EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2018
EMA/CHMP/520007/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hefiya

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/004865/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AI	Autoinjector
ANCOVA	Analysis of covariance
AS	Ankylosing spondylitis
ATE	Averaged treatment effect
AUC	Area under the serum concentration-time curve
BMI	Body mass index
BMWP	Biological Monitoring Working Party
BPS	Sandoz GmbH, Biopharmaceuticals Schaftenau
BSA	Body surface area
CD	Crohn´s Disease
CDC	Complement-dependent cytotoxicity
CE-SDS	Capillary electrophoresis sodium-dodecyl sulphate
CEX	Cation exchange chromatography
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence interval
CIPC	Critical in process parameter
CCI	Container closure integrity
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRP	C-reactive protein
CV	Coefficient of variation
DLQI	Dermatology life quality index
DMC	Data monitoring committee
DoE	Design of Experiments
DP	Drug Product
DS	Drug Substance
DSC	Differential scanning calorimetry
ECB	Extended Cell Bank
ECL	Electrochemiluminescence
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D™-5L	EuroQOL 5-dimension health status questionnaire (the trademark is omitted in the text for better readability)
ERA	Environmental Risk Assessment
EU-Humira	EU-authorized Humira
Fab	Antigen-binding fragment
FAS	Full analysis set
Fc	Complement-binding fragment
FDA	Food and Drug Administration
FMEA	Failure Modes Effects Analysis
Frel	Relative bioavailability
FTIR	Fourier transform infrared spectroscopy
GLP	Good Laboratory Practice

GM	Geometric Mean
GMP	Good manufacturing practices
GP2017	Sandoz company code for drug product for its adalimumab biosimilar product
GP2017-AI	GP2017 administered by autoinjector; combination of GP2017 in PFS assembled into the Delta autoinjector. The final combination product is referred to as Delta-GP2017_40 autoinjector.
GP2017-Cook	GP2017 drug product produced from drug substance manufactured at Cook Pharmica, LLC, in Bloomington, IN, USA
GP2017-PFS	GP2017 administered by pre-filled syringe
GP2017-Schaftenau	GP2017 drug product produced from drug substance manufactured at Sandoz GmbH, Biopharmaceuticals Schaftenau (BPS) in Langkampfen, Austria
HAQ-DI	Health assessment questionnaire disability index
HCP	Host cell protein
HDPE	High density polyethylene
HDX	Hydrogen-deuterium exchange
HMW	High molecular weight
HRQoL	Health-related quality of life
HS	Hidradenitis suppurativa
hsCRP	High sensitive C-reactive protein
huTNF	Human tumor necrosis factor
IBD	Inflammatory bowel disease
ICH	International Conference on Harmonization
IFN	Interferon
IGA	Investigator global assessment
IgG1	Immunoglobulin G1
IL	Interleukin
IMP	Investigational medicinal product
INN	International Nonproprietary Name
IPC	In process controls
JIA	Juvenile idiopathic arthritis
KIPC	Key in process control
KPP	Key Process Parameter
LAL	Limulus amoebocyte lysate
LLOQ	Lower limit of quantification
LMW	Low molecular weight
LOD	Limit of detection
LOQ	Limit of quantitation
LTα	Lymphotoxin α (also referred to as TNFβ in the literature)
MAA	Marketing authorization application
MCB	Master Cell Bank
MMC	Multimodal chromatography
MMRM	Mixed model repeated measures
MoA	Mechanism of Action
mRNA	Messenger Ribonucleic Acid
mTNF	Membrane bound TNF
mTNFα	Membrane bound TNF α
NAb	Neutralizing antibody
NK	Natural Killer (cell)
NKIPC	Non- Key in process control

NKPP	Non-key process parameter
NMR	Nuclear magnetic resonance
NSD	Needle safety device
NZW	New Zealand White
OOS	Out of specification
PACMP	Post approval change management protocol
PAR	Proven Acceptable Ranges
PASI	Psoriasis area and severity index
PASI50/75/90/100	Reduction of the PASI score by 50%, 75%, 90% or more or 100%
PASI50/PASI75	Reduction of 50%/75% or more of the Psoriasis Area and Severity Index (PASI) score
PBMC	Peripheral blood mononuclear cells
PC	Process characterisation
PD	Pharmacodynamics
PETG	Polyethylene tetraphthalate copolymer
PFS	Pre-filled syringe
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PP	Process parameters
PPS	Per-protocol analysis set
PPso	Plaque Psoriasis
PsA	Psoriatic Arthritis
PsO; Ps	Psoriasis
p.v.	Paravenous
PV	Process validation
R2 adj	Adjusted correlation coefficient
RA	Rheumatoid Arthritis
RGA	Reporter Gene Assay
s.c.	subcutaneous
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard Deviation
SEC	Size-exclusion chromatography
SmPC	Summary of Product Characteristics
SPR	Surface Plasmon Resonance
sTNF	Soluble TNF
TACE	TNFα converting enzyme
TK	Toxicokinetic(s)
tmTNF	Transmembrane TNF, also known as membrane-associated TNF
TNF	Tumor necrosis factor
TNF(α)	Tumor necrosis factor (alpha)
TNFR	Tumor necrosis factor receptor
TP2+EP FAS	Full analysis set Treatment Period 2 and Extension Period
TP2+EP SAF	Safety analysis set Treatment Period 2 and Extension Period
UC	Ulcerative colitis
UF/DF	Ultrafiltration/ Diafiltration
ULOQ	Upper limit of quantification
US-Humira	US-licensed Humira®
UV	Uveitis

WCB	Working Cell Bank
WFI	Water for Injection

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Sandoz GmbH submitted on 23 November 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Hefiya, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Hefiya in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Hefiya can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1 of the SmPC). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Hefiya is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1 of the SmPC).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Hefiya is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Hefiya is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Hefiya is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Adalimumab has been shown 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) and to improve physical function.

Psoriasis

Hefiya is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Hefiya is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Hefiya is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2 of the SmPC).

Uveitis

Hefiya is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric uveitis

Hefiya is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

The legal basis for this application refers to:

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

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

This application is submitted as a multiple of Hyrimoz simultaneously being under initial assessment.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Humira, 40 mg, solution for injection
- Marketing authorisation holder: Abbvie Deutschland GmbH & Co. KG
- Date of authorisation: 08/09/2003
  - Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/03/256/001-010, EU/1/03/256/012-021

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

- Product name, strength, pharmaceutical form: Humira, 40 mg, solution for injection
- Marketing authorisation holder: Abbvie Deutschland GmbH & Co. KG
- Date of authorisation: 08/09/2003
  - Marketing authorisation granted by: Union
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Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bio equivalence has been demonstrated by appropriate bioavailability studies:

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  - Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/03/256/001-010
- • Bioavailabilty study number(s):GP17-104

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant received scientific advice from the CHMP on 19 May 2011 (EMEA/H/SA/2108/1/2011/III). The Scientific advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2 Steps taken for the assessment of the product

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

Rapporteur: Milena Stain Co-Rapporteur: Peter Kiely

The application was received by the EMA on	23 November 2017
The procedure started on	26 December 2017
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at COOK Pharmica LLC in United States responsible for some steps in the manufacturing process of the final product has been conducted on 31.03.2017. The outcome of the inspection carried out was issued on:	19 January 2018
– A GMP inspection at Mylan Laboratories Ltd, Bangalore, India, the intended commercial manufacturing site for Hefiya FP in pre-filled syringes (PFS), has been conducted on 19.01.2018. The outcome of the inspection carried out was issued on:	2 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	30 January 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 February 2018
The CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation to be sent to the applicant on	22 February 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 March 2018

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 April 2018
The CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation to be sent to the applicant on	26 April 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 April 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 May 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 Hefiya on	31 May 2018

2 Scientific discussion

2.1 Problem statement

2.1.1 Disease or condition

Hefiya (also referred to as GP2017) is being developed as a biosimilar candidate to Humira (adalimumab).

The reference product Humira is authorised for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) (polyarticular JIA and enthesitis-related arthritis), axial spondyloarthritis (ankylosing spondylitis [AS], and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis (PsA), psoriasis (PsO), paediatric plaque psoriasis, Crohn's disease (CD), paediatric Crohn's disease, ulcerative colitis (UC), hidradenitis suppurativa (HS) including adolescent HS and non-infectious Uveitis (UV) including paediatric uveitis in the European Union.

The Applicant claims the same therapeutic indications for Hefiya as are granted for Humira in the EU, except for rheumatoid arthritis (RA), Crohn's disease (CD), pediatric Crohn's and ulcerative colitis (UC).

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Hefiya in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Hefiya can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1 of the SmPC). Adalimumab has not been studied in patients aged less than 2 years.

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Hefiya is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

As Hefiya is currently only available as a 40 mg prefilled syringe (PFS) and 40 mg pre-filled pen presentation, the Applicant claims the paediatric indications only for paediatric patients, for whom the full 40 mg dose is appropriate.

About the product

Adalimumab, the active ingredient of Hefiya (development code "GP2017") belongs to the pharmacotherapeutic group "immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors" (ATC code: L04AB04). Adalimumab is a recombinant human immunoglobulin IgG1 type monoclonal antibody specific for TNF-α. Adalimumab binds to soluble and membrane associated TNF-α, thereby inhibiting the interaction of TNF-α with the TNF-α receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events, which is considered the primary mechanism of action in all indications approved for Hefiya.

Hefiya is presented as a 0.8 mL solution for injection in a single-dose pre-filled syringe and pre-filled pen, containing 40 mg adalimumab, to be administered via subcutaneous (SC) injection. Hefiya is only available as 40 mg pre-filled syringe and pre-filled pen. Thus, it is not possible to administer Hefiya to patients that require less than a full 40 mg dose.

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.

Similarity is claimed to Humira (adalimumab) as the reference medicinal product, which has been marketed in the European Union for over 10 years. Humira 40 mg solution for injection in a prefilled syringe was first authorised in the EU on 8 September 2003; the Marketing Authorisation Holder is AbbVie Ltd.

The Applicant requested EMA scientific advice concerning quality, non-clinical and clinical development on 19 May 2011 (Procedure No.: EMEA/H/SA/2108/1/2011/III).

2.2 Quality aspects

2.2.1 Introduction

The finished product (FP) is presented as solution for injection in a pre-filled syringe or pen containing 40 mg of adalimumab as active substance (AS).

Other ingredients are adipic acid, citric acid monohydrate, sodium chloride, mannitol, polysorbate 80, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

The product is available in a prefilled syringe (single-use clear type I glass syringe with a rubber stopper and a stainless steel needle with an automatic needle guard with finger flange, rubber needle cap and plastic plunger, containing 0.8 ml of solution) or in a pre-filled pen (single-use pre-filled syringe assembled into a triangular-shaped pen with transparent window and label (SensoReady pen). The syringe inside the pen is made of type I glass with a stainless steel needle, an inner rubber needle cap, and a rubber stopper containing 0.8 ml of solution).

The finished product is presented as a similar biological application to the reference medicinal product Humira.

2.2.2 Active Substance

General information

Adalimumab (also referred to as GP2017) is an IgG antibody composed of two kappa light chains each with a molecular weight of approximately 23 kDa and two IgG1 heavy chains each with a molecular weight of approximately 51 kDa (glycosylated), forming the typical Y-shape of IgG antibodies.

Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

One adalimumab molecule contains a total of four inter-chain and twelve intra-chain disulfide bridges. The total molecular weight of adalimumab is 148 kDa (glycosylated). Each light chain consists of 214 amino acid residues and each heavy chain consists of 451 amino acid residues. In total adalimumab consists of 1330 amino acids.

Manufacture, characterisation and process controls

GP2017 active substance is manufactured according to current Good Manufacturing Practices (cGMP) at Sandoz GmbH Biopharmaceuticals Schaftenau (BPS), Biochemiestraße 10, 6336 Langkampfen, Austria and at Cook Pharmica LLC, 1300 S Patterson Dr., Bloomington, IN 47403, USA.

Description of the manufacturing process and process controls

For manufacture of GP2017, a fed-batch process with preceding expansion batches, followed by primary separation and a series of purification steps, typical for monoclonal antibodies, including chromatography steps as well as virus removal and inactivation steps, has been developed.

The manufacturing process for the AS has been adequately described. The main steps are fermentation (fed-batch), purification (using several chromatographic steps), viral inactivation nano & ultrafiltration, filling and freezing.

There are some small differences between the manufacturing process performed at Sandoz, Austria and Cook, US. Several small differences between the two processes as technical adaptations are also described and considered acceptable, as comparability between these two processes has been demonstrated (see Comparability exercise for Active Substance).

Control of materials

The applicant is using a two-tiered cell bank system in overall accordance with ICH Q 5B and Q 5D guidelines. Questions raised on the monoclonality of the MCB, use of WCB, and protocol for establishment of future WCBs have been resolved during the procedure.

Details of the various solutions and media used in the manufacturing process are described. Information and testing for raw materials are provided.

The two AS manufacturing sites, Sandoz BPS and Cook, use different raw materials. The specifications of the raw materials of the two sites correspond. All raw materials are of non-animal and non-human origin. Raw materials used for manufacturing of GP2017 AS are controlled by specifications that assure their identity, strength and purity. They are obtained from established suppliers together with a Certificate of Analysis. Upon receipt, these products are released according to Pharmacopoeia monographs or internal test procedures.

Container closure system

The GP2017 AS bulk solution is filled and stored in 2,000 mL Polyethylene tetraphthalate copolymer (PETG) bottles, closed with a High density polyethylene (HDPE) screw closure.

All components are made of well-established materials for the packaging of medicinal products and are in line with USP and Ph. Eur. monographs, as applicable. The PETG bottles with their HDPE screw closure are irradiation-sterilized and non-pyrogenic. Specifications and technical drawing of the container closure system have been provided. The compatibility of the packaging components has been demonstrated and potential extractables from the container closure system have been addressed adequately in an extractable study and as part of the toxicological assessment.

Control of critical steps and intermediates

Process controls performed during manufacture of GP2017 AS are categorized either as process parameters or as in-process controls. Based on risk assessment and results from process characterisation studies, the PPs and IPCs have been classified accordingly.

A tabulated list all critical and selected key and non-key process parameters and in-process controls of the GP2017 AS manufacturing process has been provided by the applicant. Criticality, acceptable ranges and justification of ranges are provided and considered appropriate for control of the manufacturing process.

Process validation

Process validation was carried out at the Schaftenau site (Sandoz BPS), Austria and Cook Pharmica, Bloomington, USA. GP2017 is manufactured in either one of two production lines at different scales in building 520 at Sandoz BPS.

Validation and qualification activities consisted of:

- Consistency validation (process performance qualification) of the GP2017 manufacturing process (upstream and downstream process) at manufacturing scale
- Evaluation of clearance capability of process- and product-related impurities

- Validation of intermediate hold times
- Qualification of media and buffer hold times
- Assessment of chromatographic column and membrane performance
- Validation of the limit of in vitro cell age
- Risk assessment of extractables and leachables from disposables
- Validation of the transport procedure

All validation requirements have been fulfilled. The validation program was successful and the entire manufacturing process of GP2017 AS at commercial scale is considered to be validated.

Cook Pharmica: The process validation at Cook Pharmica was carried out on essentially the same process, which was implemented at Cook Pharmica with minor adaptations due to the different facility set-up. All validation requirements have been fulfilled. Validation of the entire manufacturing process of GP2017 AS at commercial scale at Cook, including hold times and transport was confirmed.

Manufacturing process development

A process characterisation was conducted in accordance with current ICH requirements including quality by design principles. Process characterisation included large scale and small scale data mining, risk assessments, and laboratory scale studies. A process risk assessment tool based on FMEA (failure mode and effects analysis) methodology was used to assess the process- and product-related risks of the GP2017 AS manufacturing process. Based on the outcome of the risk assessment selected process parameters were further investigated during experimental process characterisation studies.

Process characterisation studies were considered adequate to establish a robust process with performance and product quality within defined ranges. The classification of the process parameters into critical, key, and non-key as well as definition of the respective acceptable ranges was considered well justified. The information presented provides sufficient evidence of a consistent and thorough approach in terms of control strategy development.

Characterisation

AS characterisation included tests for biochemical attributes such as primary structure, higher-order structures (secondary and tertiary structures), carbohydrate structure and molecular heterogeneity (e.g. by size, charge and hydrophobicity). Other attributes further including product-related substances and impurities were also determined.

For functional characterisation of GP2017, a comprehensive portfolio of cell-based potency assays as well as binding assays was used to address the possible modes of action attributed to the adalimumab molecule. TNF-α neutralization assay as well as antibody dependent cell mediated cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), apoptosis inhibition and TNF-binding assays revealed comparable results for all GP2017 FP batches analyzed. Furthermore, consistent binding to TNF-α with sub-nanomolar KD values, as well as to different human Fc gamma receptors (FcγRs) and human neonatal Fc receptor (FcRn) could be observed by surface plasmon resonance.

The AS has been sufficiently characterised by physico-chemical and biological state-of-the art methods revealing that the active substance has the expected structure of adalimumab. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the AS has been adequately characterised by analysing size and charge variants, glycosylation, and other product-related substances and impurities. Biological characterisation of GP2017 indicates that GP2017 binds to TNF and neutralizes

the biological function of TNF as expected. In summary the characterisation is considered appropriate for this type of molecule.

Specification

The AS release specifications include tests for general quality attributes, identity and quantity, testing for the purity/product- and process related impurities and finally a functional assay for the biological activity.

The proposed tests are considered appropriate to ensure that only AS of sufficiently high quality will be further manufactured to the FP. During the procedure information on the potential impact of high-mannoses variants and the level of terminal galactosylation on ADCC activity of GP2017 has been requested. The provided data indicates a linear relationship of the high mannose glycan content with ADCC. These new data also reflect the current scientific view from publications, which indicate a role of Man5 glycans in modulating ADCC activity of IgG1 antibodies.

Based on these data the Applicant has established an appropriate glycan specification which ensure that ADCC activity of GP2017 will fall within the reference range of EU-Humira.

Acceptable specification limits are in place for the controlled quality attributes. These proposed limits appropriately reflect the actual manufacturing capabilities. A justification for each specification limit based on pharmacopeial requirements as well as on the actual manufacturing capabilities was presented. As requested during the procedure certain specifications including level of residual host cell proteins and charged variants have been tightened whereas for the potency an acceptable justification for the initially proposed limits has been provided.

Analytical methods

Concerning the analytical procedures used for release testing of AS, detailed method descriptions have been provided for the non-compendial methods. These descriptions include the method principle but also summarize the procedure of the method.

Bioactivity of GP2017 is assessed with a reporter gene assay (RGA) via measurement of TNFα neutralisation.

Compendial methods are performed according to the respective Ph. Eur. monographs.

Validation summaries as well as detailed validation reports have been submitted for those methods which are not conducted according to the Ph. Eur. The provided validation results indicate that the analytical methods for AS release control are suitable for their intended use.

Batch analysis

The batch analyses data provided demonstrate that all batches complied with the specifications set at the time of testing and thus support the conclusion of the Applicant that the AS manufacturing process can perform effectively and reproducibly to produce AS material meeting its predetermined specifications and quality attributes.

Reference Standards

During early development a sequential reference standard system based on the reference medicinal product Humira and early GP2017 AS material has been in place.

This sequential reference system was then switched to a two-tiered reference standard system comprised of an in-house primary reference standard and an in-house working standard. The usage of primary and working standards as well as the concept for introduction of future in-house reference standards has been briefly outlined.

Release and periodical retests for both, the primary reference and the working reference standard have been submitted and are considered acceptable. For the primary reference standard a panel of analytical methods for additional characterisation has been presented.

Stability

The proposed shelf life of Hefiya active substance when stored at the recommended conditions is based on long-term stability data. The results demonstrate that Hefiya active substance is stable under the recommended conditions. Supporting information on accelerated and stress stability data and data from thermal freeze/thaw cycles as well as photo-stability data have been provided.

Comparability exercise for Active Substance

The development activities include the initial development of the AS manufacturing process, the following scale up and transfer from the pilot scale to the manufacturing scale at different plants and lines. Comparability was demonstrated in data between the development / clinical batches and process validation batches. Overall it is concluded, that comparability between batches produced throughout product development is demonstrated.

A comparability exercise was executed between GP2017 AS batches produced at Sandoz BPS and Cook to assess the effect of the process transfer. The study compared results obtained from routine process controls (in-process testing) and batch release testing, in-depth characterisation and stability studies of GP2017 AS produced at both sites. All acceptance criteria were fulfilled.

2.2.3 Finished Medicinal Product

Description of the product and pharmaceutical development

Hefiya FP is formulated as a solution for injection at a strength of 40 mg (40 mg/0.8 mL) for subcutaneous administration containing adalimumab as active substance. The solution is clear to slightly opalescent, colourless to slightly yellowish.

Hefiya FP is filled with a 2.5% overfill of the nominal volume which is justified by the dead volume of the syringe and the capability of the filling process.

Hefiya 40 mg solution for injection is supplied in either a single-use pre-filled syringe or a single-use pre-filled SensoReady pen. The primary packaging for both prefilled syringe and pen is 1 mL pre-filled syringes (clear, class I glass barrel with fixed needle, rigid needle shield, and a Flurotec coated bromobutyl plunger stopper) with a nominal fill volume of 0.8 mL.

Hefiya single-use pre-filled syringe is supplied in a single-use clear type I glass syringe with a rubber stopper and a stainless steel needle with an automatic needle guard with finger flange, rubber needle cap and plastic plunger, containing 0.8 ml of solution.

Hefiya single-use pre-filled pen is supplied in a single-use pre-filled syringe assembled into a triangular-shaped pen with transparent window and label (SensoReady pen). The syringe inside the pen is made of type I glass with a stainless steel needle, an inner rubber needle cap, and a rubber stopper containing 0.8 ml of solution.

The composition of Hefiya FP differs from the reference product Humira with regard to the buffer system. All excipients are of compendial quality. Except for adipic acid, which is a known excipient but novel in its use in a parenteral formulation, the excipients are widely used in the production of parenteral biopharmaceutical products. No excipients of animal or human origin are used. The following excipients are used for the composition of Hefiya: Adipic acid, citric acid monohydrate, sodium chloride, mannitol,

polysorbate 80, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), and water for injections.

The intended commercial formulation is the same as that used during clinical studies.

The excipient adipic acid has been classified as a novel excipient and the respective data package provided. Adipic acid complies with Ph. Eur. 1586 and the information provided on Chemistry, Manufacturing, and Control is considered sufficient.

The quality target product profile (QTPP) of Hefiya FP was defined to guide the biosimilar development and target ranges for relevant quality attributes (QA) were derived by testing multiple batches of the originator product EU and US Humira using orthogonal state-of-the-art analytical methods which included functional bioassays covering Fab and Fc related functions of adalimumab. An extensive set of QA was systematically evaluated for their impact on potency, PK/PD, and immunogenicity using a risk ranking approach as outlined in ICH Q9 to identify critical quality attributes (CQA) of Hefiya FP.

Formulation development

For formulation development a three step screening approach was chosen to evaluate multiple buffer/excipient combinations and their impact on selected QA. In addition, compatibility with the final primary packaging materials was evaluated. No clear differences were observed for the different combinations.

The use of adipic acid in the commercial formulation has been adequately justified.

Process development

The Applicant gained knowledge on Hefiya FP and manufacturing from development and process characterisation studies. The studies are considered adequately designed and demonstrate extensive process knowledge.

Standard materials for the primary packaging of medicinal products which are in line with pharmacopoeial requirements have been selected for primary packaging of Hefiya FP. Integrity of the container closure system and compatibility with the FP and the device parts was adequately demonstrated. Information on potential leachables and extractables from the primary packaging and process materials coming into contact with the FP has been provided.

For the administration devices (i.e. prefilled syringe and pre-filled pen) comprehensive technical and scientific information has been provided. This included detailed information on design and safety features, shelf-life, transport validation, the assembly and packaging process of the combination products including IPC and release tests, process validations, functional testing, technical drawings, and a check for compliance with the essential requirements/ essential principles as outlined in Annex I of Directive 93/42/EEC and GHTF/SG1/N68:2012.

Manufacture of the product and process controls

Manufacturing process and controls

Hefiya FP solution for injection is produced using standard manufacturing steps. After preparation of the excipient solution, the thawed AS is mixed with the excipient solution. The resulting compounded FP solution is subject to a bioburden reduction filtration, sterile filtered and aseptically filled into syringes. The stoppered filled syringes are 100% visually inspected, labelled and stored at 2-8°C. After shipment to the assembly/packaging site, the labelled PFS are assembled either with NSD or AI and labelled in an automated (NSD) or semi-automated (AI) assembly and labelling process, respectively. Packaging of the

labelled Medicinal product-device combination into shipping boxes is done manually. The FP is stored at 2-8°C.

An FP lot is manufactured from a single AS batch without pooling of different AS batches. The batch formula has been provided in the dossier. Unique batch numbers are assigned to the individual batches by the material management system which ensures traceability.

Process parameters and in-process controls with adequate limits have been established for the critical process steps which ensure consistent process performance and quality of the FP. The process design as well as the process and control limits are appropriately justified and supported by process development, characterisation studies and product knowledge.

A traditional process validation approach was chosen by the Applicant. All analytical data of IPC and release testing complied with the specifications valid at time of testing and the proposed commercial release specification. The presented analytical data from batch release, IPC testing, and additional sampling demonstrate that the manufacturing process is reliable and delivers product of consistent quality.

Hold and process times have been defined and are supported by adequate microbiological and physicochemical hold time studies.

Adequacy of the established shipment conditions was verified by a transport validation study which included four shipments of Hefiya FP PFS from Mylan to Cook using qualified shipment containers and shippers. A potential impact of mechanical stress on quality and integrity of Hefiya bulk PFS was sufficiently addressed by a second transport validation study.

A continued process verification program is in place to ensure process consistency throughout the life-cycle.

To validate the assembly and packaging process three process runs were performed at Cook for each the NSD and AI. The presented AQL, IPC, functional testing and release data demonstrate that the assembly and packaging processes produce combination products of adequate quality. Transport validations covering the different pack sizes have been conducted.

Product-related substances and impurities formed in the FP resemble the variants detected in AS and are adequately addressed.

In line with ICH Q8 the established comprehensive control strategy for FP comprises multiple control elements and links the control elements to the QA of AS. In summary, the presented control strategy address including the relevant FP attributes are considered adequate to ensure consistent quality of Hefiya FP.

The primary container closure system for Hefiya FP consists of a sterile, non-pyrogenic, single use, pre-filled syringe (PFS). Representative certificates of analysis for the components, registration of critical dimensions of the components, information on control of the silicone oil used as a lubricant and confirmation of compliance with relevant ISO standards for the syringe and rubber stopper sterilisation processes have been provided.

The PFS is assembled with either one of two functional secondary packaging components, a plunger rod with a needle safety device (NSD) with an add-on finger flange, or an autoinjector pen. Details of these devices, including descriptions of components, technical drawings and dimensions, and specifications are sufficiently described in Module 3.2.R.

Product specification

The proposed FP specification includes tests for identity, purity/impurities including microbiological attributes, content, potency, and general attributes, and is in line with Ph. Eur. 2031 and 0520 and guidelines EMA/CHMP/BWP/532517/2008 and ICH Q6B. The set of analytical methods is considered appropriate to ensure that only product of adequate quality will be released to the market.

The set of analytical methods is considered appropriate to ensure that only product of adequate quality will be released to the market. The glycosylation pattern and residual levels of HCP, host cell DNA, and Protein A are part of the AS specification and hence testing at FP release is not required.

In addition to the panel of analytical methods for release testing, the shelf life specification comprises a container closure integrity test (CCIT) by dye ingress. Specifications were based on compendial requirements, guidelines and manufacturing experience.

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

Batch analysis

A considerable number of large scale FP batches have been manufactured using the intended commercial process and production line. These batches have been produced for (pre)clinical studies, stability studies, and for process validation purposes. All batches complied with the FP specifications. In addition, release data for the three validation batches assembled with the single-use pre-filled syringe or SensoReady pen are presented and do not give raise to a concern. The batch analyses data of a considerable number of batches demonstrate that the manufacturing process reliably delivers consistent and uniform product.

Reference material

Hefiya FP the same references materials is used as for the AS.

Stability of the product

The proposed shelf life of Hefiya FP is 2 years when stored in a refrigerator (2°C–8°C).

The product should not be frozen and shaken. The product should be kept in the pre-filled syringe / pre-filled pen in the outer carton in order to protect from light.

A single Hefiya pre-filled syringe / pre-filled pen may be stored at temperatures up to a maximum of 25 ° C for a period of up to 14 days. The pre-filled syringe / pre-filled pen must be protected from light, and discarded if not used within the 14-day period.

Real time/real condition stability data from a number of FP batches in PFS and finished dosage form batches (autoinjector, needle safety device) including clinical and validation batches have been provided.

The stability studies were conducted in accordance with ICH guidelines Q1A and Q5C; statistical evaluation of stability data was performed according to ICH guideline Q1E. The analytical program followed the shelf life specifications and included appropriate stability indicating methods.

The claimed shelf life of 24 months at 5 ± 3°C including a 14 days period at 25 ± 2°C/ 60 ± 5% is supported by the presented stability data. All results were within specification for the proposed storage conditions and OOF conditions. It was confirmed that the secondary packaging protects the FP adequately against light-induced deterioration.

Stability of the novel excipient adipic acid (in parental formulations) has been demonstrated in the finished product. Any out of specification result will be reported to the Agency

Adventitious agents

Non-viral adventitious agents

The testing strategy and applied methods for testing for contamination with bacteria, mycoplasma and fungi is considered adequate.

Regarding TSE, no primary animal or human derived raw materials were used during cell banking and manufacturing of Hefiya FP.

Viral adventitious agents

Cell banks were appropriately tested for potential viral contaminants. In general, the applied test program on cell banks is deemed acceptable and in line with ICH Q5A requirements.

The Company conducted virus validation studies to assess the capacity of the manufacturing process to remove/inactivate potential viral contaminants and retroviral particles. The virus validation studies were conducted using qualified small-scale models.

The information on the selection of model viruses is considered adequate.

Significant log10 reduction values were achieved as presented in the summary of log10 virus reduction factors.

In conclusion the viral safety for Hefiya FP is considered adequately documented and ensured throughout the process.

Biosimilar comparability exercise

An analytical comparability exercise has been designed as a three-way comparison between EU-Humira, US-Humira and GP2017 and included the evaluation of structural and functional comparability of these three products.

The samples were compared head-to-head on the physico-chemical and on *in vitro* functional biological level with respect to quality, safety and efficacy. The test items were compared using a number of different/orthogonal physico-chemical and biophysical methods.

Biochemical attributes such as primary structure, higher-order structures (secondary and tertiary structures), carbohydrate structure, heterogeneity (e.g. by size, charge and hydrophobicity) and other attributes including product-related substances and impurities were determined. For the final assessment the following data have been taken into consideration:

- Historical data of EU-Humira and US-Humira generated during GP2017 development
- Historical data of multiple representative commercial scale GP2017 batches
- Data of head-to-head analyses of six GP2017 FP batches (process validation), and three batches of each EU-Humira and US-Humira

For data evaluation min-max range comparison, mean ± 3SD, and numerical or visual evaluation of data and their graphical representations were used in the analytical comparability exercise.

The analytical comparability exercise is summarised in Table 4.

Table 1.Summary of analytical comparability evaluation between GP2017 and Humira

Parameter	Quality attribute	Test method	Key findings
Primary structure	Amino acid sequence	Peptide mapping LC-UV	Identical
		Orthogonal peptide mapping LC-MS/MS	Identical
	Disulfide bonds	Non-reducing peptide mapping LC-MS	Comparable
	Thioether bonds	Reducing CE-SDS	Lower amount in GP2017[1)]
	Free thiols	Ellman's Assay	Comparable
Molecular mass and size	Molecular weight	ESI-qToF-MS	Comparable
		SEC-MALLS	Comparable
	HMW variants	SEC	Slightly higher amount of HMW variants in GP2017[1)]
		AUC	Comparable
	Dimers	AUC	Slightly higher dimer levels in GP2017[1)]
	Antibody fragments	SEC	Comparable
		Non-reducing CE-SDS	Comparable
Purity	-	SEC	Comparable
	-	Non-reducing CE-SDS	Comparable
Glycosylation	Site occupancy Fc N-glycan	Reducing CE-SDS	All GP2017 values are above those of Humira[1)]
	N-glycan galactosylation	Glycan mapping	Higher values for GP2017[1)]
	Non-focusylated N-glycans	Glycan mapping	Higher values for GP2017[1)]
	High mannose N-glycans	Glycan mapping	Lower values for GP2017[1)]
	Glycation	BAC	Slightly higher glycation in GP2017[1)]
Charge	Sum of acidic variants	CEX	Lower values for GP2017[1)]
	Sum of basic variants	CEX	Lower values for GP2017[1)]
	*p*I variants	iCE	Higher amount of lysine variants in Humira
		2D-DIGE	Comparable
Hydrophobicity	-	HIC	Lower amounts of hydrophilic variants in GP2017[1)]
Amino acid modifications / Sequence variants	Methionine oxidation	Peptide mapping LC-UV	Lower values of M_{256} in GP2017[1)], comparable for all other methionines
	Isomerization	Peptide mapping LC-MS	Comparable
	N-terminal pyro-glutamate	Peptide mapping LC-MS	Comparable
	N-terminal extension	Peptide mapping LC-MS	Low amounts of signal peptide remnants identified for GP2017 (≤ 0.5%)[1)]
	C-terminal lysine	Peptide mapping LC-UV	Lower values for GP2017[1)]
	C-terminal proline amide	Peptide mapping LC-UV	Comparable
	Deamidation	Peptide mapping LC-MS	Comparable
Secondary, tertiary and quaternary	Higher order structure	CD (FUV, NUV)	Identical
		FT-IR	Identical
		DSC	Comparable

Parameter	Quality attribute	Test method	Key findings
structure		1D ^{1}H NMR 2D ^{1}H-^{1}H NOESY NMR	Identical
		H/DX	Identical
		X-ray crystallography	Identical
Product related attributes	Concentration of active ingredient	UV absorbance	Comparable
	Particulate contamination	Visual inspection	Comparable
	Subvisible particles	RMM	Comparable
Binding assay	Target binding	SPR	Comparable
	Fcγ receptor binding	SPR	Comparable
	Neonatal Fc receptor binding	SPR	Comparable
	Off-target binding	SPR	Comparable
	C1q binding	ELISA	Comparable
In-vitro bioassay	Potency main mode of action	TNF-α neutralization RGA	Comparable
	Potency ADCC	Functional ADCC bioassay	Comparable
	Potency CDC	CDC bioassay	Comparable
	Apoptosis	Apoptosis inhibition assay	Comparable
	mTNF-α binding	mTNF-α binding assay	Comparable

[1)] Observed differences are considered to have no clinical relevance.

It is noted that a sufficient amount of EU Humira batches and Hefiya have been used for establishment of the biosimilarity ranges. The respective established ranges as well as the amount of batches can be regarded as representative for the quality of the reference product available on the market

A comprehensive set of analytical methods has been in place for characterisation and comparison of physicochemical and biological features of the adalimumab molecule. The methods are considered state-of-the art and suitable for the detection of even subtle differences between reference and biosimilar product. For most of the investigated quality attributes orthogonal methods have been used for characterisation and comparison. In summary, the analytics is sufficient for demonstration of biosimilarity and no concerns have been raised in this respect.

The characterisation of the primary structure is based on

- a comparison of the amino acid sequence with RP-HPLC-UV reducing peptide mapping and RP-HPLC-MS/MS orthogonal peptide mapping,
- a comparison of disulfide bonds with non-reducing peptide mapping and LC-MS, and
- a comparison of the content of free thiols with the Ellman's assay.

100% sequence coverage of the heavy and light chain was obtained and the results confirm that all three products, GP2017, US and EU-Humira, have identical amino acid sequences. The minor difference in the content of free thiols is not considered to be relevant, as lower amounts of free thiols lead to a more homogenous product, which is considered positive. A slightly reduced level of observed for the biosimilar FP batches were appropriately justified.

Molecular mass and size was compared by

- a descriptive comparison of the molecular weight with electrospray-ionization quadrupole time-of-flight mass spectrometer (ESI-qToF-MS) and with size exclusion chromatography with multi angle laser light scattering (SEC-MALLS)a comparison of high molecular weight variants with size exclusion chromatography (SEC) and analytical ultracentrifugation (AUC)
- a comparison of dimers with analytical ultracentrifugation
- a comparison of antibody fragments with size exclusion chromatography and non-reducing capillary gel electrophoresis with sodium dodecyl sulfate (CE-SDS)

Comparable molecular weights determined for reduced light/heavy chain and the F(ab')2 and Fc' fragments for GP2017 FP and both, EU and US Humira, confirmed the integrity of the antibody. Slightly lower levels of high molecular weight variants have been observed by AUC for some of the investigated GP2017 FP batches, whereas in contrast SEC showed slightly higher levels of high molecular weight variants in certain GP2017 FP batches. However, the observed differences were considered minor and the different outcome when using these two orthogonal methods has been explained. The comparison of EU versus US Humira showed comparable levels of high molecular weight variants. Dimers were slightly higher in GP2017; however, this minor difference was not considered relevant. The amount of antibody fragments was comparable for GP2017, EU and US Humira.

