16 September 2021
EMA/771818/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Libmyris

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/005947/0000

Note

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

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Table of contents

List of abbreviations

ACR	American College of Rheumatology
2AB	2-Aminobenzamide
Ab	Antibody
ADA	Antidrug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity.
ADR	Adverse drug reaction
AE	Adverse event
AI	Autoinjector
Alvotech	Alvotech Swiss AG
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AS	Ankylosing Spondylitis
ATP	Adenosine Triphosphate
AUC	Analytical Ultracentrifugation
AUC_{0-336}	Area under the concentration-time curve form hour 0 to hour 336
AUC_{0-inf}	Area Under the Serum Concentration-Time Curve from Time Zero (predose) Extrapolated to Infinity
AUC_{0-t}	Area Under the Serum Concentration-Time Curve from Time Zero (predose) to the Time of the Last Quantifiable Concentration
AVT02	Proposed Adalimumab Biosimilar (Alvotech)
AVT02-PFS SD	AVT02 prefilled syringe with safety device
BL	Baseline
BLA	Biologics License Application
BPD	Biosimilar Biological Product Development
BSA	Body surface area
%BSA	Percent of body surface area
BW	Body weight
C1q	Complement Component C1q
CAMs	Cellular Adhesion Molecules
CD	Crohn's Disease
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CDC	Complement-Dependent Cytotoxicity
CE-SDS	Capillary Electrophoresis-Sodium Dodecyl Sulfate
CEX	Cation Exchange
CEX-HPLC	Cation Exchange-High Performance Liquid Chromatography
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovarian
CI	Confidence interval
cIEF	Capillary Isoelectric Focusing
CDC	Complement-dependent cytotoxicity
CL	Confidence limit / Clearance
cLBA	Competitive ligand binding assay

C_{max}	Maximum serum drug concentration
CPB	Carboxypeptidase B
CQA	Critical Quality Attribute
CRP	C-Reactive Protein
CRR	Critical Risk Ranking
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Serum through drug concentrations (= lowest serum drug concentration before the next dose is administered)
CV	Coefficient of variation
DAS28 CRP	Disease Activity Score in 28 joints C-reactive protein
DHC	Deglycosylated Heavy Chain
DLQI	Dermatology Life Quality Index
DLS	Dynamic Light Scattering
DMB	1,2-diamino-4,5-methyleneoxybenzene
DP	Drug product
DS	Drug substance
DSC	Differential Scanning Calorimetry
ECG	Electrocardiogram
ECL	Electrochemiluminescence
EC50	Half-Maximal Effective Concentration
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EOS	End of study
EOW	Every other week
ERA	Enthesitis-related arthritis
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EULAR	European League Against Rheumatism
Fab	Antigen Binding Fragment (antibody region)
FAS	Full Analysis Set
Fc	Fragment Crystallizable (antibody region)
FC	Fisher's Combination Test
FcRn	Neonatal Fc Receptor
FcγR	Fragment Crystallizable Gamma Receptor
FcγRIIIa-158F	Lower IgG Binding FcγRIIIa Allele
FcγRIIIa-158V	Higher IgG Binding FcγRIIIa Allele
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
Frel	Relative bioavailability
FT-IR	Fourier Transformed Infra-Red Spectroscopy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM	Geometric mean
GMP	Good Manufacturing Practice
h	Hour
HAQ	Health Assessment Questionnaire
H2H	Head-to-Head

