions and to foreseeable excursions outside the normal operating ranges.

Data on stability of reconstituted finished product and of reconstituted finished product diluted in saline for infusion has been provided to justify a hold of reconstituted finished product for up to 24 hours at 2 - 30°C and a hold of the infusion solution at minimum or maximum recommended dilutions for 24 hours at room temperature (≤30°C) with or without light exposure.

A range of infusion preparation and administration contact materials have been stated as being compatible with the intended administration of Zessly. Additional data has been presented to support this claim.

Manufacture of the product and process controls

The manufacturers have appropriate authorisations for the manufacturing activities.

The release site is Sandoz GmbH Schaftenau, Biochemiestraße 10, 6336 Langkampfen, Austria.

The finished product manufacturing process consists of thawing of the formulated active substance, mixing, filtration, filling and lyophilisation.

The batch formula has been provided in sufficient detail. The validated duration of aseptic filling and duration of sterilizing filtration has been specified. The cumulative hold time has also been defined, based on validation data. The manufacturing process and controls have been appropriately described.

Sufficient data has been supplied to support finished product handling as described within the validated holding times. Controls for the lyophilisation are adequately defined in line with the process development data.

The microbial control strategy has been described. Data provided, including media holds and fills, support that microbial control is achieved. Process validation has been sufficiently performed and described to demonstrate a robust process with validated hold times addressing physicochemical and microbial control, with demonstrated homogeneity of the lyophilised finished product.

Validation data has been provided demonstrating adequate microbial retention capacity of the sterilizing filter.

Data to support the intended shipping conditions have been provided and are acceptable.

No significant changes have been made to the finished product manufacturing process throughout development.

In line with the recommendations of ICH Q3D, elemental impurities in the finished product have been addressed. A summary of the risk assessment is provided.

The control of excipients is adequately described and seems appropriate.

Product specification

The specifications include general tests (e.g. coloration, clarity, pH, osmolality, residual moisture, protein concentration, particulate matter, microbiology), and product-specific tests for identity, purity, content, charge heterogeneity, product related impurities and potency.

The initial approach to setting release acceptance criteria for numerical attributes was not deemed suitable. Upon request the Applicant provided additional justifications and tightened the acceptance limits. In addition, the applicant commits to re-evaluate the specifications once more experience has been gained. (see “Recommendations for future quality development”).

Analytical methods

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

Batch analysis

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

Reference Materials

See the active substance section. The same reference materials are used for the active substance and finished product.

Stability of the product

The proposed shelf life is 48 months when stored at the recommended temperature of 2 to 8°C and a single period of up to 6 months (but not exceeding the original expiration date) when stored up to a maximum temperature of 30°C. The shelf life claim is based on a stability program for both recommended and alternative temperatures.

Stability data obtained from accelerated storage temperature condition are also presented in support of the shelf life claim, as well as data from thermal stress conditions and data covering thermal cycling.

The finished product batches used for the stability studies were produced with the intended commercial process and packaged in glass vials, which are the same as the proposed commercial packaging.

The stability data at 2 - 8°C and at 30 ± 2°C / 70 ± 10% RH indicate a stable finished product up to 48 months.

Data to support storage after reconstitution has been presented.

Photostability of naked finished product vials was carried out in accordance with ICH Q1B (option two) and the commercial acceptance criteria were met.

Biosimilar comparability exercise

An extensive comparability exercise has been performed between Zessly and both EU-authorized Remicade and US-licensed Remicade. Data from a sufficient amount of US-licensed Remicade batches, EU-authorized Remicade batches and Zessly were provided. Analyses on a subset of these batches are indicated in Table 1.

Table 1 Overview of the quality comparability exercise

Attribute		Analytical procedure	Comparability outcome
Primary structure and post-translational modifications	Amino acid sequence	LC/MS/MS – Peptide Mapping Peptide Mapping/Edman Degradation	Identical amino acid sequence. 100% coverage.
	Molecular mass and size	ESI-MS	Comparable molecular mass and size at the intact molecule level.
	Post-translational modifications	ESI-MS ESI-MS– Subunit Analysis	Identical primary structure & comparable post-translational modifications at the intact molecule level. Identical primary structure & comparable identity and location of post-translational

			modifications at the subunit/domain level.
		LC/UV/MS – Peptide Mapping	Identical primary structure & comparable identity and location of post-translational modifications at the peptide level.
Biological activity Fab domain: Binding TNF	Binding to sTNF and inhibition of sTNF response	Inhibition of apoptosis assay	Comparable binding to sTNF and inhibition of sTNF response.
		Inhibition of TNF-induced endothelial adhesion molecule expression	
	Binding kinetics to TNF	Binding to sTNF Target Antigen by SPR	Comparable binding kinetics to sTNF.
		Binding to Cell Surface TNF Antigen	Comparable binding kinetics to mTNF.
Biological Activity Fc Domain: ADCC activity	ADCC activity	Primary NK Cell ADCC Assay	Comparable ADCC activity for Zessly
		FcγRIIIa Reporter Gene Assay	Overlapping biological activity
		Binding to FcγRIIIa Receptor by SPR (both receptor types)	Comparable binding to FcγRIIIa
	Dose-dependent response curve in bioassay	Mixed Lymphocyte Reaction Assay (all 3 FcγRIIIa phenotypes)	Comparable dose-dependent response.
		Natural Killer Cell Binding assay (all 3 FcγRIIIa phenotypes)	Comparable dose-dependent binding.
	Binding kinetics	Binding to FcγRI by SPR	High affinity binding kinetics. Zessly partly below infliximab range (EU & US).
		Binding to FcγRIIa (both receptor types) by SPR	Comparable/overlapping binding kinetics. Binding affinity (K_D) >2500 nM
		Binding to FcγRIIIb by SPR	Binding affinity (K_D) >2500 nM
Biological Activity Fc Domain: CDC activity	CDC activity	CDC assay	Comparable CDC activity.
		C1q ELISA assay	Comparable C1q binding.
Biological Activity Fc Domain: FcRn binding	Binding kinetics	Binding to FcRn by SPR	Overlapping binding kinetics. Zessly partly below infliximab range (EU & US). Low FcRn binding batches of Zessly used in clinical studies.
N-Linked Glycan Structure: % Total Afucosylation	Range of total afucosylation	HILIC with fluorescence detection	Comparable range of %total afucosylation.
N-Linked Glycan Structure: % Terminal Galactosylation	Range of terminal galactosylation	HILIC with fluorescence detection	Comparable range of %terminal galactosylation.
N-Linked Glycan Structure	N-linked glycan distribution profile, structure, composition and glycosidic linkages	HILIC/MS	Comparable relative proportions of major level N-linked glycans. Differences for alpha-Gal and NeuGc in infliximab (not in Zessly). Minor differences not considered clinically relevant.
		Exoglycosidase	Comparable N-linked glycan structural

		Digestion/HILIC	assignments and glycosidic linkages.
		Sialic Acid Assay	Difference in sialic acid species for Zessly is not considered clinically relevant.
Charge Heterogeneity	Ranges of %acidic, %main, and %basic species	iCE	The range of %acidic species comparable. The range of %main and % basic species different. All %main higher in Zessly and all % basic results lower for Zessly. Difference in C-terminal lysine (lower in Zessly) not considered clinically relevant.
		Carboxypeptidase B/ iCE	Comparable range of %acidic, %main and %basic after removal of C-terminal lysine.
	Major and minor charge isoforms	Cation Exchange-HPLC profile characterized by MS	Comparable major and minor charge isoform species. Differences in C-terminal lysine and sialylated glycoforms not considered clinically relevant.
Product Purity	Ranges of %monomer and %HMMS	SE-HPLC	Comparable ranges of %monomer and %HMMS.
	Ranges of %HC + LC and %fragments	CGE (reducing)	Overlapping but slightly different ranges of %HC + LC and %fragment. Slightly higher fragment content in Zessly batches. Difference did not impact biological activity and not considered clinically relevant.
	Banding pattern	SDS-PAGE (Total protein staining and Western blotting)	Comparable banding patterns.
	Dissociation constant for self-association	AUC-SE	Comparable dissociation constants for self-association.
Protein Concentration	Protein Concentration	UV spectroscopy	Overlapping protein concentration Slightly higher concentration for some Zessly batches is not considered clinically relevant.
Disulfide Bonds	State of cysteines and disulphide bonds	Sulfhydryl Analysis	Comparable, trace-level of unpaired protein sulfhydryl groups.
		LC/MS – Non-reduced Peptide Mapping	Identical disulfide bond connectivity.
Higher Order Structure	Secondary structure	Far-UV Circular Dichroism (CD) Fourier Transform Infrared (FTIR)	Comparable secondary structure.
	Tertiary structure	Near-UV CD Fluorescence Spectroscopy Intrinsic Fluorescence	Comparable tertiary structure.
	Crystal structure	X-Ray Crystallography	Comparable crystal structures.
Forced degradation	Degradation profiles at elevated temperature, photo exposure and forced deamidation	Stability indicating methods incl. bioassay, UV spectroscopy, LC/MS – Peptide mapping, and particles analysis	Comparable degradation profiles. Rate of degradation comparable for lyophilised product, but lower rate of thermal degradation for reconstituted Zessly product (different buffer to infliximab).

The comparability testing included analysis of primary structure and post-translational modifications, biological activity, N-linked glycans, charge heterogeneity, product purity, protein concentration, disulfide bonds, higher order structures and comparative forced degradation studies of Zessly, EU-authorized Remicade and US-licensed Remicade. Formulation differences between Zessly and the reference product were shown not to impact the analytical studies. Details of methods used in the characterisation and forced degradation studies, including method qualification or validation (as appropriate), are given. Methods applied

for the biological activity assays have been described in-depth and summaries of the qualification reports have been provided.

Primary, secondary and tertiary structure analysis demonstrated that Zessly, EU-authorized Remicade and US-licensed Remicade were comparable. Purity analysis shows comparable profiles for the predominant monomer peak, with only low levels of HMMS. Product-related fragment species were slightly higher in Zessly, but this did not impact the bioactivity of Zessly compared to EU-authorized Remicade and US-licensed Remicade. The mean protein concentration of Zessly is slightly higher than the mean value for EU-authorized Remicade, but there is no impact of this higher protein concentration of Zessly in vials in terms of the total dose used in clinical studies, compared with EU-authorized Remicade.

The three major N-linked glycoforms are the same with similar proportions in all 3 products. The abundance of some minor/ trace glycoforms show differences, although further information has confirmed that these slight differences are unlikely to have any clinical impact. The levels of %total afucosylation were comparable. Slight differences between FcRn binding did not have an impact on PK and half-life.

Complex biantennary structures containing alpha-Gal were only detected in the EU-authorized Remicade and US-licensed Remicade products; this is due to the use of different cell lines (SP2/0 for Remicade, compared with CHO cell line for Zessly). Zessly contains sialic acid as NeuAc, whereas EU-authorized Remicade and US-licensed Remicade contain NeuGc. These minor differences did not appear to impact the *in vitro* biological activity assays.

Differences in charge heterogeneity were observed, with higher %main and lower % basic species in Zessly compared to EU-authorized Remicade and US-licensed Remicade. This was attributed to higher levels of C-terminal lysine observed in infliximab products, which is not considered to be clinically relevant, since C-terminal lysine is rapidly cleaved *in vivo*. Trace-levels of glycation were observed in all three products. Low levels of oxidation, deamidation and succinimide intermediate were detected in all 3 products. No differences were observed in the *in vitro* biological activity and therefore the differences in charge variants for Zessly compared to EU-authorized Remicade and US-licensed Remicade are not considered to be clinically relevant.

Zessly showed comparable binding and functional Fab domain activity to EU-authorized Remicade and US-licensed Remicade, in several different assays. This included comparable binding of the Fab domain of the molecule to TNF (by SPR) and binding to cell surface TNF antigen. Comparable sTNF binding and blockade of sTNF resulting in inhibition of apoptosis were demonstrated, as well as comparable inhibition of TNF-induced endothelial adhesion molecule expression. GP1111 showed comparable binding to mTNF target antigen, which is important as the binding of infliximab to mTNF is a prerequisite for the potential Fc effector function activity. Additional details have been provided for the biological activity assays.

In most cases, Zessly showed comparable binding and functional Fc domain activity to EU-authorized Remicade and US-licensed Remicade. Any differences detected were appropriately justified with regard to their potential impact on efficacy and safety.

ADCC effector function was shown to be comparable in several cell-based functional assays and binding assays, including a primary NK cell ADCC and an FcγRIIIa Reporter Gene assay. It is noted that Zessly results are at the lower end of the range in the FcγRIIIa Reporter Gene assay. Additional mixed lymphocyte reaction and NK cell binding assays showed comparability of biological function of the Fc domain. The CDC and C1q binding data showed similar results in the assays for Zessly, compared to EU-authorized Remicade and US-licensed Remicade.

Forced degradation studies supported the claim that Zessly, EU-authorized Remicade and US-licensed Remicade are comparable, for lyophilised finished product or reconstituted product under conditions of thermal stress, photodegradation and forced deamidation. The degradation rate was higher in EU-authorized Remicade and US-licensed Remicade under thermal stress for reconstituted product, but this is likely to be due to the different formulations of the products.

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

Adventitious agents

The cell bank and routine controls to detect and prevent viral adventitious agents are typical for a monoclonal antibody.

Viral clearance studies have been described and additional data have been provided showing the clearance values and cumulative $\log_{10}$ reduction values for each model virus. This confirms the viral clearance capacity of the purification process (which includes viral inactivation and removal steps).

Sufficient detail regarding the virus filtration model has been provided to complete an assessment that routine clearance can be reasonably assured.

Assurance that the cleaning process reliably inactivates resistant non-enveloped virus has been provided.

TSE issues

No animal derived materials or excipients are used in the culture of MCB and WCB and in Zessly active substance and finished product manufacturing.

Certificates of Compliance of Zessly MCB and WCB as well as confirmation of BSE/TSE Compliance of the Zessly active substance and finished product are provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results from 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.

An extensive comparability exercise has been conducted, demonstrating high similarity with the reference product Remicade at the quality level.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

Biosimilarity to the reference product has been satisfactorily demonstrated.

2.2.6. Recommendations 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:

- To re-evaluate specifications for active substance and finished product when further manufacturing experience has been gained.
- To implement testing for endotoxin for disodium succinate hexahydrate.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

Several assays were performed to establish how the biological activity of the Fab domain of Zessly compared to that of the reference products, EU-authorized Remicade and US-licensed Remicade. The number of batches was considered adequate. For the biosimilar, Zessly, on the basis of the endpoints provided, the binding kinetics profile for soluble TNF-α, binding to membrane-bound TNF-α, inhibition of apoptosis and inhibition of endothelial adhesion molecule expression were all shown to be similar to or within the range of that observed for both EU-authorized Remicade and US-licensed Remicade.

Studies were also performed to establish how the binding and biological activity of the Fc domain of Zessly compared to that of the reference products, EU-authorized Remicade and US-licensed Remicade; the first series of studies examined some of the pathways involved in ADCC and CDC effector function. The assay formats used are listed below.

- 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).
- Natural Killer (NK) cell binding assay
- The ability to initiate ADCC and CDC using suitable cell-based assays.

These assays were developed to support comparability and are also summarized in the above sections.

The number of batches evaluated in each assay was considered adequate. For the biosimilar Zessly the results were all shown to be similar to or within the range of that observed for both EU-authorized Remicade and US-licensed Remicade.

The binding of an antibody to FcγRIIIa on effector cells is the first step (and thus plays an important role) in mediating ADCC activity; hence, the binding affinity and kinetics for Zessly vs. EU-authorized/US-licensed Remicade to two receptor types of FcγRIIIa were compared. The FcγRIIIa (CD16) receptor is distributed on several cell types; however, there is ample evidence to suggest that natural killer (NK) cells expressing the

FcγRIIIa receptor are the major cell population which mediate ADCC activity. Hence, an *in vitro* assay utilising NK cells of multiple human donors with the same FcγRIIIa heterozygous genotype (effector cell) and target cells expressing mTNF was conducted and the ADCC activity for Zessly was compared to that of the reference products. Given the challenges and inherent variability associated with the use of primary cells from multiple donors, the Applicant also used a more precise and reproducible method to measure ADCC pathway activation, though it is accepted that the assay does not directly detect target cell lysis. This assay developed by Cheng and colleagues (2014) employed target cells stably expressing human membrane bound TNFα and effector cells stably transfected with FcγRIIIa and a luciferase reporter gene. The ability of infliximab to bind to mTNFα on the target cells and to FcγRIIIa on the effector cells result in the activation of the luciferase reporter gene in a dose-dependent manner.

Minor variations in the FcγRIIIa SPR results for the individual test samples of Zessly, EU-authorized Remicade and US-licensed Remicade were apparent, when compared to that observed for the Zessly reference material. However, the relative affinity for FcγRIIIa(both receptor types), the absolute affinity for NK cells with FcγRIIIa (all three phenotypes), the relative ADCC activity as determined using primary NK cells (FcγRIIIa heterozygous genotype) and the relative FcγRIIIa activation (via Reporter Gene Assay) afforded by the biosimilar, Zessly, were all shown to be similar to or within the range of that observed for both EU-authorized Remicade and US-licensed Remicade.

The binding of the Fc region of target-cell bound antibodies to C1q protein (complement) is the first step and thus plays an important role, in mediating CDC activity; hence, the binding of Zessly vs. EU-authorized/US-licensed Remicade to C1q protein from human serum was compared. In addition, the ability of the infliximabs to cause human-complement-mediated cell lysis (of cells expressing TNF-α) was compared. The range of values reported for the relative binding to C1q and the relative CDC activity of the biosimilar, Zessly were all shown to be similar to that observed for both EU-authorized Remicade and US-licensed Remicade.

To further characterise Fc effector function, the affinity of Zessly to FcγRI, FcγRIIa(both receptor types), FcγRIIIb and FcRn was determined using SPR technology and compared to that observed with the reference products, EU-authorized Remicade and US-licensed Remicade. Literature results suggest that the affinity of IgG1 molecules to FcγRI is relatively high; this was confirmed for infliximab. The Applicant has demonstrated that the affinity of Zessly for FcγRI was comparable to EU-authorized/US-licensed Remicade.

With respect to the affinities for FcγRIIa (both receptor types) and FcγRIIIb, the affinities were said to be low, which is in line with data reported in the literature. Reliable K_D values could not be obtained for FcγRIIa 131R or FcγRIIIb (as binding saturation was not achieved at the maximum concentration evaluated); however, for FcγRIIa 131H, the ranges for the relative K_D values for Zessly, EU-authorized Remicade and US-licensed Remicade were similar. The Applicant has demonstrated that the affinity of Zessly for FcγRn is similar to that observed with the reference products.

Other effector mechanisms of anti-TNFα treatments have been proposed that are independent of TNFα neutralizing activity apart from ADCC and CDC. A mechanism for inhibition of T cell proliferation has been proposed and is thought to occur via Fc-dependent, anti-TNF-induced generation of a population of macrophages with an immunosuppressive phenotype. The Applicant has demonstrated that the observed inhibition of T-cell proliferation for Zessly is similar to that observed with EU-authorized/US-licensed Remicade.

Secondary pharmacodynamic studies

No studies to evaluate the secondary pharmacology aspects were conducted which is in line with Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues. EMEA/CHMP/BMWP/403543/2010.

Safety pharmacology programme

No studies to evaluate the safety pharmacology were conducted which is in line with Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues. EMEA/CHMP/BMWP/403543/2010.

Pharmacodynamic drug interactions

No studies to evaluate the potential pharmacodynamic interactions were conducted which is in line with Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues. EMEA/CHMP/BMWP/403543/2010.

2.3.3. Pharmacokinetics

The analytical methods used to determine serum levels of infliximab conformed to GLP, were validated over the range of 100 to 5000 ng/mL. The Applicant has stated that all samples were analysed within the established stability criteria and suggested that EU-authorized Remicade was stable at -20°C and -70°C for up to 129 days, while Zessly was considered to be stable at -70°C for 72 days (see Section 2.3.6).

Two separate electrochemiluminescence (ECL) immunoassays were validated to detect the presence of anti-drug antibodies (ADAs) in rat serum following administration of EU-authorized Remicade and administration of Zessly.

Infliximab does not bind to TNF-α from any other non-clinical species to the same extent as that observed in humans, apart from the chimpanzee and hence the CHMP Scientific advice provided in November 2012 and July 2014 questioned the relevance of the conduct of *in vivo* studies in the rat, though there is evidence that suggests that the rat can be used to characterise FcRn mediated non-target related clearance [Roopenian & Akilesh, 2007; Abdiche et al., 2015]. It is acknowledged that the 2 *in vivo* studies to evaluate the TK (and tolerability) were performed at the request of another regulatory agency outside the EU and that the studies were designed in accordance with the 3Rs.

Following a single IV dose at 10 or 50 mg/kg (n=5/group), the systemic exposures and the half-lives for Zessly were said to be comparable to those observed with EU-authorized Remicade.

A 2-week study was conducted whereby Zessly was administered once weekly on Days 1, 8 and 15 at 10 or 50 mg/kg in a non-comparative study to both male and female rats. The systemic exposures increased in a manner that was approximately proportional to dose and exposures were slightly higher on repeated dosing (Day 8). No ADAs were detected following single IV administration of Zessly or EU-authorized Remicade; however, the levels of infliximab in the samples may have affected the ADA determinations.

No studies to evaluate the distribution, metabolism, excretion or potential to cause pharmacokinetic interactions were conducted, which is in line with Guideline on similar biological medicinal products containing

monoclonal antibodies: non-clinical and clinical issues. EMEA/CHMP/BMWP/403543/2010 and/or the ICH S6 guideline (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals [EMA/CHMP/ICH/731268/1998.

2.3.4. Toxicology

In the rat, single IV administration of Zessly or infliximab at 10 and 50 mg/kg was well tolerated, whereby no effects on clinical signs, body weight or food consumption were observed. In a non-comparative, 2-week repeated-dose IV study, where rats were given Zessly once weekly at 0, 10 or 50 mg/kg on Days 1, 8, and 15, a decrease in the levels of platelets and an increase in the levels of neutrophils, monocytes, unstained large cells and fibrinogen were observed at the maximum dose tested. Minimal to mild sinusoidal cell hyperplasia was also observed at 50 mg/kg. However, the observed changes were considered not to be adverse given the magnitude of the changes (≤ 2-fold), the lack of a histological correlate and/or that similar findings have been noted during previous infliximab studies conducted in the rat.

Genotoxicity

It is not expected that IgGs would interact directly with DNA or other chromosomal material; hence, genotoxicity studies have not been conducted in accordance with ICH S6 (R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals [EMA/CHMP/ICH/731268/1998].

Carcinogenicity

Carcinogenicity studies are not required to develop the proposed biosimilar in accordance with 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 (Dec 2014)].

Reproduction Toxicity

Studies to investigate the potential to cause reproductive and developmental toxicity are not required in accordance with 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 (Dec 2014)].

Local Tolerance

Separate local tolerance studies are not recommended in accordance with 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 (Dec 2014)]. Local tolerance was evaluated as part of the repeated-dose study.

Other toxicity studies

Separate studies to evaluate the potential for antigenicity and immunotoxicity have not been performed. Separate studies to evaluate dependence and the effects of metabolites have not been performed. The conduct of toxicity studies in non-relevant species (i.e. to assess unspecific toxicity only, based on impurities) is not recommended. This is in keeping with the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues [EMEA/CHMP/BMWP/42832/2005 Rev.1 (Dec 2014)]

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, a protein and therefore unlikely to pose a significant risk to the environment. This is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

2.3.6. Discussion on non-clinical aspects

The majority of the binding and functional assays appeared to be sufficiently validated and clarification was sought where details of methods were not located. Overall the *in vitro* assays utilised can be considered to be scientifically valid and sufficiently robust.

The data as presented did not detect substantial differences between the batches of proposed infliximab biosimilar and the batches of the Remicade® sourced from the EU and US. It was noted by the CHMP that the majority of the comparisons had been made using relative potency values for e.g., where the mean endpoints for Zessly and EU-authorized/US-licensed Remicade have been compared to or expressed as a percentage of the result obtained for Zessly reference material. The Applicant clarified the calculations used to determine the relative potency. For a given test sample, it was expected that the readout would be expressed as a percentage of the result obtained with the reference material (i.e. test result/reference result * 100). However, the equations presented suggested the converse. The Applicant confirmed that potency of the standard was expressed as a percentage of the reference and thus, an inverse ratio was calculated.