Purity was assessed by

- a comparison of the monomer with size exclusion chromatography (SEC)
- a comparison of the monomer with non-reducing capillary gel electrophoresis with sodium dodecyl sulfate (CE-SDS)

With both orthogonal methods a comparable purity profile of GP2017, EU and US Humira could be demonstrated.

Glycosylation was assessed by

- a comparison of site occupancy of the Fc-located N-glycan by reducing capillary gel electrophoresis with sodium dodecyl sulfate (CE-SDS)
- a comparison of N-glycan galactosylation, non-fucosylated N-glycans and high-mannose N-glycans with glycan mapping
- a comparison of glycation with boronate affinity chromatography (BAC)

Minor differences in the glycosylation site occupancy are not expected to have any impact on the biosimilarity claim. No differences were observed between EU and US Humira in terms of glycoforms or glycan profiles. However differences have been detected for the content of galactosylated, non-fucosylated and high mannose N-glycans: The non-fucosylated N-glycans ranges for all tested batches of GP2017 largely exceeded that of of EU Humira

Concerning the galactosylated glycan variants most of the tested batches of GP2017 exceeded the range of EU Humira EU.

For M5 which represents the major high mannose structure in Humira, all tested batches of GP2017 were below the range of EU Humira.

The differences in galactosylated, non-fucosylated and high mannose N-glycans found between GP2017 and Humira were not satisfactorily justified in the initial submission. Structure-activity relationship studies with varying levels of afucosylated and high-mannose glycan variants have been conducted upon request. Based on the data provided during the procedure it was concluded that ADCC activity is impacted by high complex type afucosylated glycans, whereas a less significant influence of high mannose type

glycans on ADCC activity of GP2017 was found. In addition testing a wider range of values indicates a more pronounced, linear relationship of the high mannose glycan content with ADCC. These data also reflect the current scientific view from publications indicating a role of Man5 glycans in modulating ADCC activity of IgG1 antibodies. Notably, despite the observed difference in the Man5 content comparable ADCC activity of GP2017 and EU Humira could be established.
Furthermore, it could be shown that terminal galactosylation has no impact on ADCC activity of adalimumab.

The ranges of glycation determined by BAC are highly overlapping between EU and US Humira.

Charged variants and their distribution have been characterised by

- a comparison of the sum of acidic and basis variants with cation exchange chromatography
- a comparison of the pI variants with imaged capillary isoelectric focusing (iCE)
- a comparison with two dimensional difference gel electrophoresis (2D-DIGE)

Overall, the 2D-DIGE image of GP2017 is comparable to the ones generated for EU and US Humira which indicates a comparable charge distribution. Also the pI variants were comparable for all three products.

The sum of acidic variants of many GP2017 batches was below the lower boundary defined by the range of EU Humira; the sum of basic variants for most tested GP2017 batches was below the lower limit defined by the range of EU Humira, whereas the comparison of EU and US Humira showed comparable results. Comparative biological data of the isolated CEX fractions have been provided during the procedure and it could be concluded that minor differences in bioactivity do not translate into clinical characteristics of GP2017. Furthermore, it could be demonstrated that the differences in basic variants are indeed predominantly due to differences in C-terminal lysine.

Hydrophobicity was investigated by a descriptive comparison with hydrophilic interaction chromatography (HIC). The minor differences between GP2017 and Humira were attributed to a methionine oxidation and were considered to be irrelevant.

Amino acid modifications and sequence variants were characterised by

- a comparison of methionine oxidation with reduced peptide mapping in combination with HPLC separation and UV detection
- comparison of isomerisation of aspartate residues to iso-aspartate by the ISOQUANT kit

a comparison of N-terminal pyroglutamate, N-terminal extension, C-terminal lysine, C-terminal proline amide and deamidation with reduced peptide mapping LC-MS. The range of oxidation of Methionine determined for the GP2017 batches is in general lower than the one of EU Humira. Since Methioninoxidation occurs upon aging and stress, a lower amount is considered advantageous. As the amount of this variant is extremely low in both products it is not expected that the difference is of any relevance.Methionine oxidation in US and EU Humira is comparable.

For all other investigated amino acid modifications either comparability was shown or differences could be sufficiently justified.

Higher order structures were compared by FT-IR spectroscopy, circular dichroism (CD) spectroscopy, differential scanning calorimetry (DSC), 1D 1H nuclear magnetic resonance spectroscopy (NMR), 2 D 1H-1H NOESY NMR, X-ray crystallography and Hydrogen/deuterium exchange (H/D exchange) combined with mass spectrometry. All these methods confirmed a comparable higher order structure of GP2017, EU and US Humira.

Product-related attributes were compared by

- a comparison the concentration of active ingredient with UV absorbance

a comparison of the particulate contamination (visible and sub-subvisible) by visual inspection The content was found to be comparable between GP2017 FP and EU Humira as well as between EU and US Humira. Results for all samples of all batches tested correspond to the release specifications valid at the time of release. GP2017 and both Humira sourced in EU and US are comparable with regards to appearance of their containers. GP2017 samples exhibited a lower or equal number of sub-visible particles compared to EU Humira EU. EU Humira and US Humira are highly comparable regarding particles.

The biological activity was compared by binding assays as well as by *in vitro* bioassays.

The binding assays included

- a comparison of binding to the target by surface plasmon resonance (SPR)
- a head-to-head comparison of binding the Fcγ receptors and the neonatal Fc-receptor with SPR a comparison of Off-target binding with SPR
- a comparison of binding to C1q with an ELISA.

Based on the analysis of EU sourced Humira batches acquired it can be concluded that the range for TNF-α is fully indicative of the variability of the EU reference product on the market.

The side by side comparison of the binding to various Fcγ- as well as the neonatal FcRn receptors nevertheless revealed that the generated data does not indicate any significant differences in the above mentioned binding characteristics

Certain differences have been observed for binding to C1q, nevertheless it is agreed with the Company that this binding activity is not expected to play a role in the mode of action and thus this difference can be considered as irrelevant. All three products are comparable with respect to Off-target binding.

The functional in-vitro assays included

- a comparison of TNF-α neutralisation with a reporter gene assay (RGA)
- a comparison of the ADCC with a functional ADCC assay
- a comparison the CDC activity with CDC bioassay
- a comparison of apoptosis with an apoptosis inhibition assay
- a comparison of binding to membrane-bound TNF-α

TNF-α neutralization activity showed highly comparable results between GP2017 and EU Humira, whereas slightly lower activity was found for a very limited number of US Humira batches when

Of note, a certain shift towards lower ADCC activity values was found for GP2017 compared with EU Humira, whereas US Humira was comparable with EU Humira. This minor difference could be justified and additional measures to control ADCC activity were agreed during the procedure

No difference between GP 2017, EU and US Humira with respect to CDC potency and apoptosis could be detected.

A higher variability for GP2017, which led to values outside the established similarity range, was observed for binding to membrane-bound TNF-α. Based on the provided data and justification this difference is acceptable. GP2017, EU and US Humira are comparable with regard to apoptotic response.

In addition to the in-depth characterisation, stability studies were performed to investigate long term stability behavior of GP2017 FP and Humira EU and Humira US at intended storage condition. Furthermore, stability was tested under accelerated and stress storage conditions. The currently available stability study data demonstrate comparable stability behaviour for GP2017, EU Humira and US Humira.

2.2.4 Discussion on chemical, pharmaceutical and biological aspects

The Applicant has provided a comprehensive Module 3 within the marketing authorisation application for GP2017 as a biosimilar development to its reference product Humira.

The manufacturing process for AS and FP has been described in sufficient detail; all raw and starting materials including the cell banks used in the manufacture of GP2017 are listed identifying where each material is used in the process. Information on the quality and control of these materials has been provided. All excipients used for FP formulation including the novel excipient adipic acid comply with the Ph. Eur. Relevant process controls and in-process controls ensure a consistent routine manufacture of GP2017. Process validation supports the conclusion that the manufacturing process for AS as well as for FP reliably generates AS and FP meeting its predetermined specifications and quality attributes. The provided batch analyses data support this conclusion. Comparability of the GP2017 throughout the development has been demonstrated. An appropriate control strategy ensures that material of sufficiently high quality will enter the market.

A biosimilarity programme based on an extensive panel of standard and state-of-the-art methods has been conducted to prove similarity for relevant physicochemical and biological quality attributes. For the investigated quality attributes either similarity was shown or minor differences seen have been appropriately justified. A major concern on the extrapolation claim to other indications raised during the procedure could be resolved. A well-structured and comprehensive response document has been provided. The additional data sets as well as the provided justifications are reasonable and appropriately address the concerns raised.

Following an inspection conducted in January 2018, the Major Objection concerning the missing GMP certificate for the FP manufacturing site Mylan has been fully resolved and a GMP certificate issues for the Mylan site provided.

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.

2.2.6 Recommendation(s) for future quality development

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

- To implement release and shelf-life specifications for break-loose and gliding force
- Finalize membrane re-use study at contract manufacturing organization prior to commercial implementation.

2.3 Non-clinical aspects

The Applicant proposed a non-clinical package comprised a comprehensive panel of in vitro functional assays, a single dose PK study in rabbits and a comparative PD study in a mouse model overexpressing soluble human TNFα (Tg197 mice), and later also included a toxicological assessment in non-human primates. This was discussed in a scientific advice procedure (Procedure No.:

EMEA/H/SA/2108/1/2011/III), This proposal was accepted by the CHMP in general, with some suggestions with respect to the in vitro bio similarity exercise.

2.3.1 Pharmacology

The similarity of GP2017 to the reference product Humira was assessed by a comprehensive panel of in vitro assays as well as two comparative in vivo studies in transgenic mouse models overexpressing TNFα.

The comparative functional in vitro assays cover all relevant effector functions attributed to the Fab- and Fc-related pharmacology/mode of action of adalimumab.

The main mechanism of action of adalimumab, the binding to and neutralization of TNFα, was addressed by an SPR assay comparing the binding affinity of GP2017 and Humira, complemented by cell based assays (i.e. a TNFα neutralization reporter gene assay and an apoptosis inhibition assay with U937 cells).

In addition, reverse signalling activity is involved in the immunomodulatory mode of action of adalimumab in some indications, according to published evidence. Comparative equilibrium binding to membrane bound TNFα was assessed in a cell based competitive binding assay. On- and off-rates were not examined (as clarified as part of the EMA Scientific Advice) based on limited feasibility in recombinant expression of transmembrane target.

Overall, all TNFα binding assays showed relatively good comparability for GP2017 and EU- and US-licensed Humira, respectively. Fc-related functions were comparatively assessed by a cell-based, antibody-dependent, cell-mediated cytotoxicity (ADCC) assay and complemented by SPR-based assays for the high-affinity receptor FcγRIa and the low-affinity receptors FcγRIIa, FcγRIIb/c and FcγRIIIa/b. Complement dependent cytotoxicity (CDC) was addressed by cell-based CDC assay and an ELISA-based C1q binding assay.

Moreover, the FcRn binding affinity was assessed for GP2017 in comparison to EU- and US-licensed Humira.

Potential off-target binding of GP2017 and EU- and US-licensed Humira to cytokines structurally related to TNFα (TGF-β1, APRIL, IFN-γ, IL-1β, TNF-β, IL-6, IL-8, IL-10, sCD40L, BAFF or RANKL) was analysed by SPR without revealing any relevant effects.

In general, the results of the in vitro functional assays demonstrated that all batches of GP2017 met the predefined ± 3SD range.

In support of the in vitro comparability exercise two comparative in vivo studies have been performed in transgenic mouse models of rheumatoid arthritis with GP2017 and EU-Humira.

The efficacy of subtherapeutic doses (3 mg/kg) of GP2017 and EU-Humira on soluble TNF-α was investigated in Tg197 mice, with treatment starting shortly after onset of the disease at 6 weeks of age. Arthritic scores were evaluated on a weekly basis, histopathology scores after the end of the treatment period of 4.5 weeks (9 treatments, i.p.). GP2017 showed similar efficacy as compared to EU-Humira, and both treatment groups were significantly different from the vehicle and positive (30 mg/kg EU-Humira) controls.

The second in vivo study utilised Tg5453 mice overexpressing mTNF-α. In order to achieve a preventive effect on the disease, treatment with GP2017 and EU-Humira (2.5 mg/kg and 10 mg/kg) started when mice were 2 weeks of age and was continued for 5 weeks. Both, Humira and GP2017, positively influenced progression of the disease and revealed statistically significant higher efficacy as compared to the buffer controls. However, from the third treatment week onwards a difference in efficacy in favour of Humira was observed regarding the in vivo arthritic scores, which resulted in statistically significant differences after

5 weeks of treatment. This observation was confirmed by the histopathology scores evaluated at the end of the treatment period. The differences were more pronounced in the high dose group.

Assessment of the GP2017 batch used in this in vivo study (within the scope of the comparability exercise) revealed relatively low ADCC activity (83%) but similar or high CDC (100%), TNFα-binding (115%) and TNFα-neutralization activity (91%) as compared to the mean value of the entire range of the reference product. Compared to the GP2017 batch, the Humira batch exhibited higher ADCC (107%) and CDC activity (111%). Neither of the batches was tested for in vitro mTNFα-binding.

Based on the additional information provided by the Applicant, the reduced efficacy of GP2017 as compared to Humira in the Tg5453 mouse model for RA cannot be attributed to a difference in quality attributes analysed within the scope of the comparability exercise. Further elucidation of the difference in in vivo efficacy would in involve further animal studies which would not be in compliance with the principles of the 3Rs especially in the light of the Tg197 mouse study where similarity regarding in vivo PD was successfully demonstrated. Taking into account the limitations of the animal model as well the limited significance of in vivo studies as compared to in vitro assays in biosimilar development, this point was considered solved by the CHMP.

The Applicant did not perform any studies on secondary PD or PD drug interactions whereas safety pharmacology aspects have been addressed within the scope of the repeat-dose toxicity study. This is in line with the both the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues EMA/CHMP/BMWP/403543/2010) and the provided scientific advice (EMA/CHMP/SAWP/70331/2012). Furthermore, the non-clinical data described in the SmPC of Humira will be reflected in the SmPC for GP2017.

2.3.2 Pharmacokinetics

Comparative PK data were generated in three single-dose studies in New Zealand white (NZW) rabbits namely GP17-001 (26024), GP17-004 (8240794) and GP17-007 (28088). In addition, exposure to GP2017 was compared with the exposure to EU-Humira in the pivotal 4-week repeat-dose toxicity study GP17-002 (8240754) in cynomolgus monkeys. In the latter, serum concentrations upon first and last treatments were monitored densely, supported by analysis of trough levels throughout the remaining treatment period. The comparative PK studies GP17-004 (8240794) and GP17-007 (28088) and the TK study GP17-002 (8240754) were conducted in compliance with GLP.

All methods of analysis used for the assessment of in vivo PK parameters were sufficiently validated.

In an early phase formulation screening PK Study GP17-001 (26024) animals were administered with seven different formulations of GP2017 and Humira each dose corresponding to 10 mg/kg b.w. The ratios of Cmax, AUC0-168h, AUC0-tlast and AUC0-∞ for all formulations to Humira ranged from 0.84-1.07 and were, thus, comparable to Humira. The highest exposure to GP2017 was achieved with a formulation containing 20 mM adipic acid which was chosen for further development. The actual composition of this formulation was 23 mM adipic acid and 1.3.mM citric acid which was revealed only by retrospective analysis.

In a further PK study the selected formulation was tested head to head to Humira® resulting in a 25% higher exposure to Humira as compared to GP2017 which was in contrast to the early phase formulation study. This was attributed to either the formulation lacking citric acid (it was assumed that the selected formulation contained only adipic acid as the retrospective analysis was not performed yet) or to different handling of the animals by two different administrators.

To rule out any uncertainties a third PK study was performed comparing various formulations containing citric acid in addition to adipic acid. This study confirmed that the initially chosen formulation containing

23 mM adipic acid and 1.3 mM citric acid is biosimilar to Humira PK with respect to differences in exposure of below 5%.

The TK properties of GP2017 were also determined after single and repeated (once weekly for 4 weeks, 5 treatments) s.c. dosing to cynomolgus monkeys at the dose level of 100 mg/kg and were compared to that of EU-Humira in the GLP-compliant, pivotal 4-week repeat-dose toxicity study.

The formulation development is considered comprehensive and the nonclinical studies performed for that purpose were considered adequate by the CHMP However, they were not comparative in nature and therefore cannot be used as part of the comparability exercise to Humira.

2.3.3 Toxicology

The toxicology program performed with GP2017 and reference product Humira was part of the biosimilarity assessment and included a 4-week repeat-dose toxicity study in cynomolgus monkeys, including TK and immunogenicity assessment, a single dose local tolerance study in NZW rabbits, and a tissue cross-reactivity study with frozen human tissues. All studies were performed in compliance with GLP.

Single dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies were not performed. This is considered acceptable for biosimilar medicinal products.

The GLP-compliant comparative 4-week (29 days) repeat-dose toxicity study in cynomolgus monkeys was conducted in order to compare the safety profile of GP2017 to the reference product EU-Humira (Study GP17-002(8240754)). Repeated weekly s.c. administrations of 100 mg/kg/week for four consecutive weeks without recovery period were applied to 6 animals (3 female and 3 male) per treatment group. Observations included the assessment of clinical signs, body weight, food consumption, opthalmoscopic examination, body temperature, electrocardiography (ECG), blood pressure, clinical pathology parameters, organ weights and anatomic pathology evaluation, as well as evaluation of serum levels of adalimumab and ADA determination. The obtained safety profiles of GP2017 and EU-approved Humira are highly comparable and no new toxicities were identified for GP2017 as compared to Humira. One female monkey presented with an increase in absolute weights of liver, spleen and adrenal glands, pale lesions on liver and lung, granulomatous inflammatory areas in the femur, liver, spleen and lung, and acid fast bacteria were confirmed within areas in the lung and spleen. The actual mycobacterium tuberculosis infection was confirmed by the animal supplier to have occurred also in other animals of this one group at the test facility and was thus not regarded to be of toxicological relevance.

The dose, regimen, duration, and test species for the comparative monkey toxicology study were selected to allow detection of any meaningful toxicological differences between GP2017 and EU-Humira.

The TK profiles of GP2017 and EU-Humira were comparable throughout the duration of the study, but slightly higher exposures (AUCs and Cmax) were observed with EU-Humira on day 1 and day 29 in male monkeys compared to GP2017. On the other hand, there is a tendency towards females being higher exposed to GP2017 compared to Humira on day 1 and day 8. Larger variabilities could be detected for tmax throughout the study. The CHMP agreed with the Applicants statement, that due to the low number of animals per treatment group limited statistical power needs to be considered. Further, the batch used to supply the repeat-dose toxicity study is a preclinical batch produced at laboratory scale only, and comparative in vitro study results for target and effector functions are not available. While this of course questions the added value of the toxicity study for purposes of examining comparability, clinical PK testing is anyway part of the comparability program.

An ECL bridging immunogenicity assay for the assessment of anti-GP2017/Humira antibodies was developed and validated appropriately. No animal was identified to be positive for ADAs. Drug tolerance was estimated through spiking samples of polyclonal rabbit ADA in appropriate matrices with

adalimumab; however the samples were compared to blanks only, as the cut point was determined from pre-dosing serum values in each study. Due to the nature of the ADA response, the 'true' value for drug tolerance in a given sample is not possible to calculate and thus could be substantially different from the calculated value depending on the relative affinities of the antibodies produced and the polyclonal rabbit anti-adalimumab antibody used as the positive control in these studies. Furthermore, as the confirmatory assay acceptance criteria is set (arbitrarily) at 50% inhibition, and as relatively high concentrations of adalimumab were recorded in the repeat-dose toxicity study in cynomolgus monkeys, there is a significant risk of false negative results via this method.

For the GLP-compliant local tolerance study (Study GP17-008 (30331)) conducted in female NZW rabbits to compare the local tolerability profile of GP2017 formulation buffer, GP2017, and EU-Humira (27G and 29G needle), a single dose of 0.8 mL/injection site was administered either s.c. (intended route), i.a., i.v., p.v., respectively 0.5 mL/injection site i.m to 4 animals per treatment group. No treatment-related macroscopic or histopathological changes were observed at any of the injection sites or with any formulation tested. Thus, GP2017 is considered to be well-tolerated.

A GLP-compliant tissue-cross reactivity study was conducted to assess potential off-target binding of GP2017 to human tissues (Study GP17-005(824079)). No unexpected off-target staining was observed in any of the human tissues examined.

2.3.4 Ecotoxicity / environmental risk assessment

According to the CHMP Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2) for products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting specific ERA studies.

According to Directive 2001/83/EC, applicants are required to submit an ERA also for applications under Art 10(4) similar biological applications. However, the ERA dossier may consist of an adequate justification for the absence of specific study data. The justification of the absence of significant increase of the environmental exposure, demonstrated by suitable information, can be accepted as a justification for the absence of a complete ERA.

The Applicant provided sufficient documentation to justify that specific studies on environmental exposure are not required. The applicant concludes that the use, storage and disposal of GP2017 will not significantly alter the concentration or distribution of the substance, its metabolites or degradation products in the environment. No changes in the environmental risks that are not already identified for adalimumab are to be anticipated.

The Applicant's approach was agreed by the CHMP.

2.3.5 Discussion on non-clinical aspects

The Applicant provided a comprehensive panel of in vitro pharmacology studies in order to demonstrate comparability of GP2017 to the reference product Humira. The in vitro studies are considered suitable to investigate the reported main mechanism of action, i.e. neutralization of and binding to soluble and membrane-bound TNFα, respectively. Additional assays covering Fc-related functions were performed. In summary, GP2017 proved to be biosimilar to the reference product Humira with respect to all biological function parameters.

In vivo pharmacology studies were performed in two different murine models for RA. In the Tg197 mouse strain, which overexpresses soluble TNF-α, comparable efficacy of GP2017 and Humira with respect to inhibiting disease progression could be demonstrated. In contrast, in the Tg5453 strain, which overexpresses membrane-bound TNFα, efficacy of GP2017 was clearly inferior as compared to the

reference product. Based on the additional information provided by the Applicant, the reduced efficacy of GP2017 as compared to Humira in the Tg5453 mouse model for RA cannot be attributed to a difference in quality attributes analysed within the scope of the comparability exercise. Further elucidation of the difference in in vivo efficacy would involve further animal studies which would not be in compliance with the principles of the 3Rs especially in the light of the Tg197 mouse study where similarity regarding in vivo PD was successfully demonstrated. Taking into account the limitations of the animal model as well the limited significance of in vivo studies as compared to in vitro assays in biosimilar development, this point was considered solved by the CHMP.

The Applicant did not perform any studies on secondary PD, safety pharmacology or PD drug interactions. This is in line with the both the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues EMA/CHMP/BMWP/403543/2010) and the scientific advice received for GP2017 (EMA/CHMP/SAWP/70331/2012).

Single dose in vivo pharmacokinetics studies for the purpose of formulation development of GP2017 were performed in NZW rabbits. These studies were well conducted; however, they were not comparative in nature and therefore cannot be used as part of the comparability exercise to Humira.

In a 4-week repeat-dose toxicity study in cynomolgus monkeys, which included also TK and immunogenicity assessment, no compound-related adverse effects of GP2017 in comparison to Humira were observed. The toxicology program performed with GP2017 and the reference product Humira further included a single dose local tolerance study in NZW rabbits and a tissue cross-reactivity study with frozen human tissues. All studies were performed in compliance with GLP.

The Applicant did not submit specific ERA studies but provided sufficient documentation to justify that specific studies on environmental exposure are not required which is in line with EMA Guideline on the Environmental Risk assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr. 2). The applicant concludes that the use, storage and disposal of GP2017 will not significantly alter the concentration or distribution of the substance, its metabolites or degradation products in the environment. No changes in the environmental risks that are not already identified for adalimumab are to be anticipated. The Applicant's approach was agreed by the CHMP.

2.3.6 Conclusion on the non-clinical aspects

The Applicant provided a comprehensive panel of in vitro pharmacology studies in order to demonstrate comparability of GP2017 to the reference product Humira. Biosimilarity could be demonstrated for all parameters of biological function.

With respect to in vivo PD data, GP2017 showed good comparability to EU Humira for the mode of action exerted via soluble TNF-α. However, in vivo assessment of PD effects linked to membrane-bound TNF-α revealed inferiority of GP2017 as compared to Humira. Taking into account the limitations of the animal model as well the limited significance of in vivo studies as compared to in vitro assays in biosimilar development, this point was considered solved by the CHMP.

Toxicology data did not show any differences between GP2017 and Humira.

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

Table 2 - Summary of the clinical studies

Study No.	Study design Study objective	Study population	Treatment duration	Dosage [batch number]
GP17-104 **(pivotal PK study)**	Design: Single-center, randomized, double-blind, single-dose, three-arm, parallel group study in healthy male subjects Objective: To demonstrate PK bioequivalence (90% CI of ratio of geometric means within the margins of [0.8; 1.25]) for GP2017 and EU-Humira, and PK bioequivalence for EU-Humira and US-Humira in terms of C_{max} and AUC_{0-inf} after a single s.c. injection of 40 mg of adalimumab	Healthy male subjects N=318m GP2017: N=107m EU-Humira: N=106m US-Humira: N=105m	Up to approximately 14 weeks (including screening, treatment, and follow-up)	GP2017: 40 mg/0.8 mL, PFS, single s.c. injection [7007467] EU-Humira: 40 mg/0.8 mL, PFS, single s.c. injection [45018XD05] US-Humira: 40 mg/0.8 mL, PFS, single s.c. injection [1030241]
GP17-101 (**supportive** PK study)	Design: Single-center, randomized, double-blind, single-dose, three-arm, parallel group study in healthy male and female subjects Objective: To demonstrate PK bioequivalence of GP2017, EU-Humira and US-Humira in terms of C_{max}, AUC_{0-inf} and AUC_{0-last} after a single s.c. injection of 40 mg (0.8 mL)	Healthy male and female subjects N=219 (144m, 75f) GP2017: N=73 (49m, 24f) EU-Humira: N=73 (46m, 27f) US-Humira: N=73 (49m, 24f)	Up to approximately 14 weeks (including screening, treatment, and follow-up)	GP2017: 40 mg/0.8 mL, PFS, single s.c. injection [7006285] EU-Humira: 40 mg/0.8 mL, PFS, single s.c. injection [14270XD17] US-Humira: 40 mg/0.8 mL, PFS, single s.c. injection [131082E]
GP17-102 (**supportive** PK study - device development)	Design: Single-center, randomized, open-label, single-dose, two-arm, parallel group study in healthy subjects Objective: To describe PK of GP2017 administered by an AI or a PFS as a single s.c. injection of 40 mg to healthy adult male subjects with body weights between 50.0 and 94.9 kg in terms of AUC_{0-360h} and C_{max}	Healthy male subjects N=108m GP2017-AI: N=54m GP2017-PFS: N=54m	Up to approximately 14 weeks (including screening, treatment, and follow-up)	GP2017-AI: 40 mg/0.8 mL, PFS assembled into the Delta AI, single s.c. injection [30983842] GP2017-PFS: 40 mg/0.8 mL, PFS, single s.c. injection [30861390] One bulk drug product batch was used for the two presentations: [7007389]
GP17-103 (**supportive** PK study - technical transfer)	Design: Multi-center, randomized, double-blind, parallel group, two-arm study in healthy male subjects Objective: To demonstrate PK bioequivalence (90% CI of the ratio of the geometric means within the margins of [0.8; 1.25]) of GP2017-Cook and GP2017-Schaftenau in terms of	Healthy male subjects N=178m GP2017-Cook: N=88m GP2017-Schaftenau: N=90m	Up to approximately 14 weeks (including screening, treatment, and follow-up)	GP2017-Cook: 40 mg/0.8 mL, PFS, single s.c. injection [7007468][a] GP2017-Schaftenau: 40 mg/0.8 mL, PFS, single s.c. injection [7007467][a]

GP17-301 **(pivotal confirmatory efficacy and safety study)**	Design: multi-center, randomized, double-blind, comparator-controlled study with treatment switches in patients with moderate to severe chronic plaque-type psoriasis Objective: To demonstrate equivalent efficacy of GP2017 and Humira with respect to PASI75 response rate at Week 16 and similar safety and immunogenicity in patients with moderate to severe chronic plaque-type psoriasis	Male and female patients with moderate to severe chronic plaque-type psoriasis N=465 (284m, 181f) GP2017: N=231 (142m, 89f) Humira: N=234 (142m, 92f)) EU-Humira: N=44 (28m, 16f) US-Humira: N=190 (114m, 76f)	Up to 55 weeks (including screening, two treatment periods, and one extension period)	GP2017: 40 mg/0.8 mL, PFS [7006715, 7007139, 7007389, 7007467] EU-Humira: 40 mg/0.8 mL, PFS [20321XH04, 23342XH04, 28387XD04, 34434XD11] US-Humira: 40 mg/0.8 mL, PFS [1004010, 1017238, 1017236, 1017235, 1024661, 1030241] GP2017 and Humira were administered as s.c. injections with a loading dose of 80 mg on Day 1 and 40 mg every other week, starting with Week 1 and up to Week 49

2.4.2 Pharmacokinetics

PK biosimilarity between Humira and GP2017 was investigated in study GP17-101/GP17-104 and in the efficacy and safety study GP17-301. Further comparative PK data were generated in study GP17-102 (to describe PK of GP2017 after administration by AI versus PFS) and in study GP17-103 (to demonstrate PK biosimilarity between GP2017-Schaftenau and GP2017-Cook material from two drug substance production facilities).

Analytical methods

PK Assays

The Applicant developed a sandwich ELISA to quantify adalimumab in human serum. To ensure that the method is suitable for its intended purpose, the method was validated in line with the Guideline on bioanalytical method validation (EMEA/CHMP/EWP//192217/2009). The lower and upper limits of quantification are 0.25 µg/mL and 8 µg/mL, respectively.

For the quantification of adalimumab in human serum of patients with psoriasis, essentially the same method as for the quantification of adalimumab in human serum of healthy adults is used.

Overall, the method validation was appropriately conducted and all relevant parameters were considered for method validation.

Immunogenicity testing

The Applicant submitted a well-structured set of immunoassays to detect anti-drug antibodies (ADAs) against GP2017 and Humira. A multi-tiered approach was used for the immunogenicity assessment in the PK studies GP17-101, GP17-102, GP17-103, GP17-104 in healthy subjects and in study GP17-301 in patients with psoriasis. This included a validated bridging immunogenicity assay for the screening and confirmation of binding ADAs, followed by a validated competitive ligand binding assay for the assessment of the neutralizing capacity of antibodies.

Overall, the validation of the immunogenicity assays was appropriately conducted.

Clinical PK studies

Study GP17-101 (EudraCT Number:2012-004205-27)

Study GP17-101 was a randomized, double-blind, 3-arm parallel group phase I study conducted in healthy male and female volunteers.

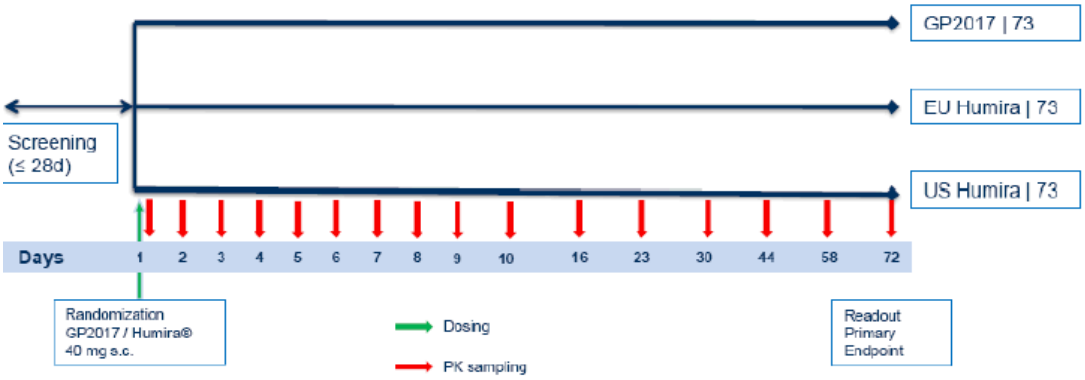


Figure 1 - Design Study GP17-101

A total of 219 healthy subjects aged 18 to 55 years were enrolled (144 male and 75 female subjects); 73 subjects in each of the three treatment groups. In each group, all subjects received a single dose of adalimumab and were then observed for 72 days during which the PK, safety, tolerability, and immunogenicity measurements were made.

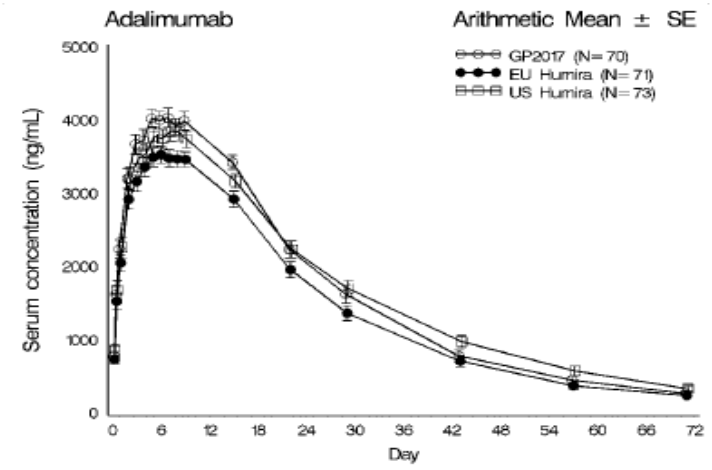
The primary objective was to demonstrate PK comparability of GP2017, EU-authorized and US-licensed Humira in terms of Cmax, AUC0-inf and AUC0-last (9 comparisons) after a single 40 mg SC injection.

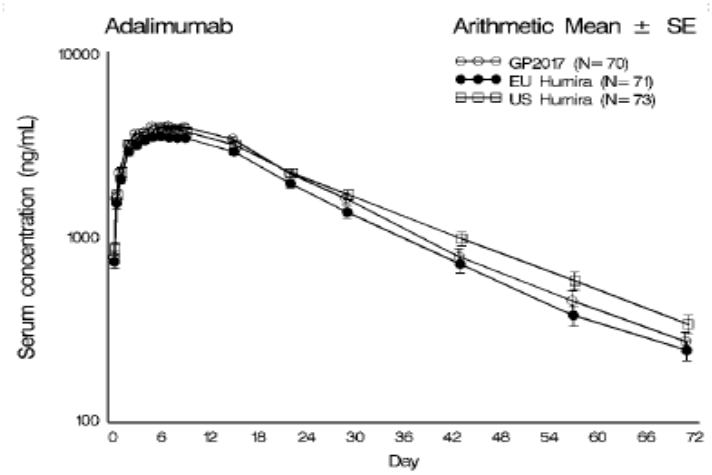
Equivalence was based on the 90% CIs for the ratio of geometric LS Means of the primary variables, which should be contained within the pre-specified acceptance range of 0.8 to 1.25.