HCP	Host Cell Protein
HCT116	Intestinal Epithelial Cells
HHL	Heavy-Heavy-Light
HLA-C	Human Leukocyte Antigen-C
HMW	High Molecular Weight
HPLC	High Performance Liquid Chromatography
HS	Hidradenitis suppurativa
HF	Human factors
HFE	Human factors engineering
HUVEC	Human Umbilical Vein Endothelial Cells
IBD	Inflammatory Bowel Disease
ICAM-1	Intercellular Adhesion Molecule-1
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IC_{50}	Half maximal inhibitory concentration
ID	Identification number
IL	Interleukin
IL-1/6/8	Interleukin-1/6/8
IP	Investigational product
IgG1	Immunoglobulin G1
iPSP	Initial Pediatric Study Plan
ISR	Injection site reaction
i.v.	Intravenous(ly)
JIA	Juvenile Idiopathic Arthritis
LC-MS	Liquid Chromatography–Mass Spectrometry
LD	Loading dose
LFA	Lymphocyte Function-Associated Antigen
LLOQ	Lower Limit of Quantitation
LOCF	Last Observation Carry-Forward
LOD	Limit of detection
LS	Least Squares
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
Met	Methionine
MFI	Micro-Flow Imaging
MLR	Mixed Lymphocyte Reaction
MMRM	Mixed Model for Repeated Measures
MSD	Meso-scale discovery
MOA	Mechanism of action
mRNA	Messenger Ribonucleic Acid
mTNF	Membrane-Bound Tumor Necrosis Factor α
MTX	Methotrexate
n	Number of Subjects in each Category
N	Sample Size / Total Number of Subjects Randomised
NAb	Neutralizing antibody
Neu5Ac	N-Acetylneuraminic Acid

Neu5Gc	N-Glycolylneuraminic Acid
NFAT	Nuclear Factor of Activated T-cells
NF-kB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NK cell	Natural killer cell
NP-HPLC	Normal Phase High Performance Liquid Chromatography
OD280	Optical Density at 280 nm
OE	Orphan exclusivity
p55 / p75	Cell Surface TNF Receptors
PASI	Psoriasis Area and Severity Index
PASI 50	50% or more improvement in the Psoriasis Area and Severity Index
PASI 75	75% or more improvement in the Psoriasis Area and Severity Index
PASI 90	90% or more improvement in the Psoriasis Area and Severity Index
PASI 100	100% improvement in the Psoriasis Area and Severity Index
PBMC	Peripheral Blood Mononuclear Cell
pCD	Paediatric Crohn's Disease
PD	Pharmacodynamic(s)
PDGF	Platelet-Derived Growth Factor
PedACR 50	50% Improvement in JIA Activity According to the American College of Rheumatology
PFS	Prefilled syringe
PGA	Physician's Global Assessment
Ph.Eur.	European Pharmacopeia
pH	Negative Logarithm of H+ Ion Concentration
pHS	Paediatric Hidradenitis Suppurativa
PHS	Public Health Service
PI	Propidium Iodide
PJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Act
pPsO	Paediatric Plaque Psoriasis
PREA	Pediatric Research Equity Act
PsA	Psoriatic Arthritis
PP	Per-Protocol
PsO	Plaque psoriasis
PT	Preferred term
pUV	Paediatric Uveitis
QC	Quality control
QoL	Quality of Life
QTPP	Quality Target Product Profile
RAPID3	Routine Assessment of Patient Index Data 3
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RP	Reference Product
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
s.c.	Subcutaneous(ly)
SD	Safety Device or Standard Deviation

SE	Standard error
SEC	Size Exclusion Chromatography
SEC-HPLC	Size Exclusion Chromatography-High Performance Liquid Chromatography
SEC-MALLS	Size Exclusion Chromatography-Multiple Angle Laser Light Scattering
SmPC	Summary of Product Characteristics
SOC	System organ class
sPGA	Static Physicians Global Assessment
SPR	Surface Plasmon Resonance
sTNF	Soluble Tumor Necrosis Factor α
$t_{1/2}$	Half-Life
TACE	TNF-α-Converting Enzyme
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TGF-β	Transforming Growth Factor beta
Th	T Helper Cell
T_{max}	Time to maximum observed concentration
TNF-α	Tumor Necrosis Factor alpha
TNFR1	Tumor necrosis factor alpha receptor 1 (p55 cell surface protein)
TNFR2	Tumor necrosis factor alpha receptor 2 (p75 cell surface protein)
Trp	Tryptophan
U937	Myeloid Cell Line
UC	Ulcerative colitis
US	United States
USA	United States of America
USP	United States Pharmacopeia
USPI	Unites States Prescribing Information
UV	Uveitis
UV CD	Ultraviolet Circular Dichroism
VCAM-1	Vascular Cell Adhesion Molecule-1
vs.	Versus
Vss	Volume of Distribution (at steady state)
WHO DDE	WHO Drug Dictionary Enhanced

1. Background information on the procedure

1.1. Submission of the dossier

The applicant STADA Arzneimittel AG submitted on 11 September 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Libmyris, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 January 2020.