It was also the view of the CHMP that definitive conclusions with respect to similarity could not be made on the basis of relative endpoints alone. Hence, the absolute data for all of the individual endpoints from the binding and functional assays (for Fab and Fc functions) were requested to allow assessment. All the absolute and relative raw data have been provided by the applicant.

For the NK binding assay, the methods used have been based upon that of Iida *and colleagues,* 2009. The Applicant provided full description of the methods used upon request and has outlined the relevant negative control groups included to help demonstrate that the binding of infliximab (Zessly or EU-authorized/US-licensed Remicade) to NK cells was dependent upon FcγRIIIa.

To further characterise Fc effector function, the affinity of Zessly to FcγRI, FcγRIIa (both receptor types), FcγRIIIb and FcRn was determined using SPR technology and compared to that observed with the reference products, EU-authorized Remicade and US-licensed Remicade. It was concluded that the mean relative values between Zessly and EU-authorized/US-licensed Remicade were comparable and the relative binding ranges overlap between Zessly and EU-authorized/US-licensed Remicade.

A mechanism for inhibition of T cell proliferation has been proposed and is thought to occur via Fc-dependent, anti-TNF-induced generation of a population of macrophages with an immunosuppressive phenotype. The Applicant has suggested that the observed inhibition of T-cell proliferation for Zessly is similar to that observed with EU-authorized/US-licensed Remicade. Upon request, the applicant has described the methods used and in the instances where the methods differ from that of Vos *et al* (2011). The assay methods/conditions have been clearly justified. In addition, the Applicant has clearly demonstrated that the observed inhibition of T-cell proliferation is dependent upon both the interaction between the antibody (infliximab) and mTNF and the presence of an Fc region. As requested, the Applicant provided detailed data to support the claim that the remaining cells at 7 days represent T-cellsThe comprehensive biological assays and results discussed above were considered comparable between Zessly and originator products, therefore a reduced non-clinical *in vivo* program was considered adequate.

After review of the amended validation report for the determination of Remicade and Zessly in rat serum by quantitative ELISA, it is noted that 2/3 of the Zessly samples at 250 ng/mL did not meet the acceptance criteria at the time point of 58 days (while the criteria for stability at the longer time point of 72 days were met). The Applicant was asked to clarify this discrepancy with the method validation and discuss how this deviation at the 58-day time point impacts upon the integrity of the results. While the Applicant confirmed that none of the samples at the low concentration of 250 ng/mL passed the acceptance criterion for recovery, the lowest concentrations observed in the single and repeat dose studies were all approximately > two-fold or higher than the tested 250 ng/mL stability validation sample. Given that long-term stability of higher concentrations of Zessly for 72 days at -70°C in rat serum has been demonstrated, it is agreed that that variability seen during long-term stability assessment at the 250 ng/mL concentration level is unlikely to have impacted the toxicokinetic results reported. For validation of the methods used to detect ADAs generated against EU-authorized Remicade, it is evident that the acceptance criteria for inter-assay precision was 25%; typically, this should be set at 20% [EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**]. In addition, anti-EU-authorized Remicade antibody was stable in rat serum for at least 4.25 hours at ambient temperature, while long-term stability does not appear to have been determined. Moreover, the acceptance criteria for stability were only met for 4 freeze/thaw cycles while it failed for 1, 2 and 6 freeze thaw cycles. The Applicant confirmed that the samples of rat serum were analysed within the established criteria of the validated method. Given that the long-term stability of anti-drug antibodies is well documented and that separate validations were conducted in human serum, it is agreed that determinations of anti-EU-authorized Remicade or anti-Zessly antibodies in human serum should not have been adversely impacted by the deficiencies observed when validating with rat serum.

A tailored toxicology package was provided: A comparative single-dose tolerability study was conducted in male rats only because non-clinical data and clinical PK data do not provide evidence of sex-related differences. A non-comparative 2-week study was conducted where Zessly was administered once weekly on Days 1, 8 and 15; the findings from this study were then compared to results from historical studies conducted with infliximab as reported during the initial registration of Remicade, or the infliximab biosimilar, Remsima. Both toxicology studies were conducted in the SD rat and conformed to the principles GLP. The non-clinical batches used (drug substance batch 94200 and drug product batch A03038) were said to be representative of the clinical drug product and were manufactured using the final commercial manufacturing process.

2.3.7. Conclusion on the non-clinical aspects

The Applicant provided a comprehensive package of *in vitro* pharmacology studies and the nature of the studies used for functional characterisation of Zessly is in line with the CHMP Scientific advice received. The pharmacology data generated during the binding and functional assays demonstrate that Zessly is similar to Remicade with respect to the function of the Fab and Fc domains.

The pharmacokinetics package for this application consisted of TK analysis from 2 toxicity studies and analytical methods to support the determination of infliximab and the anti-drug antibodies.

Overall, the approval of the proposed biosimilar can be supported with respect to the active substance non-clinical aspects. . In addition, the proposed excipients, succinate buffer, sucrose and polysorbate 80 represent pharmaceutical excipients with an established safety profile and there are no issues which preclude their inclusion.

2.4. Clinical aspects

2.4.1. Introduction

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

Study	Design	Population	Treatment	Endpoints
GP11-101 (PK study)	Phase 1, double blind, randomized, parallel-group, single-dose,3-arm, comparative pharmacokinetic study of Zessly and infliximab (=Remicade) sourced from US and EU administered to healthy volunteers	Healthy male and female subjects N=151 (all randomized subjects) Zessly: N=52 (49m, 3f) EU-authorized Remicade: N=50 (48m, 2f) US-licensed Remicade: N=49 (44m, 5f)	Dose All study drugs were administered as a single i.v. infusion of 10 mg/kg (available as 100 mg/vial, powder for injection) Study duration Up to 85 days (excluding up to 28 days of screening and ADA follow-up up to 6-months post Day 85)	Primary endpoints: 90% CIs for the test-to-reference ratios (%) in C_{max}, AUC_T, and AUC_{inf} within the pre-specified acceptance margin (80.00%, 125.00%). Secondary endpoints: $AUC_{extrap\%}$, CL, V_{SS}, and $t_{½}$ Safety and Immunogenicity: AEs, ECGs, vital signs, and other safety endpoints incl. ADA and NAb by visit
GP11-301 (therapeutic equivalence)	A Phase 3 randomized, double-blind study assessing the efficacy and safety of Zessly	Male and female patients with rheumatoid arthritis **TP1 (up to W30 pre-**	Dose Both the study drugs were dosed	Primary endpoint: The primary efficacy endpoint was the

	and EU-authorized Remicade (=EU-authorized Remicade) in combination with methotrexate in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate	**dose)** N=650 (all randomized patients) Zessly: N=324 EU-authorized Remicade: N=326 **TP2 (week 30-54)** N=566 (all re-randomised[1] at w30) Zessly/Zessly: N=280 EU-authorized Remicade/EU-authorized Remicade: N=143 EU-authorized Remicade/Zessly: N=143	i.v. infusion of 3 mg/kg as induction dose and maintenance dose (available as 100 mg/vial, powder for injection) Duration Up to 78 weeks (excluding screening period of up to 21 days.)	proportion of patients achieving a 20% or greater improvement in ACR clinical response at Week 14. Secondary efficacy endpoints: ACR20, ACR50, ACR 70 by visit, DAS28-CRP, EULAR and others. Safety and Immunogenicity: AEs, IRRs, hypersensitivity, and other safety endpoints, ADA and NAb by visit PK: Infliximab serum concentrations by visit, and Population PK PD: hs-CRP by visit

[1] Patients in the Zessly arm remained on Zessly treatment in TP2. Patients in the EU-authorized Remicade arm in TP1 were re-randomized 1:1 to treatment with either Zessly or EU-authorized Remicade in TP2.

At the time of the initial submission study GP11-301 was on-going and data were presented up to the Week 30 pre-dose assessments (TP1: data cut-off date of 08 March 2016). This included full primary efficacy endpoint data. Data up to week 54 (TP2) was submitted with the responses to the D120 list of questions.

2.4.2. Pharmacokinetics

PK data have been generated in the two clinical trials submitted in this application: the pivotal PK study in healthy volunteers (GP11-101); and supportive data from the efficacy trial in patients with Rheumatoid arthritis (GP11-301). In addition, a non-comparative pilot study using infliximab-EU only was performed to provide an estimate of overall PK variability for sample size calculation in healthy subjects (referred as B5371004). The assessment of clinical pharmacokinetics focuses on studies GP11-101 and GP11-301.

Analytical methods

Analytical methods applied during the clinical development include:

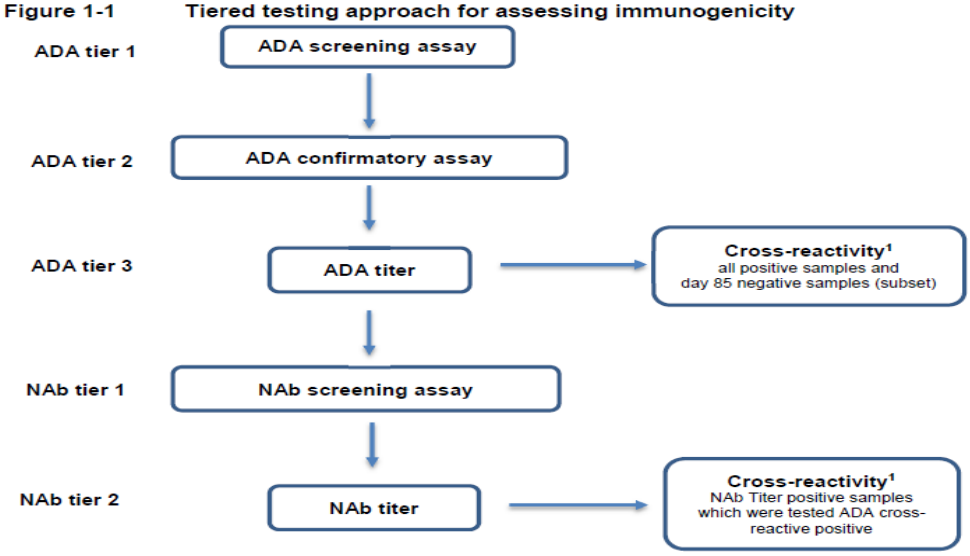
1. methods for measuring human serum levels of the active substance of Zessly and the reference product, Remicade

An enzyme linked immunosorbent assay (ELISA) was developed to quantitatively measure free (i.e. free and monovalently bound) concentrations of infliximab (US-licensed Remicade, EU-authorized Remicade and Zessly) in human serum. The validation of this assay is acceptable.

2. anti-drug antibodies and neutralising antibodies

In-line with the CHMP 'Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006)', the immunogenicity testing strategy utilizes a combination of screening, confirmatory and neutralisation assays for determining anti-drug antibodies.

Figure 1-1 Tiered testing approach for assessing immunogenicity



Anti-drug antibody detection

In study GP11-101 two ECL bridging immunogenicity assays were used for the detection of anti-US-licensed Remicade/anti-EU-authorized Remicade and anti-Zessly antibodies. As labelled US-licensed Remicade was used to assess clinical samples from Phase 1, a cross-validation study using EU-authorized Remicade to US-licensed Remicade was performed to show equivalence of assays using labelled US/EU reference product.

In the phase III study GP11-301, a single assay strategy was used: ECL bridging assay using labelled Zessly. The assay used is the same as used for Zessly treated subjects in Phase I. The applicant's justification for this strategy is that it is favourable to reduce the risk of possible different sensitivities using different assays for EU-authorized Remicade/US-licensed Remicade and Zessly. There are slight differences between the 2 assays including in sensitivity and cut-points so in principle a single assay approach would be appropriate as this would minimise variability between the RMP and Zessly. Based on the high cross-reactivity seen, the Zessly single assay is suitable for use.

Neutralising antibody detection

In study GP11-101 two cell-based assays were used. The same strategy as for the anti-Remicade ADA assay was used whereby the assay was designed starting with US-licensed Remicade and then cross-validation was undertaken with EU-authorized Remicade.

As for the ADA assay strategy, for the Phase III study GP11-301 a single cell-based NAb assay strategy was employed using the anti-Zessly NAb assay. There was high concordance seen between the two assays for samples from all 3 treated groups.

Analysis of hs-CRP in human serum of RA patients

The assay used to determine the concentration of hs-CRP in serum samples of patients in the clinical efficacy/safety study is a commercially available system (Siemens BNII Nepheometer). The validation report provided for this assay is satisfactory.

Study GP11-101

The pivotal PK study was a double-blind, randomized, parallel-group, single-dose, 3-arm, comparative PK study in healthy volunteers carried out in a clinical research unit in the United States of America. Subjects received a single dose of 10mg/kg infliximab intravenously over a period of not less than 2 hours using a calibrated infusion pump in the form of the test product (Zessly) or reference products (EU-sourced Remicade or US-sourced Remicade) as per the randomisation list.

Blood samples for PK analysis were collected prior to first dose, 2 hours, 4 hours, 24 hours (Day 2), Days 3, 4, 5, 8, 15, 22, 29, 36, 43, 50, 57, and 85. Immunogenicity was tested at baseline, Day 57 and Day 85 post dose.

The primary endpoints were C_{max}, AUC_T and AUC_{inf}. Secondary endpoints were $AUC_{extrap\%}$, CL, V_{ss} and $t_{½}$.

The PK analysis was performed in the per-protocol (PP) population based on the planned 8-week serum drug concentration-time data. The PP analysis set included all randomized subjects who received the full dose of the assigned study drug and who did not have major protocol deviations. Equivalence for the primary endpoint were determined if the 90% CI for the ratio of the adjusted geometric means of Zessly to EU sourced Remicade were within the acceptance interval of 80.0 – 125.0%. The statistical and pharmacokinetic assessment methods used are generally appropriate for non-compartmental analysis. No single subject treated with either Zessly or EU-authorized Remicade had an $AUC_{extrap\%}$ >20% and therefore no exclusions for AUC_{inf} was performed based on this criterion.

Overall, 151 subjects were randomized to the 3 study treatment groups. Five subjects discontinued prior to any study treatment; the remaining 146 subjects received the study treatment as assigned. In addition, 27 subjects (12, 5, and 10 subjects in the Zessly, EU-authorized Remicade and US-licensed Remicade treatment groups respectively) discontinued from the study after receiving the study treatment. The PP population consisted of 41 (78.8%) subjects in the Zessly treatment group, 45 (90.0%) in the EU-authorized Remicade group and 44 (89.8%) in the US-licensed Remicade group.

Sixteen subjects with incomplete profile were excluded from the PK statistical analysis. The applicant indicated that exclusion of 15 out of 16 subjects from analysis was based on the incomplete PK profiles as the excluded subjects discontinued treatment before day 29 and therefore the elimination phase was not well characterised based on infliximab long half-life of 14 days. The remaining one subject was excluded due to high ADA leading to persistent BLQ serum measurements from day 22 onwards, although it was not clear how ADA, first emerged on day 29, led to BLQ on day 22. For all the excluded 16 patients, it was acceptable to exclude analysing the PK parameters which depend on the elimination phase characterisation (e.g. half-life, Cl, AUC_{inf}) when the elimination was not well-characterised (e.g. when subjects were early withdrawn). Moreover, the applicant included those patients in the analysis of the PK parameters which are independent of the elimination phase (e.g. C_{max}). The new analysis for the C_{max} values was within the 90% CI margins of 80.0 – 125.0%. As inclusion of the C_{max} results from the excluded subjects was consistent with the previous analysis, this indicates that exclusion of other PK parameters from those subjects which depend on the elimination phase is unlikely to affect the overall study conclusions. A high proportion of subjects in the Test arm discontinued post treatment compared to the reference (EU) (12/49 vs 5/48) who discontinued because

of lack of willingness to participate in the study. No longer willing to participate was the main reason for subject discontinuation in the treated arm of Zessly. It is reassuring that no adverse events related to the IMP were reported in those subjects.

Among 146 randomized and treated subjects, 130 of which were included for PK analysis (PP analysis set) their demographic data (sex, age, race, weight and BMI) were generally comparable among the 3 treatment groups.

Results of the PK analysis

The 3 study drugs (Zessly, EU-authorized Remicade, and US-licensed Remicade) exhibited a similar PK profile, which was characterized by a rapid increase of serum drug concentration during each infusion followed by a multi-phasic decline in drug concentrations after completion of the i.v. infusion.

Arithmetic mean (+/-SD) of PK parameters in study GP11-101 (PP set).

Parameters (units)	Zessly	Remicade-EU	Remicade-US
N, n	41, 41	45, 45	44, 44
C_{max} (µg/mL)	221.9 ± 43.8	202.7 ± 46.1	209.3 ± 50.5
AUC_T[a] (µg•hr/mL)	56960 ± 12157	51180 ± 12868	53010 ± 11906
AUC_{inf} (µg•hr/mL)	61460 ± 14386	56130 ± 15972	57610 ± 14334
CL (mL/hr/kg)	0.1725 ± 0.0456	0.1918 ± 0.0527	0.1855 ± 0.0521
V_{ss} (mL/kg)	79.58 ± 20.73	92.06 ± 25.85	84.92 ± 24.52
$t_{½}$ (hr)	344.5 ± 99.72	367.6 ± 106.7	335.1 ± 124.5

The inter-subject variability for each of the PK parameters in the table represents the accurate record.

a. AUC_T was ≥80% of the corresponding AUC_{inf} in 127 of 130 subjects who were included for PK analysis.

Results of the primary endpoints (PP set)

	Adjusted Geometric Means		Ratios (Test/Reference)	90% CIs
Parameters (units)	Test	Reference	of Adjusted Means[a]	for Ratios
Zessly (Test versus Remicade-EU (Reference)				
C_{max} (µg/mL)	217.4	197.6	110.03	101.32 – 119.49
AUC_T (µg•hr/mL)	55600	49650	111.98	102.85 – 121.92
AUC_{inf} (µg•hr/mL)	59750	54080	110.49	100.67 – 121.28
Zessly (Test) versus Remicade-US (Reference)				
C_{max} (µg/mL)	217.4	203.1	107.05	98.53 – 116.31
AUC_T (µg•hr/mL)	55600	51640	107.67	98.85 – 117.28
AUC_{inf} (µg•hr/mL)	59750	55810	107.06	97.49 – 117.58
Remicade-EU (Test) versus Remicade-US (Reference)				
C_{max} (µg/mL)	197.6	203.1	97.29	89.72 – 105.50
AUC_T (µg•hr/mL)	49650	51640	96.15	88.45 – 104.53
AUC_{inf} (µg•hr/mL)	54080	55810	96.90	88.42 – 106.18

a. The ratios (and 90% Cis) are expressed as percentages

The 90% CIs for the ratio of geometric mean of Zessly and EU (and US) sourced infliximab for the primary endpoints of C_{max} , AUC_T and AUC_{inf} were within the acceptance interval of 80.0 – 125.0% and support biosimilarity in pharmacokinetics of Zessly with EU (and US) sourced infliximab.

As the 90% CI did not cross unity for all 3 PK parameters, an investigation into this observation revealed a difference in drug (protein) content of the vial containing the lyophilisate evidenced by the differences in protein concentration of the reconstituted lyophilisate between the Zessly and EU-authorized Remicade used in study GP11-101. The difference in protein concentration represents a difference in dose. Whilst not crossing unity does not preclude biosimilarity, the EMA guideline on the investigation of bioequivalence allows for content correction where a reference batch with an assay content differing less than 5% from test product cannot be found (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The protein-content corrected analysis comprised approximately 100.00% comparability between Zessly and EU sourced infliximab with 90% CIs ranging from 93% to 112% for C_{max} , AUC_T and AUC_{inf}.

Summary of statistical comparisons of primary pharmacokinetic parameters with protein-content correction (PP set)

	Adjusted Geometric Means		Ratios (Test/Reference) of Adjusted Geometric Means[a] (%)	90% CIs for Ratios (%)
Parameters (units)	**Test**	**Reference**		
Zessly (Test versus Remicade-EU (Reference)				
C_{max} (µg/mL)	211.1	208.0	101.48	93.45 – 110.21
AUC_T (µg•hr/mL)	53990	52270	103.29	94.86 – 112.45
AUC_{inf} (µg•hr/mL)	58010	56930	101.91	92.85 – 111.86
Zessly (Test) versus Remicade-US (Reference)				
C_{max} (µg/mL)	211.1	209.4	100.81	92.79 – 109.53
AUC_T (µg•hr/mL)	53990	53240	101.40	93.09 – 110.45
AUC_{inf} (µg•hr/mL)	58010	57540	100.83	91.81 – 110.73
Remicade-EU (Test) versus Remicade-US (Reference)				
C_{max} (µg/mL)	208.0	209.4	99.34	91.61 – 107.72
AUC_T (µg•hr/mL)	52270	53240	98.17	90.31 – 106.73
AUC_{inf} (µg•hr/mL)	56930	57540	98.94	90.29 – 108.41

The other PK endpoints Cl, V_{ss} and $t_{1/2}$ appear to support biosimilarity. The geometric mean ratios and the 90% CIs appeared to be within the acceptable range of 80.00% to 125.00% except for V_{ss} which had the lower bound of 90% CI slightly below 80%. The results for the additional PK endpoints are generally in support for the biosimilarity of Zessly to EU-authorized Remicade

Summary data for T_{max} was submitted and both Zessly and EU-authorized Remicade had comparable median and range for T_{max}.

Immunogenicity results

Summary of ADAs in healthy subjects in study GP11-101 (safety analysis set)

Number of Treated Subjects	Zessly N=49	Remicade-EU N=48	Remicade-US N=49
ADA at baseline (Day 1 pre-dose)			
Number of ADA-positive subjects on Day 1	0	0	0
ADA post dose			
Number (%) of ADA-positive subjects through Day 57	2/38[a] (5.3%)	0/39[a] (0%)	3/41[a] (7.3%)
Number (%) of ADA-positive subjects through Day 85	6/37[a] (16.2%)	14/43[a] (32.6%)	11/39[a] (28.2%)
Overall[b]	6/49[a] (12.2%)	14/48[a] (29.2%)	11/49[a] (22.4%)
NAb	5/6 (83.3%)	12/14 (85.7%)	9/11 (81.8%)

Five subjects tested positive for ADA during the protocol-specified 8-week PK profiling period, and therefore, the impact of ADA response on the PK similarity assessment was expected to be limited.

The rate of ADA response increased considerably from Days 57 to 85 for all 3 treatment groups, which was accompanied by a decrease in mean drug concentration from Day 57, when the mean drug concentrations ranged from 7.54 to 8.17 µg/mL to Day 85, when the mean drug concentrations ranged from 2.56 to 2.87 µg/mL. Consistent with this observation, patients with low infliximab concentrations (<2.2 µg/mL) were shown to be likely to develop ADA against infliximab.

Overall, lower immunogenicity was observed for Zessly (12%) in comparison to EU-authorized Remicade (29%) and US-licensed Remicade (22%). However, the impact of ADA on Cl during the clinical study GP11-101 was limited due to the single-dose PK and the absence of previous exposure to infliximab in the study population. Therefore, the antibody responses were primary antibody responses.

Study GP11-301

Supportive PK data is provided from the Phase III study comparing the efficacy and safety of Zessly and EU-authorized Remicade in combination with methotrexate in male and female patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate. This study was on-going when data up to Week 30 pre-dose assessments were presented. This study is described in the clinical efficacy section below.

Blood samples for measurement of serum drug concentrations were collected immediately (within 4 hours) prior to dose administration at Weeks 0, 2, 6, 14, 22, 30, 38, 54, and 62; within 5 minutes prior to the end of infusion at Weeks 0 and 14; and anytime during study visits at Weeks 4 and 78 (EOT).

C_{trough} levels at weeks 0, 2, 4, 6, 14, 22 and 30, and C_{max} levels at weeks 0 and 14 were observed directly from the data.

All patients who were treated with Zessly or EU-authorized Remicade, and provided at least 1 post-dose drug concentration measurement were included in the analysis of PK. Of the 650 randomized patients, 323 patients received Zessly and 326 patients received EU-authorized Remicade and were included in the analysis of PK.

Overall, discontinuation from treatment and from the study during treatment period 1 was similar between treatment arms. A total of 43 (13.3%) patients in the Zessly arm and 40 (12.3%) patients in the EU-authorized Remicade arm discontinued from treatment during treatment period 1, defined by the date of the

final infusion. Before Week 14, 23 (7.1%) and 13 (4.0%) patients in the Zessly and EU-authorized Remicade arms, discontinued treatment. The majority of patients were female (80.3%) and white (77.5%). The mean (SD) age of all patients was 52.8 (13.1) years, and the mean (SD) BMI was 27.4 (6.7) kg/m^2.