The study failed to demonstrate PK biosimilarity between GP2017 and EU-authorized Humira as well as between EU- and US-licensed Humira, as the upper limits of the 90% CIs of the ratios of geometric means (GM) for the primary PK endpoints AUC0-last and AUC0-inf were above 1.25. Relevant results are displayed below:

Table 3 - Results - Study GP17-101

GP2017/EU-sourced Humira	**US-/EU-sourced Humira**
AUCinf:1.156 (90% CI: 1.017 – 1,314)	AUCinf 1.231 (90% CI: 1.084 – 1.399)
Cmax: 1.151 (90% CI: 1.064 – 1,245)	Cmax 1.094 (90% CI: 1.013 – 1.183)
AUC0-last: 1.226 (90% CI: 1.085 – 1.385)	AUC0-last 1.24 (90% CI: 1.099 – 1.399)





The curves start with the value measured at 1 hour post-dose.
EU Humira = EU-authorized Humira; N = number of subjects in the PK analysis set per treatment; US Humira = US-licensed Humira

Figure 2 Arithmetic mean adalimumab serumconcentration-time profiles (linear and semi-logarihmic)

Table 4 Summary statistical analysis of bioequivalence – primary endpoints (PK analysis set)

Treatment comparison (test vs. reference)	PK parameter	Geometric LSmeans		Ratio test/reference	90% CI	
		Test	Reference	Estimate	Lower	Upper
GP2017 / EU Humira	C_{max} (µg/mL)	4.4	3.9	1.1510	1.0644	1.2446
	$AUC_{0\text{-last}}$ (h×µg/mL)	2489.0	2030.7	1.2257	1.0849	1.3847
	$AUC_{0\text{-inf}}$ (h×µg/mL)	2744.5	2374.7	1.1557	1.0166	1.3139
GP2017 / US Humira	C_{max} (µg/mL)	4.4	4.2	1.0515	0.9731	1.1362
	$AUC_{0\text{-last}}$ (h×µg/mL)	2489.0	2517.9	0.9885	0.8760	1.1156
	$AUC_{0\text{-inf}}$ (h×µg/mL)	2744.5	2923.8	0.9387	0.8273	1.0650
US Humira / EU Humira	C_{max} (µg/mL)	4.2	3.9	1.0946	1.0132	1.1826
	$AUC_{0\text{-last}}$ (h×µg/mL)	2517.9	2030.7	1.2399	1.0990	1.3989
	$AUC_{0\text{-inf}}$ (h×µg/mL)	2923.8	2374.7	1.2312	1.0839	1.3986

CI = confidence interval; EU Humira = EU-authorized Humira; LS = least squares; US Humira = US-licensed Humira

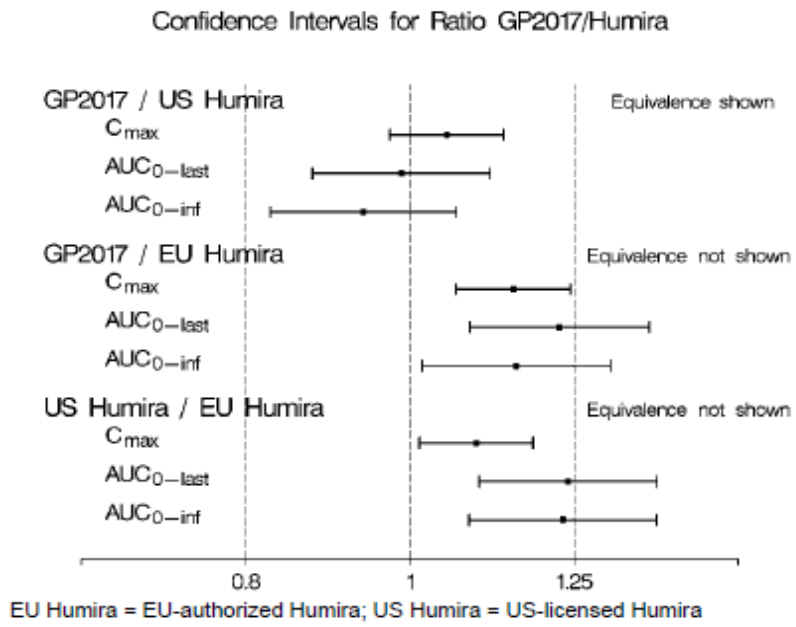


Figure 3 - 90% confidence intervals for ratio GP2017/Humira (EU authorised and US licensed)

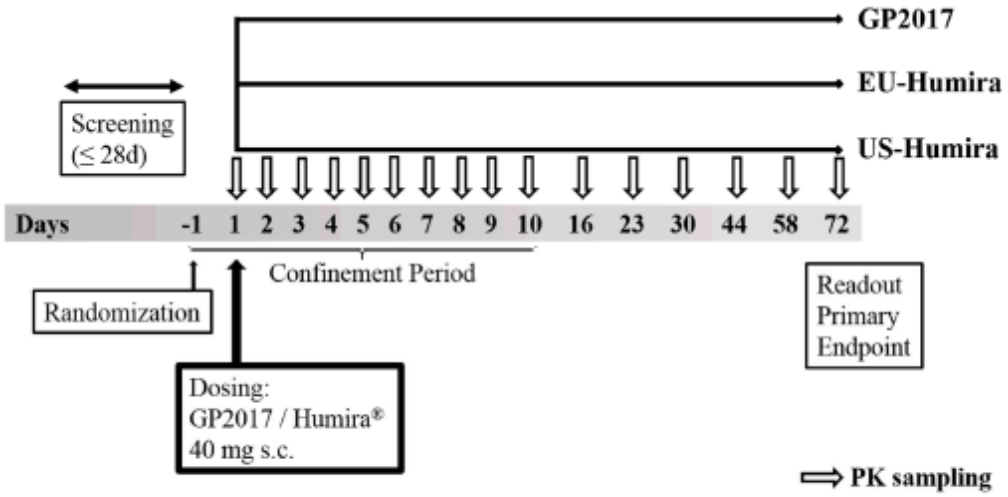
The key secondary end-point of AUC0-360h was met and was within the pre-specified range of 0.8-1.25. Descriptive statistics for other secondary end-points were also provided and in many cases proved similar across all 3 arms. However for AUC extra and Kel, a greater than 20% difference was observed between the highest and lowest geometric mean value across all three arms.

Inter-individual variability was higher than expected. Sample size calculation was based on a CV of 31% for AUC0-last based on historical literature; however, CVs for AUC0-last were approx. 10 % higher. While no root cause for the negative outcome of study GP17-101 could be identified, other reasons than the observed larger inter-subject CV for AUC0-last cannot be excluded.

The impact of ADA formation on adalimumab exposure levels following administration of single-doses was investigated and an impact was noted. In keeping with published data on Humira, smaller AUC0-last and AUC0-inf values were observed in ADA positive subjects compared to ADA negative subjects in all three treatment arms.

Study GP17-104 (EudraCT Number:2015-000579-28)

The study was a single-center, randomized, double-blind, parallel group PK study with three treatment arms to evaluate PK, safety and immunogenicity of GP2017, EU-Humira and US-Humira in 318 healthy, adult, male subjects. Randomization was stratified by body weight categories of 50.0 to 64.9 kg, 65.0 to 79.9 kg and 80.0 to 95.0 kg. Two subjects discontinued the study prematurely.



The study consisted of a screening period (Day -28 to Day -2), a "check-in" and randomization (Day -1), a treatment day (Day 1) and a follow-up period of 71 days after IMP administration (Day 2 to Day 72). The total individual study duration was up to 14 weeks.

Figure 4 – Design - Study GP17-104

The primary objective was to demonstrate PK biosimilarity (90% CI of ratio of geometric means within the margins of [0.8; 1.25]) for GP2017 and EU-Humira, and PK biosimilarity for EU-Humira and US-Humira in terms of Cmax and AUC0-inf (4 comparisons) after a single s.c. injection of 40 mg/0.8 mL of adalimumab to healthy adult male subjects.

Compared with study GP17-101 the study design was adapted in several aspects:

- restriction to only two co-primary endpoints (Cmax and AUC0-inf)
- increase of sample size
- pre-specification of descriptive comparison of AUC0-last and AUC0-inf for ADA positive and ADA negative subjects
- several restrictions with respect to baseline characteristics of the subjects, e.g. only male sex

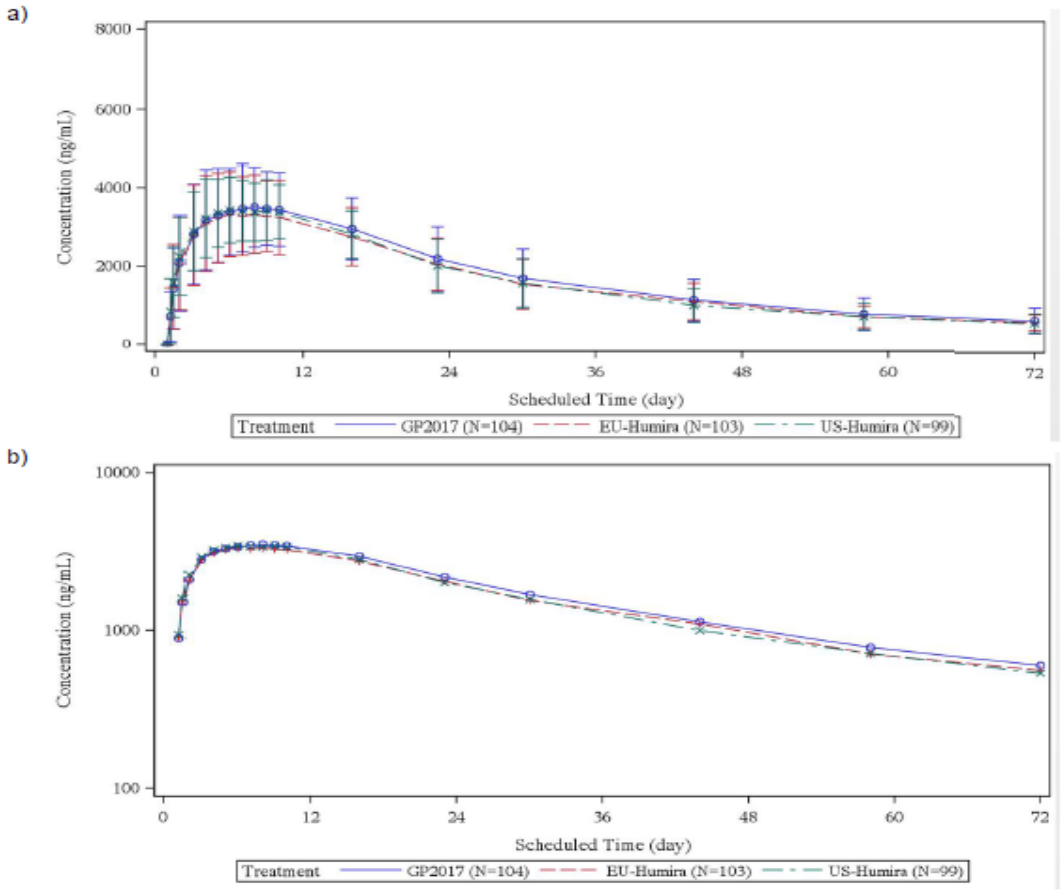
A concern was raised regarding the blinding of the study GP17-104, since 'the identity of the study treatments could not be concealed as the appearance of the syringes differed' due to use of commercially available PFS of reference product. Unblinded study site personnel not involved in any further study assessments administered treatments, whereas in study GP17-101 IMP was blinded at the pharmacy due to transfer to non-commercial tuberculin syringes. Blinding of subjects was maintained in study GP17-104 by requesting the subject "to turn his head and look in an opposite direction or to firmly close his eyes or by using an eye mask or a separation/dividing wall". Although PK levels are the key parameter of this study and are not impacted by the potential source of subjects' unblinding, the possible impact on study outcome in terms of safety was considered.

Results:

For the comparison GP2017/EU-Humira, the point estimates of the ratios of the geometric LS means for Cmax and AUC0-inf were around 1 and the corresponding 90% CIs were entirely contained within the pre-specified margin of 0.8 – 1.25.

Table 5 - Results Study GP17-104

GP2017/EU-sourced Humira	EU-/US-sourced Humira
AUCinf:1.04 (90% CI: 0.96 – 1.13)	AUCinf 1.04 (90% CI: 0.96 – 1.13)
Cmax: 1.05 (90% CI: 0.99 – 1.11)	Cmax 0.95 (90% CI: 0.9 – 1.01)



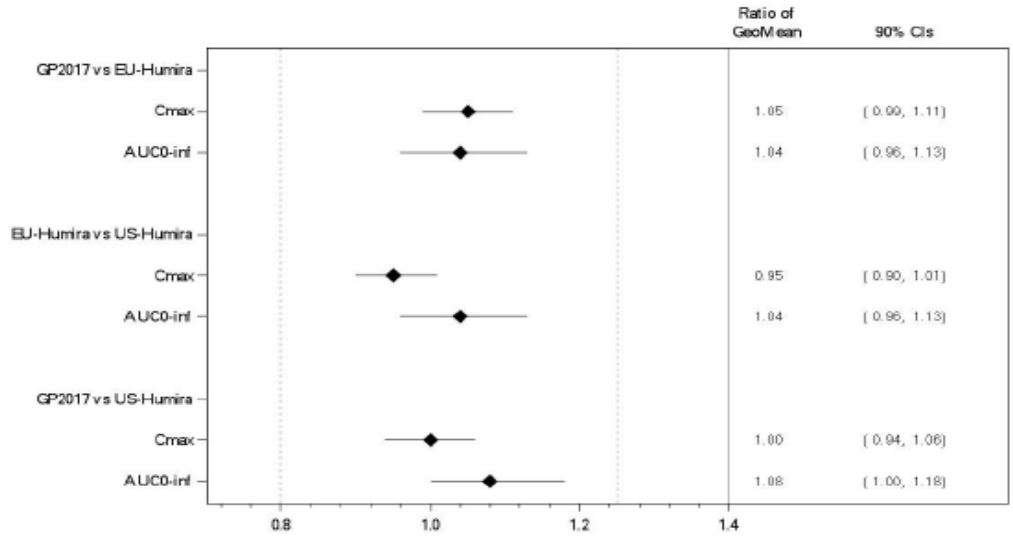
Note: The curves start with the value measured at 1 hour post-dose.
(a) linear; (b) semi-logarithmic
N=number of subjects in the PK analysis set per treatment; PK=pharmacokinetics

Figure 5 - Arithmetic mean adalimumab serum concentration-time profiles – study GP17-104 (PK analysis set)

Table 6 - Summary of the statistical results of the primary objective (PK analysis set)

Treatment comparison (Test vs reference)	PK parameter	Geometric LSmeans				Ratio test/reference	
		Test	n	Reference	n	Estimate	90% CI
GP2017 / EU-Humira	C_{max} (ng/mL)	3710.33	104	3538.11	103	1.05	0.99; 1.11
	$AUC_{0\text{-}inf}$ (h*ng/mL)	2697410.33	81	2583873.09	85	1.04	0.96; 1.13
EU-Humira / US-Humira	C_{max} (ng/mL)	3538.11	103	3715.28	99	0.95	0.90; 1.01
	$AUC_{0\text{-}inf}$ (h*ng/mL)	2583873.09	85	2489573.33	82	1.04	0.96; 1.13

CI = confidence interval; LSmean = least square mean; n = number of subjects included in the analysis; PK = pharmacokinetics.
$AUC_{0\text{-}inf}$ was not analyzed in cases where $\%AUC_{extra}$ was > 20%, < 3 data points were in the terminal phase, or the adjusted correlation coefficient (R^2 adj) was < 0.75.
The ANCOVA model included treatment as a fixed effect and body weight (Day -1) as a continuous covariate.



CI=confidence interval; PK=pharmacokinetics
For definitions of PK parameters, see Table 2-1.

Figure 6 - 90% confidence intervals for the analysis of bioequivalence between GP2017, EU Humira and US Humira – study GP17-104 (PK analysis set)

Point estimates for Cmax and AUCinf were consistently slightly greater than 1.0 in both trials GP17-101 and GP17-104, for GP2017 versus EU Humira. Additional sensitivity analyses were conducted taking the following factors into account:

- No covariate in the statistical model

- Body weight category as covariate in the statistical model

- BMI as covariate in the statistical model

- PK parameters adjusted for protein content dose received by the subject

- included all subjects for AUC0-inf (i.e. include all subjects regardless of %AUCextra value, adjusted correlation coefficient (R2 adj<0.75) values, and number of data points used in the terminal phase)

- excluding subjects based on %AUCextra value >20%, adjusted correlation coefficient (R2 adj<0.85) values, and number of data points used in the terminal phase.

The 90% CIs of the ratios of the geometric LS means were contained within the margins of 0.8 to 1.25 for Cmax and AUC0-inf (for both comparisons GP2017/EU-Humira and EU-Humira/US-Humira). It can be concluded that the above named factors did not have an impact on biosimilarity outcome.

Secondary endpoints (AUC0-360h, t1/2, tmax, %AUCextra, tmax, CL0-last and Kel) are roughly comparable across treatment arms. Results for t1/2 and tmax differ from results observed in study GP17-101.

In the body weight sub-group analysis, for the majority of the comparisons in medium and high body weight categories, the 90% CIs of the ratios of the geometric LS means were contained within the margins of 0.8 to 1.25. While for the low body weight category, the majority of the 90% CIs of the ratios of the geometric LS means were not contained within the margins of 0.8 to 1.25.

Pooled analysis of studies of PK data - exploratory analysis

A number of pooled analyses with the objective of comparing the exposure across GP2017, EU-Humira and US- Humira using a larger sample of PK data include a number of post-hoc pooled analyses of PK bioequivalence results from studies GP17-101, GP17-102, GP17-103, and GP17-104.

However, the study level data (from GP17-101 and GP17-104) should not be pooled and analysed. The level of additional relevant information coming from pooled PK (or meta-) analysis is considered limited, given the heterogeneity described for the two PK trials.

Impact of immunogenicity on pharmacokinetics (study GP17-101 and GP17-104)

The majority of healthy volunteers developed antibodies from Day 16 on. ADA formation was shown to have an impact on exposure, as in ADA positive subjects, smaller AUC0-last and AUC0-inf values were observed compared to ADA negative subjects, in all HV studies.

In study GP17-101, GP2017 shows a higher exposure in terms of AUC0-inf compared to EU-authorized Humira in both subgroups. Sub-group analyses demonstrated comparability for GP2017/EU-Humira only in ADA-positive subjects. Comparability for GP2017/US-Humira was only demonstrated for ADA-negative subjects, while comparability for EU-Humira/US-Humira was not demonstrated for any ADA sub-group analysis.

In study GP17-104, GP2017 shows a higher exposure in the ADA negative subgroup (as also seen in the overall population) compared to EU-Humira, but a lower exposure in the ADA positive subgroup compared to EU-Humira. Results of the sensitivity analysis for the primary endpoints Cmax and AUC0-inf for both ADA-subgroups however support PK comparability between GP2017 and EU-Humira, given that the 90% CIs of the ratios of the geometric LS means were contained within the pre-specified PK comparability margin of 0.8-1.25 in each subgroup and included 1.

Pharmacokinetics in target population (study GP17-301)

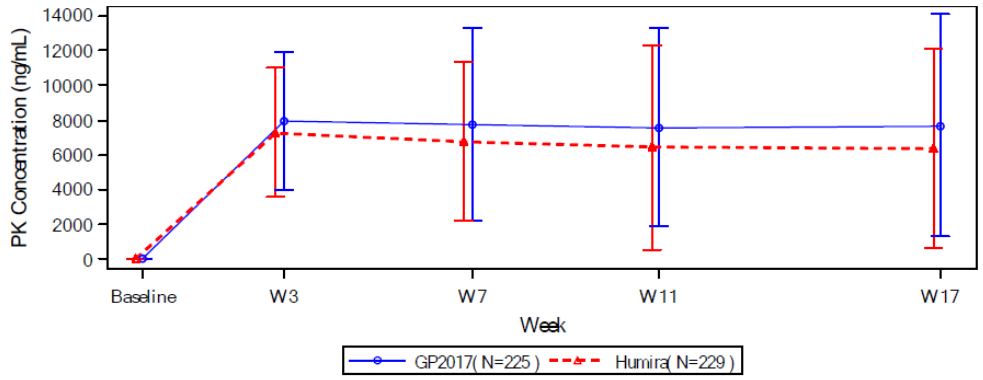
The applicant also evaluated Ctrough levels of GP2017 and EU-/US-authorised Humira in its pivotal efficacy trial GP17-301 in all patients with moderate to severe chronic plaque-type psoriasis at the following time points: at weeks 3, 7, 11, 17, 23, 29, 35, 41, 47 and 51. Steady state seems to be reached by week 3 (first measurement of Ctrough levels).

Overall, 11 patients had pre-dose concentrations of adalimumab at baseline, which might be due to previous anti TNFα therapy of these patients, as the bioanalytical test was sensitive to any anti TNFα antibody. Sensitivity analyses were performed excluding those 11 patients and were the one provided in the study report.

For 7 sites, no or incomplete temperature log data were available, therefore a *post hoc* sensitivity analysis excluding PK data of these sites was performed, which showed similar results to the primary analysis.

Some PK and ADA samples had experienced temperature excursions during storage. The presented partial validation studies indicate that PK and ADA samples are stable for up to 84 days when stored at the unintended storage condition (i.e. ≤-1°C instead of the required ≤-20°C), therefore the experienced temperature excursions during storage are not considered to impact the study outcome.

Treatment period 1



Excluding patients with pre-dose PK concentrations at baseline
PK=Pharmacokinetics; SAF=safety analysis set; SD=standard deviation; W=week

Figure 7 - Arithmetic mean (SD) adalimumab serum concentration versus time by treatment group – randomization to week 17 (SAF)

Table 7 - Summary of adalimumab trough serum concentration (ng/mL) by treatment group – randomization to week 17 (SAF)

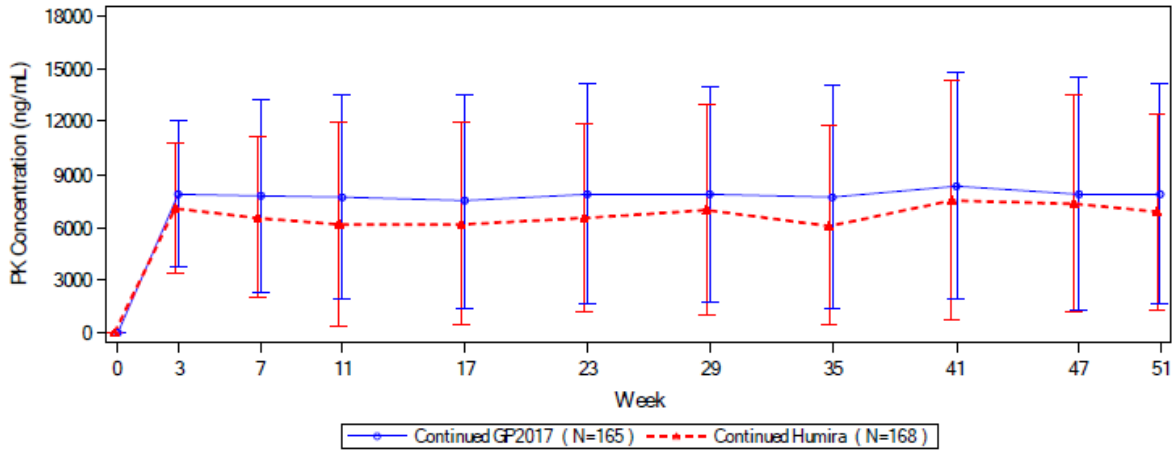
Visit	Statistics	GP2017 N=225	Humira N=229
Baseline	n	218	221
	Mean (SD)	0.0	0.0
	Median	0.0	0.0
	Min, max	0, 0	0, 0
Week 3	n	214	214
	Geometric mean	7213.5	6746.1
	Mean (SD)	7918.1 (3955.04)	7268.6 (3709.94)
	Median	7760.0	7115.0
	Min, max	0, 22100	0, 22700
Week 7	n	207	207
	Geometric mean	6373.5	5835.4
	Mean (SD)	7762.1 (5509.77)	6733.4 (4542.27)
	Median	7190.0	6490.0
	Min, max	0, 28700	0, 23100

Visit	Statistics	GP2017 N=225	Humira N=229
Week 11	n	204	196
	Geometric mean	6672.9	5380.1
	Mean (SD)	7607.0 (5729.58)	6427.2 (5852.72)
	Median	7545.0	5370.0
	Min, max	0, 24800	0, 31100
Week 17	n	187	185
	Geometric mean	7290.7	5799.2
	Mean (SD)	7687.3 (6360.63)	6370.6 (5735.38)
	Median	7280.0	5220.0
	Min, max	0, 29800	0, 25900

Summary statistics excluding patients with pre-dose concentrations at baseline. Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
max=maximum; min=minimum; n=number of patients with evaluable data; N=number of patients exposed per treatment; SAF=safety analysis set; SD=standard deviation

Means of concentration levels were higher for GP2017 compared to Humira from the first measurement at week 3 onwards. This trend was observed throughout the whole study period 1 (see Figure 9 and Table 10).

Continuous group



Excluding patients with pre-dose PK concentrations at baseline
PK=Pharmacokinetics; SAF=safety analysis set; SD=standard deviation

Figure 8 - Arithmetic mean (SD) adalimumab serum concentration versus time by continued group – randomization to week 51 (SAF)

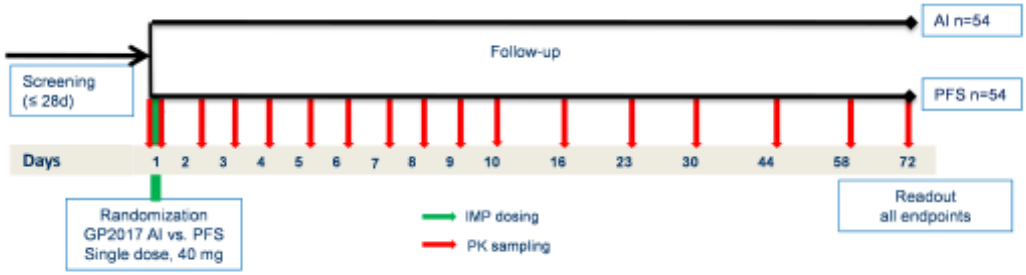
In the continuous group (excluding patients with pre-dose concentrations), Ctrough levels were also higher in the GP2017 arm compared to the Humira treatment arm. This difference was observed throughout the whole study period.

The applicant has provided as requested post-hoc descriptive analysis of the adalimumab serum concentrations for efficacy study GP17-301 as supportive to the PK studies. In Treatment period 1, the lower side of the 90% CI is contained within the 80% limit while for the upper 90% CI for 3 of 4 time-points breaches the 125% limit. For the entire study, the majority of the lower intervals are met while the majority of the upper intervals are not met. Whilst the number of subjects with evaluable serum trough concentration data (values ≥250 ng/mL) decreased during the course of the study, even by week 7, with nearly all patients evaluable, bioequivalence was not met. However this study was not powered to demonstrate PK comparability and these results should be considered descriptive in nature.

Encouragingly, across all groups, mean adalimumab trough serum concentrations were within the ranges (approximately 5000 to 10000 ng/mL) given in the Humira SmPC.

Study GP17-102 (comparison AI vs. PFS) (EudraCT Number 2014-002879-29)

Study GP17-102 was a single-center, randomized, open-label, single-dose, two-arm parallel study.



AI = Delta-GP2017_40 autoinjector; PFS = GP2017-pre-filled syringe

Figure 9 - Study GP17-102

The primary objective was to describe the PK of GP2017 administered by AI or a PFS as a single SC injection of 40 mg to healthy adult male subjects with body weights between 50.0-94.9 kg in terms of the PK parameters Cmax and AUC0-360h.

Randomization was stratified by body weight. A total of 108 subjects were randomized in the study.

The study was not powered for formal equivalence testing. There were four weight categories (ranging from 50 to 140 kg) and overall one primary weight group (weight categories from 50 to 94.9 kg) upon which the analysis of the primary endpoint was based.

Table 8-4 - Summary statistical analysis – primary PK parameters (PK analysis set; 50.0-94.9kg body weight group)

			Geometric LSmeans				Ratio test/reference 90% CI		
Treatment comparison (test vs. reference)	PK parameter	N	Test (AI)	n	Ref. (PFS)	n	Estimate	Lower	Upper
AI/PFS	C_{max} (µg/mL)	89	4.23	45	4.46	44	0.9501	0.8785	1.0275
	AUC_{0-360h} (h×µg/mL)	89	1219	45	1328	44	0.9176	0.8501	0.9905

AI = Delta-GP2017_40 autoinjector; CI = confidence interval; N = total number of evaluable subjects; n = number of evaluable subjects; LS = least squares; PFS = GP2017-pre-filled syringe; PK = pharmacokinetic; Ref. = Reference

Table 11-5 - Summary statistical analysis – secondary PK parameters (PK analysis set; 50.0-94.9kg body weight group)

			Geometric LSmeans				Ratio test/reference 90% CI		
Treatment comparison (test vs. reference)	PK parameter	N	Test (AI)	n	Ref. (PFS)	n	Estimate	Lower	Upper
AI/PFS	$AUC_{0\text{-last}}$ (h×µg/mL)	89	2799	45	2755	44	1.0159	0.8839	1.1677
	$AUC_{0\text{-inf}}$ (h×µg/mL)	89	3101	45	3002	44	1.0329	0.8946	1.1925

AI = Delta-GP2017_40 autoinjector; CI = confidence interval; N = total number of evaluable subjects; n = number of evaluable subjects; LS = least squares; PFS = GP2017-pre-filledsyringe; PK = pharmacokinetic; Ref. = Reference

Table 9 - Descriptive statistics for the GP2017 PK parameters by treatment (50.0-94.9 kg body weight group)

Parameter	Statistic	AI	PFS
C_{max} (µg/mL)	n	45	44
	geometric mean	4.20	4.49
	mean ± SD	4.39 ± 1.30	4.56 ± 0.823
	CV (%)	29.7	18.0
	min-max	1.96-7.38	3.01-6.47
$AUC_{0\text{-360}}$ (h×µg/mL)	n	45	44
	geometric mean	1209	1339
	mean ± SD	1264 ± 373	1355 ± 214
	CV (%)	29.5	15.8
	min-max	542-2089	969-1981
$AUC_{0\text{-last}}$ (h×µg/mL)	n	45	44
	geometric mean	2783	2771
	mean ± SD	3010 ± 1067	2949 ± 1017
	CV (%)	35.4	34.5
	min-max	904-4969	1164-5464
$AUC_{0\text{-inf}}$ (h×µg/mL)	n	45	44
	geometric mean	3085	3018
	mean ± SD	3358 ± 1290	3224 ± 1136
	CV (%)	38.4	35.2
	min-max	991-6092	1204-5883
AUC_{extra} (%)	n	45	44
	geometric mean	7.7	6.8
	mean ± SD	9.6 ± 6.5	8.1 ± 4.8
	CV (%)	67.9	59.7
	min-max	2.0-28.2	1.8-19.8
t_{max} (h)	n	45	44
	median	168.00	132.00
	min-max	12.00-532.38	72.00-362.17
$CL_{0\text{-last}}$ (mL/h)	n	45	44
	geometric mean	14.4	14.4
	mean ± SD	15.9 ± 8.55	15.5 ± 6.29
	CV (%)	53.6	40.7
	min-max	8.05-44.2	7.32-34.4
$t_{1/2}$ (h)	n	45	44
	geometric mean	311	256
	mean ± SD	354 ± 188	292 ± 140

Table 10 - Summary statistical analysis – primary and secondary PK parameters (total PK analysis set; 50.0-140.0 kg body weight group)

			Geometric LSmeans				Ratio test/reference 90% CI		
Treatment comparison (test vs. reference)	PK parameter	N	Test (AI)	n	Ref. (PFS)	n	Estimate	Lower	Upper
AI/PFS	C_{max} (µg/mL)	107	3.94	54	4.16	53	0.9471	0.8805	1.0187
	AUC_{0-360h} (h×µg/mL)	107	1130	54	1230	53	0.9188	0.8563	0.9858
	AUC_{0-last} (h×µg/mL)	107	2564	54	2571	53	0.9972	0.8802	1.1298
	AUC_{0-inf} (h×µg/mL)	107	2862	54	2832	53	1.0108	0.8875	1.1511

AI = Delta-GP2017_40 autoinjector; CI = confidence interval; N = total number of evaluable subjects; n = number of evaluable subjects; LS = least squares; PFS = GP2017-pre-filled syringe; PK = pharmacokinetic; Ref. = Reference

As can be seen from the tables above, for the primary body weight group (50-94.9kg), the 90%CIs for the ratios of geometric means between treatment groups were contained within 0.8-1.25 for the primary endpoints Cmax and AUC0-360h, as well as for the secondary endpoints AUC0-last and AUC0-inf.

In this weight group, the additional secondary endpoints were comparable between treatment arms except for tmax and t1/2. In light of the high variability of these measures, the observed differences in tmax and t1/2 between treatment arms are not considered to impact the comparability conclusion between PFS and AI.

Geometric LSmeans for Cmax and AUC0-360 are slightly lower for AI compared to PFS, whereas geometric LSmeans for AUC0-last and AUC0-inf are slightly higher for AI compared to PFS (total PK analysis and medium body weight group). Exposure seems roughly comparable over time and this applies to all weight categories.

In the high and very high body weight group, all named endpoints show a trend of lower exposure of AI vs. PFS. In the low body weight group, Cmax and AUC0-360h show higher values for AI vs PFS and lower values for AUC0-last and AUC0-inf for AI vs PFS.

Concomitant medications were higher in the AI arm (30%) than for the PFS arm (17%). The main difference between the treatment groups was due to paracetamol. The number of patients taking paracetamol is higher than in other studies. Paracetamol is unlikely to have any effect on PK.

The impact of ADA formation on adalimumab exposure levels was investigated and a strong impact was noted. In ADA positive subjects, smaller AUC0-last and AUC0-inf values were observed compared to ADA negative subjects in both treatment arms. AUC0-last and AUC0-inf values were comparable in ADA negative and ADA positive subjects using the AI or the PFS, respectively.

Study GP17-103 (comparison GP2017-Cook versus -Schaftenau) (EudraCT Number 2014-005229-11)

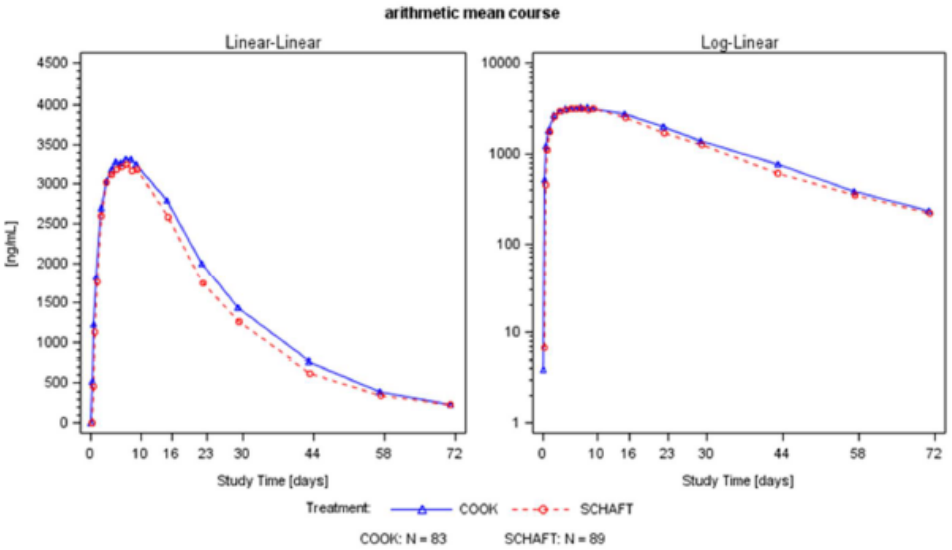
The GP17-103 study was planned to complement the analytical data supporting comparability between drug substances manufactured at the manufacturing site Sandoz GmbH, Biopharmaceuticals Schaftenau (referred to as GP2017- Schaftenau) (BPS) in Langkampfen, Austria to the manufacturing site Cook Pharmica (referred to as GP2017- Cook), LLC, in Bloomington, IN, USA, and thus, to establish both sites as drug substance manufacturing sites. For both sites, drug substance was formulated and processed to drug product at Mylan, India. Of note, drug substance of all GP2017 batches used in the other clinical PK studies and the confirmatory efficacy and safety study GP17-301 had been manufactured at Schaftenau

Austria. The GP2017 drug product batch used in study GP17-104 was the same as the GP2017-Schaftenau batch in study GP17-103 (batch number 7007467).

The primary objective of this study was to demonstrate PK biosimilarity (90% CI of the ratio of the geometric means within the margins of [0.8;1.25]) of GP2017-Cook and GP2017- Schaftenau in terms of Cmax, AUC0-inf, and AUC0-last after a single s.c. injection of 40 mg adalimumab to healthy adult male subjects.

The primary endpoints, blood sampling time points, study population (healthy male volunteers), study duration (72 days) and study design (single dose [40 mg], double-blind, two-arm parallel group) are appropriate and not further commented. Comments made for study GP17-101/-104 apply also to this study. Demographic and other baseline characteristics were comparable across treatment arms.

Overall, 178 subjects were randomized in this study. Randomization was stratified per treatment group by body weight.



N=number of evaluated subjects; Schaft=Schaftenau

Figure 10 - Mean serum concentration of adalimumab after single s.c. administration of 40mg adalimumab by treatment group (PK set)

Table 11 - Summary of primary and key secondary endpoint analyses (PK set)

Endpoint (unit)	N	GP2017-Cook		GP2017-Schaftenau		Ratio[2]	90% Confidence Interval
		LS mean[1]	n	LS mean[1]	n		
Primary							
C_{max} (ng/ml)	172	3553	83	3442	89	1.0322	0.9692;1.0993
$AUC_{0\text{-}inf}$ (h x ng/ml)	165	2456708	83	2178872	82	1.1275	1.0125;1.2555
$AUC_{0\text{-}last}$ (h x ng/ml)	172	2109082	83	1795703	89	1.1745	1.0558;1.3066
Key secondary							
$AUC_{0\text{-}360h}$ (h x ng/ml)	172	1010491	83	957642	89	1.0552	0.9871;1.1280

LS = least squares; N = total number of evaluable subjects; n = number of evaluable subjects.

[1] Geometric LS mean

[2] Geometric LS mean in the GP21017-Cook group / geometric LS mean in the GP2017-Schaftenau group

As can be seen from the table above, the ratio of the geometric means for the primary endpoint Cmax (GP2017-Cook/ GP2017-Schaftenau) was 1.0322 with a 90% CI of (0.9692; 1.0993) and was hence contained within the (0.80-1.25) bioequivalence limits.