The applicant applied for the following indications:

Rheumatoid arthritis

Libmyris in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

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

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

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Libmyris 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 DMARD. Libmyris 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). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Libmyris 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).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

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

Axial spondyloarthritis without radiographic evidence of AS

Libmyris 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 (NSAIDs).

Psoriatic arthritis

Libmyris is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous DMARD 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

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

Paediatric plaque psoriasis

Libmyris 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)

Libmyris 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).

Crohn’s disease

Libmyris is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Libmyris is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

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

Paediatric ulcerative colitis

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

Uveitis

Libmyris 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

Libmyris 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.

1.2. The legal basis for this application refers to:

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

The application submitted is

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

The chosen reference product is: Humira

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, 40mg, solution for injection in pre-filled syringe.
- Marketing authorisation holder: AbbVie Deutschland GmbH Co. KG
- Date of authorisation : 08/09/2003 (EU/1/03/256/001)
  28/07/2015 (EU/1/03/256/012)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/256/001; EU/1/03/256/012

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. *Scientific advice*

The applicant received CHMP Scientific advice on the development relevant for the indication subject to the present application pertained to the following *quality, non-clinical, and clinical* aspects:

- The agreement with applicant's revised approach to the criticality risk ranking of the quality attributes and consider the justification on each parameter substantiated and the overall strategy sufficient for 351(k) BLA submission
- The agreement with the statistical approach for comparative analytical assessment: a) agrees on the statistical approach (quality range, mean of the reference product ± X SD) for the comparative analytical assessment; b) consider the justification for the multiplier "X" sufficient for BLA/MAA submission; c) agree that the number of AVT02, EU- and US-Humira batches are adequate for pivotal analytical similarity assessment; d) agree with the general strategy for the pivotal analytical similarity assessment
- The agreement that the current comparative analytical assessment data package supports submission of AVT02 MAA as a proposed biosimilar to Humira®
- Agreement with Quality development such as: Specification and characterisation
- Agreement with Pre-clinical development: General strategy
- Agreement with Clinical development on Pharmacokinetics, on Bioequivalence, on statistical Analysis and on Safety Database

1.6. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Simona Badoi

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Ulla Wändel Liminga

The application was received by the EMA on	11 September 2020
The procedure started on	1 October 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2020

The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	4 January 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 January 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 May 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 June 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 July 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 August 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 September 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
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 Libmyris on	16 Sept 2021

2. Scientific discussion

2.1. Problem statement

Not applicable for biosimilars.

2.1.1. Disease or condition

The reference product Humira is authorised for the treatment of RA, juvenile idiopathic arthritis (JIA) (polyarticular JIA and enthesitis-related arthritis), ankylosing spondylitis (AS) and Axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis (PsA), adult and paediatric plaque psoriasis (PsO), adult and paediatric hidradenitis suppurativa (HS), adult and paediatric Crohn's disease (CD), ulcerative colitis (UC), Paediatric ulcerative colitis, Uveitis and Paediatric uveitis (UV). The same therapeutic indications are claimed for Libmyris.

2.1.1. Epidemiology

Not applicable

2.2. About the product

Libmyris (AVT02) has been developed as a biosimilar to Humira the reference medicinal product authorised in the EU on 08 September 2003, which contains adalimumab as an active substance. Adalimumab belongs to the pharmacotherapeutic group 'immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors' (ATC code: L04AB04).

Libmyris is a genetically engineered recombinant human immunoglobulin IgG1 monoclonal antibody, which binds specifically to tumour necrosis factor alpha (TNF-α) and neutralizes its biological function by inhibiting interaction with the p55 and p75 cell surface TNF receptors.