Results of the PK analysis

Serum drug concentrations in study GP11-301 (PK population TP1)

			Treatment Group	
Parameter	**Visit**	**Statistic**	Zessly	Remicade-EU
C_{trough} (ng/mL)	Week 0 (Day 1)	N	322	323
		NALQ	12	10
		Median (5^{th} – 95^{th} perc.)	0 (0-0)	0 (0-0)
	Week 2	N	316	323
		NALQ	313	320
		Median (5^{th} – 95^{th} perc.)	16830 (6241-28660)	16070 (6241-27270)
	Week 4	N	308	314
		NALQ	302	306
		Median (5^{th} – 95^{th} perc.)	23540 (4300-45750)	21250 (2258-40120)
	Week 6	N	308	315
		NALQ	293	296
		Median (5^{th} – 95^{th} perc.)	10020 (102-26650)	9266 (0-24180)
	Week 14	N	302	310
		NALQ	220	216
		Median (5^{th} – 95^{th} perc.)	1497 (0-10590)	1025 (0-7643)
	Week 22	N	295	303
		NALQ	177	176
		Median (5^{th} – 95^{th} perc.)	576 (0-7911)	433 (0-6221)
	Week 30	N	281	290
		NALQ	160	153
		Median (5^{th} – 95^{th} perc.)	413 (0-7253)	279 (0-6017)
C_{max} (ng/mL)	Week 0 (Day 1)	N	319	322
		NALQ	310	312
		Median (5^{th} – 95^{th} perc.)	64240 (31570-102000)	62200 (23260-95990)
	Week 14	N	297	299
		NALQ	288	293
		Median (5^{th} – 95^{th} perc.)	71250 (1617-150500)	68450 (3367-144500)

Serum drug concentrations in study GP11-301, TP1+TP2 (PK population TP2)

Visit	Statistic	Treatment Group		
		Zessly/ Zessly	**EU-authorized Remicade/ EU-authorized Remicade**	**EU-authorized Remicade/ Zessly**
C_{trough} (ng/mL)				
Week 0 (Day 1)	N	278	142	142
	NALQ	11	2	6
	Median (5^{th}-95^{th} perc.)	0 (0-0)	0 (0-0)	0 (0-0)
	Mean (SD)	1480 (9882.1)	457.2 (5404.7)	994.5 (8331.9)
Week 2	N	278	142	143
	NALQ	277	141	142
	Median (5^{th}-95^{th} perc.)	17010 (6585-28660)	14980 (7408-27270)	16900 (7110-26830)
	Mean (SD)	17490 (7299.5)	16790 (9440.9)	16940 (6161.6)
Week 4	N	273	140	139
	NALQ	270	138	138
	Median (5^{th}-95^{th} perc.)	24430 (4763-46600)	20390 (3611-37050)	24360 (3340-40530)
	Mean (SD)	24250 (12235)	20850 (9984.6)	23330 (10751)
Week 6	N	277	139	142
	NALQ	264	135	143
	Median (5^{th}-95^{th} perc.)	10210 (102.0-26550)	9353 (632.0-23090)	9867 (0-21970)
	Mean (SD)	11330 (9498.6)	10720 (7743.2)	10050 (7205.0)
Week 14	N	278	141	140
	NALQ	206	103	97
	Median (5^{th}-95^{th} perc.)	1610 (0-10590)	1166 (0-7974)	1171 (0-7362)
	Mean (SD)	3320 (7342.2)	3085 (8946.2)	2273 (2678.1)
Week 22	N	279	143	142
	NALQ	172	82	86
	Median (5^{th}-95^{th} perc.)	690.0 (0-8736)	359.0 (0-6681)	516.0 (0-5856)
	Mean (SD)	2129 (3507.5)	1407 (2355.7)	1759 (2253.7)
Week 30	N	278	143	142
	NALQ	161	69	82
	Median (5^{th} – 95^{th} perc.)	428.5 (0-7381)	0 (0-4757)	621.5 (0-6361)
	Mean (SD)	1801 (2773.4)	1083 (1763.6)	1819 (2393.5)
Week 38	N	272	136	133
	NALQ	152	61	68
	Median (5^{th}-95^{th} perc.)	462.0 (0-7931)	0 (0– 5926)	102.0 (0-6221)

Visit	Statistic	Treatment Group		
		Zessly/ Zessly	EU-authorized Remicade/ EU-authorized Remicade	EU-authorized Remicade/ Zessly
C_{trough} (ng/mL)				
	Mean (SD)	1855 (2871.7)	1208 (1926.5)	1620 (2413.7)
Week 54	N	248	125	125
	NALQ	145	57	67
	Median (5^{th}-95^{th} perc.)	549.5 (0-8521)	0 (0-6097)	184.0 (0-7608)
	Mean (SD)	2075 (4054.6)	1823 (6110.8)	1734 (2725.2)

Numbers are shown with up to 4 significant digits.
C_{trough} = observed pre-dose trough serum drug concentration; EU-authorized Remicade = EU-authorized Remicade; N = number of observations (non-missing concentrations); NALQ = number of observations above lower limit of quantification (LLOQ); perc. = percentile; PK = pharmacokinetics; SD = standard deviation; TP = treatment period. The LLOQ was 100 ng/mL.

Source: [Module 5.3.5.3-Table 14.4.3.1.10]

The C_{trough} and C_{max} concentrations were generally similar between the Zessly and EU-authorized Remicade treatment groups.

Immunogenicity results

TP1

Up to week 30, the proportion of patients with ADAs in the Zessly and EU-authorized Remicade study arms was similar at each specific time point of measurement. Overall, 48.6% of patients in the Zessly arm and 51.2% of patients in the EU-authorized Remicade arm were ADA-positive up to Week 30. Approximately 80% of all ADA-positive patients also tested positive for NAbs, and ADA/NAb results were balanced between treatment arms at all measured time points.

Summary of ADAs and NAbs in RA patients in study GP11-301 (safety population, Treatment Period 1)

Visit	Criteria	Zesslv (N = 323) n (%)	Remicade-EU (N = 326) n (%)
Week 0 (Baseline)	ADA positive	9 (2.8)	9 (2.8)
	NAb positive[a]	1 (11.1)	1 (11.1)
	NAb negative	8 (88.9)	8 (88.9)
	ADA negative	313 (96.9)	314 (96.3)
	ADA Not done	1 (0.3)	3 (0.9)
Week 2	ADA positive	10 (3.1)	8 (2.5)
	NAb positive[a]	3 (30.0)	3 (37.5)
	NAb negative	7 (70.0)	5 (62.5)
	ADA negative	308 (95.4)	315 (96.6)
	ADA Not done	5 (1.5)	3 (0.9)
Week 6	ADA positive	22 (6.8)	24 (7.4)
	NAb positive[a]	13 (59.1)	19 (79.2)
	NAb negative	8 (36.4)	5 (20.8)
	ADA negative	285 (88.2)	293 (89.9)
	ADA Not done	16 (5.0)	9 (2.8)
Week 14	ADA positive	96 (29.7)	100 (30.7)
	NAb positive[a]	73 (76.0)	78 (78.0)
	NAb negative	23 (24.0)	22 (22.0)
	ADA negative	206 (63.8)	214 (65.6)
	ADA Not done	21 (6.5)	12 (3.7)
Week 30	ADA positive	136 (42.1)	144 (44.2)
	NAb positive[a]	105 (77.2)	120 (83.3)
	NAb negative	31 (22.8)	23 (16.0)
	ADA negative	146 (45.2)	147 (45.1)
	ADA Not done	41 (12.7)	35 (10.7)
Overall	ADA positive	157 (48.6)	167 (51.2)
	NAb positive[a]	124 (79.0)	143 (85.6)
	NAb negative[a]	33 (21.0)	23 (13.8)
	ADA negative	163 (50.5)	158 (48.5)
	ADA Not done	3 (0.9)	1 (0.3)

The distribution of ADA titers was also similar between the treatment arms over the 30 weeks of treatment.

TP2

Summary of ADAs and NAbs in RA patients TP1+TP2 (SAF, TP2)

Visit	Criteria	Zessly/ Zessly (N=280) n (%)	Remicade-EU/ Remicade-EU (N=143) n (%)	Remicade-EU/ Zessly (N=143) n (%)
Week 0	ADA positive	7 (2.5)	6 (4.2)	2 (1.4)
(Baseline)	NAb positive[1]	1 (14.3)	0	1 (50.0)
	NAb negative	6 (85.7)	6 (100.0)	1 (50.0)
	ADA negative	272 (97.1)	136 (95.1)	140 (97.9)
	ADA not done[2]	1 (0.4)	1 (0.7)	1 (0.7)
Week 2	ADA positive	6 (2.1)	3 (2.1)	1 (0.7)
	NAb positive[1]	2 (33.3)	1 (33.3)	1 (100.0)
	NAb negative	4 (66.7)	2 (66.7)	0
	ADA negative	274 (97.9)	139 (97.2)	142 (99.3)
	ADA not done[2]	0	1 (0.7)	0
Week 6	ADA positive	19 (6.8)	7 (4.9)	9 (6.3)
	NAb positive[1]	11 (57.9)	5 (71.4)	8 (88.9)
	NAb negative	7 (36.8)	2 (28.6)	1 (11.1)
	ADA negative	257 (91.8)	133 (93.0)	134 (93.7)
	ADA not done[2]	4 (1.4)	3 (2.1)	0
Week 14	ADA positive	83 (29.6)	37 (25.9)	47 (32.9)
	NAb positive[1]	62 (74.7)	26 (70.3)	40 (85.1)
	NAb negative	21 (25.3)	11 (29.7)	7 (14.9)
	ADA negative	196 (70.0)	105 (73.4)	95 (66.4)
	ADA not done[2]	1 (0.4)	1 (0.7)	1 (0.7)
Week 30	ADA positive	132 (47.1)	77 (53.8)	65 (45.5)
	NAb positive[1]	102 (77.3)	65 (84.4)	54 (83.1)
	NAb negative	30 (22.7)	11 (14.3)	11 (16.9)
	ADA negative	147 (52.5)	66 (46.2)	78 (54.5)
	ADA not done[2]	1 (0.4)	0	0
Week 38	ADA positive	129 (46.1)	77 (53.8)	68 (47.6)
	NAb positive[1]	104 (80.6)	63 (81.8)	52 (76.5)
	NAb negative	24 (18.6)	14 (18.2)	16 (23.5)
	ADA negative	143 (51.1)	59 (41.3)	67 (46.9)
	ADA not done[2]	8 (2.9)	7 (4.9)	8 (5.6)
Week 54	ADA positive	111 (39.6)	60 (42.0)	67 (46.9)
	NAb positive[1]	85 (76.6)	45 (75.0)	49 (73.1)
	NAb negative	26 (23.4)	15 (25.0)	18 (26.9)
	ADA negative	138 (49.3)	65 (45.5)	59 (41.3)
	ADA not done[2]	31 (11.1)	18 (12.6)	17 (11.9)
EOT/ET	ADA positive	11 (3.9)	9 (6.3)	6 (4.2)
	NAb positive[1]	11 (100.0)	9 (100.0)	3 (50.0)
	NAb negative	0	0	3 (50.0)

Visit	Criteria	Zessly/ Zessly (N=280) n (%)	Remicade-EU/ Remicade-EU (N=143) n (%)	Remicade-EU/ Zessly (N=143) n (%)
	ADA negative	6 (2.1)	5 (3.5)	6 (4.2)
	ADA not done[2]	263 (93.9)	129 (90.2)	131 (91.6)
Unplanned	ADA positive	6 (2.1)	1 (0.7)	1 (0.7)
	NAb positive[1]	3 (50.0)	1 (100.0)	1 (100.0)
	NAb negative	2 (33.3)	0	0
	ADA negative	7 (2.5)	2 (1.4)	0
	ADA not done[2]	267 (95.4)	140 (97.9)	142 (99.3)
Overall TP2	ADA positive	146 (52.1)	86 (60.1)	83 (58.0)
	NAb positive[1]	118 (80.8)	73 (84.9)	65 (78.3)
	NAb negative	28 (19.2)	13 (15.1)	18 (21.7)
	ADA negative	133 (47.5)	55 (38.5)	58 (40.6)
	ADA not done[2]	1 (0.4)	2 (1.4)	2 (1.4)
Overall TP1+TP2	ADA positive	156 (55.7)	88 (61.5)	89 (62.2)
	NAb positive[1]	127 (81.4)	82 (93.2)	73 (82.0)
	NAb negative	29 (18.6)	6 (6.8)	16 (18.0)
	ADA negative	124 (44.3)	55 (38.5)	54 (37.8)
	ADA not done[2]	0	0	0

[1] NAb-positive and NAb-negative incidences are expressed as percent of ADA positive patients.
[2] ADA not done: Samples were not collected or collected but not analyzed.
ADA-positive and -negative test results were defined as ADA titer ≥1.30 and <1.30, respectively.
NAb-positive and -negative results were defined as NAb titer ≥0.70 and <0.70, respectively.
'Overall TP1+TP2' includes pooled data from the TP1 and TP2 safety population.
'Overall TP2' includes data from Week 38, Week 54, EOT/ET and Unplanned visit in TP2 (Week 30 is not included in Overall TP2 because ADA samples were obtained prior to dosing, thus representing TP1 before re-randomization).

A similar proportion of patients with ADAs, similar onset times and respective titers of ADAs were observed for the Zessly and EU-authorized Remicade arms. The proportions of patients with ADAs after dose escalation were also similar between treatment arms. The proportions of patients with NAbs in ADA-positive patients were similar between treatment arms.

PK by ADA positive and negative groups

The PK of infliximab is known to be affected by the development of ADAs.

Serum drug concentrations by ADA (PK population, TP1)

	ADA-Positive Patients		ADA-Negative Patients	
Visit **Statistic**	Zessly	Remicade-EU	Zessly	Remicade-US
C_{trough} (ng/mL)				
Week 0 (Day 1)				
N	156	166	163	156
NALQ	4	5	8	5
Median (5th – 95th perc.)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Week 2				
N	155	166	161	157
NALQ	153	163	160	157
Median (5th – 95th perc.)	15540 (5675-26780)	14230 (5243-26130)	18230 (6316-28830)	18020 (9075-29630)
Week 4				
N	151	164	157	150
NALQ	146	157	156	149
Median (5th – 95th perc.)	17760 (765-37420)	16370 (256-32450)	27850 (10660-49180)	26880 (12980-41390)
Week 6				
N	151	163	157	152
NALQ	136	144	157	152
Median (5th – 95th perc.)	6159 (0-20180)	5122 (0-17440)	14030 (3960-29890)	12790 (4321-26420)

	ADA-Positive Patients		ADA-Negative Patients	
Visit **Statistic**	Zessly	Remicade-EU	Zessly	Remicade-EU
Week 14				
N	154	159	148	151
NALQ	73	70	147	146
Median (5th – 95th perc.)	0 (0-4014)	0 (0-3428)	3351 (492-15660)	3063 (197-8440)
Week 22				
N	152	156	143	147
NALQ	36	38	141	138
Median (5th – 95th perc.)	0 (0-2262)	0 (0-1151)	2977 (206-10640)	2489 (0-7577)
Week 30				
N	143	149	138	141
NALQ	25	18	135	135
Median (5th – 95th perc.)	0 (0-533)	0 (0-575)	2846 (386-10050)	2385 (192-7580)
C_{max} (ng/mL)				
Week 0 (Day 1)				
N	154	166	162	155
NALQ	152	158	155	153
Median (5th – 95th perc.)	63830 (35630-101500)	59290 (1603-93170)	65530 (11180-102000)	66080 (29140-101200)
Week 14				
N	149	152	148	147
NALQ	140	146	148	147
Median (5th – 95th perc.)	68280 (0-157500)	62010 (1091-118200)	75640 (5633-129400)	75090 (8857-159800)

The development of ADAs lead to lower average C_{trough} and C_{max} concentrations in ADA-positive patients for both Zessly and EU-authorized Remicade. The frequency of ADA and NAbs was generally slightly lower in the Zessly arm.

Population PK modeling

A population PK model based on one clinical study (GP11-301) was developed to describe the PK of Zessly and EU-authorized Remicade in subjects with rheumatoid arthritis. The objectives were to estimate the systemic clearance (CL) and volume of distribution (V) of Zessly and EU-authorized Remicade, and evaluate potential covariates influencing the CL and V for these treatments. NONMEM (7.2.0) was used for all model estimations, Perl-speaks-NONMEM (PsN, 4.2.0) was used for stepwise covariate modeling (SCM) and R (3.0.2) and S-Plus (8.0) were used for visual predictive check (VPC), and nonparametric bootstrapping.

All technical modelling aspects were appropriately described. The population PK model described the PK of Zessly and EU-authorized Remicade with a two-compartmental model with linear elimination from central compartment. The similarity between Zessly and EU-authorized Remicade were supported by final model parameter estimates which showed similar clearance, V1 and V2 estimates for Zessly and EU-authorized

Remicade. Taking into consideration that the population PK model is of low impact in supporting biosimilarity, it has not received close Regulatory scrutiny. However, the use of popPK approach to support PK similarity and to add to the totality of evidence is acceptable.

2.4.3. Pharmacodynamics

Mechanism of action

Infliximab is an IgG1 kappa antibody that binds, via the variable region complementarity determining regions (CDRs), to both sTNF and mTNF with high avidity. Infliximab binding of TNF appears to mediate anti-inflammatory effects through multiple mechanisms of action.

Primary and Secondary pharmacology

The primary mechanism of action is binding of the Fab domain of infliximab to sTNF resulting in disruption of TNF ligand-receptor signaling and inhibition of TNF proinflammatory effects. This mechanism of action is applicable across all disease indications. However, binding of sTNF does not completely explain infliximab's effectiveness in treating CD. Binding to mTNF appears to be of additional importance in the treatment of CD. Once infliximab is bound to mTNF there are several proposed mechanisms of action. The infliximab/mTNF complex on the TNF-producing cell can block the binding to TNFR1/2 on TNF-responsive cells, thereby inhibiting TNF-induced apoptosis. Another proposed mechanism of action involves binding of the Fab domain of infliximab to mTNF resulting in a "reverse signaling" and cell apoptosis of the TNF-producing cell. Where infliximab has bound to mTNF, it is also possible that a cytotoxic effect is produced via the fragment crystallizable (Fc) domain through either antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

These mechanisms of action may play a role in neutralization of inflammatory response resulting in the effective treatment of these disorders with anti-TNF antibody therapy, supporting the consistent role of ligand-receptor interaction and function across these chronic, inflammatory disorders.

No direct pharmacodynamic effects can be attributed to anti-TNFs in patients. In the clinical efficacy and safety trial GP11-301 the only pharmacodynamic endpoint studied was CRP which is a marker of disease activity but does not have a clear relationship to therapeutic effect.

Up to week 30, mean changes from baseline in hs-CRP were similar between the treatment arms in the ITT population, with the maximal decrease of 17.2 mg/L in the Zessly arm and 16.1 mg/L in the EU-authorized Remicade arm observed at Week 2. Mean hs-CRP level decreased by 12.2 mg/L in the Zessly arm and 12.4 mg/L in the EU-authorized Remicade arm at Week 30 as compared to the baseline values. In the PP population hs-CRP levels were also similar between the 2 treatment arms at each study visit up to Week 30.

Mean hs-CRP concentrations at Week 30 pre-dose were 13.0, 14.4 and 10.6 mg/L in the Zessly/Zessly, EU-authorized Remicade/EU-authorized Remicade, and EU-authorized Remicade/Zessly groups, respectively, and minimally increased over TP2 to 13.5, 16.5 and 12.0 mg/L at Week 54. The mean changes from study baseline in hs-CRP concentrations were -12.7, -10.2 and -16.0 mg/L at Week 30 pre-dose, and -12.2, -6.9 and -15.2 mg/L at Week 54 for the Zessly/Zessly, EU-authorized Remicade/EU-authorized Remicade, and EU-authorized Remicade/Zessly groups, respectively

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

PK data have been generated in the two clinical trials submitted in this application: the pivotal PK study in healthy volunteers (GP11-101); and supportive data from the efficacy trial in patients with Rheumatoid arthritis (GP11-301).

The assay format employed by the applicant for the measurement of infliximab and immunogenicity is acceptable. For study GP11-101, the use of a single dose parallel design is acceptable considering the long half-life of infliximab and the possible generation of immunogenicity. EU sourced infliximab was used for the PK comparative study and in the pivotal clinical efficacy/safety trial. The inclusion of a US arm in the PK comparative study for the purpose of FDA requirements is regarded as supportive.

The eligibility criteria are acceptable for study GP11-101. The selection of healthy volunteers in the pivotal PK study is recommended as they represent the most sensitive and homogenous population for a comparative PK evaluation for this procedure. The use of a single dose of 10 mg/kg represents the highest possible suggested strength for patients to induce immunologic tolerance and minimize the impact of ADA was accepted by CHMP and is considered appropriate to show comparable PK profiles of the test and reference products. The objectives and primary PK endpoints are in-line with those recommended in the CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. The sample size calculation, randomisation and blinding procedures are appropriate. The collection of supportive PK data in patients is appropriate and in-line with the guidance in the CHMP biosimilar monoclonal antibody guideline (EMA/CHMP/BMWP/403543/2010).

For study GP11-101, the methods used are generally appropriate for non-compartmental analysis.

For study GP11-301, the population PK assessments and the statistical methods used are appropriate for summarising the PK data.

For study GP11-101, The 90% CIs for the ratio of geometric mean of Zessly and EU (and US) sourced infliximab for the primary endpoints of C_{max} , AUC_T and AUC_{inf} were within the acceptance interval of 80.0 – 125.0% and support biosimilarity in pharmacokinetics of Zessly with EU (and US) sourced infliximab. As the 90% CI did not cross unity for all 3 PK parameters, investigations revealed differences in protein content. While this does not preclude biosimilarity, EMA guideline on the investigation of bioequivalence allows for content correction where a reference batch with an assay content differing less than 5% from test product cannot be found (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The protein-content corrected analysis comprised approximately 100.00% comparability between Zessly and EU sourced infliximab with 90% CIs ranging from 93% to 112% for C_{max}, AUC_T and AUC_{inf}.

For study GP11-301, almost 100% of the ITT population were included in the PK subset population. The PK population is well balanced for Zessly and EU-authorized Remicade arms. C_{trough} and C_{max} concentrations were similar between the Zessly and EU-authorized Remicade treatment groups from Week 0 to 30. The development of ADAs lead to lower average C_{trough} and C_{max} concentrations in ADA-positive patients for both Zessly and EU-authorized Remicade. Of note, the frequency of ADA was generally lower in the Zessly arm.

Infliximab is a chimeric monoclonal antibody known to be immunogenic with consequences on its pharmacokinetics, safety, and efficacy. In study GP11-101, overall lower immunogenicity was observed for Zessly (12%) in comparison to EU-authorized Remicade (29%). However, the impact of ADA on Cl during the

clinical study GP11-101 was limited due to the single-dose PK and the absence of previous exposure to infliximab in the study population. Therefore, the antibody responses were primary antibody responses.

In study GP11-301, up to week 54, the proportion of patients with ADAs and NAbs in the Zessly and EU-authorized Remicade study arms was generally similar at each specific time point of measurement. The development of ADAs lead to lower average C_{trough} and C_{max} concentrations in ADA-positive patients for both Zessly and EU-authorized Remicade.

A population PK model based on study GP11-301 was also developed to describe the pharmacokinetics of Zessly and EU-authorized Remicade in patients with moderately to severely active rheumatoid arthritis. The model objectives, nature of data, missing and outlying data handling; and general modeling aspects were all appropriately described. The population PK model described the PK of Zessly and EU-authorized Remicade with a two-compartmental model with linear elimination from central compartment. The clearance and volume of distribution were estimated and the effect of number of covariates including ADA, sex and BWT. The similarity between Zessly and EU-authorized Remicade is proposed to be supported by final model parameter estimates which showed similar clearance (0.014 L/h vs 0.015 L/h for Zessly and EU-authorized Remicade, respectively), V1 (3.38 L/h vs 3.57 L/h for Zessly and EU-authorized Remicade, respectively) and V2 (1.70 L/h vs 1.65 L/h for Zessly and EU-authorized Remicade, respectively).