However, in terms of AUC0-inf and AUC0-last, PK biosimilarity between GP2017-Cook and GP2017-Schaftenau was not demonstrated. Analyses of Cmax, AUC0-inf, AUC0-last and AUC0-360h were repeated by body weight category. For medium body weight subjects, comparability was only demonstrated for Cmax, while for high body weight subjects, comparability was only demonstrated for Cmax and AUC0-360h. Secondary endpoints (AUC0-360h, tmax and AUCextrapolated [%]) were comparable across treatment arms. CL0-last and T1/2 slightly differed between treatment groups.

Three subjects had pre-dose concentrations above LLOQ (250.0 ng/ml) (n=2, GP2017-Schaftenau; N=1, GP2017-Cook group). The results from the sensitivity analysis excluding these subjects were comparable to the results from the primary analysis (negative outcome for AUC0-inf and AUC0-last).

A higher proportion of subjects in the Schaftenau group had an extrapolated part of AUC0-inf >20%: n=6 (9.5%) in GP2017-Cook vs n=15 (16.9%) in GP2017-Schaftenau group. The Applicant argued that this might have contributed to the observed results. A post-hoc analysis was performed excluding subjects with <3 data points in the terminal phase or with extrapolation of the terminal phase >20%. Although the 90% CIs of the ratio of the Geometric LS mean (Cook vs. Schaftenau) were contained within the BE limits (0.8-1.25) in this sensitivity analysis, it is not fully understood, why this imbalance in the extrapolated part of AUC0-inf was observed.

Results of this clinical PK study are difficult to interpret, given that batches from different manufacturing sites were manufactured by the same processes and comparability between batches from different manufacturing sites seems to have been adequately demonstrated at the quality level.

One notable omission from the list of quality attributes which could impact PK is the neonatal Fc receptor (FcRn). Increased binding to this receptor is known to prolong IgG half-life. Based on the data provided in the biosimilarity report, the FcRn equilibrium dissociation constants for these batches were 1.09 10^{-7}M and 1.06 10^{-7}M respectively. The difference between them is relatively minor therefore if can be concluded that differences in FcRn are unlikely to be responsible for the lack of bioequivalence.

The exclusion of 3 extreme ADA titres is somewhat rationalised, although a higher occurrence of extreme ADA titers in the Cook treatment arm could also be suggestive of “true” differences between treatments. It is noted that when all PK set subjects were included, the AUC0-inf upper side of the 90% CI was 1.255, very close to the bioequivalence limit of 1.25.

Although the primary endpoint for $AUC_{0\text{-}inf}$ was not met for study GP17-103, the applicant has adequately demonstrated that this is likely due to differences in immunogenicity and not likely due to product-related differences as demonstrated by the primary end-points being met for Cmax and AUC0-360, which are not influenced by late ADA formation (refer to “Impact of immunogenicity on PK”).

Impact of immunogenicity on PK

Subgroup analyses were performed for ADA negative and ADA positive subjects.

In the ADA negative subgroup, the 90% CIs of the ratios of the geometric means were contained within the bioequivalence limits (0.8 to 1.25) for AUC0-inf and AUC0-last.

In ADA-positive subjects, the 90% CIs for the ratios of the geometric means between GP2017-Cook and GP2017-Schaftenau were above the bioequivalence limits for both AUC0-inf and AUC0-last.The 90% CI of the geometric means ratio of AUC0-inf was contained within 0.8-1.25 in an exploratory analysis excluding those subjects with high ADA titers (4 subjects in the Schaftenau and 1 subject in the Cook group). Some

uncertainty remains, as e.g., a higher occurrence of extreme ADA titers in the Schaftenau treatment arm could also be suggestive of “true” differences between treatments.

Overall, PK biosimilarity in terms of AUC0-inf and AUC0-last could not be demonstrated between GP2017-Cook and GP2017-Schaftenau. The applicant plausibly attributed the failure of the study to demonstrate bioequivalence between GP2017-Schaftenau and GP2017-Cook to the unexpected higher rate of immunogenicity in GP2017-Schaftenau treated subjects, which impacted the demonstration of PK similarity for PK parameters affected by ADA development for AUC0-inf and AUC0-last. Although the difference in the total % of ADA positive subjects in study GP17-103 was minimal (4.1%) between the two different treatment arms, the rate of formation of ADAs differed by a maximum of 10.7% (day 30) between the two different treatment arms for study GP17-103 and differed by a maximum of 16.6% (day 44) for the same batch of GP2017-Schaftenau in studies GP17-103 and GP17-104. Thus the rationale that differences in immunogenicity resulted in a failure to demonstrate bioequivalence for $AUC_{0\text{-}inf}$ is plausible and together with the totality of the data and the lack of quality concerns over batches produced at the different manufacturing sites, this response is acceptable.

Reference is also made to section 2.6 Clinical safety, immunological events.

2.4.3 Pharmacodynamics

No clinical comparative PD study was submitted by the applicant. No accepted specific pharmacodynamic (PD) markers exist, being predictive of efficacy of adalimumab in patients. PD similarity of GP2017 and Humira in terms of TNF-α inhibition has been investigated in non-clinical in-vitro and in-vivo similarity studies.

HsCRP (High sensitivity C-reactive protein) was among the biochemistry parameters investigated in study GP17-301 up to Week 51. There were no notable differences between the treatment groups, except for one patient that had an abnormally high level of hsCRP at week 17 with Humira treatment. This patient developed a high CRP value due to necrotizing pneumonia and sepsis and the patient was discontinued from treatment. Pneumonia and sepsis are both considered expected according to the Humira SmPC. With the exception of this patient, CRP levels appear similar across all treatment groups.

2.4.4 Discussion on clinical pharmacology

Healthy volunteers studies GP17-101 and GP17-104

Study GP17-101 was conducted in healthy volunteers to establish comparability between GP2017 and EU- as well as US-licensed Humira in terms of Cmax, AUC0-inf and AUC0-last after a single SC dose of 40 mg. The study failed to demonstrate PK biosimilarity between GP2017 and EU-authorized Humira, as well as between EU- and US-licensed Humira, for the primary PK endpoints AUC0-last and AUC0-inf.

For secondary end-points AUC extra and Kel parameters there is a considerable (>20%) difference between the highest and lowest geometric mean values across the three arms. These differences are consistent with the study results, i.e. failing to meet its primary end-points.

An extensive root cause investigation was performed as requested to identify possible sources driving the negative outcome of the first PK study GP17-101: batch selection (EU- and US-Humira), IMP storage and transport, IMP preparation, IMP administration, PK sampling, PK sample shipping and testing, impact of body weight on PK, impact of ADA development on PK and impact of other subject characteristics (e.g. medical history) were investigated. No root cause driving the negative outcome of study GP17-101 could be identified.

The applicant also examined the clinical trial batches with regard to quality attributes which could potentially impact the PK (such as dose strength, Man5, Met256 oxidation and the glycovariants bGo, bG1

and gG2), and satisfactorily discussed observed quality differences potentially influencing PK. None of them appears to be responsible for the differences in PK between GP2017 and EU-Humira in study GP17-101.

The subsequently planned study GP17-104 incorporated an adapted study design with the aim to reduce inter-subject variability (by BMI-restriction and inclusion of only male subjects) and with an increased sample size (based on an observed inter- individual variability of 42% for AUC0-inf in study GP17-101, which was higher than assumed at the planning stage). Also, IMP handling and dosing was simplified by using the GP2017 PFS and the commercial PFS for EU- and US-Humira.

For both primary PK endpoints, AUC0-inf and Cmax, the 90% CIs of the ratios of the geometric means between GP2017 and EU-Humira and between EU-Humira and US-Humira were contained within the pre-specified PK comparability acceptance limits; all point estimates were close to unity. These results were confirmed by further supportive analyses including an analysis that included all AUC0-inf values. The secondary endpoints AUC0-360h, t1/2, tmax, %AUCextra, tmax, CL0-last and Kel were also roughly comparable across treatment arms.

When viewed in separation, results from study GP17-104 support biosimilarity in terms of pharmacokinetics. Point estimates for Cmax and AUCinf were consistently slightly greater than 1.0 in both trials GP17-101 and GP17-104, for GP2017 versus EU Humira.

Similarity of GP2017 and Humira is furthermore supported by the PK data from the efficacy and safety trial GP17-301 (adalimumab Ctrough levels), which seem overall comparable for Humira and GP2017 (although means of concentration levels were slightly higher for GP2017 compared to Humira troughout the whole study period).

Due to confirmed heterogeneity between both PK studies the pooled analysis that the Applicant had initially submitted is not considered informative.

The Applicant considers study GP17-104 a more sensitive and more relevant study model to detect potential differences between biosimilar candidate and reference product owing to the above mentioned study design adaptions. It is acknowledged that gender- and BMI-range restrictions were implemented in study GP17-104 as variance-reducing measures in reaction to the outcome of study GP17-101. In the context of adalimumab biosimilar exercises, inclusion of only male subjects for investigation of PK similarity is in general accepted and not criticized per se. The Applicant argued that variability in exposure may be higher in women than in man due to changes in female plasma water content during the menstrual cycle and that therefore women were not included in the second trial. This justification was endorsed by the CHMP. Indeed, by reducing the variance in the PK read-out, it can indeed be expected that the signal/noise ratio may be increased within the trial setting.

As regards the interpretation of the outcome of GP17-101, the Applicant's understanding is shared that the trial failed to demonstrate PK equivalence and that non-rejection of the null-hypothesis in this case does not necessarily imply the existence of a relevant PK-difference.

Overall, the results of the larger study GP17-104 in a more homogenous population can be accepted as supporting PK similarity of GP-2017 and EU-Humira, and also establishing the PK bridge between EU- and US-Humira.

Impact of immunogenicity on pharmacokinetics (study GP17-101 and GP17-104)

The majority of healthy volunteers developed antibodies from Day 16 onwards. ADA formation was shown to have an impact on exposure, as in ADA positive subjects, AUC0-last and AUC0-inf values were lower compared to ADA negative subjects.

PK data in patients with moderate to severe chronic plaque-type psoriasis

The Applicant also evaluated Ctrough levels of GP2017 and EU-/US-authorised Humira in the efficacy/safety trial GP17-301 in all patients with moderate to severe chronic plaque-type psoriasis. A trend towards higher Ctrough levels of GP2017 versus Humira was observed.

Given the high variability of the Ctrough measurements (in part caused by ADA development in a proportion of patients) this difference would be unlikely to be clinically meaningful.

PK similarity of PFS and autoinjector

Study GP17-102 was a two-arm parallel study to describe the PK, safety and immunogenicity of a single SC injection of GP2017 administered by AI or by PFS to adult male healthy subjects. The study was not powered for formal equivalence testing; Cmax and AUC0-360h were assessed as primary endpoints. There were four weight categories (ranging from 50 to 140 kg) and overall one primary weight group (weight categories from 50 to 94.9 kg) upon which the analysis of the primary endpoint was based.

For the primary weight group, PK similarity was shown for the primary endpoints Cmax and AUC0-360h. Secondary endpoints were supportive of PK similarity between AI and PFS in this weight group. Exposure seems relatively comparable over time and this applies to all weight categories. In the high and very high body weight group, all named endpoints show a trend of lower exposure of AI vs. PFS. In the low body weight group, Cmax and AUC0-360h show higher values for AI vs. PFS and lower values for AUC0-last and AUC0-inf for AI vs. PFS.

Conclusions to be drawn from this study are limited due to lack of power.

PK similarity of drug substance GP2017-Cook versus GP2017-Schaftenau

Study GP17-103 was a two-arm parallel trial to determine the PK, safety and immunogenicity of GP2017 from two drug substance production facilities following a single SC injection in healthy male subjects. The primary endpoints were Cmax, AUC0-inf, and AUC0-last.

The CI of the ratio of the geometric means for the primary endpoint Cmax (GP2017-Cook vs. GP2017-Schaftenau) was contained within the standard bioequivalence limits. However, in terms of AUC0-inf and AUC0-last, PK biosimilarity between the two sites could not be demonstrated. Exposure (AUC0-inf) of adalimumab was higher after administration of GP2017-Cook compared to GP2017-Schaftenau. A trend for lower exposure of GP2017 (Schaftenau) in study GP17-103 compared to the other HV studies (GP17-101, -104 and -102) using the same product was noted.

Subgroup analyses were performed for ADA negative and ADA positive subjects. In the ADA negative subgroup, BE criteria were met for AUC0-inf and AUC0-last. In ADA-positive subjects however, the 90% CIs for the ratios of the GMs between GP2017-Cook and GP2017-Schaftenau were above 0.8 to 1.25 for both AUC0-inf and AUC0-last.

Overall, although PK biosimilarity in terms of AUC0-inf and AUC0-last could formally not be demonstrated between GP2017-Cook and GP2017-Schaftenau, the applicant has adequately demonstrated that this is likely due to differences in immunogenicity and not likely due to product-related differences as demonstrated by the primary end-points being met for Cmax and AUC0-360, which are not influenced by late ADA formation.

2.4.5 Conclusions on clinical pharmacology

Study GP17-101 failed to demonstrate PK biosimilarity between GP2017 and EU-authorized Humira, as well as between EU- and US-licensed Humira, for the primary PK endpoints AUC0-last and AUC0-inf.

Ultimately, neither for the comparison GP2017/EU-Humira nor for the comparison EU-/US-Humira a clear reason/driving source for the observed differences in PK parameters in study GP17-101 was identified. However, that variability was reduced in the second PK study GP-104 and that biosimilarity was shown for all PK parameters and all comparisons.

Considering results from study GP17-104 showing PK comparability between EU- and US-Humira, it can be concluded that the scientific bridge between EU-/and US-sourced Humira has been established.

Auto-injector and pre-filled syringe showed relatively comparable PK results with regard to their exposure over time in the primary weight category. Conclusions to be drawn from study GP17-102 are limited due to lack of power.

Comparability of drug substance derived from two drug substance production facilities (Cook vs. Schaftenau), although demonstrated on the quality level, could not formally be shown in study GP17-103 in healthy volunteers. The failure to demonstrate bioequivalence between GP2017-Schaftenau and GP2017-Cook was likely due to the unexpected higher rate of immunogenicity (not likely to be product related) in GP2017-Schaftenau treated subjects, which impacted the demonstration of PK similarity for PK parameters affected by ADA development (AUC0-inf and AUC0-last).

2.5 Clinical efficacy

GP2017 has been developed as a biosimilar to US-licensed Humira and EU approved Humira. Efficacy data have only been provided by the confirmatory efficacy and safety study GP17-301 in patients with moderate to severe chronic plaque-type psoriasis.

2.5.1 Main study GP17-301

Methods

GP17-301 study design:

This study was a multicenter, randomized, double-blind, comparator-controlled, confirmatory efficacy and safety (Phase III) study to assess equivalent efficacy, safety, and immunogenicity of the proposed biosimilar GP2017 and Humira (adalimumab) after 17 weeks of treatment in patients with moderate to severe chronic plaque-type psoriasis.

The study consisted of four periods: the Screening Period (at least 2 weeks and up to 4 weeks prior to dosing), Treatment Period 1 (Randomization to Week 17), Treatment Period 2 (Week 17 to Week 35), and the Extension Period (Week 35 to Week 51). Please also refer to the table and figure below for further details on study design.

Table 12 Key features of the pivotal Efficacy trial GP17-301

Study No.	Study design Study objective	Study population	Treatment duration	Dosage [batch number]
	C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}last}$ after a single s.c. injection of 40 mg adalimumab			
GP17-301 **(pivotal confirmatory efficacy and safety study)**	Design: multi-center, randomized, double-blind, comparator-controlled study with treatment switches in patients with moderate to severe chronic plaque-type psoriasis Objective: To demonstrate equivalent efficacy of GP2017 and Humira with respect to PASI75 response rate at Week 16 and similar safety and immunogenicity in patients with moderate to severe chronic plaque-type psoriasis	Male and female patients with moderate to severe chronic plaque-type psoriasis N=465 (284m, 181f) GP2017: N=231 (142m, 89f) Humira: N=234 (142m, 92f)) EU-Humira: N=44 (28m, 16f) US-Humira: N=190 (114m, 76f)	Up to 55 weeks (including screening, two treatment periods, and one extension period)	GP2017: 40 mg/0.8 mL, PFS [7006715, 7007139, 7007389, 7007467] EU-Humira: 40 mg/0.8 mL, PFS [20321XH04, 23342XH04, 28387XD04, 34434XD11] US-Humira: 40 mg/0.8 mL, PFS [1004010, 1017238, 1017236, 1017235, 1024661, 1030241] GP2017 and Humira were administered as s.c. injections with a loading dose of 80 mg on Day 1 and 40 mg every other week, starting with Week 1 and up to Week 49

N=number of randomized subjects or patients; PASI75=reduction of Psoriasis Area and Severity Index (PASI) by 75%; PFS=pre-filled syringe; PK=pharmacokinetic; s.c.=subcutaneous

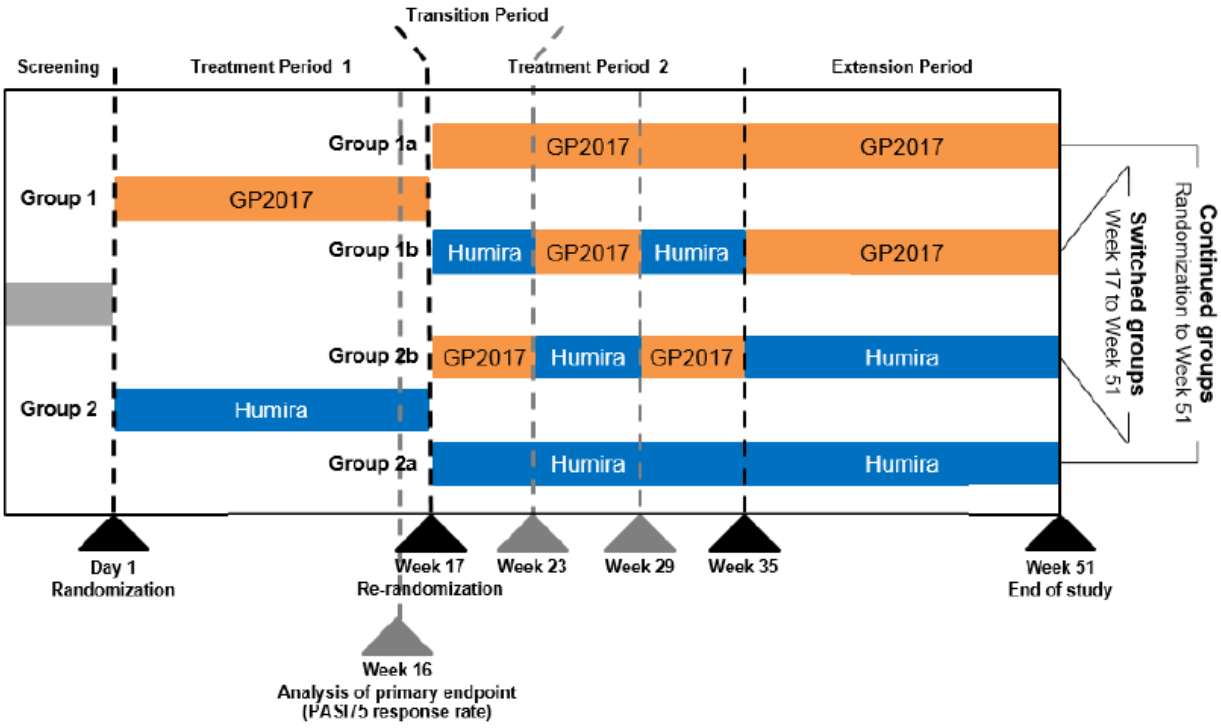


Figure 11 Study design pivotal Efficacy trial GP17-301

Study Participants

The patient population consisted of adult male and female patients who were at least 18 years of age with active, but clinically stable, moderate-to-severe chronic plaque-type psoriasis. Eligible patients had to have a PASI score of at least 12, an IGA score of at least 3 and a total BSA of minimally 10%. The inclusion and exclusion criteria describe a study population equivalent to the population for which Humira is approved.

The population is regarded as sensitive enough for the assessment of biosimilarity. Patients were recruited in the US and in the EU. For the population´s baseline characteristics, please refer to the section below.

A study in patients with moderate to severe rheumatoid arthritis is ongoing and the final study CSR is planned for September 2018.

Treatments

The proposed biosimilar GP2017 and Humira (US-Humira for patients recruited in the US and EU-Humira for patients recruited in the EU) was supplied to the investigators in prefilled syringes containing 40 mg of the active ingredient in a 0.8 mL solution.

All test materials were supplied by Novartis Drug Supply Management. The batch numbers for both GP2017 and Humira are presented below.

Table 13 - *Study medication batch numbers*

Study treatment and strength	Batch number (expiry date, end of the month)
GP2017 40 mg/0.8 mL	7006715 (Jul-2014); 7007139 (Jun-2015); 7007389 (Dec-2015); 7007467 (Apr-2016)
US-Humira 40 mg/0.8 mL	1004010 (Nov-2014); 1017238 (Oct-2015); 1017236 (Oct-2015); 1017235 (Oct-2015); 1024661 (Apr-2016); 1030241 (Jul-2016)[1]
EU-Humira 40 mg/0.8 mL	20321XH04 (Jul-2014); 23342XH04 (Oct-2014); 28387XD04 (Mar-2015); 34434XD11 (Sep-2015)

[1] Batch 1030241 was provided to study centers, but not dispensed to any patient.

One patient received expired study medication during the study.

The dose and route of administration are in accordance with the current labels of US- and EU-Humira for the therapy of moderate to severe chronic plaque-type psoriasis.

Objectives

The objective of the first treatment period was to confirm equivalent efficacy, and similar safety and immunogenicity of the proposed biosimilar GP2017 and Humira. The main objectives of the second treatment period (Week 17 to Week 35) and the extension Period (Week 35 to Week 51) were to compare long-term safety and immunogenicity and to explore effects of repeated switching of both study treatments.

Outcomes/endpoints

The Primary Endpoint was defined as the PASI75 response rate at Week 16, i.e. the proportion of patients achieving a reduction of 75% or more of the PASI score at Week 16 compared with baseline. An equivalence margin of 18% was chosen.

The key secondary efficacy variable was defined as the %-change from baseline in PASI score up to Week 16. The key secondary efficacy variable was analyzed using MMRM and ATE with ANCOVA analysis. An equivalence margin of 15% was chosen.

Secondary Efficacy Endpoints included Response Rates in PASI50, PASI75, PASI90, and PASI100, absolute and percentage change in PASI scores, proportion of IGA responders, as well as health-related quality of life assessments. Evaluation of these endpoints was done every other week until week 17 and every 6 weeks thereafter until week 51, and results were consequently presented over the whole treatment period.

Additional PASI analyses were provided in response to the EMA D180 List of Questions: absolute change in PASI score from baseline to Week 16, absolute PASI scores at week 16, and PASI assessments at week 13 (PASI75 response rate, absolute change from baseline in PASI score).

Sample size

The sample size calculation for the study was based on response rates reported in two earlier double-blind, placebo controlled studies with adalimumab for PASI75, i.e. the REVEAL study (Menter A, Tyring SK, Gordon K, et al (2008) Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. J Am Acad Dermatol; 58(1): 106-15) and the CHAMPION study (Saurat JH, Stingl G, Dubertret L, et al (2008) Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis. In similar populations, the following response rates for PASI75 after 16 weeks of treatment were observed: Adalimumab 40 mg every other week: REVEAL: 71.0% (578 out of 814 patients) vs. placebo: 6.5% (26 out of 398) and CHAMPION: 79.6% (86 out of 108 patients) vs. placebo: 18.9% (10 out of 53).

Based on these observed effect sizes of 64.5% (REVEAL) and 60.7% (CHAMPION) at Week 16, an equivalence margin of 18% was chosen so that GP2017 maintains more than 70% of the treatment effect seen for Humira. A response rate for the originator product Humira of 72% was assumed. Therapeutic equivalence in terms of PASI75 was planned be concluded if the exact confidence interval for the difference in the PASI75 rates was completely contained within the interval [−18%; 18%].

A Statistical Analysis Plan was planned to be set up for the analysis comparing US-licensed Humira to all available GP2017 patients using a 90% confidence interval. Another Statistical Analysis Plan was planned to be written to compare pooled Humira patients (US-Humira and EU-authorized Humira) to all GP2017 patients using a 95% confidence interval for EU submission purposes. Based on the above described assumptions, using a 95% confidence interval, a sample size of approximately 448 patients (to maintain 380 evaluable patients with an assumed drop-out and major protocol deviation rate of 15%, assuming a difference between treatments of 3%, was derived, providing a power of 90% to show equivalence between GP2017 and Humira.

Randomisation

Overall, 448 patients were planned to be randomized into the study. Patients were randomized at 73 study centers in the EU and the US. Patients who dropped out after they had been randomized were not replaced. A screen failure rate of 20% and a post-randomization dropout rate of 15% were anticipated.

In Treatment Period 1, eligible patients were randomized in a 1:1 ratio into either the GP2017 or the Humira treatment group. Randomization was stratified by body weight (measured during the randomization visit), prior systemic psoriasis therapy, and region.

Only patients who achieved at least a PASI50 response at Week 16, qualified for proceeding into Treatment Period 2. At Week 17, the continuing patients of both treatment groups were re-randomized each in a 2:1 ratio to either remain on their initial study treatment (groups 1a and 2a) or to receive GP2017 or Humira treatment during 3 alternating periods of 6 weeks each up to Week 35 (groups 1b and 2b). The re-randomization was stratified by region only.

The Extension Period started at the time point of the Week 35 study drug administration, and ended at Week 51. During this period, the patients continued with the same study treatment as in Treatment Period 1.

Efficacy analyses were planned to be performed including stratification factors. During the course of the study/dry runs it was noticed that some patients had been incorrectly stratified. Therefore where a patient was assigned to the incorrect stratification factor during randomization, for all statistical analyses the patient was planned be analyzed using the correct true stratification factor based on the clinical database rather than the assigned factor.

For the efficacy analysis comparing GP2017 and Humira in the pooled dataset (combined US & EU), region was planned to be included in the statistical models.

Blinding (masking)

According to the Applicant, the identity of the study treatments could not be concealed, since the appearance of the syringes used to administer GP2017 or Humira differed. To ensure blinded treatment of the patients, patients were asked not to look at the syringes during study drug administration. To maintain the blind of the assessing investigator, independent, unblinded study site personnel not involved in the study assessments handled and administered the study treatment.

Randomization data were not accessible by anyone involved in the study with the exceptions described in this section.

A blinded/unblinded team charter and tracker were prepared to provide an unblinding plan and to describe the processes to control access to unblinded confidential information. After all patients who had continued in the study after Week 17 had completed or discontinued early from Treatment Period 2 and the Extension Period, the database of the study was finally locked and the sponsor was fully unblinded to the study drug assignment.

After the database had been locked for the final Week 51 analysis, the patients, investigator staff, and persons performing the assessments at the sites were also allowed to be unblinded.

Unblinding was only permitted in the case of patient emergencies, for specific sponsor personnel involved in the Treatment Period 1/Week 17 analysis, and at the conclusion of the study.

Statistical methods

Analysis sets

Randomized set

The randomized set was planned to consist of all patients who were randomized.

Full analysis set (FAS)

The FAS was planned to consist of all randomized patients to whom study treatment had been assigned. Following the intent-to-treat principle, patients were planned to be analyzed according to the treatment assigned at randomization.

Treatment Period 2 and Extension FAS (TP2+EP FAS)

The TP2+EP FAS was planned to include all patients who were re-randomized into Treatment Period 2. Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned at re-randomization.

Extension Period FAS (EP FAS)

The EP FAS was planned to include all patients who entered into the Extension Period. Following the intent-to-treat principle, patients were to be analyzed according to the treatment assigned at randomization. The EP FAS was foreseen be used for summary of patient disposition in Extension Period only.

Per-protocol analysis set for Treatment Period 1 (PPS)

The PPS was planned as the subset of the FAS consisting of patients who complete the study up to Week 16 and have no major protocol deviations up to and including Week 16. Discontinuations due to unsatisfactory therapeutic effect (Lack of Efficacy) up to and including Week 16 were planned to be included in the PPS as non-responders provided they had received at least 4 weeks/2 doses of treatment. Patients who completed Treatment Period 1 but failed to meet the entry criteria for Treatment Period 2 - and therefore discontinued the study – were planned to be included in the PPS.

During the Week 17 Analysis BDRM meetings the following additional criteria were defined that would additionally lead to exclusion from the per-protocol analysis set:

- Patient must have a PASI score at baseline/Randomization visit
- Treatment compliance: patient must have had at least 9 (40 mg) doses of study treatment during Treatment period #1 and must have had the Week 15 dose
- PASI score to be used as primary endpoint must be within 14 days after Week 15 dose
- 2 Patient un-blinded prior to Week 16 would be excluded from PPS

Per-protocol analysis set for Treatment Period 2 and Extension PPS (TP2+EP PPS)

The TP2+EP PPS was planned as a subset of patients of the TP2+EP FAS, consisting of patients who completed the study until Week 51 or who completed TP1, TP2, and post-treatment follow-up period as per applicable protocol version (i.e. protocol versions before amendment 3), and had no major protocol deviations or additional criteria (re-randomization criteria and treatment compliance criteria) during the study. Discontinuations due to unsatisfactory therapeutic effect (Lack of Efficacy) during TP2 and EP were to be included in the TP2+EP PPS. TP2+EP PPS was be used for the analysis of secondary objectives in TP2 and EP, and for the analysis of secondary objectives in entire study.

Safety analysis set for Treatment Period 1 & entire study (SAF)

The SAF was planned to consist of all patients that received at least one dose of study treatment during Treatment Period 1. Patients were to be analyzed according to treatment received.

Treatment Period 2 and Extension SAF (TP2+EP SAF)

The TP2+EP SAF was planned to include all patients who took at least one dose of study treatment during Treatment Period 2 or the Extension Period. Patients were be analyzed according to treatment received.

Analysis methods

Summary statistics for continuous variables were planned to include N, mean, standard deviation (SD), minimum, median and maximum, if not otherwise specified. Summary statistics for discrete variables were planned to be presented in contingency tables and were to include absolute (n) and relative frequencies (%). The numbers of missing assessments were planned be displayed where appropriate. Detailed data descriptions were planned for disposition, demographics and baseline characteristics, including medical history. All study treatment and concomitant medication data was planned to be summarized using the SAF and TP2 & EP SAF.

Primary efficacy comparison

The following statistical hypotheses were defined to assess equivalence between GP2017 and US-Humira or GP2017 and Humira in the PASI 75 response at Week 16, and these were to be tested at the 5% level for GP2017 versus US-Humira or 2.5% level for GP2017 versus Humira:

$H0: |pGP2017 - pHumira| \geq 0.18$ versus $H1: |pGP2017 - pHumira| < 0.18$

where px denotes the proportion of PASI 75 responders at Week 16 for treatment group x.

Therapeutic equivalence in terms of PASI 75 was planned to be determined if the exact 95% confidence interval for GP2017 versus Humira for the difference in the PASI 75 rates was contained within the interval [−18%; 18%]. The primary analysis was planned to be performed adjusting for stratification factors (body weight, prior systemic treatment and region) using Logistic Regression. Covariate-adjusted difference in proportions and corresponding two-sided 95% confidence interval for the difference using Logistic Regression were planned to be presented.

Logistic regression model (using PROC LOGISTIC) was supposed to include following terms: Treatment group, and body-weight category ("<90 kg" or "≥90 kg"), prior systemic therapy ("no prior systemic therapy" and, "any prior systemic therapy"), and region ("US" or "EU") as factors in the model. The delta method was used to calculate a standard error for the difference and an associated confidence interval using a statistical code in SAS for the implementation of the method (method details and code are referred from Ge M, Durham LK, Meyer RD, et al (2011): Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. Drug Information Journal; 45(4): 481-93).

The analysis of the primary endpoint was planned to be based on the PPS. No imputation of missing data were seen required for the primary endpoint analysis, as by definition no patient in the PPS analysis set were expected to have missing data for the primary endpoint.

As a supportive analysis, the primary analysis was to be repeated on the FAS. For this analysis based on the FAS, missing values with respect to response variables based on PASI score will be imputed with non-response regardless of the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues).

The SAP described several other supportive (sub-group) analyses for the primary variable, including dedicated analyses to explore the impact of the randomization errors concerning stratification, and to investigate consistency of primary efficacy outcome in sub-groups of strata defined.

Secondary efficacy comparison

Key secondary variables were planned to be analyzed on the PPS and the FAS.

Therapeutic equivalence in terms of relative change from baseline in PASI score until Week 16 was planned to be determined if the exact 95% CI for GP2017 versus Humira for the difference is contained within the interval [−15%; 15%]. An MMRM model was used with treatment group, visit, treatment-by-visit interaction and body-weight category, prior systemic therapy and region were to be fitted as factors and baseline score for the PASI was to be fitted as a continuous covariate.

The mean Average Treatment Effect (ATE) of change from baseline in PASI between Week 1 and 16 was to be evaluated. The ATE was planned to be derived for each patient and then analyzed as a stand-alone endpoint to capture the overall difference between treatment groups. The ATE was defined as the average of percent change from baseline in PASI scores at Weeks 1, 3, 5, 7, 9, 11, 13, 15 and 16. This parameter is the weighted average (weights based on the time intervals between two consecutive visits in weeks) of the relative response to treatment. The ATE analysis was planned to be performed using ANCOVA (PROC MIXED).

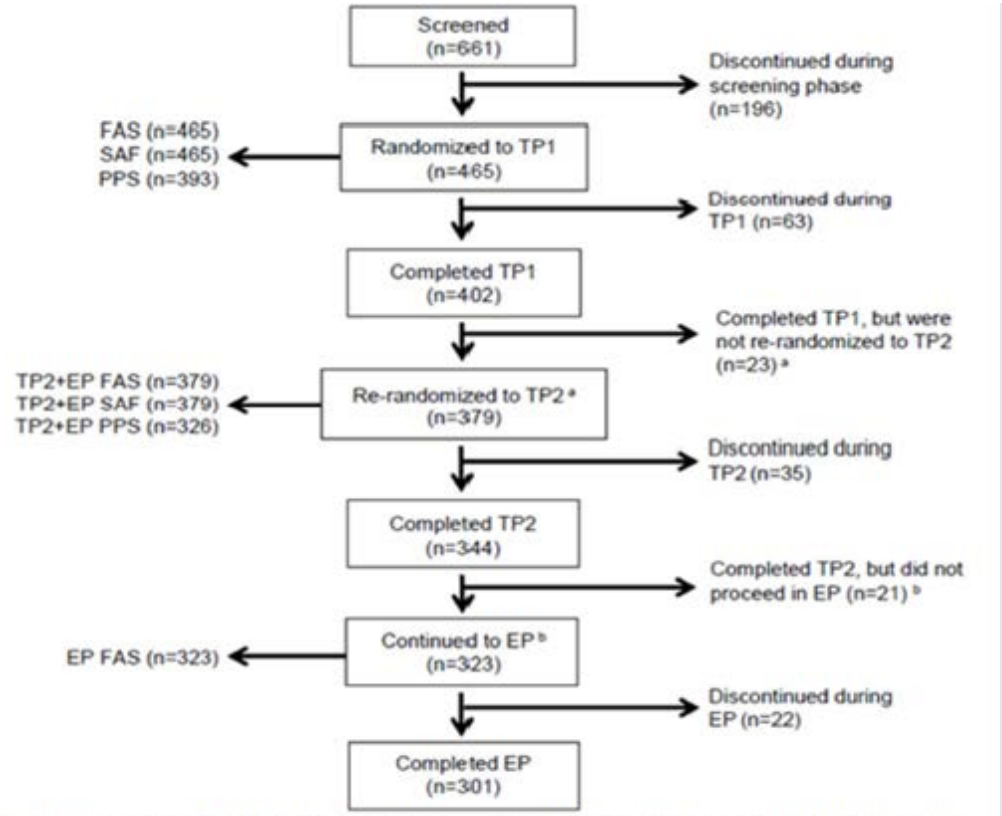
All secondary efficacy variables were planned to be analyzed on the PPS or TP2+EP PPS analysis set. In addition, summaries were to be provided for the FAS or TP2+EP FAS.

Safety analyses

Standard descriptive statistical approaches were planned in the SAP for (comparative) evaluation of safety. AEs were coded using MedDRA coding dictionary (Version 19.0). For PK and PD data, summary and plots of mean PK concentrations by visit were planned to be provided. For these analyses the SAF was planned to be used primarily.

Results

Participant flow and data sets analysed



EP=Extension Period; FAS=full analysis set; n=number of patients; PPS=per-protocol set; SAF=safety analysis set; TP=Treatment Period; TP2+EP FAS=full analysis set Treatment Period 2 and Extension Period; TP2+EP PPS=per-protocol set Treatment Period 2 and Extension Period; TP2+EP SAF=safety analysis set Treatment Period 2 and Extension Period

[a] 23 patients completed Treatment Period 1, but did not continue to Treatment Period 2, as they were non-responders of PASI50.