The proposed therapeutic indications and dosages for Libmyris are the same as those approved for EU-Humira: rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (PJIA), enthesitis-related arthritis, axial spondyloarthritis (ankylosing spondylitis [AS], and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis (PsA), adult and paediatric plaque psoriasis (PsO), adult and adolescent hidradenitis suppurativa (HS), adult and paediatric Crohn's disease (CD), adult ulcerative colitis (UC), adult and paediatric non-infectious uveitis.

Libmyris is being developed as solution for subcutaneous (s.c.) injection 100 mg/ml and presented as 40 mg/0.4 ml in a prefilled syringe (PFS) with passive safety device, 40 mg/0.4 ml in a PFS enclosed in an auto injector and 80 mg/0.8 ml in a PFS with passive safety device. The strengths are the same as those approved for Humira.

In the posology section 4.2 of the SmPC, the applicant proposes to indicate only those patients with a certain body weight that can be treated with the available presentations of Libmyris, i.e., patients weighing ≥ 30 kg.

2.3. 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.

The development of Libmyris (AVT02) followed the standard stepwise approach for establishing similarity across structural and functional quality attributes, and nonclinical and clinical data. The clinical studies supporting biosimilarity were:

- AVT02-GL-101 (Pivotal PK study for biosimilarity): A multicenter, Randomized, Double-Blind, 3-Arm, Parallel Study to Compare the Pharmacokinetics, Safety and Tolerability of AVT02 to EU-approved and US-licensed Humira® Administered as a Single Dose (40 mg Subcutaneous Injection) in Healthy Adult Volunteers (ALVOPAD FIRST)
- AVT02-GL-301 (confirmatory efficacy and safety study): A multicenter, double-blind, randomized, parallel-group, active control study to compare the efficacy, safety, and immunogenicity of AVT02 versus EU-Humira in patients with moderate-to-severe chronic plaque psoriasis (ALVOPAD PS).

The clinical studies supporting device development were:

- AVT02-GL-102 (PK study between AI and PFS): Multi-centre, Randomized, Open-Label, 2-Arm Parallel Study to Compare the Pharmacokinetics, Safety and Tolerability of AVT02 Administered Subcutaneously via Prefilled Syringe or Autoinjector in Healthy Adult Volunteers (ALVOPAD PEN)
- AVT02-GL-303 (AI usability study): Assessment of Real-life Patient Handling Experience of AVT02 Administered Subcutaneously with an Autoinjector in Patients with Moderate to Severe Active Rheumatoid Arthritis: An Open-label, Interventional, Single-arm Clinical Trial, followed by an Extension Phase of AVT02 Administered with a Prefilled Syringe (ALVOPAD-PEN)
- AVT02 HF Validation AI: Assessment of performance and function of the AVT02-AI and instructional labelling in a simulated-use setting in Adult Patients with RA, adolescent patients with JIA, caregivers and HCPs.

AVT02 has been developed in line with relevant CHMP biosimilar guidelines listed below:

- Guideline on similar biological medicinal products (CHMP/437/04)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/42832/2005)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005)
- Guideline on development, production, characterisation and specifications for monoclonal antibodies and related substances (EMEA/CHMP/BWP/157653/07)

2.4. Quality aspects

2.4.1. Introduction

The finished product (FP) is presented as solution for injection in pre-filled syringe (PFS) or pre-filled pen (PFP) containing 40 mg (40 mg / 0.4 mL) or 80 mg (80 mg /0.8 mL) of adalimumab as active substance (AS).

Other ingredients are: sodium chloride, sucrose, polysorbate 80, water for injections, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

The product is available in either in a pre-filled type I glass syringe (PFS) with a fixed 29-gauge needle, extended finger flanges and needle guard, and a plunger stopper (bromobutyl rubber, latex-free) for both strengths. The 40 mg strength is also available in pre-filled pen (PFP) autoinjector (AI) containing a pre-filled type I glass syringe with a fixed 29-gauge needle and a plunger stopper (bromobutyl rubber, latex-free). The pen is a single use, disposable, handheld, mechanical injection device. The PFS and the PFP are packed in a PVC/PE blister, together with alcohol pads.