Pharmacodynamics

In the clinical efficacy and safety trial GP11-301 the only pharmacodynamic endpoint studied was CRP which is a marker of disease activity but does not have a clear relationship to therapeutic effect. Mean hs-CRP concentration decreased in response to both Zessly and EU-authorized Remicade and the mean change from baseline was similar between the treatment arms up to week 54.

2.4.5. Conclusions on clinical pharmacology

From a PK perspective, it is considered that comparability between Zessly and Remicade has been shown. From a PD perspective, no direct pharmacodynamic effects can be attributed to anti-TNFs in patients. In the clinical efficacy and safety trial GP11-301 the only pharmacodynamic endpoint studied was CRP which is a marker of disease activity but does not have a clear relationship to therapeutic effect. Up to week 54, mean changes from baseline were similar between the treatment arms.

The immunogenicity data from the single-dose study GP11-101 in healthy volunteers and the data up to 54 weeks in the GP11-301 study in patients with RA support biosimilarity between Zessly and the reference product Remicade.

2.5. Clinical efficacy

2.5.1. Main study

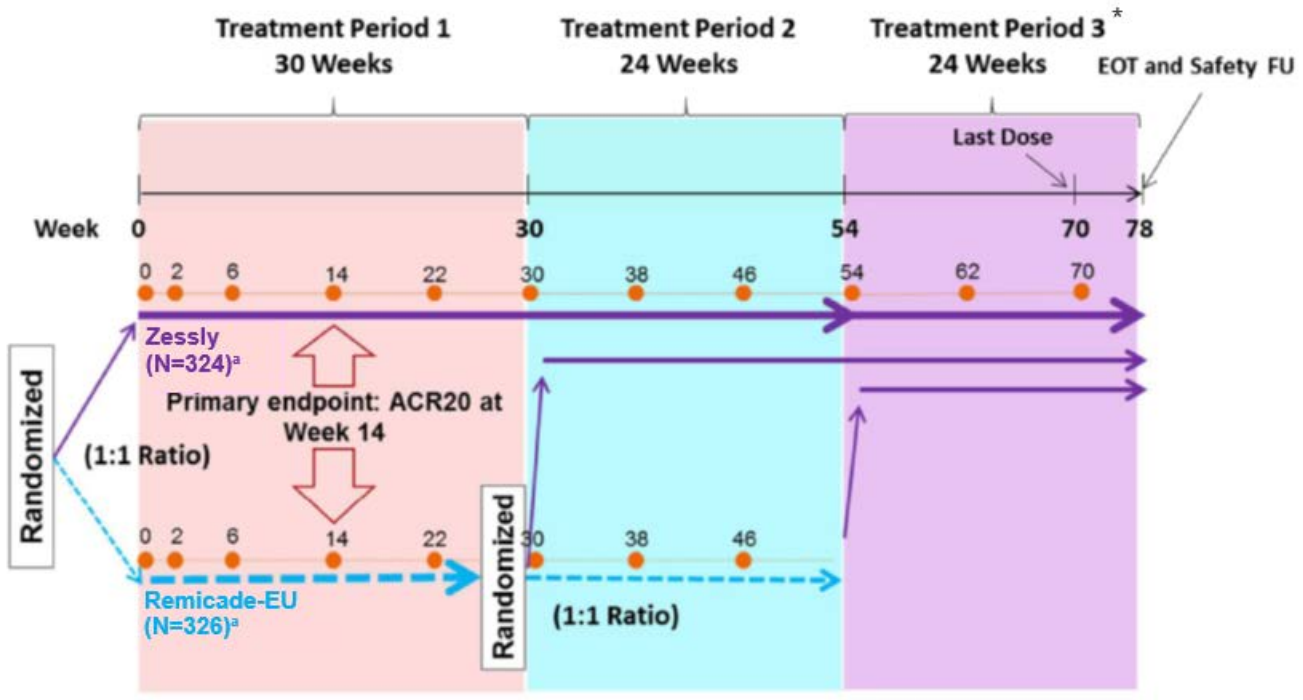
GP11-301: A Phase 3 Randomized, Double-Blind Study Assessing the Efficacy and Safety of Zessly and Infliximab in Combination with Methotrexate in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Methotrexate.

Methods

The clinical development programme to show biosimilarity between Zessly and Remicade is based on a single confirmatory efficacy and safety study (Phase III) comparing the efficacy and safety of Zessly and EU-authorized Remicade in combination with methotrexate in male and female patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate (GP11-301).

The study population (aged 18 years or older) with moderate to severely active RA with a diagnosis for at least 4 month duration and with an inadequate response to MTX was proposed based on the historical Remicade data, including the ATTRACT study.

Study design of GP11-301



Study Participants

Key inclusion criteria

- Male or female patients aged 18 years or older at the time of informed consent.
- Diagnosis of RA based on 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA for at least a 4-month duration.
- Met Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA.
- Moderately to severely active RA disease as defined by the following criteria:
  - ≥6 tender joints (of 68 assessed) and
  - ≥6 swollen joints (of 66 assessed) and
  - High-sensitive C-reactive protein (hs-CRP) ≥10 mg/L (≥1 mg/dL).
- Stable dose of oral or parenteral methotrexate of 10 to 25 mg/week. Patients who could not tolerate 10 to 25 mg/week methotrexate could take a lower dose of as low as 7.5 mg/week. In geographic regions where specified by local guidance or standard of care, a stable dose of as low as 6 mg/week was allowed. Patients were required to receive methotrexate for at least 12 weeks and were on a stable dose for at least 4 weeks prior to first dose of study drug.

Main exclusion criteria

- History of recurrent inflammatory joint disease other than RA (e.g., post infectious arthritis, gout, etc.) or history of any other autoimmune rheumatic diseases (e.g., vasculopathies, spondyloarthropathies, etc.) other than Sjogren's syndrome.
- Evidence of untreated or inadequately treated latent, or inadequately treated or active infection with tuberculosis (TB).
- Any current or prior treatment with the following disease modifying anti-rheumatic drugs (DMARDs) within the relevant washout period.
- Current or prior treatment with infliximab or lymphocyte depleting therapies (e.g., rituximab, alemtuzumab). Prior exposure to biologic therapy for RA with the exception of up to 2 doses of one biologic therapy for RA, including anti-tumour necrosis factor (anti-TNF) therapies (other than infliximab).

Treatments

All patients began their study treatment with an induction period, followed by a maintenance period.

- Induction Period: Intravenous infusion of Zessly or EU-authorized Remicade at a dose of 3 mg/kg on Weeks 0, 2, and 6. The dose remained consistent for all patients for a minimum of 3 doses (up to Week 14).
- Maintenance Period: Beginning at Week 14, patients started to receive maintenance Zessly or EU-authorized Remicade infusions every 8 weeks. The dose was maintained at 3 mg/kg for patients who achieved a minimum clinical response (20% improvement from baseline in both tender [68] and swollen [66] joint counts) at Week 14 visit. Patients who failed to achieve a minimum clinical

response received a one-time dose increase to 5 mg/kg per infusion every 8 weeks from scheduled Week 14 visit onwards. Patients who initially achieved a 20% or greater response at Week 14, but subsequently lost the response also received a one-time dose increase to 5 mg/kg per infusion every 8 weeks from the time point of such a loss of efficacy response.

Prior to infusion with study drug, pre-medications, including antihistamines, acetaminophen/paracetamol, and/or corticosteroids, could be administered at the investigator's discretion.

Stable background therapies of methotrexate and oral folic/folinic acid supplementation were required throughout the study. Patients were required to continue their stable dose of oral or parenteral methotrexate of 10 to 25 mg/week. Patients who could not tolerate 10 to 25 mg/week methotrexate were allowed to enrol with a dose as low as 7.5 mg/week. In geographic regions where specified by local guidance or standard of care, a stable dose of as low as 6 mg/week was allowed. Patients were also required to receive an adequate stable dose of oral folic acid or oral folinic acid (≥5 mg per week) for at least 21 days prior to first dose of study drug and continue on the regimen throughout the study treatment.

Permitted concomitant medications for stable pain/other arthritis therapy included:

- Stable dose (starting 4 weeks before baseline) of oral corticosteroids, equivalent to ≤10 mg/day of prednisone.
- Stable dose (starting 4 weeks before baseline) of one NSAID at a dosage less than or equal to the maximum recommended dose in the product information; in addition a cardiovascular dose of aspirin (≤325 mg/day) is permitted.
- Physical therapy and therapeutic exercise.
- Daily doses of opioids and acetaminophen/paracetamol that were required to be stable for at least 2 weeks prior to first study dose and remain on a stable dose throughout the first 54 weeks of the study treatment course unless treatment adjustment was needed to protect a subject's safety or required as rescue therapy.

Objectives

Primary objective

- To compare the efficacy between Zessly and EU-authorized Remicade in patients with moderately to severely active RA who are treated with infliximab in combination with methotrexate.

Secondary objectives

- To evaluate the overall safety and tolerability of Zessly and EU-authorized Remicade.
- To evaluate the immunogenicity of Zessly and EU-authorized Remicade.
- To evaluate the overall safety, tolerability and immunogenicity of Zessly after treatment transition from EU-authorized Remicade to Zessly.
- To evaluate the population pharmacokinetics (PK) of Zessly and EU-authorized Remicade.
- To evaluate the pharmacodynamic (PD) response to Zessly and EU-authorized Remicade.

- To evaluate the individual ACR (American College of Rheumatology criteria) parameters of clinical response to Zessly and EU-authorized Remicade.

Outcomes/endpoints

The **primary efficacy endpoint** was the proportion of patients achieving clinical response in accordance to the American College of Rheumatology (ACR) criteria of 20% improvement (ACR20) at Week 14. The trial was designed to show equivalence of the test and reference products if the 95% CI for the difference between treatments was entirely within -13.5% to +13.5% with the primary analysis in the ITT population (the PP population was used as a sensitivity analysis).

Secondary efficacy endpoints included categorical and continuous measures of clinical efficacy, including ACR20 (other than Week 14), ACR50, ACR70, change in DAS28-CRP, DAS remission (<2.6), EULAR (European League Against Rheumatism) response and ACR/EULAR remission, change from baseline in individual components of ACR response (including Health Assessment Questionnaire Disability Index [HAQ-DI]).

Sample size

The planned sample size of 614 in a 1:1 ratio was calculated using the difference in ACR20 response rates between the 2 treatment arms. With the equivalence or symmetric margin of (-13.5%, 13.5%), assuming the expected difference of 0 in Week 14 ACR20 response rates between the 2 treatment arms (response rate = 57.5% for both Zessly and EU-authorized Remicade), a total sample size of 614 patients (307 patients per arm) yields ≥85% power to demonstrate equivalence using a 2-sided 95% confidence interval (CI). Equivalence between the 2 treatment arms in this study could be declared if the 2-sided 95% CI for the observed difference in ACR20 response rates at Week 14 fell within the equivalence margin of (-13.5%, 13.5%). The equivalence margin was derived using a meta-analysis of historical published data for infliximab in RA and was accepted by the EMA. The expected ACR20 response rate of 57.5% at Week 14 was determined based on a weighted-average across the historical studies. The sample size was calculated using the method provided in Chow, et al (2008).

At the conclusion of the enrolment, 650 patients were randomized to study treatment. Under the original assumption of 57.5% ACR20 response rate for both Zessly and EU-authorized Remicade: with the symmetric equivalence margin criterion (similarity margin (-13.5%, 13.5%) and 95% 2-sided CI), the power was 87.1% for the total of 650 patients randomized (assuming 1:1 ratio).

The sample size and power calculations were done for the Intent-to-Treat (ITT) population.

Randomisation

Patients were initially randomized in a 1:1 ratio to receive Zessly or EU-authorized Remicade, prior to Day 1 dosing using an automated web-based interactive response system (IWRS). Randomization was stratified by geographic region (North America and Western Europe/Japan/South Korea/Latin America/Rest of the world). A second randomization was blindly performed prior to dosing at Week 30. All patients initially randomized to EU-authorized Remicade were re-randomized in a 1:1 ratio, with 50% of the patients in the EU-authorized Remicade arm switching to Zessly and the other 50% remaining on EU-authorized Remicade. All patients

initially assigned Zessly remained blindly assigned to continue on Zessly. All patients began open label treatment with Zessly at Week 54.

Blinding (masking)

The study patients, investigators/site staff, and Sponsor's personnel directly involved in the study conduct were blinded to the IWRS treatment assignments throughout the study conduct.

Zessly and EU-authorized Remicade were supplied packaged as blinded supplies in which the external packaging (carton) for both products appeared identical and identified with a unique container number. Zessly or EU-authorized Remicade solutions for infusion were prepared by the site's un-blinded pharmacists designated to participate in this study. Un-blinded pharmacists received study specific training on the obligations of the role and signed an agreement that would be maintained in the Site Master File.

A limited number of Sponsor's personnel were un-blinded to conduct the analyses up to Week 30 and to prepare for initial regulatory submission. The review and conduct of the study continued in a blinded manner by study team members that were blinded to all study data until all randomized patients completed the Week 54 visit or at the end of TP2. The study site personnel, investigators, and study patients also continued to be blinded until the end of TP2.

Statistical methods

Efficacy analysis sets

The **ITT population (ITT)** was defined as all patients who were randomized to study treatment. The ITT population was used as the primary analysis population.

The **Per-Protocol (PP) population** was defined as all patients who were randomized and received the study treatment as planned up to Week 14, and had no major protocol deviations.

The PP population was used as the second population for analyses of the primary and secondary endpoints and for sensitivity analyses. The list of patients with major protocol deviations or less than 100% study treatment compliance to Week 14 was determined based on blinded data review prior to database release.

Statistical tests

The primary analysis of the study was conducted after all patients have completed Week 30 assessment. An additional follow-up analysis was performed after all patients completed the Week 54 assessments and include 1 year of immunogenicity data. Both analyses support regulatory submissions and are not intended to alter the conduct of the study. Therefore, the Type 1 error rate will not be affected.

Analysis of the primary efficacy endpoint

The primary efficacy parameter was the clinical response according to the ACR definition of 20% improvement, ACR20. The proportion of patients achieving ACR20 response at Week 14 was analyzed by calculating a point estimate with 95% and 90% CIs for the difference between the 2 treatment arms.

Two exact methods were used to calculate CIs for the difference in ACR20 response rate at Week 14 between the 2 treatment arms. One was the score statistic method based on Farrington-Manning score statistic, and the other was the unconditional approach, which eliminates nuisance parameters by maximizing the p-value over all possible values of the nuisance parameters. The CI calculated by the score statistic method was used

for the inference of equivalence. The CIs for the primary efficacy endpoint calculated by the 2 methods were compared to each other for a sensitivity evaluation. The analyses were carried out using SAS® PROC FREQ (SAS/STAT® 9.3). Equivalence between the 2 arms would be declared if the 2-sided 95% CI fell within the symmetric equivalence margin (-13.5%, 13.5%); this approach was endorsed by EMA and PMDA. The FDA endorsed the alternative approach where equivalence would be declared if the 2-sided 90% CI fell within the asymmetric equivalence margin (-12%, 15%).

The ITT was the primary analysis population for ACR20 at Week 14. The same analyses were repeated for the PP population.

The primary analysis for ACR20 was performed with the missing data imputed using a non-responder imputation method. For sensitivity purposes further missing data handling rules were applied.

To account for a stratification factor (region), a sensitivity analysis was performed on the primary endpoint, utilizing a binomial model (SAS PROC GENMOD with identity link function) with treatment arm as a fixed effect and geographic region as a covariate. The "identity link function" is an option in the model that allows the difference in ACR20 response rates between the 2 arms and its confidence interval to be estimated. This analysis used all observed data at Week 14 in the ITT and PP populations, and no imputation was applied for missing ACR20 data at Week 14 for this analysis.

Descriptive statistics including number of patients (n), frequency and percentage (%) were presented for ACR20 response at Week 14 in both ITT and PP populations.

Analysis of secondary efficacy endpoints

No equivalence testing was performed on secondary endpoints. The primary analysis was, however, repeated for secondary endpoint ACR20 at Week 22 and Week 30.

Descriptive statistics were presented for all secondary efficacy endpoints for the ITT population and also presented for ACR20 response rate, DAS28-CRP and hs-CRP for the PP population. Point estimates for the difference in ACR50 and ACR70 response rates between Zessly and EU-authorized Remicade at all protocol-defined time points up to Week 30 were also summarized.

In addition, ACR20 up to Week 30 was analysed using a generalized estimating equation model with randomized treatment arm and visit as fixed effects and geographic region as covariate. Summary included point estimate and 95% CIs for the differences in ACR20 response.

Figures of changes from baseline value by visit were presented for some of the secondary efficacy endpoints including joint counts, DAS-CRP, hs-CRP, PAAP, PGA, PGAA and HAQ-DI in the ITT population.

Handling of missing data

Three imputation methods (non-responder imputation, all observed data with no imputation, and tipping point analysis based on multiple imputation) were selected to explore the potential impact of assumptions regarding missing data.

Efficacy data collected after TP 1 (i.e. in TPs 2 and 3)

This will be summarized and presented by treatment groups within each treatment period and cumulatively across periods. These efficacy data include ACR responses and other secondary efficacy endpoints. Data will be summarized only descriptive statistics, no treatment comparisons will be performed. There are three groups in TP2: i) Zessly in TPs 1 and 2, ii) EU-authorized Remicade in TP1 and Zessly in TP2 and iii) EU-authorized Remicade in TPs 1 and 2. There is only one treatment group Zessly in TP3.

Results

Participant flow

Subject disposition, ITT population (TP1)

Number (%) of Subjects	Zessly	Remicade-EU
Screened: 1603		
Randomized to study treatment	324	326
Randomized but not treated	1 (0.3)[a]	0
Treated	323 (99.7)	326 (100.0)
Completed TP1	280 (86.4)	286 (87.7)
Discontinued from treatment and continued the study	8 (2.5)	14 (4.3)
Discontinued from study	35 (10.8)	26 (8.0)

Discontinuation from treatment, safety population – TP1

Number (%) of Subjects	Zessly (N = 323)	Remicade-EU (N = 326)
Discontinued from treatment during TP1	43 (13.3)	40 (12.3)
Subject died	2 (0.6)	2 (0.6)[a]
Insufficient clinical response[b]	0	7 (2.1)
Lost to follow-up	0	1 (0.3)
No longer willing to participate in study	11 (3.4)	9 (2.8)
Non-compliance with study treatment	1 (0.3)	0
Protocol violation	5 (1.5)	1 (0.3)
Withdrawn due to pregnancy	2 (0.6)	0
Adverse event	18 (5.6)	20 (6.1)
Related to study drug	13 (4.0)	15 (4.6)
Not related to study drug	5 (1.5)	5 (1.5)
Other[c]	4 (1.2)	0

Twenty-three (7.1%) and 13 (4.0%) patients in the Zessly and EU-authorized Remicade arms, respectively, discontinued treatment before Week 14. The main reasons were adverse event (Zessly: 8, EU-authorized Remicade: 7), no longer willing to participate in study (Zessly: 7, EU-authorized Remicade: 4) and protocol violation (Zessly: 5, EU-authorized Remicade: 1).

Thirty-five (10.8%) patients in the Zessly arm and 26 (8.0%) patients in the EU-authorized Remicade arm discontinued from the study during TP1, including 18 (5.6%) and 7 (2.1%) patients in the Zessly and EU-authorized Remicade arms, respectively, discontinued the study before Week 14.

Recruitment

First subject, First visit: 26 August 2014

Last subject completing week 30 visit: 29 June 2016

Study completion date (week 78 visit): 03 June 2017

Conduct of the study

Protocol deviations

All protocol deviations recorded for TP1 were assessed by the study team in a blinded manner according to the sponsors SOP. Protocol deviations considered to be potentially important are summarised in the table below.

Potentially Important Protocol Deviations (PIPDs), ITT Population – TP1

Category of Deviations	**Zessly (n=324)**	**EU-authorized Remicade (n=326)**	**Total (n=650)**
	n (%)	n (%)	n (%)
Inclusion/Exclusion	37 (11.4)	23 (7.1)	60 (9.2)
Investigational Product	32 (9.9)	27 (8.3)	59 (9.1)
Concomitant Medications	7 (2.2)	5 (1.5)	12 (1.8)
Procedures/Tests	55 (17.0)	51 (15.6)	106 (16.3)
Visit Schedule	6 (1.9)	5 (1.5)	11 (1.7)
Safety Reporting	1 (0.3)	3 (0.9)	4 (0.6)
Informed Consent	52 (16.0)	36 (11.0)	88 (13.5)
Other	19 (5.9)	12 (3.7)	31 (4.8)

Number (%) patients are presented in this table. A subject may have been included for more than one deviation.

The PP population determination ended at Week 14 efficacy assessments for TP1.

Patients excluded from the PP population – TP1

Protocol Deviations	**Zessly n (%)**	**Remicade-EU n (%)**	**Total n (%)**
Total number of subjects excluded[a]	45 (13. 9)	36 (11.0)	81 (12.5)
Randomization error	1 (0.3)	0	1 (0.2)
Inclusion/exclusion criteria deviation	2 (0.6)	2 (0.6)	4 (0.6)
GCP non-compliance (Inadequate source documentation)	2 (0.6)	2 (0.6)	4 (0.6)
Subjects who did not receive correct doses up to Week 6	15 (4.6)[b]	16 (4.9)	31 (4.8)
Missing Week 14 RA assessment[c]	21 (6.5)[b]	12 (3.7)	33 (5.1)
Concomitant medication not allowed by the protocol[d]	13 (4.0)	12 (3.7)	25 (3.9)

a. A subject may have more than 1 protocol deviation.
b. Subject 11071011 was excluded from the PP population but the reasons for exclusion (didn't receive correct doses up to Week 6; missing Week 14 RA assessment) were omitted. See Errata for additional details.
c. Includes a Week 14 RA assessment out of protocol defined window (> 14 days); joint assessment for 1 subject occurred on Study Day 114.
d. Includes 4 patients with a protocol deviation that occurred after Week 14 efficacy assessments; these patients were eligible for inclusion in the PP population; however, this was identified after database lock and they remained excluded from PP population.

Baseline data

The distribution of enrolled patients included 69.1% in Rest of World, 15.5% in North America and Western Europe, 7.2% in Japan, 6.8% in Latin America and 1.4% in South Korea. Within each region, enrolment in the 2 study arms was balanced as region was the stratification factor used at the randomization.

Demographic characteristics at baseline, ITT population (TP1)

	Zessly (N = 324)	Remicade-EU (N = 326)	Total (N = 650)
Gender, n (%)			
Female	258 (79.6)	264 (81.0)	522 (80.3)
Male	66 (20.4)	62 (19.0)	128 (19.7)
Age (years)			
Mean (SD)	52.8 (13.3)	52.8 (12.9)	52.8 (13.1)
Median (range)	54.0 (21-86)	53.5 (23-81)	54.0 (21-86)
Weight (kg)			
Mean (SD)	73.3 (19.8)	74.2 (20.0)	73.8 (19.9)
Median (range)	70.3 (32.5-179.4)	70.8 (36.2-162.7)	70.6 (32.5-179.4)
BMI (kg/m^2)			
Mean (SD)	27.2 (6.4)	27.7 (7.0)	27.4 (6.7)
Median (range)	25.7 (15.8-62.1)	26.7 (14.5-75.0)	26.2 (14.5-75.0)
Race, n (%)			
White	257 (79.3)	247 (75.8)	504 (77.5)
Black	5 (1.5)	9 (2.8)	14 (2.2)
Asian	46 (14.2)	45 (13.8)	91 (14.0)
Other	15 (4.6)	25 (7.7)	40 (6.2)
Unspecified	1 (0.3)	0	1 (0.2)
Ethnicity, n (%)			
Hispanic/Latino	31 (9.6)	32 (9.8)	63 (9.7)
Not Hispanic/Latino	292 (90.1)	294 (90.2)	586 (90.2)
Unspecified	1.0 (0.3)	0	1.0 (0.2)

a. One subject in the EU-authorized Remicade arm was discontinued from treatment due to pneumonia during TP1 and died after TP1 and the 29 June 2016 data cut-off date.

b. Collected on the CRF and defined at the investigator's discretion.

c. Other reasons for discontinuation are listed in Table 16.2.1.2.2.