[b] 20 patients completed Treatment Period 2 before [Appendix 16.1.1-Protocol Version v03] came into effect and thus completed the study at Week 39 after receiving their last dose at Week 35. Following Protocol Version v03, 1 patient completed Treatment Period 2, but did not continue to the Extension Period.

Figure 12 - Patient disposition

The PPS data set was considered as the primary efficacy analysis set to demonstrate equivalence, with supportive analyses performed with the FAS. This is endorsed; however assessment of therapeutic equivalence equally focuses on the results both data sets.

The PPS data set for the TP1 – Randomization to week 17 (with primary analysis at week 16) consisted of 197 patients for GP2017 and 196 patients for Humira. The corresponding figures for the FAS were 231 and 234, respectively.

Table 14 - Summary of analysis sets during treatment period 1 – study GP17-301 (FAS)

Analysis set	EU-GP2017 N=43 n (%)	EU-Humira N=44 n (%)	US-GP2017 N=188 n (%)	US-Humira N=190 n (%)
Full analysis set (FAS)	43 (100.0)	44 (100.0)	188 (100.0)	190 (100.0)
Safety analysis set (SAF)	43 (100.0)	44 (100.0)	188 (100.0)	190 (100.0)
Per-protocol analysis set (PPS)	40 (93.0)	39 (88.6)	157 (83.5)	157 (82.6)

Percentages are based on the number of patients within the treatment groups in the FAS (N).

FAS=full analysis set; n=number of patients in the treatment group; PPS=per-protocol set; SAF=safety analysis set

For TP2, only PASI50 responders were re-randomized, leading to the exclusion of 23 patients (GP2017: 12 patients; Humira: 11 patients) from re-randomization. The exclusion of non-responders is acceptable and the proportion of these patients is balanced between treatment arms.

As longitudinal analysis of continuous efficacy outcomes is crucial for demonstration of biosimilarity, focus of assessment also lies on those patients who continuously received either GP2017 or Humira. Figures for the continued groups (TP2+EP) are shown in the following table:

Table 15 - Summary of analysis sets during treatment period 2 and extension period by continued treatment group – study GP17-301 (TP2+EPFAS)

Analysis set	Continued EU-GP2017 N=25 n (%)	Continued EU-Humira N=27 n (%)	Continued US-GP2017 N=101 n (%)	Continued US-Humira N=100 n (%)
TP2+EP Full analysis set (FAS)	25 (100.0)	27 (100.0)	101 (100.0)	100 (100.0)
TP2+EP Safety analysis set (SAF)	25 (100.0)	27 (100.0)	101 (100.0)	100 (100.0)
TP2+EP Per-protocol analysis set (PPS)	23 (92.0)	26 (96.3)	82 (81.2)	89 (89.0)
EP Full analysis set (EP FAS)	17 (68.0)	19 (70.4)	89 (88.1)	90 (90.0)

EP=Extension Period; FAS=full analysis set; n=number of patients in the treatment group; PPS=per-protocol set; SAF=safety analysis set; TP2=Treatment Period 2

Treatment groups – Continued: continued same treatment throughout study

Recruitment

Overall, 448 patients with moderate to severe chronic plaque-type psoriasis were planned to be randomized into the study. Patients were screened at 76 and randomized at 73 study centers in Bulgaria, France, Slovakia, and the US.

It was initially planned to recruit patients at approximately 50-100 study sites worldwide and to use US-Humira as comparator product for patients in the US and EU-Humira for patients recruited outside the US.

The first interpretable results from the phase I PK study (GP17-101) showed that GP2017 was bioequivalent to US-Humira. However, bioequivalence could formally not be shown between GP2017 and EU-Humira and between US-Humira and EU-Humira with regard to the AUC parameters, even though no relevant differences concerning safety and immunogenicity were observed between the 3 products. As EU-Humira is a well-established treatment of psoriasis with known efficacy and safety and no safety and immunogenicity issues were observed for GP2017, the study recruitment was continued in the 3 already activated countries (France, Bulgaria and Slovakia). The recruitment in Europe was to be capped at 90 patients due to the shift of enrolment to the US. This was not planned to influence the total planned number of patients to be recruited (n=448).

Conduct of the study

Protocol deviations

The proportions of patients with protocol deviations were similar across treatment groups, on an overall level as well as by category, in treatment period 1 and 2.

Major protocol deviations were defined as deviations which could have an impact either on the primary and key secondary objectives for TP1 only and/or for further secondary objectives during TP2 and EP.

Major deviations led to exclusion of patients from the PPS, which is endorsed. No remarkable difference between treatment arms was observed.

Other important protocol deviations:

- Thirty five (35) patients (15.2%) in the GP2017 group and 40 patients (17.1%) in the Humira group had been incorrectly stratified for weight and prior systemic therapy in IRT. Statistical analyses were primarily performed using the correct stratification factor based on the clinical database rather than the IRT-assigned factor.

- Eighteen (18) patients were dosed with study medication (GP2017 or Humira) that had experienced a temperature excursion. These patients were not excluded from PPS or TP2+EP PPS. Sensitivity analyses of the primary and key secondary analyses were performed excluding the 15 patients from site 1218.

- Three hundred and sixty eight (368) patients achieved PASI50 at Week 16 and 379 patients were re-randomized into Treatment Period 2. This difference of 11 patients can be explained by 13 patients who were re-randomized in error at Week 17 and 2 other patients with PASI50 response discontinuing from the study at Week 17.

Baseline data

In the reference treatment arm, EU- and US-Humira were used for patients recruited in the EU or in the US, respectively. Following a protocol amendment, treatment of patients with EU reference product was restricted to 44 patients, while US-Humira was used in 190 patients.

Demographics and baseline disease characteristics

Demographic and disease characteristic information was presented separately for both regions:

Table 16 - Baseline characteristics of patients in GP17-301 study by region and treatment group (FAS)

	EU		US	
	GP2017	EU-Humira	GP2017	US-Humira
Characteristic	N=43	N=44	N=188	N=190
Age (years), mean (SD)	43.2 (14.28)	46.9 (14.75)	46.2 (14.11)	46.9 (13.97)
Males, n (%)	30 (69.8)	28 (63.6)	112 (59.6)	114 (60.0)
Caucasian, n (%)	43 (100)	43 (97.7)	153 (81.4)	158 (83.2)
Hispanic or latino, %	7.0	6.8	25.0	26.3
Weight (kg), mean (SD)	84.60 (16.371)	85.06 (21.796)	94.62 (27.742)	92.32 (24.613)
PASI at baseline, mean (SD)	21.86 (9.653)	22.34 (8.280)	19.45 (8.240)	19.76 (7.478)
BSA (% affected), mean (SD)	28.707 (17.3028)	29.600 (13.4640)	28.924 (17.0816)	29.664 (16.0971)
Disease duration (years), mean (SD)	18.74 (13.506)	18.42 (14.117)	14.51 (12.341)	16.57 (14.782)
PsA, present, %	30.2	15.9	20.7	20.5
PsO Hand and Feet, yes, %	2.3	4.5	43.6	43.2
Prior systemic therapy yes, %	55.8	54.5	42.0	41.6
Prior biologics, yes, %	18.6	13.6	24.5	20.0

Baseline characteristics provided in table above indicate that there are relevant differences between both regions´ patient populations, e.g. in hand and feet involvement at baseline (4% vs. 45%, respectively), body weight (85 kg vs. 95 kg, respectively), duration of psoriasis (18 y vs. 15–16 y, respectively), mean baseline PASI score (22 vs. 20, respectively) and rate of prior systemic treatment (55% vs 42%, respectively). The latter three baseline disease characteristics could be the consequence of the EU-Humira label at the time of study set-up in 2013, approved at that date as 2nd line treatment (in contrast to US-Humira). This might have led to recruitment of a somewhat different patient population in the EU compared to the US, as reflected by longer duration of psoriasis, a slightly higher mean baseline PASI score, and a higher rate of prior systemic treatment.

Concomitant medication

Data about prior and concomitant medication were presented for the SAF.

Concomitant medication was allowed according to predetermined criteria. Comparative data between the groups indicate that non-restricted concomitant treatments were mostly balanced between the GP2017 and Humira arms. A slight imbalance was noted in the frequency of concomitant treatment with ibuprofen (17.3% vs. 9.9% for GP2017 and Humira continuous arms, respectively).

Prohibited medication was broadly defined in the clinical study protocol and included medication with an active ingredient in the class of biologic immunomodulating therapy, other systemic immunomodulating therapy, other systemic psoriasis treatments, photochemotherapy, phototherapy, topical steroids or other topical treatment that is likely to impact signs and symptoms of psoriasis. Overall only 3 patients received prohibited medication between randomization and the primary efficacy assessment at week 16 and no impact on efficacy in these patients has been observed.

A higher proportion of patients took concomitant medication in US region compared to the EU region. However, within the regions, prior and concomitant medications were overall balanced between the

treatment arms. Focusing only on patients recruited in the US (based on which the conclusion on equivalent efficacy is drawn), a numerical difference was detected with regard to the percentage of patients taking concomitant medication: 78.7% vs. 69.5% for the GP2017 and Humira groups, respectively. This difference could mainly be attributed to ibuprofen and acetylsalicylic acid use (17% vs. 11.1%; and 11.7% vs. 7.4% for both medications and groups, respectively). The clinical impact of this slight imbalance is regarded as marginal by the CHMP.

Outcomes and estimation

Primary Efficacy Analysis

Comparison GP2017 vs. Humira (pooled)

For the primary endpoint analysis, the 95% CI for the difference in the PASI75 response rates at Week 16 (GP2017 – Humira) was contained within the interval [-18%; 18.

Table 17 - Logistic regression analysis on PASI75 response at week 16 (primary endpoint analysis) – GP2017 vs. Humira (PPS)

	N	n	Adjusted response rate[1] (SE) [%]	Adjusted response rate difference (SE) GP2017 – Humira [%]	95% CI
GP2017	197	132	66.8 (3.33)	1.8 (4.75)	[-7.46, 11.15]
Humira	196	127	65.0 (3.38)		

To conclude equivalent efficacy, the 95% CI had to be entirely within the interval [-18%, 18%].
CI=confidence interval; N=number of patients per treatment group; n=number of patients per treatment group achieving PASI75 response; PASI=psoriasis area and severity index; PPS=per-protocol set; SE=standard error

[1] Adjusted response rates were estimated using a logistic regression model including treatment, body weight strata, region and prior systemic therapy. The 95% CI for the rate difference was derived based on the normal approximation and standard error computed using the delta method.

Table 18 - Logistic regression analysis on PASI75 response at week 16 (primary endpoint analysis) – GP2017 vs. Humira (FAS)

	N	n	Adjusted response rate[1] (SE) [%]	Adjusted response rate difference (SE) GP2017 – Humira [%]	95% CI
GP2017	231	134	58.1 (3.23)	2.2 (4.56)	[-6.79, 11.10]
Humira	234	131	55.9 (3.23)		

CI=confidence interval; FAS=full analysis set; N=number of patients per treatment group; n=number of patients per treatment group achieving PASI75 response; PASI=psoriasis area and severity index; SE=standard error

[1] Adjusted response rates were estimated using a logistic regression model including treatment, body weight strata, region and prior systemic therapy. The 95% CI for the rate difference was derived based on the normal approximation and standard error computed using the delta method.

Comparison GP2017 vs. US-/EU-Humira (both separated per region)

Table 19 - Primary endpoint analysis by region: logistic regression analysis on PASI75 response at week 16 – GPS2017 vs. Humira – study GP17-301 (PPS)

	N	n	Adjusted response rate[1] (SE) [%]	Adjusted response rate difference (SE) [%] (EU-GP2017 – EU-Humira)	95% CI (%) of difference
EU region					
GP2017	40	25	60.4 (6.75)	-15.7 (9.01)	[-33.34, 1.99]
Humira	39	29	76.1 (5.95)		
US region					
GP2017	157	107	68.0 (3.72)		
Humira-	157	98	62.6 (3.84)	5.3 (5.35)	[-5.14, 15.81]

To conclude equivalent efficacy the 95% CI had to be entirely within the interval [-18%, 18%].

CI=confidence interval; n=number of patients per treatment group and subgroup achieving PASI75 response; N=number of patients per treatment group and subgroup; PASI=Psoriasis Area and Severity Index; PPS=per-protocol analysis set; SE=standard error

[1] Adjusted response rates were estimated using a logistic regression model including treatment, body weight strata, region and prior systemic therapy in the model. The 95% CI for the rate difference was derived based on the normal approximation and SE computed using the delta method.

Subgroup analyses - pooled analyses

For bodyweight group <90 kg or ≥90 kg and prior systemic therapy no or yes, the adjusted response rates each were similar across groups, but due to the low number of patients in these subgroups, the analyses were not powered for the formal treatment comparisons and are therefore considered descriptive.

The results of the supportive analyses in ADA negative patients also corroborated the primary analysis.

The adjusted response rates at Week 16 in ADA positive patients were lower than in ADA negative patients, but similar across groups: 42.8% vs. 39.2% for GP2017 and Humira, respectively. Criteria for equivalence were not met (upper margin of the CI of the difference: 25.28). However, the analysis was not powered for the formal treatment comparison and is therefore considered descriptive. Furthermore, results analysing patients with ADA positive samples at week 3/7/11 are in favour for GP2017. Of note, these results are only representative for the region pooled data. No information about the impact on ADA status on efficacy in EU patients is available. Due to the very limited number of patients in the EU, further analyses in this direction would be inconclusive.

Additional supportive analyses

According to the Applicant, the following additional supportive analyses corroborated the main treatment comparison results:

- analysis of patients enrolled in the US,
- analysis of ADA negative patients at baseline,
- analysis using assigned stratification factors as per IRT,
- analysis excluding patients with pre-dose serum adalimumab concentration values,
- analysis excluding patients dosed with study drug that had experienced a temperature excursion, and
- analysis excluding patients enrolled at site 1268.

For the following analyses there was a similar trend in adjusted response rates between treatment groups, but the numbers of patients were low and therefore results should be interpreted with caution:

- analysis of patients enrolled in the EU,
- analysis of ADA positive patients at baseline, and
- analyses of patients with transient ADA, or progressive ADA development.

Table 20 - Statistical analysis (logistic regression) of patients with PASI 75 response at week 16 by subgroup per-protocol set

Subgroup	Endpoint	Treatment group	N	n	Adjusted response rate/ SE (%)	Adjusted response rate difference/SE (%) (GP2017 - Humira)	95% Confidence Interval
Body Weight							
< 90 kg	PASI 75 response	GP2017	104	73	69.8 (4.45)	0.9 (6.33)	[-11.54, 13.26]
		Humira	102	70	69.0 (4.49)		
>= 90 kg	PASI 75 response	GP2017	93	59	62.8 (4.85)	1.4 (6.84)	[-11.99, 14.83]
		Humira	94	57	61.3 (4.82)		
Prior Systemic Therapy (biologic and non-biologic)							
No	PASI 75 response	GP2017	113	80	70.8 (4.26)	1.0 (6.16)	[-11.10, 13.04]
		Humira	106	74	69.8 (4.44)		
Yes	PASI 75 response	GP2017	84	52	61.9 (5.19)	2.9 (7.27)	[-11.31, 17.17]
		Humira	90	53	58.9 (5.08)		
Region							
US	PASI 75 response	GP2017	157	107	68.0 (3.72)	5.3 (5.35)	[-5.14, 15.81]
		Humira	157	98	62.6 (3.84)		
EU	PASI 75 response	GP2017	40	25	60.4 (6.75)	-15.7 (9.01)	[-33.34, 1.99]
		Humira	39	29	76.1 (5.95)		
ADA status at baseline							
Negative	PASI 75 response	GP2017	191	126	65.8 (3.41)	-0.1 (4.85)	[-9.63, 9.38]
		Humira	187	123	65.9 (3.44)		
Positive		GP2017	2	2	NE	NE	NE
		Humira	3	0	NE		
ADA status upto Week 16							
Negative	PASI 75 response	GP2017	149	111	74.3 (3.58)	2.2 (5.16)	[-7.87, 12.35]
		Humira	146	105	72.1 (3.70)		
Positive	PASI 75 response	GP2017	40	17	42.8 (7.72)	3.7 (11.03)	[-17.96, 25.28]
		Humira	38	15	39.2 (7.80)		

N- number of patients per treatment group and subgroup, n- number of patients per treatment group and subgroup achieving PASI 75 response, NE= Not estimable.
1. To conclude equivalent efficacy the 95% CI must be entirely within the interval [-18%, 18%].
2. Adjusted response rates are estimated using a logistic regression model including treatment effect and covariate effects (covariates for body weight subgroups: region and prior systemic therapy; covariates for prior systemic therapy subgroup: region and body weight; covariates for others: region, body weight, and prior systemic therapy). The 95% CI for the rate difference is derived based on the normal approximation and standard error (SE) computed using the delta method.

Key Secondary Efficacy Analysis

Comparison GP2017 vs. Humira (pooled)

The 95% CI for the difference in the percentage change from baseline in PASI up to Week 16 was contained within the interval [-15%; 15%], for the PPS as well as for the FAS data sets.

Table 21 - Statistical analyses of percentage change from baseline in PASI score up to week 16 – GP2017 vs. Humira (PPS)

	N	n	LS means (SE) [%]	LS means difference (SE) GP2017 – Humira [%]	95% CI for LS means difference [%]
Mean percent change from baseline in PASI score (MMRM)[1]					
GP2017	197	191	-60.7 (1.54)	0.8 (2.03)	[-3.15, 4.84]
Humira	196	192	-61.5 (1.55)		
Mean ATE of percent change from baseline in PASI score (ANCOVA)[2]					
GP2017	197	197	-59.7 (1.59)	1.2 (2.00)	[-2.78, 5.08]
Humira	196	196	-60.8 (1.61)		

Table 22 - Statistical analyses of percentage change from baseline in PASI score up to week 16 – GP2017 vs. Humira (FAS)

	N	n	LS means (SE) [%]	LS means difference (SE) GP2017 – Humira [%]	95% CI for LS means difference [%]
Mean percent change from baseline in PASI score (MMRM)[1]					
GP2017	231	196	-60.1 (1.61)	-0.7 (2.12)	[-4.85, 3.47]
Humira	234	200	-59.4 (1.61)		
Mean ATE of percent change from baseline in PASI score (ANCOVA)[2]					
GP2017	231	231	-58.0 (1.69)	-0.5 (2.07)	[-4.57, 3.55]
Humira	234	233	-57.5 (1.68)		

Comparison GP2017 vs. US-/EU-Humira (both separated per region)

Table 23 - Statistical analyses of percentage change from baseline in PASI score up to week 16 by region – GP2017 vs. Humira – study GP17-301 (PPS)

	N	n	LS means (SE) [%]	LS means difference (SE) GP2017 – Humira [%]	95% CI for LS means difference [%]
EU region					
Mean percent change from baseline in PASI score (MMRM)[1]					
GP2017	40	40	-65.0 (2.24)	1.1 (3.17)	[-5.26, 7.39]
Humira	39	39	-66.1 (2.25)		
Mean ATE of percent change from baseline in PASI score (ANCOVA)[2]					
GP2017	40	40	-61.4 (2.18)	1.3 (3.05)	[-4.82, 7.35]
Humira	39	39	-62.6 (2.17)		
US region					
Mean percent change from baseline in PASI score (MMRM)[1]					
GP2017	157	151	-59.6 (1.67)	0.9 (2.35)	[-3.77, 5.48]
Humira	157	153	-60.5 (1.66)		
Mean ATE of percent change from baseline in PASI score (ANCOVA)[2]					
GP2017	157	157	-56.8 (1.65)	1.3 (2.31)	[-3.22, 5.88]
Humira	157	157	-58.1 (1.64)		

ANCOVA=analysis of covariance; ATE=average treatment effect; CI=confidence interval; LS=least squares; MMRM=mixed-model repeated measures; N=number of patients per treatment group and subgroup; n=number of patients with evaluable data per treatment group and subgroup; PASI=psoriasis area and severity index; PPS=per-protocol set; SE=standard error

[1] LS means, standard errors and 95% CI were estimated by a Mixed-Effects Repeated Measures (MMRM) model with treatment, visit, treatment-by-visit interaction, body weight strata, prior systemic therapy, as fixed factors and baseline PASI score as covariate. An unstructured covariance matrix is used to model the within-patient variance-covariance matrix.

[2] ATE is the weighted average of % change from baseline in PASI scores between Week 1 and Week 16 (weights based on the time interval between two consecutive visits).

[2] For mean ATE percent change from baseline in PASI score, LS means, standard errors and 95% CI were estimated using an ANCOVA model with treatment, body weight strata and prior systemic therapy as fixed effects and baseline PASI score as covariate.

No imputation of missing values was performed.

Subgroup analyses - pooled analyses

For bodyweight group <90 kg or ≥90 kg and prior systemic therapy no or yes, the LS means each were similar across groups, but due to the low number of patients in these subgroups, the analyses were not powered for the formal treatment comparisons and are therefore considered descriptive.

The results of the supportive analyses in ADA negative patients and ADA positive patients corroborated the primary analysis. The LS means up to Week 16 in ADA positive patients were lower than in ADA negative patients, but similar across groups. However, due to the low numbers of patients in this subgroup, the analysis was not powered for the formal treatment comparison and is therefore considered descriptive.

Please refer to the table below for detailed subgroup figures (MMRM).

According to the Applicant, the following additional supportive analyses corroborated the main treatment comparison results:

- analysis of patients enrolled in the US,
- analysis of ADA negative patients at baseline, analysis using assigned stratification factors as per IRT,
- analysis excluding patients with pre-dose serum adalimumab concentration values,
- analysis excluding patients dosed with study drug that had experienced a temperature excursion, and
- analysis excluding patients enrolled at site 1268.

Table 24 - Statistical analysis (MMRM) of % change from baseline in PASI score up to week 16 by subgroup per-protocol set

Subgroup	Treatment group	n	LS Means (standard error - SE)	LS Mean Difference/ SE (GP2017 - Humira)	95% Confidence Interval (CI) of Difference	AIC criteria value
Body Weight < 90 kg	GP2017 (N=104)	101	-62.4 (2.26)	0.0 (3.06)	[-5.99, 6.07]	14045.3
	Humira (N=102)	100	-62.4 (2.30)			
Body Weight >= 90 kg	GP2017 (N= 93)	90	-57.7 (2.07)	1.9 (2.62)	[-3.28, 7.05]	12587.7
	Humira (N= 94)	92	-59.6 (2.03)			
Prior Systemic Therapy(biologic and non-biologic): No	GP2017 (N=113)	111	-62.3 (2.13)	0.5 (2.76)	[-4.94, 5.94]	14564.0
	Humira (N=106)	104	-62.8 (2.19)			
Prior Systemic Therapy(biologic and non-biologic): Yes	GP2017 (N= 84)	80	-59.2 (2.18)	1.0 (2.93)	[-4.79, 6.78]	12003.1
	Humira (N= 90)	88	-60.2 (2.14)			
Region: US	GP2017 (N=157)	151	-59.6 (1.67)	0.9 (2.35)	[-3.77, 5.48]	21454.6
	Humira (N=157)	153	-60.5 (1.66)			
Region: EU	GP2017 (N= 40)	40	-65.0 (2.24)	1.1 (3.17)	[-5.26, 7.39]	5148.9
	Humira (N= 39)	39	-66.1 (2.25)			
ADA status at baseline: Negative	GP2017 (N=191)	185	-60.2 (1.56)	1.7 (2.07)	[-2.34, 5.81]	25671.4
	Humira (N=187)	183	-62.0 (1.58)			
ADA status at baseline: Positive	GP2017 (N= 2)	2	NE	NE	NE	-
	Humira (N= 3)	3	NE			

ADA status up to Week 16: Negative	GP2017 (N=149)	147	-62.9 (1.63)	2.6 (2.19)	[-1.75, 6.86]	19800.5
	Humira (N=146)	144	-65.4 (1.63)			
ADA status up to Week 16: Positive	GP2017 (N= 40)	38	-51.2 (3.88)	-4.0 (5.10)	[-14.13, 6.22]	5405.5
	Humira (N= 38)	38	-47.3 (4.07)			

Secondary Analyses

Secondary Endpoints included Response Rates in PASI50, PASI75, PASI90, and PASI100, absolute and percentage change in PASI scores, proportion of IGA responders, as well as health-related quality of life assessments.

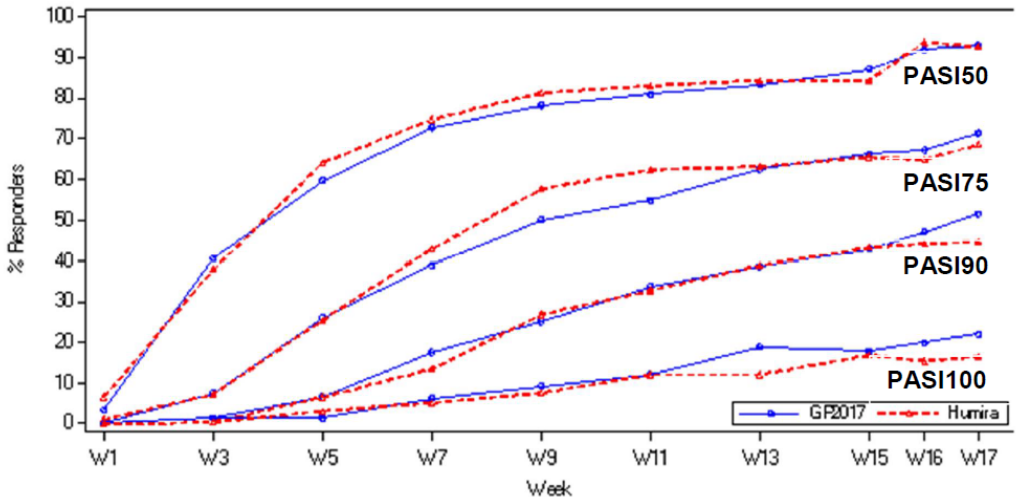
Evaluation of these endpoints was done every other week until week 17 and thereafter every 6 weeks until week 51, and results were presented over the whole treatment period.

As for the primary and key secondary efficacy analyses, it was requested to complement the presented data with results only for the EU region, i.e. separating the regions also for the test arm and not pooling those patients together in one analysis.

PASI50, PASI75, PASI90, and PASI100 response rates

EU and US regions pooled: PASI response rates in the PPS were similar over time across treatment groups. Up to Week 16, the adjusted response rates for all evaluable assessments were similar and their 95% CI margins each within [-18%, 18%]. PASI response rates in the TP2+EP PPS were also similar over time across continued and switched groups. The analysis on the FAS was consistent with the results in the PPS.

Comparison GP2017 vs. Humira (pooled)

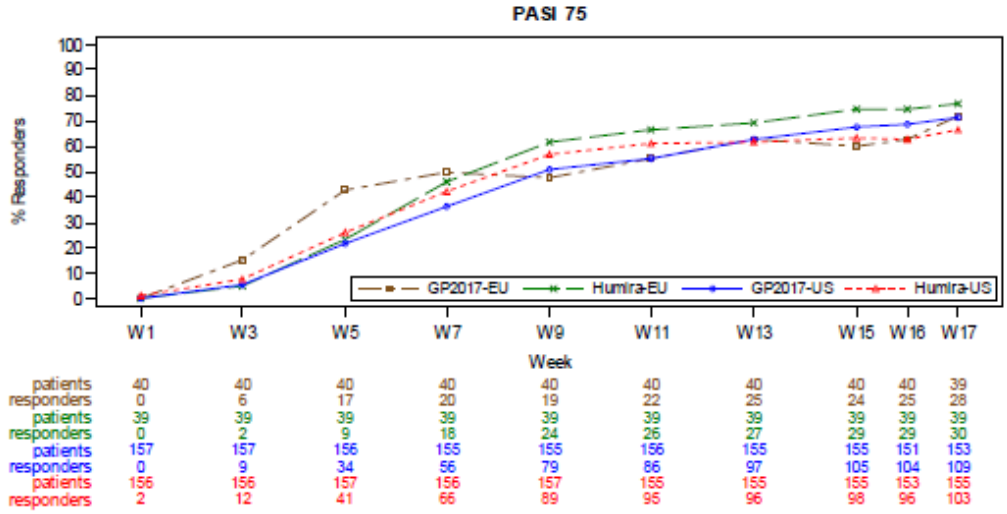


PASI=Psoriasis Area and Severity Index; PPS=per-protocol analysis set; W=week

Figure 13 Plots of PASI50, PASI75, PASI90 and PASI100 response rates (randomisation to week 17) – study GP17-301 (PPS)

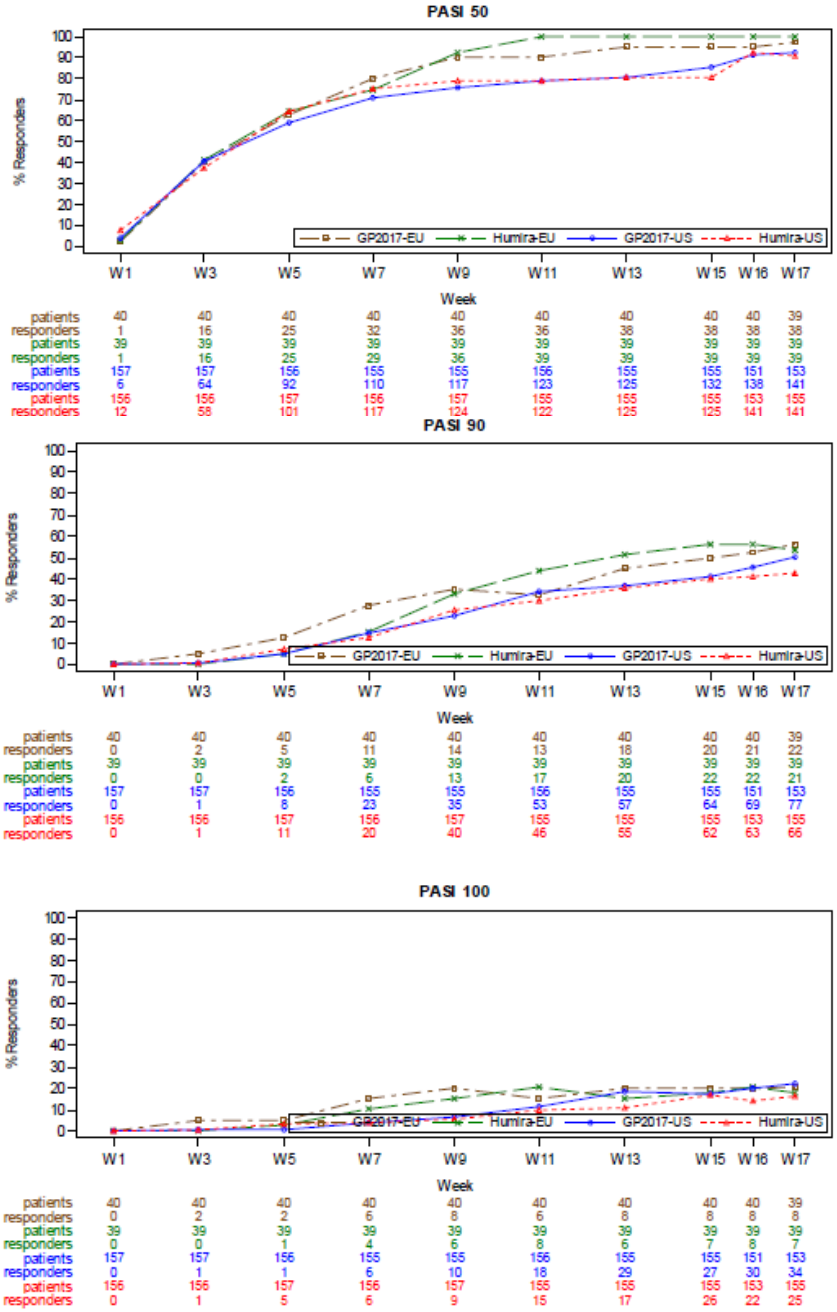
Comparison GP2017 vs. EU-/US Humira (both separated per region)

With the Day 121 Responses, the Applicant provided additional graphs, as requested, separating the GP2017 arm for the patients recruited in the US and EU, respectively:



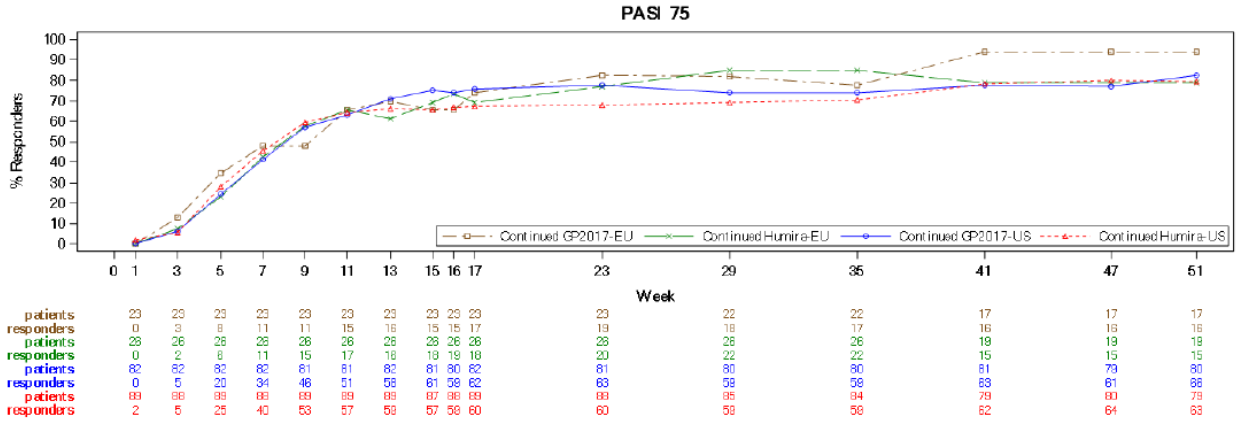
PASI=psoriasis area severity index; PPS=per-protocol set

Figure 14 - Plot for response rate for PASI 75 during treatment period 1 by treatment groups – study GP17-301 (PPS)



PASI=psoriasis area severity index; PPS=per-protocol set; W=Week

Figure 15 - Plot for response rate for PASI 50, PASI90 and PASI100 during treatment period 1 by treatment groups – study GP17-301 (PPS)



PASI=Psoriasis Area and Severity Index; TP2+EP PPS=per-protocol set Treatment Period 2 and Extension Period

Treatment groups – Continued: continued same treatment throughout study.

Figure 16 Plot for response rates for PASI75 for entire study by continued treatment groups and region – study GP17-301 (TP2+EP PPS)

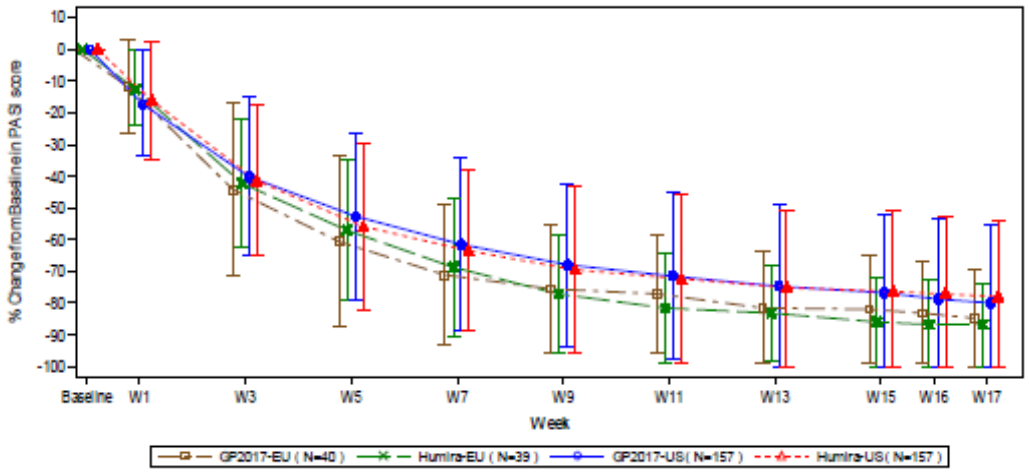
Change in PASI scores

EU and US regions pooled:

The mean absolute PASI scores and percent changes from baseline were similar across groups at visits up to Week 17.

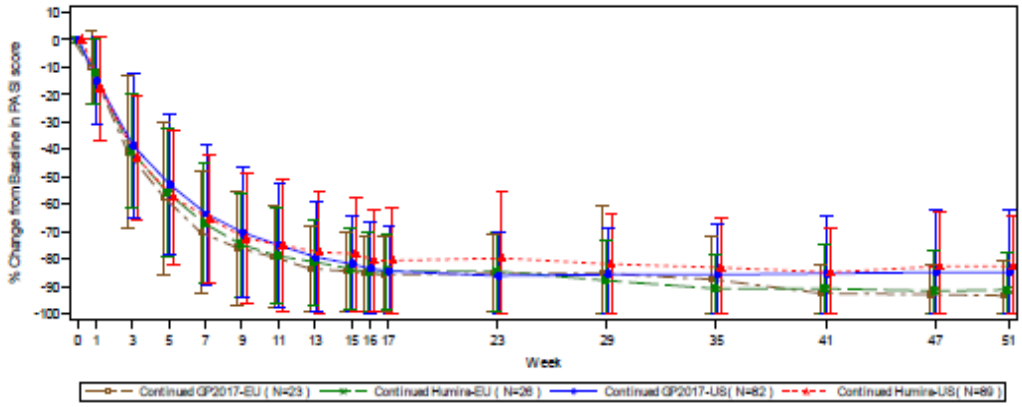
Comparison GP2017 vs. EU-/US Humira (both separated per region)

Comparable results for GP2017 and Humira are generally shown, but generally a slight greater efficacy for the biosimilar and the reference product in the EU stratum were seen.