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

2.4.2. Active Substance

2.4.2.1. General information

Adalimumab (also referred to as AVT02) is a recombinant, fully human monoclonal immunoglobulin G1 (IgG1) kappa monoclonal antibody consisting of two identical heavy (H) chains of 451 amino acids paired with two identical light (L) chains of 214 amino acids. Adalimumab binds specifically to TNF, thereby inhibiting the binding of TNF with its receptor.

The antibody bears one N-glycosylation site on each heavy chain within the constant region at asparagine (Asn) 301. The N-linked glycosylation consensus sequence, in the CH2 region is essentially fully occupied with asialo, core-fucosylated, complex-type biantennary N-linked glycans with zero and one terminal galactose residues, abbreviated as FA2 and FA2G1, respectively. C-terminal lysine is encoded by the H chain expression vector cDNA sequence, and is observed in the mature, secreted form of AVT02. The penultimate glycine residue is the predominant H chain C-terminus in AVT02.

2.4.2.2. Manufacture, characterisation and process controls

AVT02 active substance is manufactured according to current Good Manufacturing Practices (cGMP) by Alvotech hf, Reykjavik, Iceland.

Description of manufacturing process and process controls

The AS manufacturing process is a straightforward monoclonal antibody production process that consists of 9 sequential upstream processing (USP) and 7 sequential downstream processing (DSP) steps. AVT02 is produced in a Chinese Hamster Ovary (CHO)-S cell line. The manufacturing process begins with thawing of a single WCB vial followed by serial cell culture expansion in shake flasks and bioreactors leading to production scale bioreactor. The material from the production bioreactor is harvested and clarified with depth filtration followed by inline bioburden reduction filtration prior to further processing. The purification process includes Protein A chromatography, Low pH viral

inactivation, Multimodal chromatography and bioburden reduction, nanofiltration, and UF/DF filtration prior to final formulation, dilution, fill and freeze steps. The AS is stored in the container closure system. There are no reprocessing steps in the DS manufacturing process. No design space is claimed.

The manufacturing process, with in-process controls, has been outlined in flow diagrams and additional information and input process parameters have been provided for each step in sufficient detail. In general, the presented in-process controls and tests for AS manufacturing are appropriate.

Control of materials
The applicant is using a two-tiered cell bank system in overall accordance with ICH Q 5B and Q 5D guidelines. Descriptions of the methods used to characterise the MCB, WCB and PPCB (Post-Production Cell Banks) have been provided. Any materials of animal origin comply with the Note for Guidance EMA/410/01 and a valid EDQM certificate was provided. Therefore, the risk of transmissible spongiform encephalopathy (TSE) contamination is considered minimal. Overall, appropriate safety precautions and controls concerning the absence of bacteria, mycoplasma, and viruses has been considered for all source material, including reagents, media, and cells. The cell banking system and its characterisation and testing were adequately presented.

Process validation
The manufacturing process for AVT02 DS has been validated at the intended production site, on several consecutive commercial scale batches. The validation study covered both the USP and DSP covered. Impurity clearance was also evaluated as part of process performance qualification (PPQ) activities.

For all PQ batches CQAs remained within pre-defined In-process and Release specifications. However, two batches showed higher than expected levels of aggregates and as a consequence a lower purity (SEC) although both parameters remained within the acceptance criteria. Critical Process Parameters (CPPs) were maintained within established acceptable ranges during the qualification runs. Overall, validation acceptance criteria were met, and no manufacturing deviations were generated which impacted the validation, even though a number of deviations were raised. Consistency data from several at scale batches was presented in the dossier. The USP and DSP in-process data, combined with the batch data indicate that the process is capable of operating within defined parameters to generate product of the required product quality.

In addition, the applicant has provided information on potential extractables/leachable from the single-use equipment used, and a risk assessment in line with EMA/CHMP/BWP/187338/2014 has been performed.