Baseline rheumatoid arthritis characteristics, ITT population (TP1)

	Zessly (N = 324)	Remicade-EU (N = 326)	Total (N = 650)
RA duration (years)			
Mean (SD)	7.3 (8.6)	6.4 (6.7)	6.9 (7.7)
Median (range)	4.0 (0.3 - 45.0)	4.2 (0.3 - 40.0)	4.1 (0.3 - 45.0)
RF or anti-CCP antibody positive (n%)	249 (76.9)	267 (81.9)	516 (79.4)
Replaced and/or fused joint, n (%)	23 (7.1)	35 (10.7)	58 (8.9)
Swollen joint count			
Mean (SD)	16.1 (9.4)	16.3 (8.7)	16.2 (9.1)
Median (range)	13.0 (3 - 62)	14.0 (6 - 53)	14.0 (3 - 62)
Tender joint count			
Mean (SD)	24.7 (13.9)	25.7 (12.9)	25.2 (13.4)
Median (range)	21.0 (3 - 68)	23.0 (6 - 67)	22.0 (3 - 68)
hs-CRP (mg/L)			
Mean (SD)	25.8 (24.3)	25.3 (28.4)	25.6 (26.4)
Median (range)	17.9 (0.5 - 135.0)	16.5 (0.8 - 203.0)	17.4 (0.5 - 203.0)
DAS28-CRP			
Mean (SD)	6.0 (1.0)	6.0 (0.9)	6.0 (0.9)
Median (range)	5.9 (3 - 8)	6.0 (3 - 8)	6.0 (3 - 8)
HAQ-DI			
Mean (SD)	1.6 (0.6)	1.6 (0.7)	NC
Median (range)	1.6 (0 - 3.0)	1.6 (0 - 3.0)	NC
PAAP			
Mean (SD)	63.6 (20.6)	63.2 (21.6)	NC
Median (range)	66.0 (4.0 - 99.0)	67.5 (3.0 - 100.0)	NC
PGA			
Mean (SD)	65.4 (20.7)	63.9 (23.0)	NC
Median (range)	69.0 (5.0-100.0)	68.0 (2.0-99.0)	NC
PGAA			
Mean (SD)	65.4 (16.2)	64.2 (16.8)	NC
Median (range)	68.0 (19.0 - 100.0)	67.0 (1.0 - 98.0)	NC
Prior use of 1 biologic drug[a], n (%)	6 (1.9)[a]	3 (0.9)	9 (1.4)[a]
Anti-malarial drug use[b], n (%)	2 (0.6)	5 (1.5)	7 (1.1)
Sulfasalazine drug use[b], n (%)	2 (0.6)	2 (0.6)	4 (0.6)
Prior traditional DMARDs (non-biologic) other than methotrexate			
Mean (SD)	0.2 (0.5)	0.2 (0.5)	0.2 (0.5)
Median (range)	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)
Methotrexate dose (mg/week)[a]			
Mean (SD)	14.2 (4.5)	14.4 (4.5)	14.3 (4.5)
Median (range)	15.0 (8 - 32)	15.0 (6 - 25)	15.0 (6 - 32)
Duration of methotrexate use, n (%)			
<6 months	52 (16.0)	58 (17.8)	110 (16.9)
≥6 months to <1 year	78 (24.1)	83 (25.5)	161 (24.8)
≥1 year to <3 years	86 (26.5)	93 (28.5)	179 (27.5)
≥3 years	107 (33.0)	92 (28.2)	199 (30.6)
Corticosteroids use, n (%)	178 (54.9)	192 (58.9)	370 (56.9)

Overall for TP1, the baseline demographic characteristics, baseline disease characteristics and prior and concomitant medication use were generally balanced across the 2 treatment arms.

Patients receiving dose adjustment in TP1

Status	**Zessly (n=324)**	**EU-authorized Remicade (n=326)**
Patients receiving increased dose before week 14	0	0
Patients eligible and receiving increased dose at week 14	58 (17.90)	65 (19.94)
Patients eligible and receiving increased dose at week 22	12 (3.70)	7 (2.15)
Patients not eligible and receiving increased dose at week 14	2 (0.62)	3 (0.92)
Patients not eligible and receiving increased dose at week 22	11 (3.40)	8 (2.45)
Total	**83 (25.62)**	**83 (25.46)**

The number of patients that were eligible and received a one-time dose escalation at week 14 or 22 was similar between the two treatment groups. A small number of additional patients also received a one-time dose increase at week 14 or 22 that, in accordance with the protocol, were not eligible. These patients were balanced across the treatment groups.

Numbers analysed

Numbers analysed for efficacy

Number (%) patients	**Zessly (n=324)**	**EU-authorized Remicade (n=326)**
ITT population	324 (100)	326 (100)
PP population	279 (86.1)	290 (89.0)

Outcomes and estimation

Primary efficacy endpoint

Primary endpoint: Exact binomial approach for ACR20 response rate at Week 14 in study GP11-301

Visit	Exact Method[1]	Zessly	Remicade-EU	Difference in ACR20 response rate (GP1111 – Infliximab-EU)
		n (%)	n (%)	Point estimate (95% CI)
ITT population: primary endpoint				
Week 14	N	324	326	
	Score statistic method[a]	198 (61.1)	207 (63.5)	−2.39 (−9.92, 5.11)
	Unconditional approach	198 (61.1)	207 (63.5)	−2.39 (−9.98, 5.38)
PP population				
Week 14	N	279	290	
	Score statistic method[a]	186 (66.7)	195 (67.2)	−0.58 (−8.42, 7.23)
	Unconditional approach	186 (66.7)	195 (67.2)	−0.58 (−8.81, 7.66)

[1] The primary analyses for ACR20 at Week 14 were performed with the missing data imputed using a non-responder imputation method. For patients who discontinued (treatment/study) prior to Week 14, a non-responder was assigned to their Week 14 ACR20 assessment. A non-responder was also assigned to patients who were on study treatment and had a missing Week 14 ACR20 assessment.
a. Score statistic was the primary inference for equivalence.

Equivalence was shown for the ACR20 at Week 14 for both the ITT and PP populations, with the confidence intervals being well contained within ± 13.5%, so the study met its primary endpoint and supports biosimilarity in efficacy between Zessly and Remicade. Furthermore, the 95% confidence intervals for the treatment differences in ACR response rates between the 2 treatment groups were less than +/- 10%, which is considered not clinically relevant.

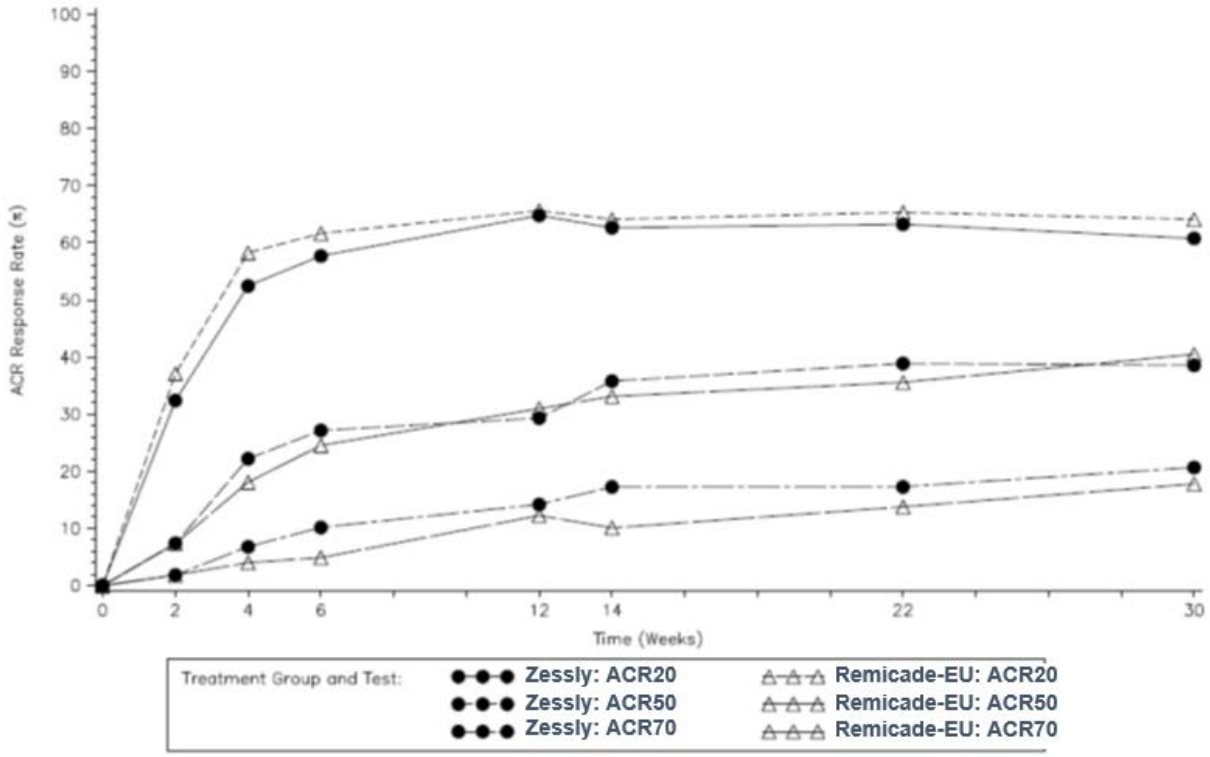
The results of the supportive and sensitivity analyses reflect those in the primary analysis and support the robustness of the primary efficacy analysis. The ACR20 response rates at week 14 in the primary analysis were similar to the applicant's assumption (57.5%) determined based on a weighted average across historical studies.

Secondary efficacy endpoints

ACR20, ACR50 and ACR70 responses by visit

Up to week 30 the ACR20, ACR50 and ACR70 responses were generally similar at all study visits.

Figure S1. ACR20, ACR50 and ACR70 Response Rate by Visit, ITT Population – TP1



For each of the individual ACR components the mean baseline value, mean absolute value and change from baseline at each timepoint was generally similar between both treatment arms. With the exception of hs-CRP where the maximal effect was seen at week 2, the maximal effect was seen at week 30.

DAS28-CRP response

In both the ITT and PP populations, at each study visit, DAS28-CRP responses and changes from baseline were similar between the Zessly and EU-authorized Remicade arms with the maximum effect being observed at Week 30 for both treatments.

DAS remission

The proportion of patients with DAS remission (DAS<2.6) was similar between the 2 treatment arms at each visit. In the ITT population, a total of 62 patients (19.1%) and 54 patients (16.6%) achieved DAS remission in the Zessly and EU-authorized Remicade arms, respectively, at Week 30.

European league against rheumatism (EULAR) response.

The proportions of patients in each response category were similar between the 2 arms. In the ITT population a total of 101 patients (31.2%) and 94 patients (28.8%) achieved good EULAR response in the Zessly and EU-authorized Remicade arms, respectively, at Week 30.

ACR/EULAR remission

At each study visit, a similar proportion of patients reached ACR/EULAR remission in the Zessly and EU-authorized Remicade arms, with a Week 30 response in 30 patients (9.3%) and 23 patients (7.1%), respectively in the ITT population.

Efficacy results in sub-populations

ACR20 and DAS28-CRP response for eligible patients with dose escalation

Taking into consideration the smaller numbers in the subgroups that received a dose increase, it is agreed that the ACR20 and DAS28-CRP response rates were similar at weeks 22 and 30 in both treatment groups in the 3mg/kg and 5mg/kg subgroups.

Demographic and other characteristics (ACR20 response rate at week 14)

Overall, no significant differences were observed in ACR20 response rates between the subgroups.

TP2

Participant flow

Subject disposition, TP 2 ITT

	Zessly/ Zessly (N = 280) n (%)	Remicade-EU/ Remicade-EU (N = 143) n (%)	Remicade-EU/ Zessly (N = 143) n (%)	Total (N = 566) n (%)
Treated during TP2	280 (100.0)	143 (100.0)	143 (100.0)	566 (100.0)
Completed TP2	254 (90.7)	126 (88.1)	126 (88.1)	506 (89.4)
Discontinued from treatment and remained in the study	0	1 (0.7)	1 (0.7)	2 (0.4)
Discontinued from study	26 (9.3)	16 (11.2)	16 (11.2)	58 (10.2)

Source: Table 14.1.1.1.2
Abbreviations: ITT = Intent-to-Treat; n = number of subjects; N = number of subjects in the TP2 ITT population; TP2 = Treatment Period 2.

Discontinuation from study, TP2 safety population

	Zessly/ Zessly (N = 280) n (%)	Remicade-EU/ Remicade-EU (N =143) n (%)	Remicade-EU/ Zessly (N =143) n (%)	Total (N = 566) n (%)
Discontinued from study	26 (9.3)	16 (11.2)	16 (11.2)	58 (10.2)
Subject died	1 (0.4)	0	0	1 (0.2)
Insufficient clinical response[a]	4 (1.4)	3 (2.1)	1 (0.7)	8 (1.4)
Lost to follow-up	1 (0.4)	1 (0.7)	0	2 (0.4)
No longer willing to participate in study	8 (2.9)	8 (5.6)	10 (7.0)	26 (4.6)
Non-compliance with study treatment	1 (0.4)	0	0	1 (0.2)
Adverse event	10 (3.6)	4 (2.8)	4 (2.8)	18 (3.2)
Related to study drug	7 (2.5)	3 (2.1)	4 (2.8)	14 (2.5)
Not related to study drug	3 (1.1)	1 (0.7)	0	4 (0.7)
Other[b]	1 (0.4)	0	1 (0.7)	2 (0.4)

Source: Table 14.1.1.2.2

Abbreviations: eCRF = electronic case report form; N = number of subjects in the TP2 safety population; n = number of subjects; TP2 = Treatment Period 2.

a. Collected on the eCRF and defined at the investigator's discretion.

b. Other reasons for discontinuation from the study are listed in Table 16.2.1.2.1.

Six hundred and fifty patients were included in TP1 and 566 patients continued on to TP2, of who 89.4% completed TP2. The number of patients in TP2 who discontinued treatment/discontinued from the study was balanced across the 3 treatment arms.

Baseline data

The demographic characteristics were similar between the 3 treatment groups in TP2. All baseline RA disease characteristics were generally similar between the three treatment groups in TP2 and the cumulative TP1+TP2 analysis. However, there were some numerical differences in the RA characteristics at the start of TP2 from the Week 30 value for the original EU-authorized Remicade arm.

A one-time dose escalation for patients who had not experienced a minimal improvement was possible from Week 14 study visit onwards, with a dose increase to 5 mg/kg. Similar numbers of patients had a one-time dose escalation in TP1 (Zessly: 83 patients [25.6%], EU-authorized Remicade: 83 patients [25.5%]). In TP2 one-time dose escalation occurred in the following: Zessly/Zessly: 22 patients [7.9%], EU-authorized Remicade/EU-authorized Remicade: 19 patients [13.3%], and EU-authorized Remicade/Zessly: 12 patients [8.4%])

Numbers analysed

Subject evaluation groups – TP2

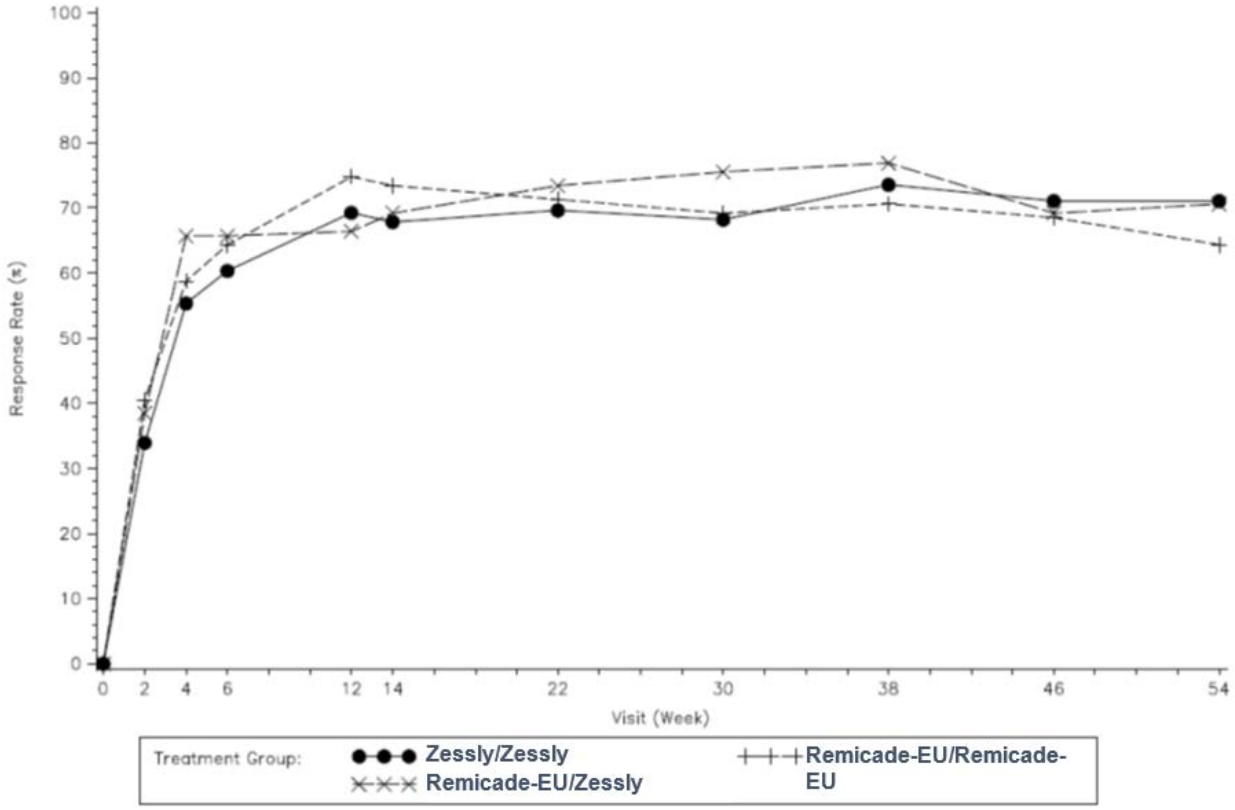
	Zessly/ Zessly n (%)	Remicade-EU/ Remicade-EU n (%)	Remicade-EU/ Zessly n (%)	Total n (%)
Analyzed for efficacy				
ITT population	280 (100.0)	143 (100.0)	143 (100.0)	566 (100.0)
Analyzed for PK				
PK population	280 (100.0)	143 (100.0)	143 (100.0)	566 (100.0)
Analyzed for safety				
Safety population	280 (100.0)	143 (100.0)	143 (100.0)	566 (100.0)

Source: Table 14.1.1.1.2
Abbreviations: ITT = Intent-to-Treat; n = number of subjects; PK = Pharmacokinetics; TP2 = Treatment Period 2.

Key secondary endpoints

ACR response

ACR20 response by visit in study GP11-301, TP1+TP2 (ITT, TP2)

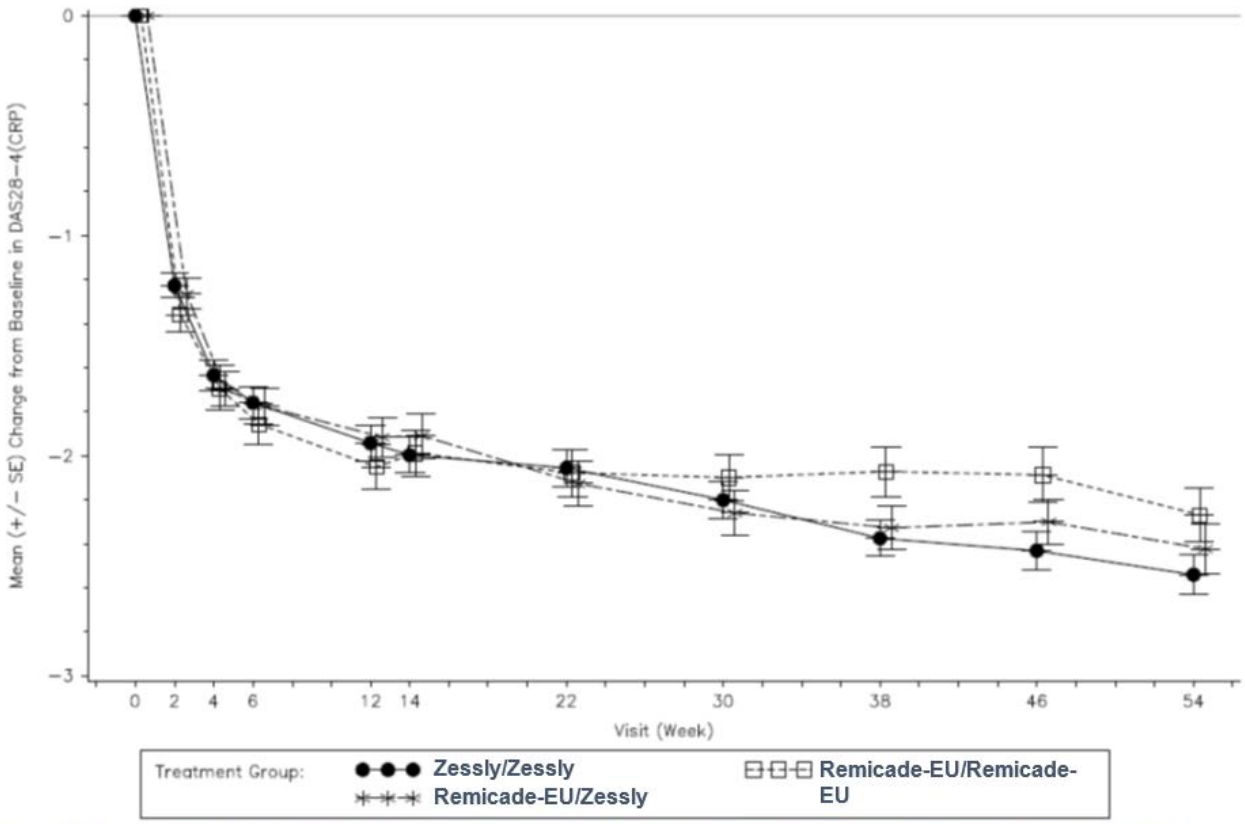


ACR20 = American College of Rheumatology; ITT = Intent-to-treat; TP = treatment period

Up to week 54 the ACR20, ACR50 and ACR70 responses were generally similar across all study groups.

DAS28-CRP

Mean change from baseline in DAS28-CRP by visit in study GP11-301, TP1+TP2 (ITT, TP2)



DAS28-CRP = Disease Activity Score 28; 4 components based on high sensitivity C-reactive protein; ITT = Intent-to-treat; TP = treatment period; SE = standard error

The decreases from Week 30 pre-dose to Week 54 were comparable among the 3 treatment groups, and the differences between the treatment groups were all less than the minimal clinically important difference of 0.6 for DAS28-CRP.

DAS remission

The percentage of patients who had achieved DAS remission at Week 30 pre-dose was 22.5%, 20.3% and 17.5% in the Zessly/Zessly, EU-authorized Remicade/EU-authorized Remicade, and EU-authorized Remicade/Zessly treatment groups, respectively. The value increased over TP2 in all treatment groups to 28.2%, 23.1% and 20.3% at Week 54.

Impact of immunogenicity on efficacy

ACR20 response rate for ADA and NAb subgroups in study GP11-301 (ITT population, up to week 54)

Visit	Subgroup	Zessly (N=324)			Remicade-EU (N=326)			Difference in ACR 20 response rate (Zessly vs Remicade-EU)
		N	n	n/N (%)	N	n	n/N (%)	Point estimate (95% CI)
Week 14	ADA-positive	100	51	51.0	103	51	49.5	1.49 (-12.27, 15.24)
	ADA-negative	220	152	69.1	222	158	71.2	-2.08 (-10.61, 6.45)
	NAb-positive	74	37	50.0	81	37	45.7	4.32 (-11.41, 20.05)
	NAb-negative	246	166	67.5	244	172	70.5	-3.01 (-11.20, 5.17)
Week 30	ADA-positive	157	91	58.0	167	94	56.3	1.67 (-9.11, 12.46)
	ADA-negative	163	106	65.0	158	115	72.8	-7.75 (-17.84, 2.33)
	NAb-positive	124	69	55.7	143	78	54.6	1.10 (-10.86, 13.06)
	NAb-negative	196	128	65.3	181	131	72.4	-7.07 (-16.39, 2.25)
		Zessly/Zessly (N=280)			Remicade-EU/ Remicade-EU (N=143)			Difference in ACR 20 response rate (Zessly/Zessly vs Remicade-EU/ Remicade-EU)
Week 30	ADA-positive	140	87	62.1	78	46	59.0	3.17 (-10.39,16.72)
	ADA-negative	140	104	74.3	65	53	81.5	-7.25 (-19.14,4.64)
	NAb-positive	111	66	59.5	67	40	59.7	-0.24 (-15.12,14.64)

Visit	Subgroup	Zessly (N=280)			Remicade-EU (N=143)			Difference in ACR 20 response rate (Zessly vs Remicade-EU)
		N	n	n/N (%)	N	n	n/N (%)	Point estimate (95% CI)
	NAb-negative	169	125	74.0	75	59	78.7	-4.70 (-16.09,6.69)
Week 54	ADA-positive	156	103	66.0	88	50	56.8	9.21 (-3.53,21.95)
	ADA-negative	124	96	77.4	55	42	76.4	1.06 (-12.37,14.48)
	NAb-positive	127	83	65.4	82	46	56.1	9.26 (-4.30,22.82)
	NAb-negative	153	116	75.8	61	46	75.4	0.41 (-12.35,13.17)

Table displays ACR20 response rate within ADA positive and negative groups for the ITT population of TP1 for visits in TP1 (Week 14 and Week 30) and for the continued arms of ITT population of TP2 for visits in TP2 (Week 30 and Week 54) as well as the difference in response rate with 95% CIs.