N=number of patients per treatment group; PASI=Psoriasis Area and Severity Index; PPS=per-protocol analysis set; SD=standard deviation; W=week

Figure 17 - Arithmetic mean (+/-SD) plot of % change from baseline in PASI score during treatment period 1 by treatment group and region – study GP17-301 (PPS)



N=number of patients per treatment group; PASI=Psoriasis Area and Severity Index; SD=standard deviation; TP2+EP PPS=per-protocol set Treatment Period 2 and Extension Period

Treatment groups – Continued: continued same treatment throughout study.

Figure 18 - Arithmetic mean (+/-SD) plot of % change from baseline in PASI score for entire study by continued treatment group and region – study GP17-301 (TP2+EP PPS)

Proportion of IGA responders (with IGA 0 or 1)

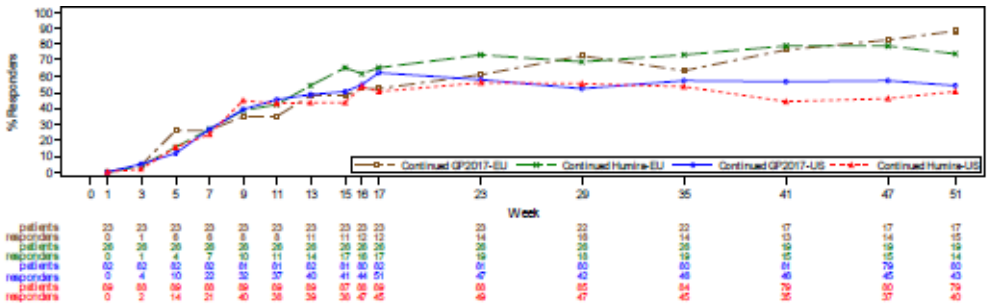
EU and US regions pooled:

Patients who achieved a clear (0) or almost clear (1) disease state and improved by at least 2 points of the IGA scale compared with baseline score were considered IGA responders. All randomized patients had an IGA score of 3 or 4 at baseline.

In the PPS and FAS, the IGA response rates increased over time and were similar in both treatment groups.

Comparison GP2017 vs. EU-/US Humira (both separated per region)

IGA responder rates support the finding that patients in the EU show a superior efficacy compared to the US population.



IGA=Investigator's global assessment; PPS=per-protocol analysis set; TP2+EP PPS=per-protocol set Treatment Period 2 and Extension Period

Treatment groups – Continued: continued same treatment throughout study.

Figure 19 - IGA response rates for entire study by continued treatment group and region – study GP17-301 (TP2+EP PPS)

Absolute change from baseline in PASI score at Week 16

Table 25 - Statistical analysis of absolute change from baseline in PASI score at Week 16, overall and by region – GP2017 vs. Humira, study GP17-301 (PPS)

	Treatment	N	LS means (SE)	LS mean difference (SE) GP2017- Humira	95% CI for LS mean difference
Overall	GP2017 (N=197)	191	-15.67 (0.452)	0.13 (0.622)	[-1.090, 1.359]
	Humira (N=196)	192	-15.80 (0.454)		
US region	GP2017 (N=157)	151	-14.99 (0.480)	-0.11 (0.676)	[-1.444, 1.220]
	Humira (N=157)	153	-14.88 (0.478)		
EU region	GP2017 (N=40)	40	-18.48 (0.714)	0.88 (1.013)	[-1.185, 2.938]
	Humira (N=39)	39	-19.35 (0.720)		

CI=confidence interval; LS=least squares; MMRM=mixed-model repeated measures; N=number of patients per treatment group and subgroup; n=number of patients with evaluable data per treatment group and subgroup; PASI=psoriasis area and severity index; PPS=per-protocol set; SE=standard error

[1] LS means, standard errors and 95% CI were estimated by a Mixed-Effects Repeated Measures (MMRM) model with treatment, visit, treatment-by-visit interaction, body weight strata, prior systemic therapy, (and region for overall analysis only) as fixed factors and baseline PASI score as covariate. An unstructured covariance matrix is used to model the within-patient variance-covariance matrix.

No imputation of missing values was performed.

Efficacy assessment at earlier time point (Week 13)

Table 26 - Statistical analysis of absolute change from baseline in PASI score at Week 13 in US region only – GP2017 vs. Humira, study GP17-301 (PPS)

	N	n	LS means (SE) [%]	LS means difference (SE) GP2017 – Humira [%]	95% CI for LS means difference [%]
GP2017	157	155	-14.07 (0.49)	0.25 (0.69)	[-1.10, 1.60]
Humira	157	155	-14.32 (0.49)		

CI=confidence interval; LS=least squares; MMRM=mixed-model repeated measures; N=number of patients per treatment group; n=number of patients with evaluable data per treatment group; PASI=psoriasis area and severity index; PPS=per-protocol set; SE=standard error

LS means, standard errors and 95% CI were estimated using a Mixed-Effects Repeated Measures (MMRM) model with treatment, visit, treatment-by-visit interaction, body weight strata, prior systemic therapy, as fixed factors and baseline PASI score as covariate. An unstructured covariance matrix is used to model the within-patient variance-covariance matrix.

No imputation of missing values was performed.

Summary of main study(ies)

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 27 - Summary of Efficacy for trial GP17-301

Title: A randomized, double-blind, multicenter study to demonstrate equivalent efficacy and to compare safety and immunogenicity of a biosimilar adalimumab (GP2017) and Humira in patients with moderate to severe chronic plaque-type psoriasis		
Study identifier	Protocol No.: **GP17-301** (GPN017A2301), EudraCT number: 2013-000747-11	
Design	This study was a multicenter, randomized, double-blind, comparator-controlled, confirmatory efficacy and safety (Phase III) study to assess equivalent efficacy, safety, and immunogenicity of the proposed biosimilar GP2017 and Humira (adalimumab) after 17 weeks of treatment in patients with moderate to severe chronic plaque-type psoriasis. In addition, the long-term effects including safety and immunogenicity up to Week 51 and the effect of repeated switching between GP2017 and Humira were to be analyzed. In this study US-licensed Humira was used to treat patients enrolled in the US and EU-authorized Humira was used to treat patients enrolled in the EU.	
	Duration of study: Duration of main phase (treatment period 1): Duration of Run-in phase: Duration of Extension phase:	51 weeks (end of active treatment) 16 weeks (primary endpoint) not applicable 16 weeks
Hypothesis	Equivalence for comparison GP2017 vs. Humira Equivalence for comparison GP2017 vs. US-Humira Primary: Margin for the difference in PASI 75 response rate at week 16: [−18%; 18%] Key Secondary: Margin for the difference in relative change from baseline in PASI score until Week 16: [−15%; 15%]	
Treatment groups	GP2017 in Treatment Period 1	GP2017 40 mg, every other week, up to week 17 Randomized: n=231

	Humira in Treatment Period 1		Humira 40 mg, every other week, up to week 17 Randomized: n=234
	Continued GP2017 in Treatment Period 2		GP2017 40 mg, every other week, up to week 51 Re-randomized: n=126
	Continued Humira in Treatment Period 2		Humira 40 mg, every other week, up to week 51 Re-randomized: n=127
	GP2017 to Humira in Treatment Period 2		GP2017 or Humira 40 mg (switch every 6 weeks), every other week, up to week 35 Re-randomized: n=63
	Humira to GP2017 in Treatment Period 2		Humira or GP2017 40 mg (switch every 6 weeks), every other week, up to week 35 Re-randomized: n=63
Endpoints and definitions	Primary endpoint	PASI75	PASI75 response rate at Week 16
	Key Secondary Efficacy Endpoint	PASI	%-change from baseline in PASI score up to Week 16
	Secondary Efficacy Endpoint	PASI50, PASI75, PASI90, PASI100	PASI50, PASI75, PASI90, and PASI100 response rates over the whole study duration
	Secondary Efficacy Endpoint	PASI	PASI score over the whole study duration
	Secondary Efficacy Endpoint	IGA	IGA response rates over the whole study duration
	Secondary Efficacy Endpoint	HRQoL	Assessment of health-related QoL by DLQI and the EQ-5D-5L Health status questionnaire
Main Results and Analysis			
Analyses description	**Primary / Secondary Analyses**		

Effect estimate per comparison	**Primary endpoint** (PPS) PASI75 at week 16	Comparison groups	GP2017 (n=197) vs. Humira (n=196)
		Treatment difference	1.8%
		95% CI	[−7.46%, 11.15%]
		Test	-0.18 < CI < 0.18
	Primary endpoint (FAS) PASI75 at week 16	Comparison groups	GP2017 (n=231) vs. Humira (n=234)
		Treatment difference	2.2%
		95% CI	[−6.79%, 11.10%]
		Test	-0.18 < CI < 0.18
	Primary endpoint (PPS) PASI75 at week 16 **EU region**	Comparison groups	GP2017 (patients only recruited in the EU) (n=40) vs. EU-Humira (n=39)
		Treatment difference	-15.7%
		95% CI	[−33.34%, 1.99%]
		Test	-0.18 < CI < 0.18
	Primary endpoint (PPS) PASI75 at week 16 **US region**	Comparison groups	GP2017 (patients only recruited in the US) (n=157) vs. US-Humira (n=157)
		Treatment difference	5.3%
		95% CI	[−5.14%, 15.81%]
		Test	-0.18 < CI < 0.18
	Key Secondary endpoint (PPS) %change from baseline in PASI75 score up to week 16	Comparison groups	GP2017 (n=191) vs. Humira (n=192)
		Treatment difference (MMRM)	-0.8%
		95% CI	[−3.15%, 4.84%]
		Test	-0.15 < CI < 0.15
	Key Secondary endpoint (FAS) %change from baseline in PASI75 score up to week 16	Comparison groups	GP2017 (n=196) vs. Humira (n=200)
		Treatment difference (MMRM)	-0.7%
		95% CI	[−4.85%, 3.47%]
		Test	-0.15 < CI < 0.15

	Key Secondary endpoint (PPS) %change from baseline in PASI75 score up to week 16 **EU region**	Comparison groups	GP2017 (n=40) vs. Humira (n=39)
		Treatment difference (MMRM)	1.1%
		95% CI	[−5.26%, 7.39%]
		Test	-0.15 < CI < 0.15
	Key Secondary endpoint (PPS) %change from baseline in PASI75 score up to week 16 **US region**	Comparison groups	GP2017 (n=151) vs. Humira (n=153)
		Treatment difference (MMRM)	0.9%
		95% CI	[−3.77%, 5.84%]
		Test	-0.15 < CI < 0.15

2.5.2 Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data have been provided from a randomized, double-blind, multicentre study GP17-301, intended to demonstrate similar efficacy and to compare safety and immunogenicity of GP2017 and Humira in patients with moderate to severe chronic plaque-type psoriasis.

As part the EMA Scientific Advice (EMEA/H/SA/2108/1/2011/III), the Applicant was originally planning to perform the confirmatory study in patients with moderate to severe rheumatoid arthritis. Based on CHMP and FDA interaction the approach was adapted and psoriasis was selected as the indication, in which to demonstrate similarity of GP2017 with Humira.

In general, the study is adequately designed for a biosimilar exercise and consistent with the study aim. The focus of assessment for a MA in the EU is on patients who continuously received the biosimilar product or Humira.

The patient population consisted of adult male and female patients with active, but clinically stable, moderate-to-severe chronic plaque-type psoriasis. Eligible patients had to have a PASI score of at least 12, an IGA score of at least 3 and a total BSA of minimally 10%. The selected population is considered sensitive to detect differences in efficacy.

Patients were recruited in the EU and in the US. US-Humira was used as comparator product for patients in the US and EU-Humira for patients recruited outside the US. However, recruitment in Europe was capped at 90 patients and enrolment shifted to the US. This did not influence the total planned number to be recruited (n=448).

For the primary and key secondary objective to be met, equivalence had to be demonstrated for both treatment comparisons: comparing all Humira and GP2017 treated patients (EU and US region pooled), as well as comparing patients treated with US-Humira (in the US region) and patients treated with GP2017 (EU and US region pooled).

The primary endpoint was defined as the PASI75 response rate at Week 16; with an equivalence margin of 18%. The key secondary efficacy variable was defined as the %-change from baseline in PASI score up to (i.e. averaged over time points) Week 16 and was analysed using MMRM and ATE with ANCOVA

analysis. An equivalence margin of 15% was chosen. Secondary endpoints included Response Rates in PASI50, PASI75, PASI90, and PASI100, absolute and %-change in PASI scores, proportion of IGA responders, as well as health-related quality of life assessments.

With regard to the primary endpoint, the use of a continuous variable (absolute PASI score) would have been preferred. The defined margin is considered rather wide and an earlier time point could have been more sensitive to detect differences between treatments. While the key secondary endpoint represents a continuous variable, which is in principle endorsed, it is expected to provide limited additional insight in the evaluation of equivalent efficacy due to the statistical methodology chosen. Evaluation of other secondary endpoints was done in regular time intervals from randomization until end of study, which is strongly endorsed. The CHMP concluded that the definition of the endpoints was not optimal, but acceptable.

Overall, the design of the study was considered appropriate for a biosimilar setting by the CHMP.

Efficacy data and additional analyses

The sample sizes in the FAS (safety data set) as well as PPS (primary data set for efficacy analysis) seem to be overall balanced and sufficiently large. With regard to discontinuations per region, it is noted that more patients discontinued in the US region (14.4% and 15.3%) than in the EU region (7.0% and 9.1%) in TP1, for GP2017 and Humira, respectively. However, within regions no imbalances were seen between the treatment arms and the reasons for discontinuation were generally equally distributed. Therefore this was not further pursued by the CHMP.

In the reference treatment arm, EU- and US-Humira were used for patients recruited in the EU or in the US, respectively.

Following the results of the first PK equivalence study, the recruitment in Europe was to be capped at 90 patients due to the shift of enrolment to the US. Consequently, treatment of patients with EU reference product was restricted to 44 patients, while US-Humira was used in 190 patients. This intervention was seen critically from a methodological perspective, as the shift of recruitment to the US and use of US-Humira in the majority of patients might influence the result of the phase 3 study.

Efficacy results initially submitted by the Applicant strongly focussed on the treatment comparison GP2017 vs. Humira (i.e. data from patients treated with EU-Humira and data from patients treated with US-Humira were pooled into one Humira group), as well as on separate results for the US region. Overall pooled data analyses were planned to be the basis for the MAA in the EU.

For the primary endpoint (PASI75 response rate at week 16), overall pooled data analysis showed a point estimate of the difference between treatments of 1.8, with 95% CI of [-7.46, 11.15] (PPS). Corresponding adjusted response rates were 66.8% for GP2017 and 65.0% for Humira. GP2017 is equivalent to Humira with regard to the primary efficacy endpoint. Analysis of the FAS data set support that result.

During the assessment procedure, the Applicant was requested to present all relevant comparative efficacy data (primary, key secondary and secondary) by region. The provision of such data was considered important due to initial concerns related to signals for inconsistency of the treatment effect among regions and inferior efficacy of GP2017 compared to EU-Humira. These issues could be resolved during the assessment procedure. On a region level, the comparison between GP2017 (in patients recruited in the US) and US-Humira also met the criteria for equivalence. In contrast, the comparison in the EU region showed greater efficacy of the reference product compared to GP2017 at isolated visits including Week 16. It is however noted that the sample size in the EU was too small to draw any firm conclusions.

Mean %-change from baseline up to w16 (key secondary endpoint) was -60.7% for GP2017 and -61.5% for Humira (MMRM model, adjusted values). The point estimate was 0.8, with 95% CI of [-3.15; 4.84]. In order to complete the whole picture of equivalent efficacy, the Applicant was requested to provide additional analysis on the differences between treatments in absolute change from baseline in PASI score at week 16 (single time point), for the pooled and region-separated populations. The LS means were similar between GP2017 and Humira treatment groups for the overall study population as well as for both the EU and US regions. The differences between treatment arms were as follows: US region -0.11 [-1.444, 1.220]; EU region 0.88 [-1.185, 2.938].

Other secondary endpoints, especially different PASI scores (50, 75, 90 and 100) mostly corroborate the findings and conclusion drawn from the primary and key secondary endpoints. The CHMP agreed that PASI75 response rates at time points other than week 16 as well as secondary endpoints generally demonstrate similar efficacy between biosimilar and reference product within the EU and US regions. Signals for inconsistencies in terms of a (not statistically significant) treatment*region interaction seen for the primary analysis seemed only to be exhibited at isolated visits and was found to be compatible with a chance-finding (mainly due to the small sample size).

Efficacy results based on the US region only

A concern with regard to patient homogeneity emerged. Information on baseline characteristics indicated that there were relevant differences between the EU and US region patient populations. At the time of study set-up, EU-Humira was approved as 2nd line treatment in contrast to US-Humira. Hence, a patient population with a longer duration of psoriasis, a slightly higher mean baseline PASI score, and a higher rate of prior systemic treatment could have been recruited in the EU compared to the US population. In response to the CHMP's concern, the Applicant submitted a conclusive line of argument, a comprehensive overview of all available US results and a thorough discussion on the appropriateness of basing the decision of the EU marketing authorization on US data only.

The majority of patients (n=378, 81%) in study GP17-301 were randomized in the US region and treated either with GP2017 (188 patients) or with US-Humira (190 patients). Patient disposition and discontinuation rates were similar in both treatment groups within the US: 14.4% vs. 15.3% discontinuations in treatment period 1 and 10.9% vs. 10% in treatment period 2, for the GP2017 and Humira groups, respectively. The reasons for discontinuations were also in general equally distributed between both arms.

With regard to the US analysis sets, the full, safety and per-protocol analysis sets comprise highly similar numbers of patients in both treatment groups. It is agreed that similar proportions of patients were excluded from the PPS due to major protocol deviations in both treatment arms.

The baseline characteristics are well balanced between both treatment groups in the US region. External validity (which however does not necessarily represent a prerequisite in a biosimilar exercise) is also given by similar characteristics of the US population studied in study GP17-301 as compared to the general psoriasis population and the patients studied in the clinical study of Humira.

The analysis based on US data only concluded that the study population recruited in the US region was representative of the moderate to severe psoriasis population in the EU. Comparable efficacy of GP2017 and US-Humira was consistently demonstrated based on the primary (PASI75 response rate at Week 16), key secondary (%change from baseline in PASI score up to Week 16) and other secondary endpoints. Equivalent efficacy was further supported by analyses of absolute change from baseline in PASI score and assessment of additional analyses of efficacy at an earlier time point (Week 13). In view of the totality of data provided in this application, the CHMP concluded that the US region results adequately support a marketing authorization in the EU.

Subgroup analyses evaluating the impact of ADA status on primary efficacy endpoint generally show similarity between treatments. While in ADA positive patients, criteria for equivalence were not met, interpretation should be done with caution due to the low number of patients included in the analyses. Adjusted PASI75 Response Rates were similar between treatments in ADA positive patients: 42.8% vs. 39.2% for GP2017 and Humira, respectively. Further efficacy data separated by ADA status for the secondary endpoints were requested. The CHMP concluded that GP2017 and Humira exhibited similar and homogenous treatment effects within both the ADA-negative and ADA-positive subgroups.

2.5.3 Conclusions on the clinical efficacy

The CHMP concluded that GP2017 and US-Humira show similar efficacy in the treatment of moderate to severe psoriasis, and in view of the totality of data provided in this application, the US region results adequately support a marketing authorization in the EU.

2.6 Clinical safety

As outlined in the EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 Rev. 1) and "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010), clinical evidence on comparability/similarity needs to be provided with respect to safety.

The safety part of the clinical dossier for GP2017 includes data from 5 clinical studies, whereof 3 studies provide comparative information (GP2017 vs. Humira); studies GP17-104, GP17-101 (both PK) and study GP17-301 (efficacy and safety).

For safety analyses, data from the healthy volunteer's studies are presented as pooled data which is considered acceptable as study designs are sufficiently comparable. Separate analyses of safety aspects according to the respective reference product (EU- Humira or US- Humira) are available from studies GP17-104 and GP17-101 (the comparative PK studies) which enables more detailed assessment with this regard.

The focus of the safety assessment, however, is on the pivotal, confirmative efficacy and safety trial in psoriasis patients (study GP17-301). For the reference product(s), the data of patients treated with either EU-Humira or US-Humira were pooled and analysed as a single Humira treatment group in this trial and this is acceptable in principle. However, safety data from the PK studies indicate differences in the safety profiles of US- and EU Humira. Therefore, separate analyses according to treatment group (EU-Humira or US-Humira) have been requested for study GP17-301 to gain further insight and exclude major divergences.

Patient exposure

In the studies included in this application, safety of GP2017 was investigated in 466 adult healthy subjects (single dose of 40 mg) and in 294 adult patients with chronic plaque-type psoriasis (multiple doses, initial dose of 80 mg followed by 40 mg every other week).

Exposure in healthy subjects

In the PK studies in healthy subjects, GP2017 was administered as a single s.c. dose of 40 mg/ 0.8 mL either by PFS (GP17-104, GP17-101, GP17-102, and GP17-103) or by AI (GP17-102). Apart from study GP17-103, where patients received GP2017 manufactured at Cook Pharmica, USA (referred to as GP2017-Cook) or at Sandoz GmbH, Austria (referred to as GP2017-Schaftenau), GP2017 drug product manufactured at Sandoz GmbH, Biopharmaceuticals Schaftenau, was used.

Table 28 - Exposure in healthy subjects

	GP2017[1]	Humira[2]
Duration of drug exposure	single injection	single injection
Dose administered	40 mg	40 mg
Subjects dosed	466	357

IMP=investigational medicinal product; SAF=safety analysis set

[1] Includes GP2017 groups from studies GP17-104, GP17-101, GP17-102, and GP17-103.

[2] Includes EU-Humira and US-Humira groups from studies GP17-104 and GP17-101.

Exposure in patients with psoriasis

Patients received SC injections by PFS with a fixed dose of 40 mg (except for the initial loading dose, which was 80 mg) via a prefilled syringe. Trough serum levels were evaluated to provide supportive data on similarity with regard to systemic exposure.

In the following sections, for study GP17-301 data are presented separately by treatment period and continued/switched groups. Please refer to the efficacy section for an overview on study design.

Treatment Period 1

During Treatment Period 1, there were no relevant differences in the exposure to study treatment between the two treatment groups. The mean (± SD) duration of exposure was 99.2 ± 21.19 days overall, and 390 patients (83.9%) received the maximum number of 10 doses (the loading dose of 80 mg was counted as 2 doses): 193 patients (83.5%) in the GP2017 treatment group and 197 patients (84.2%) in the Humira treatment group.

Continued groups (Randomization to Week 51)

During the entire study, there were no relevant differences in the exposure to study treatment between the two groups (table below). The mean (± SD) duration of exposure was 254.6 ± 120.92 days overall in the continued groups; 168 patients (49.6%) received the maximum number of 27 doses (the loading dose of 80 mg was counted as 2 doses): 81 patients (48.2%) in the continued GP2017 group and 87 patients (50.9%) in the continued Humira group.

Table 29 - Summary of exposure to study treatment by continued group – randomisation to week 51 (SAF)

Drug administration details	Continued GP2017 N=168	Continued Humira N=171
Duration of exposure (days)		
Mean	256.2	253.1
SD	118.57	123.51
Median	343.0	344.0
Range (min, max)	1, 358	1, 354
Exposure[1] (in weeks) – n (%)		
≥2 weeks	163 (97.0)	166 (97.1)
≥4 weeks	162 (96.4)	164 (95.9)
≥8 weeks	158 (94.0)	150 (87.7)
≥12 weeks	146 (86.9)	144 (84.2)
≥15 weeks	141 (83.9)	141 (82.5)
≥17 weeks	126 (75.0)	127 (74.3)
≥25 weeks	118 (70.2)	120 (70.2)
≥33 weeks	111 (66.1)	115 (67.3)
≥41 weeks	105 (62.5)	105 (61.4)
≥49 weeks	89 (53.0)	96 (56.1)
Patient exposure (years)	117.8	118.5

Continued groups include patients who continued the same treatment throughout the study.
n=number of patients in the sub-category; max=maximum; min=minimum; N=number of patients exposed to study treatment; SAF=safety analysis set; SD=standard deviation
[1] Exposure is defined in terms of last dose of study drug.

Individual groups (Week 17 to Week 51)

During Week 17 to Week 51, there were no relevant differences in the exposure to study treatment among the four individual groups (Humira to GP2017; continued Humira; GP2017 to Humira; and continued GP2017; Table below). The mean (± SD) duration of exposure was 198.1 ± 56.50 days overall in the individual groups; 252 patients (66.5%) received the maximum number of 17 doses: 37 patients (58.7%) in the Humira to GP2017 group, 89 patients (70.1%) in the continued Humira group, 42 patients (66.7%) in the GP2017 to Humira group, and 84 patients (66.7%) in the continued GP2017 group. Due to the 2:1 ratio at re-randomization patient exposure (in years) was about twice as high in the continued as in the switched groups.

A sufficient number of patients were included in the “switched” groups to allow for reasonable comparison of safety profiles after switching of products.

Table 30 - Exposure across groups (week 17 to 51)

Drug administration details	Humira to GP2017 N=63	Continued Humira N=127	GP2017 to Humira N=63	Continued GP2017 N=126
Duration of exposure (days)				
Mean	195.6	198.0	203.2	197.0
SD	53.60	59.27	48.69	59.11
Median	225.0	225.0	225.0	224.0
Range (min, max)	16, 238	1, 235	16, 233	1, 239
Exposure[1] (in weeks) – n (%)				
≥1 weeks	63 (100.0)	124 (97.6)	63 (100.0)	124 (98.4)
≥9 weeks	61 (96.8)	118 (92.9)	62 (98.4)	118 (93.7)
≥17 weeks	52 (82.5)	108 (85.0)	55 (87.3)	106 (84.1)
≥25 weeks	49 (77.8)	103 (81.1)	52 (82.5)	103 (81.7)
≥33 weeks	1 (1.6)	3 (2.4)	1 (1.6)	4 (3.2)
Patient exposure (years)	33.7	68.8	35.1	68.0

The continued groups include patients who continued the same treatment throughout the study; the switched groups include patients who switched treatment between GP2017 and Humira during Treatment Period 2.

n=number of patients in the sub-category; max=maximum; min=minimum; N=number of patients exposed to study treatment; TP2+EP SAF=safety analysis set Treatment Period 2 and Extension Period; SD=standard deviation

[1] Exposure is defined in terms of last dose of study drug.

Though the extent of exposure was comparable between the GP2017 and the pooled Humira groups throughout the whole study duration, there was a difference in exposure between the EU- and the US-reference product. When differences in PK-performances between EU- and US- Humira were discovered in study GP-17-101 during the recruitment stage of study GP17-301, recruitment in the EU-Humira arm was stopped As a result, the number of patients exposed to EU-Humira in this pivotal study is low (only 44 patients were included in the EU-Humira arm at baseline).

Hundred and four (104) patients from the continued Humira group and 100 patients from the continued GP2017 completed the phase III study. Eighty nine (89) patients in the continued GP2017 arm and 96 patients in the continued Humira arm were exposed to study treatment for ≥ 49 weeks. While this is considered only borderline sufficient (100 patients exposed for a minimum of one-year are expected according to ICH E1), the numbers could be acceptable, considering the known safety profile of Adalimumab and the frequency of key AEs. Also, data from the switched groups are available and provide supportive evidence on long-term exposure. Fifty one (51) weeks is considered a sufficiently long duration of exposure to enable meaningful assessment of long-term safety and provide reasonable assurance for this known substance.

Demographics and baseline characteristics and concomitant medication

Inclusion and exclusion criteria did differ between the trials, in GP17-101 and GP17-301 male and female subjects were included while in all other (PK-) trials only male subjects were included.

Due to the inclusion criteria, significantly more male than female subjects were exposed (especially in the PK studies at single dose) and there were also notable differences in distribution of subjects' body weight across studies (body weight is assumed to be correlated to sex). No relationship of adalimumab safety and sex or body weight is presumed based on historical data (e.g. Menter A et al.; J Am Acad Dermatol. 2010). The population is considered sensitive to detect differences between products on a safety level and therefore adequate for this biosimilarity exercise.

There were no clinically relevant differences between the treatment groups in the use of concomitant medication in any study. The most frequently (>7% of patients in either group) used concomitant medications were ibuprofen, acetylsalicylic acid, paracetamol and lisinopril.

Adverse events

In all studies, the occurrence of AEs was sought by non-directive questioning of the subject or patient at each visit during the study. AEs may also have been detected when they were reported by the subject during or between visits or identified through physical examination, laboratory test, or other assessments.

In the following sections, only treatment-emergent AEs are presented. Treatment-emergent AEs were defined as AEs started on or after the administration of the IMP, or which were present prior to the administration of IMP but increased in severity, changed from being not suspected to being suspected of IMP relationship, or developed into SAEs after the IMP administration. All AEs including those reported before (first) administration of IMP were listed in the individual clinical study reports. Relationship of study treatment to AEs (suspected or not suspected) was assessed by the investigators.

Healthy subjects

In the pooled analysis of PK studies GP17-104, GP17-101, GP17-102 and GP17-103 in healthy subjects, the nature of AEs was similar between the GP2017 groups and the Humira groups. The most commonly affected primary system organ classes were infections and infestations, nervous system disorders, gastrointestinal disorders, musculoskeletal and connective tissue disorders, and respiratory, thoracic and mediastinal disorders.

Overall, GP2017 performed similarly or better (e.g. for Nasopharyngitis) in terms of AE frequencies when compared to the pooled Humira group (Table below).

Table 31 - Adverse events by preferred term (at least 2% of subjects in any group) in healthy subjects – pooled studies (safety set)

Preferred term	GP2017[1] N=466 n (%)	Humira[2] N=357 n (%)
Subjects with at least 1 adverse event	292 (62.7)	264 (73.9)
Nasopharyngitis	68 (14.6)	89 (24.9)
Headache	74 (15.9)	73 (20.4)
Rhinitis	26 (5.6)	32 (9.0)
Oropharyngeal pain	22 (4.7)	23 (6.4)
Back pain	21 (4.5)	8 (2.2)
Myalgia	20 (4.3)	19 (5.3)
Diarrhoea	16 (3.4)	14 (3.9)
Nausea	15 (3.2)	11 (3.1)
Neutropenia	14 (3.0)	4 (1.1)
Abdominal pain	12 (2.6)	16 (4.5)
Fatigue	12 (2.6)	11 (3.1)
Toothache	12 (2.6)	8 (2.2)
Upper respiratory tract infection	10 (2.1)	3 (0.8)
Dizziness	9 (1.9)	9 (2.5)
Pharyngitis	7 (1.5)	21 (5.9)
Oral herpes	7 (1.5)	10 (2.8)
Presyncope	6 (1.3)	8 (2.2)
Cough	5 (1.1)	13 (3.6)
Abdominal distension	5 (1.1)	12 (3.4)
Rash	3 (0.6)	7 (2.0)

Preferred terms are sorted by descending frequency in the GP2017 group.
[1] Includes GP2017 groups from studies GP17-104, GP17-101, GP17-102, and GP17-103.
[2] Includes EU-Humira and US-Humira groups from studies GP17-104 and GP17-101.
n=number of subjects that experienced the adverse event per treatment; N=number of randomized subjects per treatment group per treatment

When taking a closer look at AE frequencies according to the respective reference product (EU- or US), recognisable numerical differences in certain system organ classes become evident: infections and infestations were reported more frequently for subjects in the EU-Humira groups (45.3% and 42%) than for the subjects in the GP2017 (34.6% and 32%) and US-Humira groups (38.1% and 29%).

The most commonly affected preferred terms were headache, nasopharyngitis, rhinitis, myalgia, nausea, abdominal pain, fatigue, and pharyngitis, all of which of mild or moderate severity. In study GP17-104, nasopharyngitis and rhinitis were driving the difference among groups observed in this system organ class as both AEs were reported more frequently in the EU-Humira group, and rhinitis also more frequently in the US-Humira group as compared to the GP2017 group. In study GP17-101, nasopharyngitis and pharyngitis were the most frequently affected preferred terms in this system organ class for subjects in the EU-Humira group, whereas rhinitis was most frequently affected preferred term for subjects in the GP2017 group. These findings are in line with that from other, recently published studies in healthy subjects using EU Humira and US-Humira as comparators, where differences between the proportions of EU-Humira or US-Humira treated subjects receiving reporting AEs, particularly nasopharyngitis, were described (Shin et al 2015, Hyland et al 2016, Wynne et al 2016, Kaur et al 2017). The Applicant argues that, as EU-Humira and US-Humira are analytically indistinguishable, there is no clear explanation for the imbalance in infections and infestations observed between the two groups. The Applicant further considers these differences clinically irrelevant as these only pertain to rather mild events of infections and infestations, which could in principle be agree upon. It is also noteworthy that GP2017 performed best when comparing frequencies of AEs to either reference group (EU- or US-Humira) and therefore these imbalances seem indeed of minor concern for the characterisation of GP2017.

However, these imbalances as regards safety performance are seen critically in light of the pooling of reference products.

There were no clinically relevant differences pertaining to severity of events between the treatment groups in any of the studies.

In trial GP17-102 (comparison AI vs. PFS), minor bleeding and injection fluid loss was seen at the injection site and was not considered to be clinically significant (e.g. bleeding was observed at a rate of 6 and 7% in the PFS and AI arms and fluid loss was observed for 15% and 0% in the PFS and AI arms for this trial). The As explained by the Applicant bleeding or fluid loss at the injection site was only assessed in Trial GP17-102 comparing PK in healthy subjects receiving GP2017 via Autoinjector (AI) or Prefilled Syringe (PFS). There was no such specific focus on this type of hazard assessments in other PK studies, as this was a device related question. For all 8 cases where fluid loss from the injection site was reported in the PFS group, the hazard assessment was negative, implying that the amount of fluid lost was minimal, not impacting the total amount of medication received. For the autoinjector, one case of fluid loss potentially leading to less than the full dose being administered was noted. No manufacturing or assembling defects were detected in the syringe and the sponsor considers the fluid loss was most likely attributable to the skinny physical built of the subject and lack of adequate adipose tissue to absorb the injected IMP.

Patients with psoriasis

Treatment Period 1 (Randomization to Week 17)

There were no clinically relevant differences between the GP2017 and Humira groups with respect to the proportions of patients reporting AEs (overall and treatment related). The proportions of patients reporting SAEs (overall and related), severe AEs, AEs of special interest, AEs requiring study drug interruption, and discontinuations due to AEs were similar between the two treatment groups. Overall, 239 patients (51.4%) reported a total of 541 AEs. The most commonly affected primary system organ class was infections and infestations (reported for 111 patients (23.9%) overall). The proportions of patients with AEs at system organ class and preferred term levels were similar between the treatment groups. The proportion of patients with gastrointestinal disorders (mainly diarrhoea) was higher in the Humira group than in the GP2017 group. Injection site reactions, including injection site erythema, were reported for a small number of patients. In GP17-301 study a slightly higher number of events were reported in GP2017 as compared to Humira group however almost all ISR were mild or moderate in intensity. Only one patient (1.6%) in the GP2017 to Humira group experienced severe injection site pain.

AEs suspected of being related to study drug were reported for 61 patients (13.1%) total during Treatment Period 1. The most commonly affected primary system organ class was general disorders and administration site conditions (reported for 26 patients (5.6%)), including the most commonly affected preferred term injection site erythema (reported for 12 patients (2.6%)). The proportions of patients with AEs suspected of being related to study drug were generally small on system organ class and preferred term levels and similar between treatment groups.

Continued groups (Randomization to Week 51)

There were no clinically relevant differences between the continued GP2017 and Humira groups with respect to the proportions of patients with AEs, treatment related AEs or SAEs, and AEs leading to discontinuation of study drug. The proportions of patients reporting severe AEs, SAEs (irrespective of relationship) or AEs of special interest were smaller, and the proportion of patients with AEs requiring study drug interruption was higher in the GP2017 group than in the continued Humira group (differences >5%).

Primary system organ classes and preferred terms reported by ≥3% of patients in any treatment group are presented in the table below. The proportions of patients with AEs at system organ class and preferred term levels were generally similar between the treatment groups except for gastrointestinal disorders, which were less frequently (with a difference of >10%) reported in the continued GP2017 group than in the continued Humira group. At the preferred term level, the gastrointestinal disorders that mainly contributed to this difference were diarrhoea (1.2% vs. 5.3%), dental caries (1.2% vs. 2.9%), abdominal pain (0.6% vs. 2.3%), constipation (0.6% vs. 2.3%), and gastrooesophageal reflux disease (0.0% vs. 2.3%); other preferred terms in this system organ class were reported in similar proportions of patients or as single observations. Injection site erythema was reported for 7 patients (4.2%) in the continued GP2017 groups and for 5 patients (2.9%) in the continued Humira group.