Resin ageing studies were performed in scale-down models for the two chromatography steps in AVT02 DS manufacturing demonstrating overall robust performance and resin stability. Information on the scale down models used in resin ageing studies was provided.

Manufacturing process development
Three different processes (0.1, 1.0 and 1.1) have been described and used during the different development phases of AVT02 active substance. The modifications introduced to the manufacturing processes during the development have been adequately described and sufficient details and rationale for each step has been provided.

A high-level summary of USP and DSP manufacturing process characterisation was provided in the dossier. USP and DSP unit operations were risk assessed by Failure Mode Effect Analysis (FMEA). Based on the risk assessment, the potential critical process parameters (pCPPs) were identified. These pCPPs were assessed during the process characterisation and subsequently classified as CPP or non-Critical Process Parameters (nCPP). For parameters that are established as critical, a Proven Acceptable Range (PAR) was established based either on the parameters characterised, or limitations based on impact on CQAs.

Several significant changes were implemented between active substance (AS) manufacturing process 0.1 and manufacturing process 1.0. Therefore, process 0.1 material used only in very early development is not considered fully representative of process 1.0 or 1.1 material; this is acceptable.

Adjustments were made to the DSP process for process optimisation and closer alignment to the reference product between manufacturing process 1.0 and the intended commercial manufacturing process 1.1. No major process adjustments were made to the USP process. A comparability study was performed on AS as well as the respective finished product (FP) level for relevant pre- and post-change batches. Product quality was compared in terms of release data (AS and FP), in-process data (AS), additional characterisation (AS/FP), stability (AS and FP) and forced degradation (FP) behaviour. In-process DS data showed comparable clearance rates for pre- and post- change batches in terms of product related variants (high molecular weight species, fragments and acidic species) and process-related impurities (residual host cell protein (rHCP), leached recombinant protein A (rProtA) and host cell DNA (hcDNA)). Comparable primary and higher order structure were confirmed, including disulfide linkages and comparable free thiol levels. Deamidation and oxidation analysis showed comparable levels in pre- and post- change batches. Comparable efficacy of pre- and post- change batches was supported by comparable potency by cell viability assay, comparable binding to sTNFα and FcγRIIIa F158, as well as comparable ADCC and CDC activity and C1q binding. Additionally, binding to FcRn was comparable for pre- and post- change batches.

DS and DP stability data showed comparable degradation pathways and trends for pre- and post-change batches.

Based on the provided results, it is overall agreed that process 1.0 batches can be considered representative of process 1.1.

Characterisation
The characterisation studies were presented as a tabulated list in CTD section S.3.1 as the studies are also a part of analytical biosimilarity assessment described in CTD section 3.2.R. AVT02 has been characterised using state-of-the-art methodology. Data for primary, secondary and higher-order structure, post-translational forms (e.g., glycoforms), biological and functional activity, purity, and immunochemical properties have been generated and assessed. The detailed data, analysis and conclusions are presented in CTD Section 3.2.R.3.

Impurities
The applicant has summarised and discussed all product-related impurity variants with regards to their impact on AVT02 biological activity, safety, and efficacy. As the main product-related impurities, Size Variants (HMW Species and Fragments) and Charge Variants have been considered. Post-Translational Modifications (e.g., glycosylation and oxidation variants, deamidation, and N/C-terminal variants) are considered as product-related substances absent or present in very low amounts or shown to have no impact on efficacy and safety.

As process-related impurities, Residual host cell protein, Residual host cell DNA, Residual Protein A, poloxamer 188 (pluronic F68), dimethyl sulfoxide (DMSO), and simethicone have been considered. Overall, no safety risks were identified. Descriptions and qualification of the analytical methods used to study poloxamer 188 (pluronic F68), and simethicone in AVT02 DS are provided.

Container closure
An appropriate description of the container closure system has been provided and compliance with relevant requirements has been confirmed. Satisfactory information regarding leachable and extractables has been provided. The compatibility of the AVT02 DS with the container has been evaluated

Overall, the Container Closure system used for AVT02 is acceptable.