Abbreviations: ACR20 = 20% improvement by American College of Rheumatology definition of improvement criteria; ADA = anti-drug antibody; CI = confidence interval; Infliximab-EU = EU-authorized Remicade; ITT = Intent-to-Treat; n = number of patients in each subgroup with ACR20 response; N = number of patients in each subgroup; NAb=neutralizing antibody, OBS = observed cases.

In-line with historical data on Remicade, in all treatment groups up to week 54, the response rates were higher in patients that were ADA negative compared to those that were ADA/NAb positive.

Ancillary analyses

Efficacy results in sub-populations

ACR 20 and DAS28-CRP response for patients with dose escalation

A total of 166 patients (25.5%) received an increased dose during TP1 with similar proportion between 2 treatment arms: 83 patients (25.6%) in the Zessly arm and 83 patients (25.5%) in the EU-authorized Remicade arm.

ACR20 response rate at Weeks 22 and 30

Similar response rates at Week 22 were observed for patients between the Zessly and EU-authorized Remicade arms who continued on 3 mg/kg, and for patients who received 5 mg/kg at Week 14. For patients who were eligible and dose escalated first at Week 22, similar Week 30 response rates were observed between the Zessly and EU-authorized Remicade arms.

Descriptive summary of ACR20 response rate at Weeks 22 and 30 in study GP11-301 (ITT population excluding patients not dosed at Week 14, TP1)

Visit	Dose	ACR20 Response	Zessly (N=300)	Remicade-EU (N=312)	Difference in ACR20 Response Rate (Zessly vs Remicade-EU)
			n (%)	n (%)	%
Week 22	3 mg/kg	Yes	180 (75.0)	185 (75.8)	−0.82
		No	58 (24.2)	58 (23.8)	
		Missing	2 (0.8)	1 (0.4)	
	5 mg/kg	Yes	23 (38.3)	27 (39.7)	−1.37
		No	36 (60.0)	36 (52.9)	
		Missing	1 (1.7)	5 (7.4)	
Week 30	3 mg/kg	Yes	169 (70.4)	181 (74.2)	−3.76
		No	65 (27.1)	55 (22.5)	
		Missing	6 (2.5)	8 (3.3)	
	5 mg/kg	Yes	27 (45.0)	27 (39.7)	5.29
		No	29 (48.3)	30 (44.1)	
		Missing	4 (6.7)	11 (16.2)	

Treatment comparisons for ACR20 response rate using the observed data (without missing data imputation) were conducted for patients who dose escalated first at Week 14 and Week 22, respectively. No statistically significant differences were observed between the 2 arms

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application.

These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 2 Summary of Efficacy for trial GP11-301

Title: A Phase 3 Randomized, Double-Blind Study Assessing the Efficacy and Safety of Zessly and Infliximab in Combination with Methotrexate in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Methotrexate				
Study identifier	GP11-301			
Design	Double-blind, randomized, multi-center study			
	Duration of main phase:		TP1: 30 weeks (Patients randomized 1:1 to receive Zessly or EU-authorized Remicade) TP2: 24 weeks (Patients on EU-authorized Remicade re-randomized 1:1 to receive Zessly or continue on EU-authorized Remicade. Patients on Zessly all remain on Zessly))	
	Duration of Run-in phase:		not applicable	
	Duration of Extension phase:		24 weeks (open-label extension with all patients receiving Zessly)	
Hypothesis	Equivalence			
Treatments groups	Zessly		3mg/kg IV at Week 0, 2, 6, 14, 22, 30 combined with methotrexate number randomized: 324	
	EU-authorized Remicade		3mg/kg IV at Week 0, 2, 6, 14, 22, 30 combined with methotrexate number randomized: 326	
Endpoints and definitions (TP1)	Primary endpoint	ACR20 W14	% patients achieving ACR20 response at week 14	
	Secondary endpoint	ACR20 W30	% patients achieving ACR20 response at week 30	
	Secondary endpoint	ACR50 W14	% patients achieving ACR50 response at week 14	
	Secondary endpoint	ACR50 W30	% patients achieving ACR50 response at week 30	
	Secondary endpoint	ACR70 W14	% patients achieving ACR70 response at week 14	
	Secondary endpoint	ACR70 W30	% patients achieving ACR70 response at week 30	
	Secondary endpoint	DAS28-CRP W14	DAS28-CRP change from baseline at week 14	
	Secondary endpoint	DAS28-CRP W30	DAS28-CRP change from baseline at week 30	
Database lock (TP1)	TBC (last patient completed their week 30 visit on 29 June 2016)			
Results and Analysis (TP1)				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (All) Per protocol (primary EP only)			
Descriptive statistics and estimate variability	Treatment group	Zessly	EU-authorized Remicade	
	Number of subject	324	326	

	ACR20 W14 (%) ITT PP	198/324 (61.1) 186/279 (66.7)	207/326 (63.5) 195/290 (67.2)	
	ACR20 W30 (%) ITT	197/324 (60.8)	209/326 (64.1)	
	ACR50 W14 (%) ITT	116/324 (35.8)	108 (33.1)	
	ACR50 W30 (%) ITT	125/324 (38.6)	132 (40.5)	
	ACR70 W14 (%) ITT **ACR70 W30** (%) ITT	56 (17.3) 67 (20.7)	33 (10.1) 58 (17.8)	

Effect estimate per comparison	Primary endpoint **ACR20 W14** ITT	Comparison groups	Zessly vs EU-authorized Remicade
		Treatment difference	-2.39
		95% CI	-9.92, 5.11
		Test	- 13.5% < CI < + 13.5%
	Primary endpoint **ACR20 W14** PP	Comparison groups	Zessly vs EU-authorized Remicade
		Treatment difference	-0.58
		95% CI	-8.42, 7.23
		Test	- 13.5% < CI < + 13.5%
	Secondary endpoint **ACR20 W30** ITT	Comparison groups	Zessly vs EU-authorized Remicade
		Treatment difference	-3.31
	Secondary endpoint **ACR50 W14** ITT	Comparison groups	Zessly vs EU-authorized Remicade
		Treatment difference	2.67
	Secondary endpoint **ACR50 W30** ITT	Comparison groups	Zessly vs EU-authorized Remicade
		Treatment difference	-1.91
	Secondary endpoint **ACR70 W14** ITT	Comparison groups	Zessly vs EU-authorized Remicade
		Treatment difference	7.16
	Secondary endpoint **ACR70 W30** ITT	Comparison groups	Zessly vs EU-authorized Remicade
		Treatment difference	2.89
Analysis description	**ACR20 and secondary endpoints through to week 54 (TP2)**		
	Treatment group: Zessly/GP111 N=280 Treatment group: EU-authorized Remicade/EU-authorized Remicade N=143 Treatment group: EU-authorized Remicade/Zessly N=143 The efficacy results up to week 54 continue to support the conclusion of biosimilarity between Zessly and EU-authorized Remicade		

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme to show biosimilarity between Zessly and Remicade is based on a single Phase III study comparing the efficacy and safety of Zessly and EU-authorized Remicade in combination with methotrexate in male and female patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate (GP11-301).

A single pivotal Phase III equivalence trial comparing the test and reference product is considered adequate to support this biosimilar application.

The design of the study including the choice of the indication (rheumatoid arthritis), the clinical setting (patients not adequately controlled with methotrexate), dose regimen, the primary endpoint (ACR20 at week 14) and the equivalence margin (± 13.5%) are in line with the CHMP guidance and were endorsed in CHMP Scientific Advice. Indeed, this clinical model was considered sufficiently sensitive to enable the detection of differences between the two products.

The study was conducted in 5 geographic regions: North America and Western Europe, Japan, Republic of Korea, Latin America, and Rest of the world. Only 15.5% of the enrolled patients were from the North America and Western Europe geographic region. However, within each region, enrolment in the 2 study arms was balanced as region was the stratification factor used at the randomization and this is acceptable for a biosimilar exercise, provided that similar results are shown across geographical regions.

This study is on-going but data on the double-blind period of the study up to week 54 is complete. The final 24 weeks of the study comprise an open-label period where all patients will receive Zessly.

Efficacy data and additional analyses

In treatment period 1, baseline patient demographics and disease characteristics were well balanced across the two treatment groups, as were prior and concomitant medications. The number of patients that were eligible in accordance with the protocol and received a one-time dose escalation at week 14 or 22 was similar between the two treatment groups. The number of patients during TP1 that discontinued from study treatment and that discontinued from the study was comparable across the two treatment arms. The number of patients that discontinued treatment/the study due to adverse events was low and balanced across the 2 treatment arms.

Of the 650 patients randomized in TP1, 566 patients continued on to TP2, of who 89.4% completed TP2. The number of patients in TP2 who discontinued treatment/discontinued from the study was balanced across the 3 treatment arms. The demographic characteristics were similar between the 3 treatment groups in TP2. All baseline RA disease characteristics were generally similar between the three treatment groups in TP2 and the cumulative TP1+TP2 analysis. However, there were some numerical differences in the RA characteristics at the start of TP2 from the Week 30 value for the original EU-authorized Remicade arm. In TP2 one-time dose escalation occurred in the following: Zessly/Zessly: 22 patients [7.9%], EU-authorized Remicade/EU-authorized Remicade: 19 patients [13.3%], and EU-authorized Remicade/Zessly: 12 patients [8.4%]).

Equivalence was shown for the ACR20 at Week 14 in both the ITT and PP populations, with the confidence intervals being well contained inside ± 13.5%, so the study met its primary endpoint and supports biosimilarity in efficacy between Zessly and Remicade. Furthermore the 95% confidence intervals for the treatment differences in ACR response rates between the 2 treatment groups were less than +/- 10% which is considered not clinically relevant. The ACR20 response rates at week 14 in the primary analysis were similar to the applicant's assumption (57.5%) determined based on a weighted average across historical studies. The results of the supportive, sensitivity and sub-group analyses (including patients with dose escalation and by demographics including region) reflect those in the primary analysis and support the robustness of the primary efficacy analysis.

Furthermore, the results of secondary endpoints, in particular ACR50, ACR70 and DAS28-CRP, were all consistent with the results of the primary endpoint and were similar between both treatment groups up to week 54.

In-line with historical data on Remicade, in all treatment groups up to week 54, the response rates were higher in patients that were ADA negative compared to those that were ADA/NAb positive.

2.5.3. Conclusions on the clinical efficacy

The single pivotal efficacy equivalence trial met its primary endpoint with the 95% confidence intervals of the treatment difference well contained within the equivalence margin. The robustness of this result is supported by the sensitivity, supportive and subgroup analyses, together with the results of the secondary endpoints up to week 54.

These results demonstrate equivalence in clinical efficacy between the proposed biosimilar Zessly (Zessly) and the reference product Remicade (EU-authorized Remicade).

2.6. Clinical safety

The comparative safety of Zessly was investigated in two studies:

- The PK study GP11-101 in healthy volunteers;
- The confirmatory efficacy and safety study GP11-301 in patients with RA.

Safety data are presented by study. Due to the different objectives, design and populations in these 2 clinical studies, no combined or integrated analyses were planned or performed. In both studies, the safety population comprised all subjects/patients treated with at least 1 dose of study drug.

For study GP11-301 data up to pre-dose week 30 comparing the Zessly and EU-authorized Remicade treatment groups is presented (TP1). Data from week 30-54 comparing the Zessly/Zessly, EU-authorized Remicade/EU-authorized Remicade and EU-authorized Remicade/Zessly treatment groups is also presented, together with a combined analysis of TP1 and TP2 where appropriate/available.

Patient exposure

In study **GP11-101** 146 subjects received a single IV dose of 10mg/kg infliximab: 49 subjects received Zessly, 48 received EU-sourced Remicade and 49 received US-sourced Remicade.

In study **GP11-301** patients received 3 mg/kg body weight administered IV at Weeks 0, 2, and 6, followed by a maintenance regimen of every 8 weeks, which is the approved dosing regimen for US-licensed Remicade in RA therapy. A one-time dose escalation for patients who had not experienced a minimal improvement was possible from Week 14 study visit onwards, with a dose increase to 5 mg/kg.

TP1

Drug exposure in study GP11-301 (TP1), safety population

	Zessly (N = 323)	Remicade-EU (N = 326)	Total (N = 649)
Total dose administered (mg)			
Median (range)	1068.0 (138.3-2690.8)	1103.5 (217.2-3091.3)	1078.0 (138.3-3091.3)
Mean (SD)	1110.8 (389.52)	1137.2 (377.16)	1124.1 (383.29)
Missed doses			
Number of patients [n (%)]	14 (4.3)	15 (4.6)	29 (4.5)
Due to AE[1], n (%)	10 (3.1)	11 (3.4)	21 (3.2)
Number of missed doses			
Median (range)	0.0 (0.0-2.0)	0.0 (0.0-3.0)	0.0 (0.0-3.0)
Mean (SD)	0.1 (0.26)	0.1 (0.31)	0.1 (0.29)
Infusion interruption [n (%)]	15 (4.6)	18 (5.5)	33 (5.1)
Due to AE [1]	12 (3.7)	15 (4.6)	27 (4.2)
Dose reduction [n (%)]	0	1 (0.3)	1 (0.2)
Due to AE [1]	0	0	0

The administered total dose was similar between treatment arms: Zessly mean (SD) 1110.8 mg (389.52) and EU-authorized Remicade 1137.2 mg (377.16). Less than 5% of the total number of patients (14 [4.3%] patients on Zessly and 15 [4.6%] patients on EU-authorized Remicade) missed a dose and the main reason was due to AEs. The maximum number of missed doses was 3. There were no dose reductions due to AEs in either treatment arm. A total of 60 (18.5%) patients in the Zessly arm and 68 (20.9%) patients in the EU-authorized Remicade arm had dose escalation to 5 mg/kg at Week 14. Twenty-three (23) (7.1%) in the Zessly arm and 15 (4.6%) patients in the EU-authorized Remicade arm had dose escalation to 5 mg/kg first at Week 22.

The dosing instructions for Remicade vary depending on the indication and include dose escalation for patients with insufficient response or loss of clinical response. In patients with RA, studies with Remicade with doses ranging up to 10 mg/kg indicate a broad therapeutic window for infliximab with regards to the safety profile (Maini et al 1999, Westhovens et al 2006). Therefore, and also due to similar numbers of

patients with one-time dose escalation to 5mg/kg in TP1 in both treatment arms, no further safety subgroup analysis in patients with dose escalation has been undertaken.

TP2

Drug exposure in TP2, SAF

	Zessly/ Zessly (N=280) n (%)	Remicade-EU/ Remicade-EU (N=143) n (%)	Remicade-EU/ Zessly (N=143) n (%)	Total (N=560) n (%)
Total dose administered (mg)				
Median (range)	707.3 (170.4-2106.0)	684.0 (60.0-2169.0)	738.9 (189.0-2446.5)	703.4 (60.0-2446.5)
Mean (SD)	784.2 (328.7)	749.9 (332.5)	789.2 (316.1)	776.8 (326.3)
Missed doses				
Number of patients [n (%)]	12 (4.3)	4 (2.8)	4 (2.8)	20 (3.5)
Due to AE[1], n (%)	9 (3.2)	4 (2.8)	0	13 (2.3)
Number of missed doses				
Median (range)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
Mean (SD)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)
Infusion interruption [n (%)]	8 (2.9)	10 (7.0)	4 (2.8)	22 (3.9)
Due to AE[1]	7 (2.5)	9 (6.3)	4 (2.8)	20 (3.5)
Dose reduction [n (%)]	7 (2.5)	1 (0.7)	2 (1.4)	10 (1.8)
Due to AE[1]	0	0	0	0

[1] Study treatment could be temporarily withheld at the discretion of the investigator for safety reasons.
Abbreviations: AE=adverse event; Infliximab-EU=EU-authorized Remicade; n=number of patients; N=number of patients in SAF; SAF = safety population; SD=standard deviation; TP2=Treatment Period 2.

In TP2 exposure to the IP is generally comparable across the three treatment groups.

Adverse events

Study GP11-101

The number of subjects reporting TEAEs was 17 (34.7%) in the Zessly arm compared to 21 (43.8%) in the EU-authorized Remicade arm and 18 (36.7%) in the US-licensed Remicade arm. TEAEs were most commonly reported with PTs belonging to the SOCs nervous system disorders (6.1%, 6.3% and 8.2% respectively) as well as infections and infestations (6.1%, 4.2% and 0% respectively); the most common PTs within these SOCs were headache, and upper respiratory tract infection, reported for similar proportions of subjects in both treatment arms.

Treatment-related AEs were reported for 5 subjects (10.2%) in the Zessly arm, 12 subjects (25.0%) in the EU-authorized Remicade arm and by 11 subjects (22.4%) in the US-licensed Remicade arm.

No Grade 4 or 5 TEAEs occurred in study GP11-101. Eight subjects had grade 3 AEs. The most common grade 3 TEAE was granulocytopenia, reported for 5 subjects (3.4%) overall: 3 subjects (6.3%) in the EU-authorized Remicade arm and 2 subjects (4.1%) in the US-licensed Remicade arm. Two further grade 3 PTs were increased AST and myalgia, reported for 1 subject each (2.0%) in the US-licensed Remicade arm. Grade 3 mental disorder (not related to study drug) was reported for 1 subject (2.0%) in the Zessly arm.

The overall safety profile appears generally comparable between treatment groups in study GP11-101. The number of AEs/subjects with AEs assessed as treatment-related was lower in the Zessly arm compared with the EU-authorized Remicade and US-licensed Remicade arms, although it is acknowledged that the total numbers are small.

Study GP11-301

TP1

As of 29 June 2016, 185 (57.3%) patients reported 486 TEAEs in the Zessly treatment arm and 176 (54%) patients reported 492 TEAEs in the EU-authorized Remicade treatment arm.

All-causality TEAEs by SOC and PT in study GP11-301 (TP1), occurring in 3% or more of patients with RA in any arm at PT level, safety population

System Organ Class Preferred Term	Zessly (N = 323) n (%)	Remicade-EU (N = 326) n (%)
Any AEs	**185 (57.3)**	**176 (54.0)**
Blood and lymphatic system disorders	**19 (5.9)**	**18 (5.5)**
Anemia	7 (2.2)	10 (3.1)
Gastrointestinal disorders	**41 (12.7)**	**36 (11.0)**
Nausea	7 (2.2)	10 (3.1)
General disorders and administration site conditions	**22 (6.8)**	**22 (6.7)**
Pyrexia	3 (0.9)	10 (3.1)
Infections and infestations	**86 (26.6)**	**72 (22.1)**
Bronchitis	14 (4.3)	6 (1.8)
Nasopharyngitis	14 (4.3)	13 (4.0)
Upper respiratory tract infection	12 (3.7)	13 (4.0)
Injury, poisoning and procedural complications	**36 (11.1)**	**36 (11.0)**
Infusion-related reaction (IRR)	19 (5.9)	21 (6.4)
Investigations	**37 (11.5)**	**26 (8.0)**
ALT increased	19 (5.9)	15 (4.6)
AST increased	14 (4.3)	11 (3.4)
Nervous system disorders	**17 (5.3)**	**23 (7.1)**
Headache	10 (3.1)	9 (2.8)
Skin and subcutaneous tissue disorders	**38 (11.8)**	**41 (12.6)**
Rash	8 (2.5)	10 (3.1)
Vascular disorders	**20 (6.2)**	**23 (7.1)**
Hypertension	14 (4.3)	11 (3.4)

In-line with the known safety profile of infliximab, TEAEs were most commonly reported in the SOC 'infections and infestations' with 86 (26.6%) patients in the Zessly arm and 72 (22.1%) patients in the EU-authorized Remicade arm.

Similar percentages of patients in both treatment arms had treatment-related TEAEs (Zessly: 81 patients [25.1%] and EU-authorized Remicade: 75 patients [23.0%]). Four patients (1.2%) in each treatment arm had treatment-related SAEs. Less than 5% of patients in each arm had treatment-related TEAEs of grade 3 or higher. The most common drug-related PTs were IRR with 17 (5.3%) TEAEs reported in the Zessly arm and 20 (6.1%) in the EU-authorized Remicade arm; and increased ALT with 12 (3.7%) TEAEs reported in the Zessly arm and 8 (2.5%) in the EU-authorized Remicade arm, this is in-line with the overall most common PTs. Whilst a slightly higher number of treatment-related TEAEs were seen in the Zessly arm in the investigations SOC (23 [7.1%] vs 10 [3.1%]; with the exception of the AEs 'ALT', 'AST' and 'lymphocyte morphology abnormal' which were essentially balanced across the treatment arms, this slight imbalance came from single AEs per preferred term.

Within the Zessly treatment arm, 33 (10.2%) and 3 (0.9%) patients reported TEAEs of Grade 3 and Grade 4-5, respectively. In the EU-authorized Remicade arm, 30 (9.2%) and 6 (1.8%) patients reported TEAEs of Grade 3 and Grade 4-5, respectively.

Within the Zessly treatment arm, 15 (4.6%) patients reported Grade 3 treatment-related TEAEs. No treatment-related TEAEs of Grade 4-5 were reported. In the EU-authorized Remicade arm, 12 (3.7%) and 3 (0.9%) patients reported treatment-related TEAEs of Grade 3 and Grade 4-5, respectively. IRR was the only treatment-related TEAE of Grade 3 or higher that occurred in ≥1% of patients in any treatment arm. It was reported by 5 (1.5%) and 2 (0.6%) patients in the Zessly and EU-authorized Remicade treatment arms, respectively.

During TP1, the overall safety profile appears generally comparable between treatment groups in study GP11-301.

TP2

All-causality TEAEs by SOC and PT, occurring in 3% or more of patients with RA in any treatment group at PT level, SAF, TP2

System Organ Class Preferred Term	Zessly/ Zessly (N=280) n (%)	Remicade-EU/ Remicade-EU (N=143) n (%)	Remicade-EU/ Zessly (N=143) n(%)
Any AEs	**103 (36.8)**	**48 (33.6)**	**54 (37.8)**
Infections and infestations	**45 (16.1)**	**21 (14.7)**	**19 (13.3)**
Nasopharyngitis	9 (3.2)	5 (3.5)	2 (1.4)
Injury, poisoning and procedural complications	**18 (6.4)**	**16 (11.2)**	**9 (6.3)**
Infusion-related reaction (IRR)	9 (3.2)	12 (8.4)	6 (4.2)

Abbreviations: AE=adverse event; Infliximab-EU=EU-authorized Remicade; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients in each category; N=number of patients included in the safety population; PT=preferred term; RA = rheumatoid arthritis; SAF=safety population; SOC=system organ class; TEAE=treatment-emergent AE; TP2=Treatment Period 2. MedDRA (version 19.1) coding dictionary was applied.