Most patients in either continued group reported AEs of mild or moderate severity during the entire study.

Table 32 - Adverse events regardless of study treatment relationship by system organ class and preferred term (at least 3% of patients in any treatment group) by continued group – study GP17-301 – randomisation to week 51 (SAF)

System organ class Preferred term	Continued GP2017 N=168 n (%)	Continued Humira N=171 n (%)
Number of patients with at least one AE	103 (61.3)	111 (64.9)
Infections and infestations	67 (39.9)	62 (36.3)
Nasopharyngitis	15 (8.9)	18 (10.5)
Upper respiratory tract infection	13 (7.7)	13 (7.6)
Sinusitis	12 (7.1)	8 (4.7)
Bronchitis	7 (4.2)	1 (0.6)
Urinary tract infection	5 (3.0)	2 (1.2)
Nervous system disorders	24 (14.3)	15 (8.8)
Headache	13 (7.7)	8 (4.7)
Musculoskeletal and connective tissue disorders	23 (13.7)	19 (11.1)
Arthralgia	7 (4.2)	3 (1.8)
Back pain	6 (3.6)	5 (2.9)
General disorders and administration site conditions	19 (11.3)	20 (11.7)
Injection site erythema	7 (4.2)	5 (2.9)
Fatigue	3 (1.8)	7 (4.1)
Skin and subcutaneous tissue disorders	18 (10.7)	22 (12.9)
Dermatitis contact	5 (3.0)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	15 (8.9)	20 (11.7)
Cough	3 (1.8)	6 (3.5)
Gastrointestinal disorders	13 (7.7)	31 (18.1)
Diarrhoea	2 (1.2)	9 (5.3)
Injury, poisoning and procedural complications	13 (7.7)	14 (8.2)
Psychiatric disorders	8 (4.8)	10 (5.8)
Investigations	11 (6.5)	19 (11.1)
Immune system disorders	6 (3.6)	7 (4.1)
Metabolism and nutrition disorders	6 (3.6)	7 (4.1)
Blood and lymphatic system disorders	6 (3.6)	6 (3.5)
Reproductive system and breast disorders	5 (3.0)	6 (3.5)
Vascular disorders	3 (1.8)	12 (7.0)
Hypertension	3 (1.8)	10 (5.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.2)	7 (4.1)

The proportions of patients in the continued groups who experienced AEs suspected of being related to study drug were <8% at system organ class level and <3% at preferred term level and similar between treatment groups during Randomization to Week 51.

Individual groups (Week 17 to Week 51)

There were no clinically relevant differences across the four treatment groups (Humira to GP2017, continued Humira, GP2017 to Humira, and continued GP2017) with respect to the proportions of patients reporting AEs and SAEs during Week 17 to Week 51.

The proportions of patients with AEs were similar for most system organ classes and preferred terms. At system organ class level, differences between groups were <10%. At preferred term level, except for nasopharyngitis, upper respiratory tract infection, and headache, <5% of patients were reported per AE in any of the system organ classes.

Most patients in any of the individual reported AEs of mild or moderate severity.

The proportions of patients in the four individual groups (Humira to GP2017, continued Humira, GP2017 to Humira, and continued GP2017) who experienced AEs suspected related to study drug during Week 17 to Week 51 were <6.5% at system organ class level and <3.5% at preferred term level and similar among treatment groups.

Serious adverse event / deaths / other significant events

Deaths

There were no deaths reported in the PK studies in healthy subjects.

In the confirmatory efficacy and safety study GP17-301 in patients with psoriasis, 1 patient with a known history of depression in the continued GP2017 treatment group died on Day 178 (Treatment Period 2) as a result of completed suicide. The investigator did not consider the death to be related to study treatment and this can be endorsed.

Other serious adverse events

Healthy subjects

No SAEs were reported in studies GP17-101 and GP17-103.

In study GP17-104, 2 subjects (0.6%) experienced SAEs. One subject in the GP2017 group with a known history of pollinosis developed a moderate angioedema (known AE for Humira as per Humira SmPC and Humira US PI), which was reported 3 days after the single dose administration of 40 mg GP2017 and was suspected to be related to study treatment; the subject received treatment and the event was resolved after 13 days. Another subject, in the US-Humira group, experienced a severe femoral neck fracture after an accident, which occurred 4 weeks after single dose administration of US-Humira and was not suspected to be related to study treatment; the patient underwent surgical treatment and event resolved. Neither SAE led to discontinuation from the study.

In study GP17-102, 1 subject in the GP2017-PFS group experienced mild appendicitis on Day 12, which was reported as an SAE and resulted in discontinuation of the subject from the study. The appendicitis was not considered to be related to study treatment; the patient underwent surgery and the event was resolved.

Patients with psoriasis

In the clinical study GP17-301 in patients with psoriasis, no safety signal or issues of concern have been identified. One patient (0.4%) in the Humira group experienced an SAE of toxic skin eruption during Treatment Period 1, which was reported as a suspected unexpected serious adverse reaction to the competent authorities and independent ethics committees/institutional review boards. The patient

discontinued the study as a result of this SAE. One patient (0.6%) in the continued Humira group was reported to experience pulmonary tuberculosis during Treatment Period 2, which is listed as an adverse reaction in the Humira SmPC. The patient had been screened negative for tuberculosis prior to randomization.

Overall, the proportions of patients reported with SAEs were low across all treatment groups and treatment periods. Throughout the study, 29 patients experienced 38 SAEs, one of which occurred pre-dose (preferred term: anal abscess). Of the remaining 37 SAEs, 11 were suspected to be related to study drug and 14 resulted in permanent discontinuation of study treatment.

Treatment Period 1 (Randomization to Week 17)

Overall, 13 patients (2.8%) reported SAEs during Treatment Period 1. Three patients (1.3%) in GP2017 group and 10 patients (4.3%) in the Humira group experienced SAEs. On system organ class, ≤1.3% of patients reported SAEs in either treatment group. Except for basal cell carcinoma, which was reported for 2 patients (0.9%) in each of the treatment groups, no more than 1 patient reported a specific SAE.

Continued groups (Randomization to Week 51)

Five patients (3.0%) in the continued GP2017 treatment group and 15 patients (8.8%) in the continued Humira group experienced SAEs. At the preferred term level, SAEs were all single observations except for abdominal pain, which was reported for 2 patients (1.2%) in the continued Humira group.

Individual groups (Week 17 to Week 51)

There were no clinically relevant differences across the four individual groups (Humira to GP2017, continued Humira, GP2017 to Humira, and continued GP2017) with respect to the proportions of patients reporting SAEs during Week 17 to Week 51. AEs were most frequently reported in the system organ class infections and infestations. At preferred term level, none of the SAEs were reported by more than 1 patient in any treatment group.

Adverse Events of special interest

AEs of special interest were defined based on the Humira PI and included infections malignancies, allergic reactions, immune system disorders/autoimmune events, neurological events, hematological reactions, and congestive heart failure and are endorsed as such. The AE profile for adverse events of special interest revealed no obvious differences between the treatment groups. AEs of special interest were not defined in the healthy subject studies, which is acceptable. It is noted that two cases of hypersensitivity were reported in the GP2017 group and not in the Humira group. All cases suggesting allergic reaction to the treatment with GP2017 were thoroughly discussed and the ADA status for these patients was clarified. The reaction rates where very low, balanced across groups, mostly of moderate to mild intensity and seemed not related with immunogenicity findings.

Treatment Period 1 (Randomization to Week 17)

Overall, AEs of special interest were reported for 30 patients (6.5%) during Randomization to Week 17. The proportions of patients with AEs of special interest were similar between treatment groups (GP2017: 13 patients (5.6%); Humira: 17 patients (7.3%)). The most commonly affected primary system organ class was infections and infestations (reported for 15 patients (3.2%)). At preferred term level, except for basal cell carcinoma (GP2017: 3 patients (1.3%); Humira: 2 patients (0.9%)), AEs of special interest were reported by 2 patients or less in any treatment group. One patient (0.4%) in the GP2017 group experienced a severe hypersensitivity, which was considered related to study treatment and led to permanent treatment discontinuation. No ADAs were identified in this patient.

Continued groups (Randomization to Week 51)

The proportions of patients with AEs of special interest were similar between the continued groups, with 13 patients (7.7%) in the continued GP2017 group and 22 patients (12.9%) in the continued Humira group. At preferred term level, AEs of special interest were reported for 3 patients (thrombocytopenia in the continued Humira group) or less in either treatment.

Individual groups (Week 17 to Week 51)

The proportions of patients with AEs of special interest were similar across the individual groups (Humira to GP2017: 3 patients (4.8%); continued Humira: 12 patients (9.4%); GP2017 to Humira: 6 patients (9.5%); and continued GP2017: 7 patients 5.6%)). At preferred term level, except for 2 patients (1.6%) each reporting herpes zoster or anaemia in the continued GP2017 group and thrombocytopenia in the GP2017 to Humira group, AEs of special interest were reported for not more than 1 patient per group.

Injection site reactions

Injection site reactions in healthy subjects

Overall, the numbers and proportions of subjects with injection site reactions were similar among the GP2017, EU-Humira and US-Humira groups across all time points. Mainly mild injection site reactions were reported in any of the treatment groups (two moderate reactions were recorded, one in study GP17-101 in a subjects receiving EU-Humira and one in study GP17-102 in the GP2017-AI group). The majority of the subjects experienced no pain after administration.

In study GP17-103, mild AEs of injection site pruritus were reported for 2 subjects in the GP2017-Schaftenau group.

Concerning study GP17-102 5 subjects developed ISRs, one was moderate and the others mild.

Injection site reactions in psoriasis patients (study GP17-301)

In the confirmatory efficacy and safety study GP17-301, the investigator or designee assessed injection site reactions such as itching, redness, swelling, pain, or ulceration. Injection site reactions reported in the study included injection site erythema, pain, swelling, pruritus, bruising, haematoma, oedema, induration, urticaria, mass, and injection site reaction.

The proportion of patients with injection site reactions was slightly higher in the GP2017 group (15 patients (6.5%)) than in the Humira group (8 patients (3.4%)) during randomization to week 17. This difference disappears over time and no imbalance was recorded at later time points of safety assessment. There is no indication for an increased potential for injection site reactions from the preclinical studies. Though this finding is considered of minor clinical relevance, it is noted that injection site reactions could be an AE especially prone to be affected by defective blinding measures.

Laboratory findings

Healthy subjects

In the PK studies in healthy subjects, no clinically meaningful differences were observed among the treatment groups in the four studies according to the Applicant. Abnormal laboratory findings were listed for several subjects, and according to the investigator's medical judgement, all were considered as "not clinically significant (n)". Events were overall too rare to enable meaningful comparison between groups.

Patients with psoriasis

As for AE reporting, the main assessment of safety laboratory evaluations focuses on the phase III efficacy and safety trial GP17-301. Haematology, clinical chemistry and urine analysis data yielded similar results in the different treatment groups. No important treatment group differences were noted in the mean change from baseline for any parameter. There were no anomalies in the switched groups (Humira to Hymiroz or GP2017 to Humira).

The following hematology parameters were analysed for all treatment groups: mean band neutrophils (% and absolute), basophils (% and absolute), eosinophils (% and absolute), lymphocytes (% and absolute), monocytes (% and absolute), mean neutrophils (% and absolute), hematocrit, hemoglobin, platelets, red blood cells, and white blood cells. The following clinical chemistry parameters were analyzed for all treatment groups: albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, bilirubin, blood urea nitrogen, calcium, creatinine, gamma glutamyltransferase, glucose, high sensitivity C-reactive protein, potassium, phosphate, sodium, total protein, and uric acid. The choice of parameters investigated is endorsed.

Hematology

No clinically relevant changes over time or differences between treatment groups were observed for hematology parameters (including erythrocytes, platelets, white blood cells and neutrophils). Across treatment periods, the proportions of patients with newly occurring clinically notable values of hematology parameters were low and there were no clinically relevant differences among groups.

One patient in the Humira group experienced a severe neutropenia on Day 120 (Treatment Period 1), which was not considered related to study treatment and led to temporary interruption of study treatment.

Shifts from baseline to low or high post-baseline values occurred similarly in all treatment groups and in a small number of patients across the treatment periods.

Clinical chemistry

No clinically relevant changes over time or differences between treatment groups were observed for clinical chemistry parameters (including liver function tests and creatinine). Across treatment periods, the proportions of patients with newly occurring clinically notable values of clinical chemistry parameters were low and there were no relevant differences among groups.

Shifts from baseline to low or high post-baseline values occurred similarly in all treatment groups and in a small number of patients across the treatment periods.

Urinalysis

The following parameters were analyzed for all treatment groups: blood, glucose, ketones, protein, pH, specific gravity, urine pregnancy. No clinically relevant differences among groups were observed for urinalysis parameters among groups and across treatment periods.

Safety in special populations

The effect of intrinsic and extrinsic factors as well as the effect on fertility, pregnancy and lactation were not evaluated with GP2017 and will be extrapolated from the reference product EU-Humira, which is in accordance with regulatory guidance. GP2017 was developed as a biosimilar medicinal drug product; therefore respective information from the reference product EU-Humira also applies to GP2017. The respective PI wordings are in line with the originator PI and are adequate.

Immunological events

Pooled PK studies in healthy subjects

In healthy subjects, the samples for ADA measurement were collected pre-dose on Day 1, and on Days 16, 30, 44, and 72. The time points and frequency of immunogenicity sampling appear adequate.

Sixteen subjects (1.9%) had ADA positive results at pre-dose on Day 1. The ADA response was balanced between the pooled GP2017 and Humira groups, and the proportion of subjects with NAbs at the last positive ADA sample was similar in the two groups (see table below).

Table 33 - Summary of immunogenicity results – pooled studies (safety analysis set)

		GP2017[1] N=466 n (%)	Humira[2] N=357 n (%)
	Visit		
ADA	Day 1, pre-dose	7 (1.5)	9 (2.5)
	Day 16	137 (29.4)	104 (29.1)
	Day 30	107 (23.0)	69 (19.3)
	Day 44	125 (26.8)	95 (26.6)
	Day 72	284 (60.9)	233 (65.3)
	Total (# of subjects with at least one positive result)	310 (66.5)	252 (70.6)
NAb	Total (# of subjects with a positive result)[3]	275 (59.0)	217 (60.8)

ADA=anti-drug antibody; n=number of positive results; N=number of randomized subjects per treatment group; NAb=neutralizing antibody

[1] Includes GP2017 groups from studies GP17-104, GP17-101, GP17-102, and GP17-103.

[2] Includes EU-Humira and US-Humira groups from studies GP17-104 and GP17-101.

[3] NAb was only analyzed for the last confirmed positive ADA sample that was collected per subject.

Study GP17-104

Positive ADA results were seen from Day 16 until Day 72 with the highest incidence seen on Day 72. Nine subjects had ADA positive results at pre-dose on Day 1. The proportions of subjects with ADAs and NAbs were lower in the GP2017 group than in the EU-Humira and US-Humira groups.

Study GP17-101

Positive ADA results were seen from Day 16 until Day 72 with the highest incidence seen on Day 72 and were similar in the three groups. Three subjects had ADA positive results at predose on Day 1. The proportions of subjects with ADAs and NAbs were similar in the three groups.

The incidences of anti-drug antibodies and neutralising antibodies seem sufficiently comparable in healthy volunteers. GP2017 had lowest total ADA rates in both studies compared to the two reference groups (EU-Humira and US-Humira).

Study GP17-102

The ADA response was balanced between the GP2017-AI and GP2017-PFS groups, and the proportion of subjects with NAbs at the last positive ADA sample was similar in the two treatment groups. No subject had ADA positive results at pre-dose on Day 1. Positive ADAs were seen from Day 16 until Day 72 with the highest incidence seen on Day 72.

ADA rates are considered comparable over time. Differences at some (earlier) time points are noted but are hard to interpret considering the small sample sizes of the groups.

Study GP17-103

Positive ADA results were seen from Day 16 until Day 72 with the highest incidence seen on Day 72. Four subjects had ADA-positive results at pre-dose on Day 1. The proportions of ADA-positive subjects were higher by 6.5-10.7% in the GP2017-Schaftenau group than in the GP2017-Cook group at each measured time point. The investigation of the difference in immunogenicity between GP2017-Cook and GP2017-Schaftenau groups did not reveal an underlying reason. There can be subject related risk factors, which were not investigated but might have played a role in the observed difference in immunogenicity between the two treatment groups. However, the overall proportions of subjects with ADA-positive results and with NAbs were similar in both groups. Higher proportions of ADA-positive subjects per each measured time point were observed in the GP2017-Schaftenau group in study GP17-103 as compared to the GP2017 group in study GP17-104. This is of note as one and the same GP2017 batch was used in studies GP17-103 and GP17-104. Both studies were carried out in a healthy subject population with similar inclusion and exclusion criteria, and the same analytical assay for detection of ADA was used.

Though the same batch of IP was used in study GP17-103 in study GP17-104, higher proportions of ADA-positive subjects per each measured time point were observed in study GP17-103 for unknown reasons.

Fewer patients with psoriasis developed the ADA response as compared to healthy volunteers. In the GP2017 treatment group overall 35.8% patients developed the ADA responses in comparison to 66.5% of healthy volunteers (pooled PK studies). Several factors such as chronic dosing, greater age and disease-related immunocompromised status may lead to a lower proportion of patients with psoriasis developing anti-drug antibodies as compared to healthy volunteers.

Immunogenicity in patients with psoriasis (study GP17-301)

The time points and frequency of immunogenicity sampling in the pivotal, comparative phase III trial appear adequate.

While ADA data according to EU- and US Humira are displayed for the (pooled) PK studies, for study GP17-301 comparison to one pooled Humira reference group and by region is available. To exclude major differences between the products on an immunogenicity level and thus to recognize if comparison to a pooled reference group is reasonable and to enable assessment of a possible ‘region effect’, separate analyses of immunogenicity data according to the respective reference product (EU- or US- Humira) and GP2017 group (recruited in US or EU) were requested. ADA positive samples were further characterized in an ADA titer assay by the Applicant which is helpful to characterize the magnitude of the ADA response. The titer values are not continuous but semi-quantitative values for dilution steps (for example 1, 2, 6, 10, 12 and so on without limit) and the Applicant argues that summary statistic calculated would not provide any clinically meaningful conclusion. In addition they say that the number of ADA titer values per visit and treatment group are too low (in particular for the EU region) to allow meaningful interpretation.

Table 34 - Summary of ADA and ADA titer levels during entire study by continued treatment groups and region (SAF)

Visit	Statistic	Continued EU-GP2017[1] N=30	Continued EU-Humira N=31	Continued US-GP2017[1] N=138	Continued US-Humira N=140
Overall during entire study - ADA positive patients	n/N' (%)	12/29 (41.4)	11/30 (36.7)	50/131 (38.2)	61/129 (47.3)
Baseline[2]	n	0	0	2	3
	Median			1.5	2.0
	(Min-Max)			(1-2)	(2-10)
Week 3	n	3	3	25	23
	Median	10.0	6.0	10.0	10.0
	(Min-Max)	(6-10)	(1-12)	(2-45000)	(1-1000)
Week 7	n	2	1	14	14
	Median	23.0	2.0	8.0	10.0
	(Min-Max)	(10-36)	(2-2)	(1-8000)	(1-300)
Week 11	n	7	5	25	24
	Median	6.0	10.0	10.0	24.0
	(Min-Max)	(2-30)	(6-30)	(1-600)	(2-3000)
Week 17	n	6	6	25	25
	Median	75.0	10.0	50.0	30.0
	(Min-Max)	(6-360)	(2-150)	(2-300)	(2-4000)
Week 23	n	4	5	11	19
	Median	109.0	50.0	30.0	10.0
	(Min-Max)	(6-600)	(2-360)	(2-900)	(2-60)
Week 29	n	5	5	15	17
	Median	10.0	30.0	10.0	18.0
	(Min-Max)	(2-100)	(6-50)	(2-2000)	(2-360)
Week 35	n	4	5	11	17
	Median	33.0	2.0	50.0	30.0
	(Min-Max)	(6-00)	(2-180)	(2-900)	(2-1000)
Week 41	n	2	5	12	18
	Median	1.5	10.0	27.0	30.0
	(Min-Max)	(1-2)	(2-200)	(6-900)	(2-600)
Week 47	n	1	5	14	16
	Median	2.0	2.0	20.0	34.0
	(Min-Max)	(2-2)	(1-50)	(2-200)	(1-300)
Week 51	n	3	2	13	17
	Median	2.0	6.0	50.0	30.0
	(Min-Max)	(2-6)	(2-10)	(2-300)	(6-1200)

Continued groups include patients who continued the same treatment throughout the study.

ADA=anti-drug antibody; Min-Max=minimum-maximum; N=number of patients per treatment group; N'=number of patients with evaluable data, n=number of patients with ADA titer at visit; SAF=safety analysis set

[1] The same GP2017-drug product batches were used for treatment of EU and US patients.

[2] Patients with ADA positive responses at baseline were excluded from later visits.

The provided table shows that there are rather large differences between the EU and the US region as regards ADA titers. The reasons for the drift of values between regions is not clear, might be a chance finding or caused by differences in baseline characteristics or correlated with earlier systemic therapy (higher rate of prior systemic therapy in the EU groups) The Applicant did not further elaborate on this difference. The US groups are larger and show considerably higher titers and might therefore be the more suitable groups for comparison (detecting a difference), however, within each regions (EU or US) the titer

values are quite consistent. ADA (or nAB) titers seem not to have influenced AEs considerably; however, for an approval in Europe it is reassuring that in the EU both products have produced lower ADA titers. All patients with high ADA titer values ≥1800 were from the US region (7 GP2017 and 4 Humira patients).

While a region effect on titer values could be observed, this seems of no relevance for the comparability exercise. There is no difference in the AE profile reported between ADA positive and negative patient subgroups. There was no signal that higher ADA titer values had a greater impact on safety or efficacy.

Treatment Period 1 (Randomization to Week 17)

During Randomization to Week 17, the numbers and proportions of patients with positive ADA responses were similar between the GP2017 and Humira groups at the individual visits, and the numbers and proportions of patients with at least one positive ADA response from Week 1 and up to Week 17 were also similar between treatment groups; NAbs were detected in similar proportions between groups (see table below).

Table 35 - Summary of patients with confirmed positive anti-drug antibody response by treatment group – study GP17-301 – randomization to week 17 (SAF)

ADA response	GP2017 N=231 n/N' (%)	Humira N=234 n/N' (%)
Anti-drug antibodies		
Baseline[a]	3/224 (1.3)	3/225 (1.3)
Week 3	41/214 (19.2)	32/211 (15.2)
Week 7	26/207 (12.6)	20/206 (9.7)
Week 11	45/204 (22.1)	38/196 (19.4)
Week 17	48/187 (25.7)	43/182 (23.6)
Neutralizing antibodies		
Baseline[a]	0/3	0/3
Week 3	9/41 (22.0)	8/32 (25.0)
Week 7	21/26 (80.8)	19/20 (95.0)
Week 11	45/45 (100.0)	35/38 (92.1)
Week 17	46/48 (95.8)	42/43 (97.7)
Overall from Week 1[b]		
Negative	139/220 (63.2)	145/220 (65.9)
Positive	81/220 (36.8)	75/220 (34.1)
Neutralizing	65/81 (80.2)	60/75 (80.0)
Transient[c]	23/81 (28.4)	20/75 (26.7)

ADA=anti-drug antibody; n=number of patients per treatment group with ADA response; N'=number of patients with evaluable data; N=number of randomized patients; SAF=safety analysis set

[a] Patients with ADA positive results at baseline were excluded from the rows for subsequent visits.

[b] 'Overall from Week 1' indicates that patients had at least one ADA positive result (recorded as positive) or had consistently negative results (recorded as negative) post-baseline.

[c] Patients experiencing a final negative ADA result at any visit following a positive ADA result; patients were counted as both positive and transient.

Source: [Module 5.3.5.1 GP17-301-Table 12-43]

Up to Week 17, 81 patients (36.8%) in the GP2017 group and 75 patients (34.1%) in the Humira group had at least one ADA-positive result. There were no clinically meaningful differences in the proportions of

patients reporting AEs (overall and treatment related), SAEs (overall and related), severe AEs, AEs of special interest, AEs requiring study drug interruption, and discontinuations due to AEs between ADA-positive and ADA-negative patients and between the GP2017 and Humira groups within each subgroup. The nature of AEs reported for ADA-positive patients was similar to that reported for ADA-negative patients, therefore ADA development is not considered to have an impact on patients' safety in this study.

The relationship between ADA status (positive or negative) and adverse events was assessed over the whole study duration for all 4 groups (EU GP2017, EU Humira, US GP2017, US Humira). In the ADA negative subgroups, the overall incidence of TEAEs was higher than in ADA positive subgroups (continuous dataset). The Applicant argues that this difference was caused by seasonal viral exposure (driven by system organ class "Infections and infestations" and by preferred terms "nasopharyngitis, upper respiratory tract infection and sinusitis"). From AE data per region we know that the US groups had higher "Infections and infestations" rates than the EU groups. This could make sense as patients with high ADA rates (the majority of ADAs were of neutralizing nature) could have an impaired efficacy (less tnf-alpha inhibition) and thus a better immune response than patients with no ADAs (or nABs). However, these are theoretical assumptions which are not supported by efficacy data.

Interestingly, the rate of "Injury, poisoning and procedural complications" in the ADA-negative groups was higher than in the ADA positive groups (continuous dataset). The reason or impact of this finding is unknown.

Overall some differences between groups were found but no clear pattern that would be considered clinically meaningful was noted.

Continued groups (Randomization to Week 51)

The numbers and proportions of patients with positive ADA responses were similar between the continued groups at post-baseline time points up to Week 17 and lower in the continued GP2017 group compared to the continued Humira group at later time points visits. The numbers and proportions of patients with at least one positive ADA response from Week 1 and up to Week 51 were lower in the continued GP2017 than in the continued Humira group at each time point, and NAbs were detected in similar high, proportions (see table below).

Individual groups (Week 17 to Week 51)

Differences in relation to the ADA response were observed between treatment groups. At week 51 (overall from week 1) in the continued GP2017 groups ADA response was reported in 35.8 % of patients whereas in the continued Humira group ADAs were found in 45.1 % of patients (see table below). The proportions of patients with positive ADA responses were higher in the switched groups compared with the continued groups at individual time points during Week 17 to Week 51 (see table below). In the GP2017 to Humira group this could be due to a higher rate of ADA positive patients being re-randomized to this group at week 17, however, this does not explain similar observation in the Humira to GP2017 group. Overall, the differences were small and likely not of clinical significance. The differences are believed to be a chance finding.

There is no clear indication for an increase in immunogenicity after transition from Humira to GP2017 or vice versa. The majority of ADAs was, again, neutralizing. The proportion of patients with at least one sample that was positive for NAbs from Week 1 was slightly higher in the Humira to GP2017 group than in the other three groups.

Table 36 - Summary of patients with confirmed positive anti-drug antibody response by individual group – study GP17-301 – randominsation to week 51 (TP2+EP SAF)

ADA response	Humira to GP2017 N=63 n/N' (%)	Continued Humira N=127 n/N' (%)	GP2017 to Humira N=63 n/N' (%)	Continued GP2017 N=126 n/N' (%)
Anti-drug antibodies[a]				
Week 17	12/57 (21.1)	26/118 (22.0)	17/59 (28.8)	23/118 (19.5)
Week 23	14/56 (25.0)	24/112 (21.4)	18/57 (31.6)	15/106 (14.2)
Week 29	15/56 (26.8)	22/104 (21.2)	17/56 (30.4)	20/104 (19.2)
Week 35	17/53 (32.1)	22/104 (21.2)	14/54 (25.9)	15/101 (14.9)
Week 41	14/45 (31.1)	23/97 (23.7)	16/49 (32.7)	14/98 (14.3)
Week 47	16/45 (35.6)	21/99 (21.2)	12/46 (26.1)	15/95 (15.8)
Week 51	15/45 (33.3)	19/98 (19.4)	13/46 (28.3)	16/96 (16.7)
Neutralizing antibodies[a]				
Week 17	12/12 (100.0)	25/26 (96.2)	16/17 (94.1)	23/23 (100.0)
Week 23	14/14 (100.0)	24/24 (100.0)	18/18 (100.0)	15/15 (100.0)
Week 29	15/15 (100.0)	22/22 (100.0)	17/17 (100.0)	20/20 (100.0)
Week 35	17/17 (100.0)	21/22 (95.5)	14/14 (100.0)	15/15 (100.0)
Week 41	14/14 (100.0)	23/23 (100.0)	16/16 (100.0)	14/14 (100.0)
Week 47	16/16 (100.0)	18/21 (85.7)	12/12 (100.0)	15/15 (100.0)
Week 51	15/15 (100.0)	18/19 (94.7)	13/13 (100.0)	16/16 (100.0)
Overall from Week 1[b]				
Negative	37/61 (60.7)	67/122 (54.9)	32/60 (53.3)	79/123 (64.2)
Positive	24/61 (39.3)	55/122 (45.1)	28/60 (46.7)	44/123 (35.8)
Neutralizing	24/24 (100.0)	47/55 (85.5)	21/28 (75.0)	38/44 (86.4)
Transient[c]	4/24 (16.7)	25/55 (45.5)	11/28 (39.3)	19/44 (43.2)

The incidences of anti-drug antibodies and neutralising antibodies in psoriasis patients are mostly comparable across the groups. It is noteworthy, however, that in the continued GP2017 group the lowest ADA incidence of all 4 groups was measured at each time point.

In the phase III trial, ADA incidences are significantly higher than those reported in the Psoriasis studies for the initial MAA of Humira (SmPC Humira). This is to be expected as more sensitive assays for the detection of anti-adalimumab antibodies were developed in the meantime. In addition, the incidence of ADAs is high but comparable in the GP2017 and Humira treatment groups.

At the end of study GP17-301 at week 51, close to 100% of all ADA positive subjects had neutralising antibodies (across all treatment groups). It is noted that the assessment of ADA/nAB positivity on a qualitative level leads to limitations because it does not allow for stratification of ADA/nAB levels. Positive antibody and nAB responses should therefore generally also be reported as a titer to allow elucidation of the relationships between ADA/nAB levels and their impact on safety (and efficacy) for all three products used in this study. The assay used to evaluate neutralizing quality was a qualitative assay only, but highly sensitive and the result is the high rate of nABs. The assay is considered state of the art and deemed acceptable.

According to the Applicant, the determined rate of neutralizing antibodies was expected. Comparable incidence rates are reported in the literature, the majority of binding anti-adalimumab antibodies (ADAs) are capable of neutralizing adalimumab (van Schouwenburg et al 2013). It is further described that ADAs against adalimumab are usually anti-idiotype antibodies that target the drug binding site, as this does not belong to the immunoglobuline repertoire of the host. The humoral response to adalimumab, for e.g. in RA patients was found to be highly restricted and limited to epitopes located in the TNF-binding region. As a result, anti-adalimumab antibodies are mostly neutralizing (i.e. they block the binding of the therapeutic agent to its target, TNF-α). In addition it was shown that more than 94% of the binding of anti-adalimumab antibodies could be blocked by the Fab fragment of a single monoclonal

anti-adalimumab antibody (van Schouwenburg et al 2013). Furthermore, according to the available literature, more than 97% of the anti-idiotype antibody response to adalimumab, could be inhibited by TNF (van Schie et al 2015), additionally supporting their neutralizing character. In the single dose study in healthy volunteers, almost all subjects were ADA-positive. The incidence of subjects with post-dose ADA to adalimumab was observed in 98.4% of subjects in the SB5 treatment group, 95.2% of subjects in the EU-ADL treatment group and all subjects in the US-ADL treatment group. Most ADA-positive subjects had NAbs, approximately 80% in each treatment group (Shin et al 2017).

As the rate of nAB was close to 100%, the assessment and distribution of ADA titers per visit was considered as a surrogate for titers of Nabs, and this seems an acceptable approach. No impact of nABs on safety profile of the products was observed.

Safety related to drug-drug interactions and other interactions

Interactions with other medicinal products were not evaluated with GP2017 and this information will be extrapolated from the reference product EU-Humira, which is in line with regulatory guidance. GP2017 was developed as a biosimilar medicinal drug product; therefore respective information from the reference product EU-Humira also applies to GP2017. The respective PI wordings are in line with the originator PI and are adequate.

Discontinuation due to adverse events

There is no significant dysbalance for subjects terminating their study participation due to adverse events.

Adverse events leading to discontinuation in healthy subjects

There were no AEs leading to discontinuation reported in studies GP17-101, GP17-103, and GP17-104. In study GP17-102, 1 SAE (appendicitis) not related to study treatment led to study discontinuation.

Adverse events leading to study drug discontinuation in patients with psoriasis (study GP17-301)

Overall, the proportions of patients reported with AEs leading to discontinuation were low across treatment groups and across treatment periods.

During Treatment Period 1 (Randomization to Week 17), 11 patients (2.4%) overall experienced AEs that led to permanent discontinuation of study treatment. Proportions of patients experiencing AEs leading to discontinuation of study treatment were similar between the treatment groups.

At preferred term level, none of the AEs leading to discontinuation were reported by more than 1 patient in any treatment group, except for psoriasis (verbatim: worsening of psoriasis), which was reported by 2 patients (0.9%) in the Humira treatment group. Five of the 11 patients experienced SAEs that led to permanent discontinuation of study treatment. In the GP2017 group, 1 patient experienced severe staphylococcal infection and hypersensitivity. Both events were considered related to study treatment. In the Humira group, 4 patients experienced SAEs that led to discontinuation of study treatment. These were SAEs of severe cellulitis and severe toxic skin eruption, which were both considered to be related to study treatment, and severe, unrelated SAEs of ectopic pregnancy and prostate cancer. The toxic skin eruption was reported as a suspected unexpected serious adverse reaction to the competent authorities and independent ethics committees/institutional review boards as required. In the GP2017 and Humira groups, 1 patient each experienced a non-serious AE, which was considered to be treatment related and led to permanent discontinuation of study treatment during Treatment Period 1. These were a moderate AE of increased body temperature in the GP2017 group and a moderate AE of hypoaesthesia in the Humira group. One patient (0.4%) in the GP2017 group and 2 patients (0.9%) reported unrelated, mild

or moderate AEs of psoriasis (verbatim: worsening of psoriasis), which were considered to be unrelated to study treatment and led to treatment discontinuation. Another patient in the GP2017 group permanently discontinued treatment due to a moderate skin infection, which was considered to be unrelated tostudy treatment.

During Week 17 to Week 51, 12 patients (3.2%) overall experienced AEs that led to permanent discontinuation of study treatment, and 7 of these 12 patients (5 in the continued and 2 in the switched groups) experienced SAEs that led to treatment discontinuation. The proportion of patients reporting AEs leading to discontinuations was similar across the four individual groups (Humira to GP2017, continued Humira, GP2017 to Humira, and continued GP2017). At preferred term level, none of the AEs leading to discontinuation were reported by more than 1 patient in any group.

During Week 17 to Week 35 (Treatment Period 2), in the continued GP2017 group, 1 patient committed suicide on Day 178. The death was not considered to be related to study treatment.

2.6.1 Discussion on clinical safety

The safety profile of GP2017 was explored in five clinical studies. In the four PK studies 466 adult healthy subjects provided data on single dose (40 mg) exposure in healthy volunteers, who were followed for 72 days. The phase III study in 294 subjects (126 on continued GP2017, 127 on continued Humira, 63 on Humira and switching to GP2017 (week 17) and 63 on GP2017 switching to Humira (week 17)) provided comparative data on multiple dose treatment (initial dose of 80 mg followed by 40 mg every other week) with adalimumab for up to 51 weeks in patients with moderate to severe chronic plaque-type psoriasis. Data from this study thus provides safety data on transitioning from Humira to the biosimilar and vice versa. The phase III study GP17-301 is pivotal for the safety assessment of this application.

Hundred and four (104) patients from the continued Humira group and 100 patients from the continued GP2017 completed the phase III study. Eighty nine (89) patients in the continued GP2017 arm and 96 patients in the continued Humira arm were exposed to study treatment for $\geq$ 49 weeks. While this is considered only borderline sufficient (100 patients exposed for a minimum of one-year are expected according to ICH E1), the numbers could be acceptable, considering the known safety profile of Adalimumab and the frequency of key AEs. Also, data from the switched groups are available and provide supportive evidence on long-term exposure.

Data on adverse events, serious adverse events and adverse events of special interest were provided in a descriptive manner. The characteristics of adverse events were overlapping in all arms and mirror the safety profile as described in the SmPC of Humira.

From the comparative PK trials, separate analyses according to the reference product used (EU- or US Humira) are available. Recognisable numerical differences in the frequency of certain AEs were detected between treatment groups: infections and infestations were reported more frequently for subjects in the EU-Humira groups (45.3% and 42%) than for the subjects in the GP2017 (34.6% and 32%) and US-Humira groups (38.1% and 29%). These differences pertained only to mild events and GP2017 performed best when comparing frequencies of these AEs to either reference group.

Due to the low number of recruited EU-patients in the reference group there is also a shift towards the US population in study GP17-301. The factor ‘region’ could theoretically have an influence on certain safety aspects such as e.g. infection rates (which could differ at baseline pertaining to geographic area). Actually, a higher proportion of patients experienced AEs in the US region, largely driven by infections (rhinitis, nasopharygitis, sinusitis), which might have been a reflection of seasonal viral exposure.

Within each region (EU or US), baseline data as well as safety results (apart from the infections and infestations system organ class) are quite comparable and seem each sufficiently similar to support assumption of similarity from a safety perspective. It remains unknown if one population (US or EU) is

more “sensitive” in detecting differences in safety between the two products than the other, but both populations seem each equally appropriate for the comparison. However, it has to be considered that the overall incidence of events is low and also that the number of patients exposed to EU-Humira is rather low, possibly compromising the meaningfulness of results. Therefore the US comparison was finally considered more suitable to detect differences. For an approval in the EU however, it is important that the safety profile of the biosimilar is comparable or better than the safety profile of the originator in the EU population and this was supported by the AE data from the EU population.

When considering EU- and US Humira as a single reference group, numbers of adverse events in the phase III study are not only comparable between the GP2017 and Humira treatment group but also overall comparable with PI information. The AE profiles remain overall similar for the continued groups and the groups who transitioned from Humira to GP2017 and vice versa.

The proportion of patients with injection site reactions was slightly higher in the GP2017 group (15 patients (6.5%)) than in the Humira group (8 patients (3.4%)) during randomization to week 17 in study GP17-301. This difference disappears over time and no imbalance was recorded at later time points of safety assessment. Also, there is no indication for an increased potential for injection site reactions from the preclinical studies. Though this finding is considered of minor clinical relevance, it is noted that injection site reactions could be an AE especially prone to be affected by defective blinding measures.

Blinding was an issue in some of the studies included in this application and also in GP17-301. Although the Applicant argues that blinding was done in the best possible way, it is still considered suboptimal and maintain of the blind couldn’t be ensured. Serum drug concentrations are the key PK parameter of the biosimilar exercise and these measurements are considered robust against this kind of bias. However, biased assessment of subjective endpoints (e.g. safety endpoints) couldn’t be excluded.

Small differences in relation to the ADA response were observed between treatment groups in study GP17-301. At week 51 (overall from week 1) in the continued GP2017 groups ADA response was reported in 35.8 % of patients whereas in the continued Humira group ADAs were found in 45.1 % of patients. The proportions of patients with positive ADA responses were slightly higher also in the switched groups compared with the continued groups at individual time points during Week 17 to Week 51. In the GP2017 to Humira group this could be due to a higher rate of ADA positive patients being re-randomized to this groups at week 17; nonetheless, this does not explain similar observation in the Humira to GP2017 group. However, overall the differences, probably chance findings, were small, disappeared over time and were likely not of clinical significance. Currently there is no clear indication for an increase in immunogenicity after transition from Humira to GP2017 or vice versa.

Fewer patients with psoriasis developed ADA response as compared to healthy volunteers. In the GP2017 treatment group overall 35.8% patients developed the ADA responses in comparison to 66.5% of healthy volunteers (pooled PK studies). Several factors such as chronic dosing, greater age and disease-related immunocompromised status may lead to a lower proportion of patients with psoriasis developing anti-drug antibodies as compared to healthy volunteers.

At the end of study GP17-301 at week 51, close to 100% of all ADA positive subjects had neutralising antibodies. This was observed across all treatment groups. ADA positive samples were further characterized in an ADA titer assay by the Applicant which is helpful to characterize the magnitude of the ADA response. While a region effect on titer values could be observed, this seems of no relevance for the comparability exercise, titers were comparable within each region (EU and US). There is no difference in the AE profile reported between ADA positive and negative patient subgroups. There was no signal that higher ADA titer values had a greater impact on safety or efficacy.

2.6.2 Conclusions on the clinical safety

The safety and immunogenicity profiles for GP2017 and Humira are mostly comparable, supporting the notion of biosimilarity for the two products in principle. The trials revealed the well-known adalimumab safety profile/AEs in comparable proportions across treatment groups. GP2017 was well tolerated and AE rates were low.

A possible impact of regional differences on safety outcomes could be examined based on separate analyses for EU- and US Humira. Though a certain region effect could be observed, the US population, which is the major share of patients in study GP17-301, could be sufficiently representative also for the EU population. Major differences in frequencies of AEs and thus, safety performance between (i) regions or (ii) products can be excluded. Looking at Europe region data alone, EU-GP2017 was well tolerated and showed a comparable safety profile to EU-Humira. While some minor uncertainties (e.g. suboptimal blinding measures, impact of region effect) have to be considered in the benefit/risk balance of the product, the amount and quality of safety data is considered satisfactory.

2.7 Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Serious infections including diverticulitis and opportunistic infection, eg invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB) Reactivation of hepatitis B Pancreatitis Lymphoma Hepatosplenic T-Cell Lymphoma (HSTCL) Leukemia Non melanoma skin cancer (NMSC) Melanoma Merkel cell carcinoma (Neuroendocrine carcinoma of skin) Demyelinating disorders (including Multiple sclerosis (MS), Guillain-Barre syndrome (GBS), and optic neuritis Immune reactions (including lupus-like reactions and allergic reactions) Sarcoidosis Congestive heart failure (CHF) Myocardial Infarction (MI) Cerebrovascular accident (CVA)

Summary of safety concerns	
	Interstitial lung disease (ILD) Pulmonary embolism Cutaneous vasculitis Stevens-Johnson syndrome and erythema multiforme Worsening and new onset of Ps Hematological disorders Intestinal perforation Intestinal stricture in Crohn's disease [applicable for marketing authorization with indication CD] Liver failure and other liver events Elevated Alanine transaminase (ALT) levels Autoimmune hepatitis Medication errors and maladministration
Important potential risks	Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, and melanoma and Merkel cell carcinoma) Vasculitis (non-cutaneous) Progressive multifocal leukoencephalopathy (PML) Reversible posterior leukoencephalopathy syndrome (RPLS) Amyotrophic lateral sclerosis (ALS) Colon cancer in ulcerative colitis patients [applicable for marketing authorization with indication CD] Infections in infants exposed to adalimumab in utero Off-label use
Missing information	Subjects with immune-compromised conditions either due to underlying conditions (i.e. diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, antirejection drugs for organ transplant) may have increased known risks of

Summary of safety concerns	
	infection or other unknown risks related to the condition or to the concomitant medications. Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD Pregnant and lactating women Remission - withdrawal – retreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and JIA Long-term safety information in the treatment of adults with HS Long-term safety information in the treatment of adults with uveitis

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
RABBIT (DE): Rheumatoid Arthritis Observation of Biologic Therapy	Evaluation of long-term safety and effectiveness of tumor necrosis factor (TNFα)-inhibitor therapies in the treatment of rheumatoid arthritis (RA). Data for TNF–inhibitor therapies in the treatment of RA patients will be compared to a cohort of RA patients who are treated with nonbiologic	Monitoring of all safety concerns for adult population described in RMP including Serious infections including diverticulitis and opportunistic infection, e.g. invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB) Reactivation of hepatitis B Pancreatitis Lymphoma Hepatosplenic T-cell lymphoma (HSTCL) Leukemia Non melanoma skin	Registry participation start date Registry participation end date: Final report	Planned: At time of drug availability in country following approval in EU After review of data in PSURs; subject to variation After agreed end of registry participation

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	DMARDs.	cancer (NMSC) Melanoma Merkel cell carcinoma (neuroendocrine carcinoma of skin) Immune reactions (including lupus-like reactions and allergic reactions) Sarcoidosis Congestive heart failure (CHF) Liver failure and other liver events Elevated alanine transaminase (ALT) levels Autoimmune hepatitis Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, and melanoma and Merkel cell carcinoma) Infections in infants exposed to adalimumab in utero		
BADBIR (UK): British Association of Dermatologists Biological Interventions Register	A long-term prospective, observational, cohort study whose objectives are to ascertain the safety and efficacy of biologic agents compared to nonbiologics agents in the treatment of adult psoriasis.	Monitoring of all safety concerns for adult population described in RMP including Serious infections including diverticulitis and opportunistic infection, e.g. invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB), Reactivation of hepatitis B, Pancreatitis, Lymphoma, Hepatosplenic T-cell lymphoma (HSTCL), Leukemia, Non melanoma skin cancer (NMSC), Melanoma, Merkel cell carcinoma (neuroendocrine carcinoma of skin), Sarcoidosis, Congestive heart failure (CHF), Other malignancies	Registry participation start date Registry participation end date: Final report	Planned: At time of drug availability in country following approval in EU After review of data in PSURs; subject to variation After agreed end of registry participation

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		(except lymphoma, HSTCL, leukemia, NMSC, and melanoma and Merkel cell carcinoma), Infections in infants exposed to adalimumab in utero		
UKIBD (UK): Inflammatory Bowel Disease (IBD) Registry	The UKIBD Registry provides the first ever UKwide repository of anonymized IBD adult and pediatric patient data for prospective audit and research purposes. Bringing this data together for the first time will: • Drive continuous improvement in patient care and access to care across the UK • Inform commissioning and service design • Improve our understanding of long term outcomes • Provide local & national data in order to better define the pattern of ulcerative colitis and Crohn's disease • Support IBD research	Monitoring of all safety concerns for adult and pediatric population described in RMP Serious infections including diverticulitis and opportunistic infection, e.g. invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB), Reactivation of hepatitis B, Pancreatitis, Lymphoma, Hepatosplenic T-cell lymphoma (HSTCL), Leukemia, Non melanoma skin cancer (NMSC), Melanoma, Merkel cell carcinoma (neuroendocrine carcinoma of skin), Sarcoidosis, Congestive heart failure (CHF), Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, and melanoma and Merkel cell carcinoma), *Colon cancer in ulcerative colitis patients [applicable for marketing authorization with indication CD],* Infections in infants exposed to adalimumab in utero Subjects with immunecompromised conditions either due to underlying conditions (i.e. diabetes, renal or	Registry participation start date Registry participation end date: Final report	Planned: At time of drug availability in country following approval in EU After review of data in PSURs; subject to variation After agreed end of registry participation

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, antirejection drugs for organ transplant), Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD, Pregnant and lactating women, Remission - withdrawal – retreatment nr-axSpA data and episodic treatment in psoriasis, CD, UC, and JIA.		

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infections including diverticulitis and opportunistic infection, e.g. invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation, 4.8 Undesirable effects. PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Before initiation of therapy with GP2017, all patients must be evaluated for both active and inactive (“latent”) TB infection. Legal status: Prescription only **Additional risk minimization measures:** To educate prescribers and patients about the risks of serious infections associated with the use of Hefiya: Patient alert card – adult and pediatric, HCP educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Reactivation of hepatitis B	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC section 4.4: Close monitoring of patients who develop signs of infections and carriers of HBV Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Pancreatitis	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC. PL section 4. Routine risk minimization activities recommending specific clinical measures to address the risk: Close monitoring of patients who develop signs of infections Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Lymphoma	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.3 Preclinical safety data Legal status: Prescription only **Additional risk minimization measures:** To educate prescribers and patients about the risks of lymphoma associated with the use of Hefiya: Patient alert card – adult and pediatric, HCP educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Hepatosplenic T-cell lymphoma (HSTCL)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.3 Preclinical safety data PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** To educate prescribers and patients about the risks of	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	HSTCL associated with the use of Hefiya: Patient alert card – adult and pediatric, HCP educational material	
Leukemia	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.3 Preclinical safety data PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** To educate prescribers and patients about the risks of leukemia associated with the use of Hefiya: Patient alert card – adult and pediatric, HCP educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Non-melanoma skin cancer (NMSC)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, where recommendations are done to all patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non- melanoma skin cancer prior to and during treatment with Adalimumab, 4.8 Undesirable effects and 5.3 Preclinical safety data PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** To educate prescribers and patients about the risks of NMSC associated with the use of Hefiya: Patient alert card – adult and pediatric, HCP educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Melanoma	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.3 Preclinical safety data	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** To educate prescribers and patients about the risks of melanoma associated with the use of Hefiya: Patient alert card – adult and pediatric, HCP educational material	RABBIT (DE), BADBIR (UK), UKIBD (UK)
Merkel cell carcinoma (neuroendocrine carcinoma of skin)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.3 Preclinical safety data PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** To educate prescribers and patients about the risks of merkel cell carcinoma (neuroendocrine carcinoma of skin) associated with the use of Hefiya: Patient alert card – adult and pediatric, HCP educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Demyelinating disorders (including multiple sclerosis (MS), Guillain-Barre syndrome (GBS), and optic neuritis)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. PL sections 2 and 4 Legal status: Prescription only Routine risk minimization activities recommending specific clinical measures to address the risk: Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation **Additional risk minimization measures:** To educate prescribers and patients about the risks of demyelinating disorders (including MS, GBS, and optic neuritis) associated with the use of Hefiya: Patient alert card – adult and pediatric, HCP educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Immune reactions (including lupus-like	**Routine risk minimization measures:**	Routine pharmacovigilance activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
reactions and allergic reactions)	Guidance is provided in the following sections of the SmPC: 4.3 Contraindications, 4.4 Special warnings and precautions for use, where recommendations are done to stop the treatment with Hefiya if a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Hefiya and is positive for antibodies against double-stranded DNA or present any allergic reaction, and 4.8 Undesirable effects. PL sections 2 and 4 Legal status: Prescription only	beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE)
Sarcoidosis	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. PL sections 2 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: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Congestive heart failure (CHF)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.3 Contraindications, 4.4 Special warnings and precautions for use, where it is recommended that reatment with Hefiya must be discontinued in patients who develop new or worsening symptoms of congestive heart failure, and 4.8 Undesirable effects. PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** To educate prescribers and patients about the risks of CHF associated with the use of Hefiya: Patient alert card – adult and pediatric, HCP educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Myocardial infarction (MI)	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC.PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none

Safety concern	Risk minimization measures	Pharmacovigilance activities
Cerebrovascular accident (CVA)	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC.PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Interstitial lung disease (ILD)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. PL sections 2 and 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Pulmonary embolism	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC.PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Cutaneous vasculitis	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC.PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Stevens-Johnson syndrome and erythema multiforme	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC.PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Worsening and new onset of psoriasis	**Routine risk minimization** **Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC.PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Hematological disorders	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. PL sections 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: All patients	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none

Safety concern	Risk minimization measures	Pharmacovigilance activities
	should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on Hefiya (SmPC section 4.4). Legal status: Prescription only	
Intestinal perforation	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC.PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Intestinal stricture in Crohn's disease (CD)	***Routine risk minimization measures:*** *Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 5.1 Pharmacodynamic properties.PL sections 2 and 3.* *Legal status: Prescription only*	*Routine pharmacovigilance activities* *beyond adverse reactions reporting and* *signal detection: none* *Additional pharmacovigilance activities:* *participation in registries: none*
Liver failure and other liver events	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.2 Pharmacokinetic properties PL sections 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: Patients should be tested for HBV infection before initiating treatment with Hefiya. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE)
Elevated alanine transaminase (ALT) levels	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC. PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Autoimmune hepatitis	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC.PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none

Safety concern	Risk minimization measures	Pharmacovigilance activities
Medication errors and maladministration	**Routine risk minimization measures:** Guidance is provided in the section 4.2 Posology and method of administration of the SmPC.PL section 3. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, melanoma, and Merkel cell carcinoma)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.3 Preclinical safety data PL sections 2 and 4. Legal status: Prescription only **Additional risk minimization measures:** To educate prescribers and patients about the risks of other malignancies (except lymphoma, HSTCL, leukemia, NMSC melanoma and Merkel cell carcinoma) associated with the use of Hefiya: Patient alert card – adult and pediatric, HCP educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Vasculitis (noncutaneous)	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC.PL section 4 Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Progressive multifocal leukoencephalopathy (PML)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. PL sections 2 and 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Reversible posterior leukoencephalopathy syndrome (RPLS)	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC. PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none
Amyotrophic lateral sclerosis (ALS)	**Routine risk minimization measures:** Guidance is provided in the section 4.8 Undesirable effects of the SmPC.PL section 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
		participation in registries: none
Colon cancer in ulcerative colitis (UC) patients	***Routine risk minimization measures:*** *Guidance is provided in the section 4.4 Special warnings and precautions for use of the SmPC.* *PL section 4.* *Routine risk minimization activities recommending specific clinical measures to address the risk: All patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations (SmPC section 4.4).* *Legal status: Prescription only*	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none* *Additional pharmacovigilance activities: participation in registries: UKIBD (UK)*
Infections in infants exposed to adalimumab in utero	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation, where it is recommended that administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy, and 5.3 Preclinical safety data. PL sections 2 and 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Off-label use	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.1 Therapeutic indications, and 4.2 Posology and method of administration. PL sections 1, 2, and 7. Routine risk minimization activities recommending specific clinical measures to address the risk: Treatment should be initiated and supervised by specialist	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: none

Safety concern	Risk minimization measures	Pharmacovigilance activities
	physicians experienced in the diagnosis and treatment of conditions for which Hefiya is indicated (SmPC section 4.2). Legal status: Prescription only	
Subjects with immunecompromised conditions either due to underlying conditions (i.e. diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, antirejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, and Section 5.2 Pharmacokinetic properties. PL sections 2 and 4. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE), BADBIR (UK), UKIBD (UK)
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration. PL section 2. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: UKIBD (UK)
Pregnant and lactating women	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: Section 4.6 Fertility, pregnancy and lactation.PL section 2. Recommendation to suspend the therapy with Adalimumab while pregnant or breastfeeding in SmPC section 4.6. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: RABBIT (DE) (pregnant women), BADBIR (UK) (pregnant women), UKIBD (UK)
Remission - withdrawal – retreatment nraxSpA data and episodic treatment in Ps, CD, UC, and JIA	**Routine risk minimization measures:** Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: UKIBD (UK)
Long-term safety information in the treatment of adults with HS	**Routine risk minimization measures:** Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and

Safety concern	Risk minimization measures	Pharmacovigilance activities
		signal detection: none Additional pharmacovigilance activities: participation in registries: none
Long-term safety information in the treatment of adults with uveitis	**Routine risk minimization measures:** Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: participation in registries: 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 Humira 40 mg solution for injection in pre-filled syringe, Humira 40 mg solution for injection in pre-filled pen as the scientific content of the drug product part of the package leaflet is identical except for GP2017 specific differences (design/layout) and Cosentyx 150 mg solution for injection in a pre-filled syringe, Cosentyx 150 mg solution for injection in a pre-filled pen as the instructions for use of the pre-filled syringe are identical except for MAH specific differences (design/layout). 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, Hefiya (adalimumab) is included in the additional monitoring list as new biological product.

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

3 Biosimilarity assessment

3.1 Comparability exercise and indications claimed

The proposed biosimilar GP2017 is intended for some of the therapeutic indications approved for Humira in the EU: juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), axial spondyloarthritis (ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa (HS), uveitis and paediatric uveitis.

Hefiya is currently only available as a 40 mg prefilled syringe (PFS) or AI, and the Applicant intends to claim the paediatric indications only for patients, for whom the full 40 mg dose is suitable, depending on age, weight or body surface area.

To support the biosimilarity claim the Applicant performed a comprehensive biosimilarity exercise at the quality level. An extensive panel of standard and state-of-the art techniques has been used for characterisation and comparison of relevant quality attributes of the adalimumab molecule. The panel includes analytical tests for physicochemical features as well as biological characteristics including binding to membrane-bound TNF-α and ADCC activity, and is considered appropriate for a robust comparison of the quality profiles of GP2017 with its reference medicinal product.

In addition to the in vitro comparability exercise two comparative in vivo PD studies have been performed in two different mouse models, overexpressing soluble TNFα (Tg197 mice) and membrane-bound TNFα (Tg5453 mice), respectively.

Table 37 Summary of the main clinical studies included in this submission

Study No.	Study design Study objective	Study population	Treatment duration	Dosage [batch number]
GP17-104 **(pivotal PK study)**	Design: Single-center, randomized, double-blind, single-dose, three-arm, parallel group study in healthy male subjects Objective: To demonstrate PK bioequivalence (90% CI of ratio of geometric means within the margins of [0.8; 1.25]) for GP2017 and EU-Humira, and PK bioequivalence for EU-Humira and US-Humira in terms of C_{max} and AUC_{0-inf} after a single s.c. injection of 40 mg of adalimumab	Healthy male subjects N=318m GP2017: N=107m EU-Humira: N=106m US-Humira: N=105m	Up to approximately 14 weeks (including screening, treatment, and follow-up)	GP2017: 40 mg/0.8 mL, PFS, single s.c. injection [7007467] EU-Humira: 40 mg/0.8 mL, PFS, single s.c. injection [45018XD05] US-Humira: 40 mg/0.8 mL, PFS, single s.c. injection [1030241]
GP17-101 (**supportive** PK study)	Design: Single-center, randomized, double-blind, single-dose, three-arm, parallel group study in healthy male and female subjects Objective: To demonstrate PK bioequivalence of GP2017, EU-Humira and US-Humira in terms of C_{max}, AUC_{0-inf} and AUC_{0-last} after a single s.c. injection of 40 mg (0.8 mL)	Healthy male and female subjects N=219 (144m, 75f) GP2017: N=73 (49m, 24f) EU-Humira: N=73 (46m, 27f) US-Humira: N=73 (49m, 24f)	Up to approximately 14 weeks (including screening, treatment, and follow-up)	GP2017: 40 mg/0.8 mL, PFS, single s.c. injection [7006285] EU-Humira: 40 mg/0.8 mL, PFS, single s.c. injection [14270XD17] US-Humira: 40 mg/0.8 mL, PFS, single s.c. injection [131082E]

GP17-301 **(pivotal confirmatory efficacy and safety study)**	Design: multi-center, randomized, double-blind, comparator-controlled study with treatment switches in patients with moderate to severe chronic plaque-type psoriasis Objective: To demonstrate equivalent efficacy of GP2017 and Humira with respect to PASI75 response rate at Week 16 and similar safety and immunogenicity in patients with moderate to severe chronic plaque-type psoriasis	Male and female patients with moderate to severe chronic plaque-type psoriasis N=465 (284m, 181f) GP2017: N=231 (142m, 89f) Humira: N=234 (142m, 92f)) EU-Humira: N=44 (28m, 16f) US-Humira: N=190 (114m, 76f)	Up to 55 weeks (including screening, two treatment periods, and one extension period)	GP2017: 40 mg/0.8 mL, PFS [7006715, 7007139, 7007389, 7007467] EU-Humira: 40 mg/0.8 mL, PFS [20321XH04, 23342XH04, 28387XD04, 34434XD11] US-Humira: 40 mg/0.8 mL, PFS [1004010, 1017238, 1017236, 1017235, 1024661, 1030241] GP2017 and Humira were administered as s.c. injections with a loading dose of 80 mg on Day 1 and 40 mg every other week, starting with Week 1 and up to Week 49

Clinical studies to demonstrate similarity of GP2017 to (EU-sourced) Humira were conducted in healthy volunteers (PK, safety and tolerability), as well as in patients with psoriasis (efficacy, safety, tolerability, PK).

The applicant performed two 3-arm, comparative PK studies in healthy volunteers (study GP17-101 and GP17-104). In both studies, similarity in PK, safety and immunogenicity between GP2017 and EU-Humira, between GP2017 and US-Humira, as well as between US and EU originator was studied. The Applicant also submitted an analysis pooling results from both PK studies GP17-101 and GP17-104.

The confirmatory efficacy and safety trial GP17-301 was a randomised, double blind study in patients with moderate to severe chronic plaque-type psoriasis (n=465) over 51-weeks of treatment. The primary objective was to evaluate similarity in efficacy between GP2017 and Humira based on a statistical comparison of the proportion of patients meeting the PASI75 response criteria at Week 16 (primary endpoint).

Apart from the main clinical trials investigating biosimilarity between Humira and GP2017, two supportive trials were performed, aiming to describe the PK of GP2017 administered by an AI or a PFS in healthy volunteers and to compare GP2017 drug substances manufactured by two different manufacturing sites, respectively.

In addition the applicant presented a discussion on the extrapolation to the indications of Humira, for which no comparative clinical data are available. The scientific justification for extrapolation includes structural, physico-chemical and functional analyses as well as nonclinical data, complemented with clinical data in psoriasis patients and a literature review of the mechanism of action of adalimumab.

3.2 Results supporting biosimilarity

Quality

A similar quality profile between US and EU Humira could be demonstrated. Observed differences in critical quality attributes between GP2017 and the reference product (which have been raised as part of a multidisciplinary Major Objection at day 120) have been appropriately addressed by providing additional data sets as well as reasonable justifications:

Of particular concern were differences in glycosylation variants, which are reported to impact Fc-related biological activities, as well as biological assays relevant for the mode-of-action, including binding to membrane-bound TNF-α and ADCC activity.

These bioassays are important for claiming extrapolation to indications, for which no comparative clinical data are available. In addition, no further in vitro data were available in support of the extrapolation to indications where mTNFα-mediated mechanisms may play a more prominent role. Additional evidence and convincing justification was needed to rule out the possibility that these differences might alter the clinical performance of the biosimilar candidate (quality aspect of the multidisciplinary MO at day 120). With the responses, a well-structured and comprehensive response document has been provided. The additional data sets provided as well as the provided justifications are reasonable and appropriately address the previous concerns.

In summary all concerns have been resolved and biosimilarity on the quality level has been demonstrated.

Non-clinical

Similar efficacy of GP2017 and Humira was shown in a murine *in vivo* model for RA overexpressing soluble TNFα. *In vivo* TK and toxicology studies showed comparable results for both, GP2017 and Humira.

Pharmacokinetics

Results from study GP17-104 support biosimilarity in terms of pharmacokinetics: For the comparison GP2017/EU-Humira, the point estimates of the ratios of the geometric LS means for Cmax and AUC0-inf were around 1 and the corresponding 90% CIs entirely contained within the equivalence margin of 0.8 – 1.25 [AUCinf: 1.04 (90% CI: 0.96 – 1.13), Cmax: 1.05 (90% CI: 0.99 – 1.11)]. Comparability was also shown for EU vs. US-sourced Humira in study GP17-104. These results were confirmed by all requested supportive analyses including the one which included all AUC0-inf values. The secondary endpoints AUC0-360h, t1/2, tmax, %AUCextra, tmax, CL0-last and Kel were also roughly comparable across treatment arms.

Similarity of GP2017 and Humira is furthermore supported by the PK data in the target population from the efficacy and safety trial GP17-301 (adalimumab Ctrough levels), which seem overall comparable for Humira and GP2017.

Efficacy

The confirmatory efficacy study GP17-301 was adequately designed for a biosimilar exercise.

In the primary analysis pooling results from patients recruited in the EU and in the US (i.e. pooling GP2017 administered to patients in EU and US as well as pooling EU- and US-Humira), biosimilarity between GP2017 and Humira was shown for the primary efficacy endpoint (PASI75 response rate at week 16) (in the PPS as well as for the FAS data set). The point estimate of the difference between treatments was 1.8, with 95% CI [-7.5; 11.15].

Equivalence between both treatment arms with regard to the primary efficacy endpoint was also shown in the population subset only recruited in the US.

Biosimilarity was also shown in the key secondary endpoint “mean %-change from baseline up to week 16”, for the pooled analysis as well as for the region-specific subgroup analyses (including the comparison GP2017 vs. EU-Humira for patients only recruited in the EU). The point estimate of the difference between treatments for the pooled analysis was 0.8, with a 95% CI [-3.15; 4.84].
Evaluation of secondary endpoints over the whole treatment period shows that GP2017 and US-Humira, as well as GP2017 and EU-Humira, are (descriptively) similar.

Safety

The comparative safety results of the studies in healthy volunteers as well as in psoriasis patients largely support the biosimilarity of GP2017 to Humira; no major difference in the occurrence of unfavourable effects was identified in the programme. GP2017 performed comparably or better compared with the pooled reference Humira group in the pivotal efficacy and safety trial GP17-301. Incidence of ADAs was mostly comparable for GP2017 and Humira. The incidence of neutralising antibodies (59% for GP2017 vs 60.8% for Humira, pooled studies, safety analysis set - Table 36) was rather high but balanced over the treatment groups.

The adverse events captured in comparative clinical studies mirror those described in the SmPC for Humira.

3.3 Uncertainties and limitations about biosimilarity

Quality

For some of the quality attributes the comparative tests were initially conducted with a limited number of batches using wide comparability ranges. These data were supplemented with additional datasets and overall, no concerns on biosimilarity remain.

Non-clinical

In transgenic mice overexpressing membrane-bound TNF-α, the PD effects of GP2017 were significantly lower than those of Humira. However, the contribution of the mTNF-α RA model to the overall assessment of biosimilarity is considered to be of limited value.

Pharmacokinetics

In study GP17-101, PK biosimilarity between GP2017 and EU-authorized Humira as well as between EU- and US-licensed Humira could not be demonstrated, as the upper limits of the 90% CIs of the ratios of GMs for the primary PK endpoints AUC0-last and AUC0-inf were above 1.25. An extensive root cause investigation was conducted, but was not able to explain the outcome of GP17-101. The applicant also examined the clinical trial batches with regard to quality attributes which could potentially impact the PK (such as dose strength, Man5, Met256 oxidation and the glycovariants bGo, bG1 and gG2), and satisfactorily discussed observed quality differences potentially influencing PK. None of them appears to be responsible for the differences in PK between GP2017 and EU-Humira in study GP17-101.

Although GP17-101 failed to demonstrate PK equivalence, the CHMP concluded that non-rejection of the null-hypothesis in this case does not necessarily imply the existence of a relevant PK difference. Indeed, when concluding on PK similarity, results of the PK investigations should always be interpreted and weighed in the context of all other data. It is therefore important to consider also the quality characteristics and data on binding properties when judging the likelihood of potential pharmacokinetic differences.

Study GP17-103 failed to demonstrate bioequivalence in PK between GP2017-Schaftenau and GP2017-Cook. The primary end-points for AUC0-inf and AUC0-last were not met most likely due to differences in the rate of ADA development; this assumption is supported by the fact that the primary end-points for Cmax and AUC0-360, which are not influenced by late ADA formation, have been met.

Efficacy

The recruitment of the confirmatory efficacy and safety trial GP17-301 in Europe was to be capped at 90 patients due to the shift of enrolment to the US. This intervention is seen critically from a methodological perspective by the CHMP, as shift of recruitment to the US and use of US-Humira in the majority of patients might influence the result of the phase 3 study.

During the assessment procedure, the CHMP raised a concern regarding the signal for inconsistency of the treatment effect among the US and EU regions, in terms of a (not statistically significant) treatment*region interaction and inferior efficacy of GP2017 vs. EU-Humira at isolated visits including Week 16. However, it was concluded that this 'interaction' was only exhibited at isolated visits and that due to the small sample size in the EU subgroup, small differences in the number of patients achieving PASI75 response resulted in large differences in response rates (a difference of 4 patients resulted in a 15% difference in response rates). The isolated results were considered to be compatible with a chance-finding.

Concern emerged that populations included in study GP17-301 the EU and in the US differ in certain baseline characteristics, e.g. hand and feet involvement at baseline (4% vs. 45%), body weight (85 kg vs. 95 kg), duration of psoriasis (18 y vs. 15–16 y), mean baseline PASI score (22 vs. 20) and rate of prior systemic treatment (55% vs 42%). This might be partly a consequence of a difference in the Humira labels at the time of study set-up in 2013 (approved then as 2nd line treatment in the EU, in contrast to US). A somewhat different patient population might have been recruited in the EU.

Safety

Some regional differences between the EU and the US population could be observed at baseline (e.g. differences in body weight, baseline PASI -both accounted for by stratification- but also others), which is not considered ideal for comparability exercise. Also, some regional differences occurred in safety events (e.g. a higher rate of infections in the US areas, differences in ADA titres).

Blinding measures were not ideal in studies GP17-104 and GP17-301. Biased assessment of subjective endpoints (e.g. local tolerance, other potentially treatment-related AEs) cannot be entirely excluded; the impact of this is however considered to be minor.

3.4 Discussion on biosimilarity

Similarity was shown for the investigated quality attributes; small differences which have been observed for critical glycan variants as well as for certain mode-of-action relevant biological assays, including binding to membrane-bound TNF-α and ADCC activity, have been appropriately justified. Taking the additional data sets including additional data on ADCC activity as well as the provided justifications into account, the initial concerns have been adequately resolved.

The Applicant intends to manufacture the drug substance at two different sites: Biopharmaceuticals Schaftenau (BPS), Austria; and Cook Pharmica, USA. In all clinical studies (except study GP17-103) GP2017 manufactured from drug substance produced at Schaftenau was used. In a comprehensive comparability exercise the applicant has provided evidence of an adequate bridge between both manufacturing sites. On a quality level, comparability of biosimilar drug substance produced at the different lines and sites was shown. Comparable efficacy of Humira and GP2017 was demonstrated in a murine model for RA based on the overexpression of soluble TNFα. However, in mice overexpressing membrane-bound TNF-α, PD effects of GP2017 were significantly lower than those of Humira. However, the murine mTNF-α model is of limited value for the overall assessment of biosimilarity.

Neither for the comparison GP2017/EU-Humira nor for the comparison EU-/US-Humira any clear reason/driving source for the observed differences in PK parameters in study GP17-101 was identified. The applicant also examined the clinical trial batches with regard to quality attributes which could potentially impact the PK and discussed observed quality differences potentially influencing PK. A larger study (GP17-104) was conducted, and the variability was reduced and biosimilarity was shown in the second PK study.

When concluding on PK similarity, results of the PK investigations should always be interpreted and weighed in the context of all other data. It is important to consider also the quality characteristics and data on binding properties when judging the likelihood of potential pharmacokinetic differences.

EU- and US-Humira have been shown to be highly similar at the quality level and considering results from the successful study GP17-104, showing PK comparability between EU- and US-Humira, the scientific bridge between EU- and US-sourced Humira has been established.

For study GP17-301, the pooled efficacy data show comparability with regard to the primary and key secondary endpoints; the point estimates as well as CI are contained within the predefined equivalence margins. However, results at the region level were found to be indicative of inconsistencies of the treatment effect and the populations included in the EU and in the US differed in certain baseline disease characteristics (hand and feet involvement, duration of psoriasis, mean baseline PASI score and rate of prior systemic treatment). This might have contributed to a heterogeneous treatment response between both regions, as efficacy results also indicate a trend towards higher efficacy of both products (biosimilar and reference product) in the EU region.

A comprehensive overview of all available US results and a thorough discussion on the appropriateness of basing the decision of the EU marketing authorization on US data only was submitted. For the US region, comparable efficacy of GP2017 and US-Humira was consistently demonstrated based on the primary, key secondary and other secondary endpoints. Equivalent efficacy was further supported by analyses of absolute change from baseline in PASI score and assessment of efficacy at an earlier time point (Week 13). Furthermore, the study population recruited in the US region is regarded as representative of the moderate to severe psoriasis population. Based on the presented US data, it can be concluded that GP2017 and Humira show similar efficacy in the treatment of moderate to severe psoriasis, and that in view of the totality of data provided in this application the US region results adequately support a marketing authorization in the EU.

The safety and immunogenicity results of the comparative studies in healthy volunteers and psoriasis patients broadly support biosimilarity of GP2017 and Humira; only some minor differences were identified. The observed adverse events mirror those described in the Humira SmPC.

3.5 Extrapolation of safety and efficacy

The Applicant presented a comprehensive set of models on the quality, preclinical and clinical level to justify extrapolation to all indications of Humira.

3.6 Conclusions on biosimilarity and benefit risk balance

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

4 Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that

the benefit-risk balance of Hefiya is favourable in the following indication:

"Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Hefiya in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Hefiya can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1 of the SmPC). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Hefiya is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1 of the SmPC).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Hefiya is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Hefiya is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Hefiya is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Adalimumab has been shown 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 of the SmPC) and to improve physical function.

Psoriasis

Hefiya is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Hefiya is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Hefiya is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2 of the SmPC).

Uveitis

Hefiya is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult

patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric uveitis

Hefiya is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Additional risk minimisation measures

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

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

- Physician educational material
- Patient information

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient alert card

The Guide for healthcare professionals shall contain the following key elements:

- Relevant information on the safety concerns of serious infections, sepsis, tuberculosis and opportunistic infections; congestive heart failure; demyelinating disorders; malignancies to be addressed by the additional risk minimisation measures (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable).

The patient alert card shall contain the following key messages:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Hefiya.
- That Hefiya treatment may increase the potential risks of serious infections, sepsis, tuberculosis and opportunistic infections; congestive heart failure; demyelinating disorders; malignancies.
- Signs or symptoms of the safety concern and when to seek attention from a HCP
- Contact details of the prescriber

The patient information pack should contain:

Patient information leaflet

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

Not applicable.