All-causality TEAEs by SOC and PT (TP1+TP2), occurring in 3% or more of patients with RA in any treatment group at PT level, SAF, TP2

System Organ Class Preferred Term	Zessly/ Zessly (N=280) n (%)	Remicade-EU/ Remicade-EU (N=143) n (%)	Remicade-EU/ Zessly (N=143) n(%)
Any AEs	**189 (67.5)**	**85 (59.4)**	**91 (63.6)**
Blood and lymphatic system disorders	**19 (6.8)**	**6 (4.2)**	**13 (9.1)**
Anemia	9 (3.2)	4 (2.8)	8 (5.6)
Gastrointestinal disorders	**37 (13.2)**	**20 (14.0)**	**19 (13.3)**
Nausea	5 (1.8)	7 (4.9)	5 (3.5)
Diarrhoea	7 (2.5)	5 (3.5)	3 (2.1)
General disorders and administration site conditions	**20 (7.1)**	**10 (7.0)**	**6 (4.2)**
Pyrexia	1 (0.4)	5 (3.5)	3 (2.1)
Infections and infestations	**98 (35.0)**	**40 (28.0)**	**41 (28.7)**
Bronchitis	13 (4.6)	5 (3.5)	3 (2.1)
Nasopharyngitis	20 (7.1)	12 (8.4)	5 (3.5)
Upper respiratory tract infection	18 (6.4)	7 (4.9)	8 (5.6)
Urinary tract infection	9 (3.2)	5 (3.5)	7 (4.9)
Injury, poisoning and procedural complications	**38 (13.6)**	**24 (16.8)**	**17 (11.9)**
Infusion-related reaction (IRR)	15 (5.4)	14 (9.8)	9 (6.3)
Contusion	2 (0.7)	7 (4.9)	0
Fall	9 (3.2)	3 (2.1)	0
Investigations	**39 (13.9)**	**12 (8.4)**	**15 (10.5)**

System Organ Class Preferred Term	Zessly/ Zessly (N=280) n (%)	Remicade-EU/ Remicade-EU (N=143) n (%)	Remicade-EU/ Zessly (N=143) n(%)
ALT increased	18 (6.4)	6 (4.2)	9 (6.3)
AST increased	15 (5.4)	3 (2.1)	8 (5.6)
Musculoskeletal and connective tissue disorders	**45 (16.1)**	**19 (13.3)**	**21 (14.7)**
Arthralgia	6 (2.1)	3 (2.1)	5 (3.5)
Rheumatoid arthritis	9 (3.2)	9 (6.3)	4 (2.8)
Nervous system disorders	**18 (6.4)**	**16 (11.2)**	**12 (8.4)**
Headache	8 (2.9)	6 (4.2)	6 (4.2)
Skin and subcutaneous tissue disorders	**36 (12.9)**	**21 (14.7)**	**19 (13.3)**
Rash	10 (3.6)	6 (4.2)	4 (2.8)
Vascular disorders	**20 (7.1)**	**10 (7.0)**	**11 (7.7)**
Hypertension	13 (4.6)	6 (4.2)	6 (4.2)

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; Infliximab-EU=EU-authorized Remicade; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients in each category; N=number of patients included in the safety population; PT=preferred term; RA=rheumatoid arthritis; SAF=safety population; SOC=system organ class; TEAE=treatment-emergent AE; TP1=Treatment Period 1, TP2=Treatment Period 2.
MedDRA (version 19.1) coding dictionary was applied.

In TP2 similar proportions of patients experienced all causality TEAEs, treatment-related TEAEs: Zessly/Zessly 32 (11.4%), EU-authorized Remicade/EU-authorized Remicade 20 (14.0%) and EU-authorized Remicade/Zessly 16 (11.2%) and all causality TEAEs of grade 3 or higher: Zessly/Zessly 20 (7.1%), EU-authorized Remicade/EU-authorized Remicade 11 (7.7%) and EU-authorized Remicade/Zessly 6 (4.2%) across the 3 treatment groups.

In the TP1+TP2 analysis the number of all causality TEAEs was numerically slightly higher in the Zessly/Zessly group (67.5%) compared with the EU-authorized Remicade (59.4%) and EU-authorized Remicade/Zessly (63.6%) groups. However, the number of treatment-related TEAEs and all causality TEAEs of grade 3 or higher across the 3 treatment groups is generally balanced. The potential effect of the smaller size of the 2 infliximab arms (EU-authorized Remicade/EU-authorized Remicade and EU-authorized Remicade/Zessly) following re-randomisation at Week 30 also needs to be taken into consideration.

During TP1 and TP2, the overall safety profile appears generally comparable between treatment groups in study GP11-301.

Serious adverse event / deaths / other significant events

Study GP11-101

No deaths were reported. Two patients experienced an SAE: one unrelated case of ‘mental disorder’ in the Zessly treatment arm and one related case of ‘myalgia’ in the EU-infliximab arm.

Study GP11-301

TP1

Up to 29 June 2016, 4 deaths were reported, two in each treatment arm. One of the deaths in the EU-authorized Remicade arm occurred outside of the TP1 data cut-off. None of the deaths were assessed by the sponsor or the investigator as treatment-related.

The number of all-causality treatment-emergent SAEs was low, with 16 (5%) patients reporting SAEs in the Zessly arm and 20 (6.1%) in the EU-authorized Remicade arm, and generally comparable between the two treatment arms. In keeping with the known safety profile of infliximab, the SOC with the highest proportion of patients who had SAEs was 'Infections and infestations' with 6 (1.9%) patients in the Zessly group and 9 (2.8%) patients in the EU-authorized Remicade group. Within the SAEs in this SOC, in the EU-authorized Remicade group one SAE 'Community-acquired pneumonia' was fatal; this death was assessed as not related to study treatment by the sponsor and investigator.

In addition, there were 2 pregnancy cases reported during TP1 in the Zessly treatment arm that were considered significant AEs. In one case the outcome was the birth of a healthy male infant, in the other case the subject underwent induced abortion. No changes to the proposed information in section 4.6 of the SmPC are proposed or considered required based on these 2 pregnancy cases.

TP2

One death occurred in TP2 in the Zessly/Zessly treatment group. This was assessed by the investigator and sponsor as not related to the study drug.

The number of all-causality treatment-emergent SAEs was low and generally comparable between the three treatment arms with 13 (4.6%) patients reporting SAEs in the Zessly/Zessly arm, 11 (7.7%) in the EU-authorized Remicade/EU-authorized Remicade arm, and 4 (2.8%) in the EU-authorized Remicade/Zessly arm.

Similarly, for the combined TP1+TP2 analysis the number of all-causality treatment-emergent SAEs was generally comparable between the three treatment arms.

Adverse events of interest

Study GP11-101

Among AESIs, only infectious AEs were reported in this study. There were 6 (12.2%), 3 (6.3%) and 2 (4.1%) subjects in the Zessly, EU-authorized Remicade and US-licensed Remicade treatment groups respectively, who experienced AEs under the SOC of "Infections and infestations". Of these 3 (6.1%), 3 (6.3%) and no (0%) subjects respectively experienced treatment-related AEs. No tuberculosis or pneumonia cases were reported.

Although more subjects experienced AEs under the SOC of "Infections and infestations" in the Zessly treatment group, all of these AEs were Grade 1. Two subjects experienced Grade 2 AEs; 1 in the EU-authorized Remicade treatment group who experienced groin abscess (treatment-related), and 1 in the US-licensed Remicade treatment group who experienced cellulitis (not treatment-related).

Study GP11-301

Infusion related reactions, infections (including TB and pneumonia), malignancy (including lymphoma) and hypersensitivity were identified as adverse events of special interest for infliximab. At the request of the

CHMP, taking into consideration section 4.4 of the Remicade SmPC and the identified risks in the RMP, the following were also included as AESI in the updated assessment of safety (up to week 54) submitted with the responses to the D120 LoQ: 'Hepatobiliary events', 'SLE/lupus-like syndrome', demyelinating disorders', 'Heart failure', 'Haematological disorders' and 'delayed hypersensitivity (serum sickness)'.

TP1

Infusion-related reactions

Low and similar proportions of patients in each treatment arm experienced an IRR: 19 (5.9%) in the Zessly arm and 21 (6.4%) in the EU-authorized Remicade arm. No patients experienced an SAE and the number of patients that discontinued treatment (6 [1.9%] Zessly vs 6 [1.8%] EU-authorized Remicade) or temporarily discontinued (7 [2.2%] Zessly vs 11 [3.4%] EU-authorized Remicade) due to AEs related to IRRs was similar across the 2 treatment groups. There were no dose reductions in either treatment arm due to IRRs. The majority of IRRs were attributed to study treatment by the investigator.

IRR in ADA-positive patients

Overall 157 (48.6%) of patients in the Zessly arm and 167 (51.2%) patients in the EU-authorized Remicade arm were ADA positive up to week 30. Less than 10% of patients had an IRR after testing positive for ADA and the rates were similar in each treatment arm (11 [7.0%] Zessly vs 14 [8.4%] EU-authorized Remicade).

Infections

There were no clinically meaningful differences between infectious AEs between the two treatment arms.

All-causality treatment-emergent infectious AEs, safety population – TP1

	Zessly (N = 323) n (%)	Remicade-EU (N = 326) n (%)
Number of AEs[a]	108	95
Subjects with AEs	87 (26.9)	73 (22.4)
Subjects with SAEs	6 (1.9)	9 (2.8)
Subjects with Grade 3 AEs	8 (2.5)	9 (2.8)
Subjects with Grade 4 AEs	0	5 (1.5)
Subjects with Grade 5 AEs	0	0
Subjects discontinued from treatment due to AEs	5 (1.5)	7 (2.1)
Subjects discontinued from study due to AEs	3 (0.9)	4 (1.2)
Subjects with temporary discontinuation[b] due to AEs	19 (5.9)	7 (2.1)

a. Includes 5 positive QuantiFERON®-TB test results under the investigations SOC

During TP1 the number of patients with all-causality treatment-emergent infectious AEs was numerically slightly higher in the Zessly treatment arm (87 [26.9%]) compared with the EU-authorized Remicade group (73 [22.4%]). The number of patients with infectious SAEs was numerically slightly lower with 6 patients (1.9%) in the Zessly group and 9 (2.8%) in the EU-authorized Remicade group.

More patients in the EU-authorized Remicade group required the use of antimicrobial drugs, including parental (35 [47.9%]) and required hospitalization due to infectious AEs (10 [13.7%]) compared with the Zessly group (28 [32.2%] and 5 [5.7%] respectively).

There were 6 cases of pneumonia reported, distributed equally between the 2 treatment arms. There were 2 cases of tuberculosis; one case of latent TB in the Zessly group and one case of active TB in the EU-authorized Remicade group.

Malignancy and lymphoma-related AEs

One grade 3 colon cancer was reported in each treatment arm. The investigator considered both cases not related to the study drug. One additional subject in the EU-authorized Remicade arm was diagnosed with a non-malignant lipoma.

Hypersensitivity reactions

There were no clinically meaningful differences in the pattern of hypersensitivity reactions in the 2 treatment arms.

All-causality treatment-emergent hypersensitivity AEs, safety population – TP1

	Zessly (N = 323) n (%)	Remicade-EU (N = 326) n (%)
Number of AEs	52	64
Subjects with AEs	44 (13.6)	51 (15.6)
Subjects with SAEs	1 (0.3)	1 (0.3)
Subjects with Grade 3 AEs	5 (1.5)	2 (0.6)
Subjects with Grade 4 AEs	0	0
Subjects with Grade 5 AEs	0	1 (0.3)
Subjects discontinued from treatment due to AEs	10 (3.1)	9 (2.8)
Subjects discontinued from study due to AEs	6 (1.9)	3 (0.9)
Subjects with temporary discontinuation[a] due to AEs	4 (1.2)	7 (2.1)

There were no dose reductions due to hypersensitivity AEs in either treatment arm. One subject from the EU-authorized Remicade arm had a Grade 5 SAE of “shock multi-organ failure” captured using the hypersensitivity search criteria. The event was secondary to perforated diverticulitis and peritonitis and not due to hypersensitivity.

Hypersensitivity AEs in ADA-positive patients

A total of 11 (7.0%) and 19 (11.4%) patients reported 14 and 25 hypersensitivity AEs in the Zessly and EU-authorized Remicade treatment arms, respectively. Three (1.9%) patients in the Zessly arm reported Grade 3 AEs including cyanosis, blood pressure decreased, dyspnoea, hypotension and urticaria. Two (1.2%) patients in the EU-authorized Remicade arm reported Grade 3 rash and dyspnoea. No AEs of Grade 4-5 or SAEs were reported. Five patients each in the Zessly and EU-authorized Remicade arms discontinued treatment due to hypersensitivity AEs; 3 (1.9%) and 2 (1.2%) patients, respectively, discontinued from the study. Two (1.3%) patients in the Zessly arm and 6 (3.6%) patients in EU-authorized Remicade arm

temporarily discontinued from the treatment. There were no dose reductions due to AEs in either treatment arm.

In ADA positive patients, the number of patients with hypersensitivity reactions and the severity and seriousness of these was balanced across the 2 treatment groups.

TP2

In TP2 and the combined TP1+TP2 analysis, no clinically meaningful differences were seen in AESI between the three treatment groups.

Percentages of patients with all-causality treatment-emergent AESIs (TP1+TP2), SAF, TP2

AESI[1]	Zessly/ Zessly (N=280) n (%)	Remicade-EU/ Remicade-EU (N=143) n (%)	Remicade-EU/ Zessly (N=143) n (%)
Infusion-related reaction (IRR)	15 (5.4)	14 (9.8)	9 (6.3)
Infectious AE	99 (35.4)	40 (28.0)	42 (29.4)
Tuberculosis			
(PT) Latent tuberculosis	2 (0.7)	2 (1.4)	2 (1.4)
(PT) Mycobacterium tuberculosis complex test positive	2 (0.7)	0	3 (2.1)
Pneumonia			
(PT) Pneumonia	0	2 (1.4)	0
(PT) *Pneumocystis jirovecii* pneumonia	1 (0.4)	1 (0.7)	0
Neoplasms	1 (0.4)	1 (0.7)	3 (2.1)
Malignancies			
(PT) Colon cancer	0	1 (0.7)	0
(PT) Laryngeal squamous cell carcinoma	1 (0.4)	0	0
(PT) Lipoma	0	0	1 (0.7)
(PT) Ocular lymphoma	0	0	1 (0.7)
Hypersensitivity	46 (16.4)	31 (21.7)	22 (15.4)
Hepatobiliary events	21 (7.5)	7 (4.9)	11 (7.7)
Hepatobiliary disorders			
(PT) Hepatic steatosis	0	0	1 (0.7)
(PT) Hepatic function abnormal	0	0	2 (1.4)
Investigations			
(PT) Hepatic enzyme increased	1 (0.4)	0	0
(PT) Transaminases increased	1 (0.4)	0	1 (0.7)
(PT) Alanine aminotransferase increased	18 (6.4)	6 (4.2)	9 (6.3)
(PT) Aspartate aminotransferase increased	15 (5.4)	3 (2.1)	8 (5.6)
Haematologic reactions	19 (6.8)	6 (4.2)	13 (9.1)
Blood and lymphatic system disorders			
(PT) Iron deficiency anaemia	2 (0.7)	0	2 (1.4)

AESI[1]	Zessly/ Zessly (N=280) n (%)	Remicade-EU/ Remicade-EU (N=143) n (%)	Remicade-EU/ Zessly (N=143) n (%)
(PT) Anaemia	9 (3.2)	4 (2.8)	8 (5.6)
(PT) Anaemia macrocytic	1 (0.4)	0	0
(PT) Anaemia of chronic disease	1 (0.4)	0	0
(PT) Hypochromic anaemia	1 (0.4)	0	0
(PT) Leukopenia	2 (0.7)	2 (1.4)	3 (2.1)
(PT) Lymphopenia	1 (0.4)	1 (0.7)	0
(PT) Neutropenia	5 (1.8)	1 (0.7)	4 (2.8)
(PT) Blood disorder	0	1 (0.7)	0
(PT) Pancytopenia	0	0	1 (0.7)
(PT) Thrombocytopenia	1 (0.4)	1 (0.7)	0

Abbreviations: AE=adverse event; AESI=adverse event of special interest; Infliximab-EU=EU-authorized Remicade; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients in each category; N=number of patients included in the safety population; PT=preferred term; SAF=safety population; TP1=Treatment Period 1; TP2=Treatment Period 2.

MedDRA (version 19.1) coding dictionary was applied.

[1] Hepatobiliary events, SLE/lupus-like syndrome, demyelinating disorders, heart failure, haematological disorders, and delayed hypersensitivity (serum sickness) were analyzed *post hoc*. No cases of SLE/lupus-like syndrome, demyelinating disorders and delayed hypersensitivity (serum sickness) and single cases of heart failure were reported.

Infusion-related reactions

Although the overall number of IRRs was slightly higher in the EU-authorized Remicade/EU-authorized Remicade group compared with the Zessly/Zessly group, there were no clinically meaningful differences in the percentage of patients that had an IRR in each of the three treatment groups in TP2 or the combined TP1+2 analysis.

Only a small fraction of the IRRs was grade 3 or 4 in either the ADA positive or negative groups. A low and comparable portion of patients among the 3 treatment groups discontinued treatment due to IRRs.

Infectious AEs

Whilst in the TP1+TP2 analysis there was a slight numerical imbalance between the groups, with the percentage of infectious AEs being numerically slightly higher in the Zessly/Zessly group, the vast majority of the AEs were grade 1-2 and the number of SAEs was very low and balanced between the groups.

In TP2 the percentage of patients in the Zessly/Zessly group that required antimicrobials was numerically lower than in the other 2 treatment groups. Three patients in the EU-authorized Remicade/EU-authorized Remicade treatment group in TP2 were reported with treatment-emergent pneumonia. The number of patients with a negative quantiFERON®-TB test result at screening and reported with treatment-emergent latent TB in TP2 was very low and generally balanced across the treatment groups.

Hypersensitivity reactions

Although the overall number of hypersensitivity reactions was slightly higher in the EU-authorized Remicade/EU-authorized Remicade group compared with the Zessly/Zessly group, there were no clinically

meaningful differences in the percentage of patients that had a hypersensitivity reaction in each of the three treatment groups in TP2 or the combined TP1+2 analysis

The number of hypersensitivity reactions that were grade 3 or above and the number of serious hypersensitivity reactions was very low and balanced across the groups. Similarly, the number of patients that required dose reduction/temporary or permanent discontinuation of treatment due to hypersensitivity reactions was low.

The incidence and severity of hypersensitivity reactions across the treatment groups did not appear to be increased by ADA status.

Congestive heart failure

Up to week 54, 3 cases of heart failure were reported: 1 patient in the Zessly arm that later continued into the Zessly/Zessly group; 1 patient in the EU-authorized Remicade arm experienced a grade 1 TEAE of cardiac failure during TP1; and 1 patient in the EU-authorized Remicade/EU-authorized Remicade group experienced a grade 1 TEAE of heart failure during TP2. None of the events were considered related to study drug.

SLE/lupus-like syndrome, Demyelinating disorders and Delayed hypersensitivity (serum sickness)

No cases of any of these 3 AESI were reported during TP1 or TP2.

Laboratory findings

Overall the profile of laboratory parameters in study **GP11-101** and **GP11-301** was similar across the treatment groups.

Impact of Anti-drug antibodies on safety

In accordance with the Remicade SmPC, it is known that patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop IRRs. Use of concomitant immunosuppressant agents appeared to reduce the frequency of IRRs and development of ADA. In clinical studies, delayed hypersensitivity reactions have been reported.

In study GP11-301, in-line with the known safety profile of infliximab, the percentage of patients that had IRRs was greater in the subjects that were ADA positive. The incidence and severity of hypersensitivity reactions across the treatment groups did not appear to be increased by ADA status.

The impact of immunogenicity on safety was evaluated with respect to IRR and hypersensitivity. There were no treatment related differences on the effect of immunogenicity for IRR and hypersensitivity.

Safety in special populations

No studies in special populations were submitted.

Safety related to drug-drug interactions and other interactions

In accordance with the EMA biosimilar guideline (EMEA/CHMP/BMWP/42832/2005), no further specific studies on the potential impact of drug interactions were submitted with Zessly.

Discontinuation due to adverse events

Study GP11-101

This was a single dose study. There were no permanent discontinuations due to AEs.

Study GP11-301

TP1

Permanent discontinuation of treatment due to adverse events

Twenty-three (7.1%) and 24 (7.4%) patients from the Zessly and EU-authorized Remicade arms permanently discontinued treatment due to AEs, respectively; 16 (5.0%) and 14 (4.3%) patients, respectively, discontinued from the study. The SOCs with the highest proportion of patients who had AEs leading to permanent treatment discontinuations were Skin and Subcutaneous Tissue Disorders (8 [2.5%] patients on Zessly and 7 [2.1%] patients on EU-authorized Remicade), Injury, Poisoning and Procedural Complications (6 [1.9%] patients on Zessly and 6 [1.8%] patients on EU-authorized Remicade) and Infections and Infestations (5 [1.5%] patients on Zessly and 6 [1.8%] patients on EU-authorized Remicade).

Eleven SAEs led to permanent treatment discontinuation in TP1, 4 in the Zessly arm and 7 in the EU-authorized Remicade arm.

Temporary discontinuation due to adverse events

During TP1, 31 (9.6%) patients in the Zessly arm and 28 (8.6%) patients in the EU-authorized Remicade arm temporarily discontinued due to TEAEs. The majority of the TEAEs were Grade 1 or 2, and resolved by the time of reporting. There were 7 SAEs that led to temporary treatment discontinuation during TP1, 3 in the Zessly arm and 4 in the EU-authorized Remicade arm

During TP1 the incidence, type and severity of all-causality TEAEs that resulted in temporary or permanent treatment discontinuation, including patients that discontinued the study was essentially comparable between treatment arms.

TP2

Similar percentages of patients across treatment groups permanently discontinued treatment due to AEs (Zessly/Zessly: 14 patients [5.0%]; EU-authorized Remicade/EU-authorized Remicade: 10 patients [7.0%], EU-authorized Remicade/Zessly: 7 patients [4.9%]). The percentage of patients who discontinued from the study was also similar across groups (Zessly/Zessly: 12 patients [4.3%]; EU-authorized Remicade/EU-authorized Remicade: 6 patients [4.2%], EU-authorized Remicade/Zessly: 5 patients [3.5%])

In keeping with the data from TP1, the number of patients across treatment groups that permanently discontinued treatment/discontinued from the study was similar in both the TP2 and TP1+TP2 analyses.

2.6.1. Discussion on clinical safety

The main safety data are derived from study GP11-301 in patients with Rheumatoid arthritis. In addition, safety data is provided from the phase I PK study in healthy volunteers which is considered supportive in characterising the short-term safety profile of Zessly.
Overall, 49 healthy volunteers in study GP11-101 and 323 patients with RA in study GP11-301 were treated with at least one dose of Zessly. The extent of exposure to the IP is comparable for the Zessly and EU-

Infliximab treatment groups.
The overall safety profile as reflected by the most frequently reported TEAEs, severity of the TEAEs and number reported as related, appears similar between Zessly and Remicade and in line with that expected based on the EU-authorized Remicade SmPC.
In study GP11-301, up to week 30 the most frequently affected SOCs were infections and infestations; gastrointestinal disorders; skin and subcutaneous disorders; and injury, poisoning, and procedural complications. The most frequently occurring TEAEs were IRR, ALT increased and nasopharyngitis.
In study GP11-101, no deaths were reported. Two patients experienced an SAE: one unrelated case of 'mental disorder' in the Zessly treatment arm and one related case of 'myalgia' in the EU-infliximab arm.
Up to week 54, 5 deaths have been reported in study GP11-301, two in each treatment arm in TP1 and one in the Zessly/Zessly treatment arm in TP2. None of the deaths were assessed by the sponsor or the investigator as treatment-related. The number of all-causality treatment-emergent SAEs was low and generally comparable between the treatment arms.
The overall incidence of TEAEs that affected IP administration in study GP11-301 was comparable in both treatment arms. The number of patients that experienced TEAEs that led to IP discontinuation, including patients that discontinued the study, was also comparable.
In study GP11-301 IRRs, Infections (including tuberculosis and pneumonia), Malignancy (including lymphoma) and Hypersensitivity were identified by the applicant as TEAEs of special interest. At the request of the CHMP, the following were also included as AESI in the updated assessment of safety (up to week 54): 'Hepatobiliary events', 'SLE/lupus-like syndrome', demyelinating disorders', 'Heart failure', 'Haematological disorders' and 'delayed hypersensitivity (serum sickness)'. There were no clinically meaningful differences in AESI between the treatment groups.
In accordance with the known safety profile of infliximab, it is recognised that patients who develop antibodies to infliximab are more likely to develop IRRs. In study GP11-101, there were no AEs in any arm reasonably attributable to immunogenicity. In study GP11-301, over 54 weeks, the percentage of patients that had IRRs was balanced between treatment arms within the ADA positive subgroup. Only a small proportion of these IRRs were grade 3, 4 or serious and a low and comparable proportion of patients discontinued treatment due to IRRs.

2.6.2. Conclusions on the clinical safety

Based on the data from study GP11-301 in patients up to week 54, together with supportive data from the single dose study in healthy volunteers, the overall safety and immunogenicity profile of Zessly is acceptable and supports biosimilarity between Zessly and Remicade (EU-authorized Remicade).

2.6.3. Extrapolation to the indications of the reference product

Remicade has a number of indications in chronic inflammatory conditions in adults (RA, Crohn's disease, UC, ankylosing spondylitis, psoriatic arthritis and psoriasis) and children (Crohn's disease and UC). In line with CHMP guidance (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - EMEA/CHMP/BMWP/42832/2005 Rev1), extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data.

Pharmacokinetics

The PK profiles are well characterized and essentially similar across all indications for Remicade.

Pharmacokinetics in adults

Infliximab exhibits a dose proportional and linear PK profile over the studied dose range (1 – 20 mg/kg) and similar PK characteristics across RA, AS, PsA, PsO, CD and UC indications.

PK data and Population PK analysis of Remicade collected in RA, AS, PsO, PsA, and adult and paediatric CD and UC indicate that the overall PK properties of Remicade across all approved indications are comparable. Population PK analyses of infliximab in various populations showed that clearance of infliximab was higher in patients who developed ADAs and influenced by body weight. In patients with RA receiving repeated infliximab dosing, concomitant administration of methotrexate resulted in higher serum infliximab concentrations at the low infliximab dose of 1 mg/kg, possibly by suppressing ADA formation and preventing its impact on infliximab PK. Similar findings have been generally reported in other indications, even though the extent of ADA formation, its response to concomitant immunosuppressants, and its impact on PK parameters may differ across indications. Accounting for those factors, the pharmacokinetics of infliximab is similar in patients with RA, PsO and CD.

Based on all the above, it is reasonable to conclude that the PK of infliximab is linear and similar across disease indications in the tested dose range.

Pharmacokinetics in paediatric population

Infliximab PK characteristics (including peak and trough concentrations and terminal half-life) were similar in paediatric and adult patients with CD or UC following the administration of 5 mg/kg infliximab. Population PK analysis based on the data obtained in two Phase 3 studies comprising paediatric and adult patients showed that weight influenced the pharmacokinetics, however, age was not found to influence infliximab PK in age range tested (6-76 years). The effect of body weight on the PK of infliximab was corroborated in another population PK analysis conducted on data obtained from paediatric patients with a subgroup of patients aged 6 years to 17 years showing mild decrease (20%) in steady state area under the concentration-time curve (AUC). The recommended dosing regimen of Remicade in USPI and SmPC in paediatric CD patients is generally consistent with that in adult patients, which further affirms PK similarity between paediatric and adult patients.

Distribution

The distribution/disposition of infliximab in humans is expected to be through the same mechanisms as other monoclonal antibodies. These disposition mechanisms are expected to be shared by patients of the different licensed indications of infliximab.

Conclusion

These data suggest no major differences in infliximab PK across the indications of Remicade. A similar PK profile of Zessly and Remicade in healthy volunteers was demonstrated in study GP11-101 with supportive data in RA patients from study GP11-301. From a PK perspective, it is considered that equivalence is confirmed and sufficient data are available to support extrapolation, based on the totality of the data supporting similarity of Zessly and the reference product, to all indications of Remicade.

Efficacy

The RA indication is considered a sensitive clinical model for the detection of potential differences in efficacy between a biosimilar candidate to Remicade and the reference product. Study GP11-301 met its primary endpoint and these results are supported by the sensitivity analyses and the secondary endpoint data up to week 54.

From a PD perspective, extrapolation to all other indications of Remicade, based on the totality of the data supporting similarity of Zessly and the reference product, especially those of inflammatory bowel diseases, depends on convincing evidence of the comparability of binding and effector functions, including those in the setting of membrane bound TNFα and is considered justified.

Safety

Remicade has a well-established safety profile in all approved indications based on the clinical trial experience in 4955 paediatric and adult patients and over 18 years of post-marketing experience. The important identified and potential risks for Remicade include infections, malignancies, heart failure and infusion reactions. The most common adverse events (>10%) include infections, infusion-related reactions, headache, and abdominal pain. Generally, the types and frequencies of adverse reactions observed were similar in Remicade-treated RA, AS, PsA, PsO, and CD patients. Overall, the adverse reactions reported in the paediatric UC trial and adult UC studies were generally consistent. Studies in paediatric patients receiving Remicade found a higher rate of infections, haematological disorders such as anaemia, leukopenia, and neutropenia, flushing, bone fracture and respiratory tract allergic reactions compared to those observed in adults with CD.

Conclusion

The overall pattern of safety events is generally consistent across the multiple approved clinical indications of Remicade and differences due to posology, patient population, indication, or patient factors are described in the prescribing information. The key safety concerns are common to all TNF inhibitors and reflect the primary MOA of Remicade (i.e., neutralization of the biological activity of TNF and the immunosuppressive effect). While potential qualitative or quantitative differences between the various indications are conceivable, those would be expected to result from unique disease specific factors, clinical and post-marketing exposure, and not from differences in the mechanistic effects of infliximab.

Based on the data up to Week 54 from study GP11-301 in patients, together with supportive data from the single dose PK study in healthy volunteers, the overall safety profile is acceptable, supports biosimilarity and extrapolation to the other indications of Remicade based on the totality of the data supporting similarity of Zessly and the reference product is considered justified.

Immunogenicity

The rate of ADAs reported in literature varies from study to study according to the format, sensitivity and specificity of the assay, the cut-point used, or other factors such as dose or dosing regimen, concomitant medication and the underlying disease(s).

There are differences between patient populations regarding the dose of infliximab (with the development of ADAs being inversely associated with infliximab dose), dosing regimen or the concomitant medications (e.g. immunosuppressive treatments). Inflammatory burden, thought to favour the production of ADAs, also differs among the disease populations. The effect of age on the ADAs has not been extensively studied. It has been reported that in patients with CD the prevalence of infliximab ADAs may be lower in children than adults

(2.9% versus 11% in one of the studies), but community-based studies of paediatric and older populations find similar prevalence, suggesting that patient age may only play a limited role in anti-infliximab antibody production.

From an efficacy perspective, infliximab ADAs may reduce treatment effects by two possible mechanisms: 1) neutralizing ADAs block binding of infliximab to its target, reducing treatment efficacy; 2) binding of both neutralizing and non-neutralizing ADAs to infliximab can result in the formation of immune complexes, which are then cleared from the circulation reducing the exposure to active drug contributing to changes in drug pharmacokinetics.

Other important safety consequences of the development of ADAs are acute infusion reactions and delayed hypersensitivity.

The clinical experience with Remicade is consistent with the above considerations. ADAs have been detected in studies with Remicade in different patient populations. The frequency of ADA formation reported in the Remicade SmPC is summarized in the table below:

Table 4-2 Incidence of ADAs in different patient populations treated with infliximab (SmPC, 2015) ADAs were detected using an ELISA assay

Patient Population	Concomitant Treatment	Frequency of ADA
Rheumatoid arthritis	With Immunosuppressants	8%
Crohn's disease (with maintenance treatment)	With Immunosuppressants	3.3%
	Without Immunosuppressants	13.3%
Psoriatic arthritis	With Immunosuppressants	4%
	Without Immunosuppressants	26%
Psoriasis	Without Immunomodulators	28%

As expected, the antibody titers varied according to the patient population and the concomitant use of immunosuppressant therapies within specific indications.

Conclusion

In conclusion, it follows that immunogenic response to infliximab is not expected to be the same in all patient populations. However, considering the totality of the data supporting similarity of Zessly and the reference product, and, the comparable immunogenicity profiles in RA extrapolation to the other indications of Remicade.

2.7. Risk Management Plan

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hepatitis B reactivation	Routine risk minimization measures: SmPC section 4.4 where recommendations are given for testing on hepatitis B virus (HBV) infection before initiating treatment with infliximab; and 4.8 PL section 2 where recommendation is given to inform the doctor on medical history of hepatitis B and on test for HBV; and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Legal status: Prescription only Additional risk minimization measures: Patient alert card	
Congestive Heart Failure (CHF)	Routine risk minimization measures: SmPC section 4.3; 4.4 where recommendation on close monitoring and infliximab discontinuation in patients who develop new or worsening symptoms of heart failure; and 4.8 PL section 2 where recommendation is given to inform the doctor on medical history and symptoms of heart failure and for close monitoring of heart function; and 4 Legal status: Prescription only Additional risk minimization measures: Patient alert card.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Opportunistic infection (OI)	Routine risk minimization measures: SmPC section 4.3; 4.4 where recommendation is given to discontinue infliximab treatment if a patient develops a new serious infection or sepsis; and 4.8 PL section 2 where recommendation to inform the doctor on symptoms of infections is given, and 4. 8 Legal status: Prescription only Additional risk minimization measures: Patient alert card Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for serious infections and opportunistic infections Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Serious infection/sepsis (excluding OI and TB)	Routine risk minimization measures: SmPC section 4.3; 4.4 where recommendations are given to discontinue infliximab treatment if a	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for serious infections and opportunistic infections

Safety concern	Risk minimization measures	Pharmacovigilance activities
	patient develops a new serious infection or sepsis; 4.5, 4.6 and 4.8 PL section 2 where recommendation is given to the patient to inform the doctor on symptoms of infections Legal status: Prescription only Additional risk minimization measures: Patient alert card Educational material	Specific AE targeted follow-up questionnaire for progressive multifocal leukoencephalopathy. Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Tuberculosis (TB)	Routine risk minimization measures: SmPC section 4.3; 4.4 where recommendations are given to evaluate all patients for both active or inactive (‘latent’) tuberculosis; 4.6, and 4.8 PL section 2 where recommendations are given to inform the doctor if the patient ever had TB or was in close contact with someone who had TB or if the patient gets signs of TB during treatment; and 4 Legal status: Prescription only Additional risk minimization measures: Patient alert card Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for tuberculosis Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Serum sickness (delayed hypersensitivity)	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only Additional risk minimization measures: Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hematologic reactions	Routine risk minimization measures: SmPC section4.4 where	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	recommendation is given to discontinue infliximab in patients with confirmed significant hematologic abnormalities; 4.6, 4.8, and 5.1 PL section 4 Legal status: Prescription only Additional risk minimization measures: None	None
SLE/lupus-like syndrome	Routine risk minimization measures: SmPC section 4.4 where recommendations are given not to give further treatment with infliximab if patient develops symptoms suggestive of a lupus-like syndrome following treatment with Zessly and is positive for antibodies against double-stranded DNA; and 4.8 PL section 4 Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Demyelinating disorders	Routine risk minimization measures: SmPC section 4.4 where recommendation is given to discontinue infliximab if disorders develop; and 4.8 PL section2.2 where recommendation is given to the patient to tell the doctor straight away if the patients gets symptoms of a nerve disease during treatment with Zessly; and 4 Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Lymphoma (excluding	Routine risk minimization	Routine pharmacovigilance activities beyond

Safety concern	Risk minimization measures	Pharmacovigilance activities
HSTCL)	measures: SmPC section 4.4 where recommendation is given to consider continuing treatment in patients who develop a malignancy; 4.8, and 5.3 PL section 2 where recommendation is given the patient to tell the doctor if the patient has or has ever had lymphoma or any other cancer before Zessly is given; and 4 Legal status: Prescription only Additional risk minimization measures: Educational material	adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for lymphoma Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Hepatobiliary events	Routine risk minimization measures: SmPC section 4.4 where recommendation is given to discontinue infliximab if jaundice and/or ALT elevations ≥5 times the UL develop(s) and to undertake a thorough investigation of the abnormality; and 4.8 PL section 4 Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Hepatosplenic T-cell lymphoma (HSTCL)	Routine risk minimization measures: SmPC section 4.4 where recommendation is given to carefully consider the potential risk with the combination of AZA or 6-MP and infliximab; 4.8, and 5.3 PL sections 2 and 4 Legal status: Prescription only Additional risk minimization measures: Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for lymphoma and malignancies Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Intestinal or perianal	Routine risk minimization	Routine pharmacovigilance activities beyond

Safety concern	Risk minimization measures	Pharmacovigilance activities
abscess (in CD)	measures: SmPC section 4.3, 4.4 where recommendation is given not to initiate infliximab therapy until a source for possible infection, specifically abscess, has been excluded; 4.8, and 5.1 PL section 4 Legal status: Prescription only Additional risk minimization measures: None	adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Serious infusion reactions during a re-induction regimen following disease flare	Routine risk minimization measures: SmPC section 4.2, 4.4, and 4.8 Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Sarcoidosis/sarcoid-like reaction	Routine risk minimization measures: SmPC section 4.8 PL section 4 Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Pediatric malignancy	Routine risk minimization measures: SmPC section 4.4 where recommendation is given to carefully consider the potential risk with the combination of AZA or 6-MP and infliximab; 4.8, and 5.3 PL section 2 and 4 Legal status: Prescription only Additional risk minimization measures: Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for lymphoma Specific AE targeted follow-up questionnaire for malignancy Additional pharmacovigilance activities: Participation in UKIBD (UK)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Leukemia	Routine risk minimization measures: SmPC section 4.4 where recommendation is given to exercise caution when considering continuing treatment in patients who develop a malignancy; 4.8, and 5.3 PL section 2 and 4 Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for malignancy Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Merkel cell carcinoma (MCC)	Routine risk minimization measures: SmPC section 4.4,4.8, and 5.3 PL section 4 Legal status: Prescription only Additional risk minimization measures: Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for malignancy Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Melanoma	Routine risk minimization measures: SmPC section 4.4 where recommendation is given for periodic skin examination; 4.8, and 5.3 PL section 2 and 4 Legal status: Prescription only Additional risk minimization measures: Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for malignancy Additional pharmacovigilance activities: Participation in RABBIT (UK), BADBIR (UK), UKIBD (UK)
Acute hypersensitivity reaction (including anaphylactic shock)	Routine risk minimization measures: SmPC section 4.3, 4.4 where recommendation is given to interrupt the infusion immediately if acute infusion reactions occur; and 4.8 PL sections 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Legal status: Prescription only Additional risk minimization measures: Educational material	
Bacillus Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure	Routine risk minimization measures: SmPC section 4.4 where recommendation is given not to concurrently administer live vaccines and for an at least six month waiting period following birth before the administration of live vaccines to infants exposed in utero to infliximab; 4.5, 4.6, and 4.8 PL sections 2 and 4 Legal status: Prescription only Additional risk minimization measures: Patient alert card (BCG only) Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Cervical cancer	Routine risk minimization measures: SmPC section 4.4 and 4.8 PL section 2 where recommendation for cervical cancer screening is made; and 4 PL section 2 and 4 Legal status: Prescription only Additional risk minimization measures: Educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Malignancy (excluding lymphoma, HSTCL, pediatric malignancy, leukemia, melanoma, Merkel cell carcinoma and cervical cancer)	Routine risk minimization measures: SmPC section 4.4 where recommendation is given to exercise caution when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy; 4.8, and 5.3 PL section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for malignancy Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Legal status: Prescription only Additional risk minimization measures: Educational material	
Colon carcinoma/dysplasia (in UC)	Routine risk minimization measures: SmPC section 4.4 where recommendation to screen patients screened for dysplasia at regular intervals before therapy and throughout their disease course; and 5.3 PL section: none Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for malignancy Additional pharmacovigilance activities: Participation in UKIBD (UK)
Skin cancer (excluding melanoma and Merkel cell carcinoma)	Routine risk minimization measures: SmPC section 4.4 where recommendation for periodic skin examination is made; and 5.3 PL section 2 Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE targeted follow-up questionnaire for malignancy Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)
Exposure during pregnancy	Routine risk minimization measures: SmPC section 4.6 where recommendation is given not to administer infliximab during pregnancy and women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last Zessly treatment; and 5.3 PL section 2 Legal status: Prescription only Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Participation in RABBIT (DE), BADBIR (UK), UKIBD (UK)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None	
Infusion reaction associated with shortened infusion	Routine risk minimization measures: SmPC section 4.2 where recommendation to consider a slower infusion rate for future infusions if an infusion reaction occurs in association with a shortened infusion, if treatment is to be continued; and 4.8 PL section: none Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety in adult patients with UC, PsA, or Ps	Routine risk minimization measures: SmPC section 4.8 Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Participation in BADBIR (UK), UKIBD (UK)
Long-term safety in pediatric CD and pediatric UC patients	Routine risk minimization measures: None Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Participation in UKIBD (UK)
Long-term safety in children	Routine risk minimization measures: None. Legal status: Prescription only Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Participation in UKIBD (UK)
Safety in very young children (<6 years)	Routine risk minimization measures: SmPC section 4.2 and 5.1 Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures:	
	None	
Use of drug during lactation	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
	SmPC section 4.6	None
	PL section 2	Additional pharmacovigilance activities:
		Participation in UKIBD (UK)
	Legal status: Prescription only	
	Additional risk minimization measures:	
	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.

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

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 Remicade. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zessly (infliximab) is included in the additional monitoring list as it is a biologic product.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Zessly has been developed as a similar biological medicinal product to Remicade. The European reference medicinal product is Remicade 100mg powder for concentrate for solution for infusion, MA numbers EU/1/99/116/001-005, MA holder Janssen Biologics B.V., NL, authorised 13 August 1999.

The proposed clinical use of Zessly is identical to that of the reference medicinal product, Remicade. Zessly is proposed for the treatment of adult patients with Rheumatoid arthritis, Crohn's disease, Ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis; and the treatment of paediatric patients with Crohn's disease and Ulcerative colitis.

3.1.2. Available therapies and unmet medical need

This is a biosimilar application to Remicade.

3.1.3. Main clinical studies

The clinical trial programme to show biosimilarity between Zessly and Remicade is based on two trials:

- Study GP11-101, Phase I PK study in healthy volunteers.
- Study GP11-301, Phase III study comparing the efficacy and safety of Zessly and Remicade in combination with methotrexate in adult male and female patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate.

3.2. Favourable effects

From a quality perspective, it is considered that high similarity between Zessly and Remicade was shown with regard to:

- primary, secondary and tertiary structures
- binding to sTNF and inhibition of sTNF response (apoptosis assay, inhibition of TNF-induced endothelial adhesion molecule expression)

- binding kinetics to TNF (sTNF and mTNF)
- glycosylation profile (only minor differences in the relative content of N-glycans)
- comparable total afucosylation and terminal galactosylation
- glycans of complex biantennary type, with low levels of high mannose glycans
- product purity
- HC + LC (slightly higher fragment content in Zessly, low levels overall)
- degradation profile (lower rate of degradation for Zessly after reconstitution, attributed to different buffer systems)

There is a lack of alpha-Gal and NeuGc in Zessly (low levels in EU-authorized Remicade) which is considered favourable as these are potentially immunogenic.

From a non-clinical perspective, the following endpoints for the proposed biosimilar, Zessly were all shown to be similar to or within the range of that observed for both EU-authorized Remicade and US-licensed Remicade:

- Relative affinity for FcγRIIa and FcγRIIIa (both receptor types)
- (Absolute) affinity to NK cells with FcγRIIIa (all 3 phenotypes)
- Relative ADCC activity as determined using primary NK cells with the same FcγRIIIa heterozygous genotype
- Relative FcγRIIIa activation (as observed during a normal ADCC response) via reporter gene assay
- Relative binding to C1q and the relative CDC activity
- (Absolute) inhibition of T-cell proliferation

From a clinical perspective:

- The pivotal PK trial in healthy volunteers showed comparable PK profile with 90% confidence intervals for the ratios of all 3 primary parameters (C_{max}, AUC_T and AUC_{inf}) being well contained within the standard bioequivalence interval of 80% – 125%;
- PK data from the phase III clinical efficacy and safety study were also supportive of similarity.
- The pivotal efficacy trial in patients with rheumatoid arthritis achieved its primary endpoint since the 95% confidence interval for the difference in ACR20 was well-contained within the predefined equivalence margin (± 13.5%) in both the ITT and PP populations;
- The results of sensitivity and sub-group analysis of the primary endpoint data, together with the results of the secondary endpoints up to week 54 reflect those of the primary endpoint and support biosimilarity.

3.3. Uncertainties and limitations about favourable effects

From a quality perspective, some differences were observed between Zessly and Remicade:

- lower C-terminal lysine content in Zessly compared with infliximab; however, rapid cleavage of the C-terminal lysine occurs in blood
- differences in the levels of minor and trace glycans
- trace levels VHS signal peptide and amidated proline in Zessly, not present in EU-authorized Remicade
- %main isoforms higher and % basic isoforms lower in Zessly (attributed to difference in C-terminal lysine levels)
- reduced FcRn binding for Zessly (some batches below EU-authorized Remicade range)
- protein content higher in Zessly than EU-authorized Remicade

3.4. Unfavourable effects

The type and incidence of ADRs to the test and reference products were broadly comparable and in line with those expected on the basis of the Remicade SmPC.

3.5. Uncertainties and limitations about unfavourable effects

There are no remaining uncertainties and limitations about the unfavourable effects.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Data from the two clinical trials support PK, efficacy and safety similarity between Zessly and Remicade with both studies meeting their primary endpoints. The pivotal PK trial in healthy volunteers showed comparable PK profile with 90% confidence intervals for the ratios of all 3 primary parameters (C_{max}, AUC_T and AUC_{inf}) being well contained within the standard bioequivalence interval of 80% – 125%; PK data from the phase III clinical efficacy and safety study in patients with Rheumatoid Arthritis were also supportive of similarity.

The single pivotal efficacy equivalence trial met its primary endpoint with the 95% confidence intervals of the treatment difference well contained within the equivalence margin. The robustness of this result is supported by the sensitivity, supportive and subgroup analyses, together with the results of the secondary endpoints up to week 54

Based on the data from study GP11-301 in patients up to week 54, together with supportive data from the single dose study in healthy volunteers, the overall safety and immunogenicity profile of Zessly is acceptable and supports biosimilarity between Zessly and Remicade (EU-authorized Remicade).

3.6.2. Balance of benefits and risks

The clinical trial programme to show biosimilarity between Zessly and Remicade is based on two trials: Study GP11-101, a Phase I PK study in healthy volunteers and Study GP11-301, a Phase III study in patients with rheumatoid arthritis.

Remicade has a number of indications in chronic inflammatory conditions in adults (RA, Crohn's disease, UC, ankylosing spondylitis, psoriatic arthritis and psoriasis) and children (Crohn's disease and UC). In line with CHMP guidance (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - EMEA/CHMP/BMWP/42832/2005 Rev1), extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data.

Extrapolation to the other indications of Remicade is justified based on the totality of the data supporting similarity of Zessly and the reference product including the pharmacokinetic and safety data which were generated in the PK study in healthy volunteers, and the PK, efficacy, safety and immunogenicity data which were generated in the confirmatory efficacy and safety study (phase III) in RA.

3.7. Conclusions

The overall B/R of Zessly 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 Zessly is favourable in the following indications:

Rheumatoid arthritis

Zessly, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see section 5.1).

Adult Crohn's disease

Zessly is indicated for:

- treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Paediatric Crohn's disease

Zessly is indicated for treatment of severe, active Crohn's disease, in children and adolescents aged 6 to 17

years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Ulcerative colitis

Zessly is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis

Zessly is indicated for treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

Ankylosing spondylitis

Zessly is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis

Zessly is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.

Zessly should be administered

- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated

Infliximab 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 (see section 5.1).

Psoriasis

Zessly is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA (see section 5.1).

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 in each Member State, the MAH shall agree the final educational material with the Competent authority in that Member State, consisting of information provided to all healthcare professionals expected to prescribe the product.
The healthcare professional's educational material should contain the following key elements:

- The risk of opportunistic infections and tuberculosis (TB) in patients treated with Zessly.
- The need to assess the risk of TB in patients prior to treating with Zessly.
- The risk of acute hypersensitivity reactions (including anaphylactic shock) and delayed hypersensitivity reactions.
- The risk of lymphoma, melanoma, Merkel cell carcinoma, and other malignancies.
- The risk of disseminated BCG infection after BCG vaccination of infants up to 6 months of age who were exposed in utero to infliximab.
- The patient alert card, which is to be given to patients using Zessly.

Prescribers of Zessly for paediatric Crohn's disease and paediatric ulcerative colitis shall additionally be made aware:

- That children may be at increased risk of developing infections and that their immunisations need to be up-to-date.