2.4.2.3. Specification

The AS release and shelf-life specifications include tests for general attributes (clarity, colour, and pH), an identity test (peptide mapping), a test for protein content (OD280), a potency cell-based luminescence assay (*in vitro* TNFα neutralisation assay), purity tests (CEX for charge heterogeneity, CE-SDS (reducing and non-reducing) and SEC-HPLC for charge variants), test for N-glycosylation, tests for process related impurities (HCP ELISA, Host cell DNA qPCR, and Residual Protein A), and safety tests (Bacterial endotoxins and Bioburden).

The test parameters proposed to be included in the AVT02 AS specification have been discussed separately and a very brief justification and historical data has been provided for each parameter. Overall, the test parameters included in the specification are considered relevant and in line with current guidance. Since ADCC is considered as a likely mechanism of action for adalimumab in certain indications, in order to ensure that AVT02 will maintain an ADCC activity similar to EU Humira, AS release testing for glycosylation will be performed using two methods with respective limits until further experience is gained. The CHMP requested and the applicant committed to revisit the acceptance limits for glycan structures once a certain number of batches of AS has been manufactured (REC).

According to the applicant the specification acceptance criteria were initially established by literature review, pharmacopoeia monographs, and the specified quality target product profile (QTPP), as well as evaluating analytical results from development batches. The acceptance criteria have been further adjusted based on available development data and data from full-scale batches. Stability data has been reviewed and the specifications set to establish the targeted quality throughout the DS and DP shelf life.

Analytical procedures
AVT02 is tested using a combination of compendial and non-compendial analytical tests. Compendial analytical methods used for AVT02 batch release testing and stability are clarity, colour, pH, endotoxin (LAL test), and bioburden (membrane filtration). The methods are conducted as described by the relevant sections in the Ph. Eur. and have been verified under actual conditions of use (measuring a standard or reference) and then product verified by measuring a product to verify that the method is fit for purpose.

Non-compendial analytical methods used for AVT02 batch release and stability studies include CE-SDS, CEX-HPLC, HCP ELISA, Host Cell DNA, OD280, Peptide Mapping, Potency, Glycosylation (N-glycans), Residual Protein A, and SEC-HPLC. Method descriptions and other relevant information have been provided for the non-compendial methods. The applicant has also described how consistent performance of the analytical methods is ensured after method changes.

The non-compendial analytical methods have been validated according to ICH Q2 (R1) at Alvotech, Reykjavik and full validation reports and a validation summary have been provided for all methods with the exception with the exception of one. The CHMP requested and the applicant committed to validate that method at the release site (REC).

Reference standards
The strategies for establishing the reference material during the active substance development have been provided. The reference material used throughout the product development and the bridging between two reference material have been adequately described. A two tiered reference material system

consisting of a primary reference material and a working reference material has been implemented; this is acceptable.

Batch analysis
Batch data for several AVT02 AS batches have been presented. The results obtained from all the batches are within the proposed commercial specification. Batch data was also presented for the early development process batch.

2.4.2.4. Stability

A shelf-life claim of 24 months when stored at -70±10°C in the commercial container is proposed for the AS.

Stability data at the long-term storage condition (-70 ±10°C), at the accelerated storage condition (5±3°C) and stressed storage condition 25±2°C /60±5% RH was presented. The presented stability data has been generated using material from manufacturing processes 1.0 and 1.1, considered representative of commercial product. The stability samples have been stored in reduced size bags with the same interior product contact layer as the actual AS container. However, the fill volume has varied (60-97%). The 60% fill volume represents a worst-case fill with greatest headspace. The studies at long-term conditions are planned to continue up to 24 months for most batches. For PPQ batches the stability studies are planned to be continued until the 60-month time point has been reached.

Real-time, accelerated and stressed storage condition stability data has been provided on several batches from process versions 1.0 and 1.1.

No trends were observed in the tested parameters in the long-term conditions. However, in the provided data a possible slight decrease in potency by *in vitro* TNF neutralisation assay can be seen for some batches, even though the data remains within specification. The data from stressed stability studies show that the non-reduced CE SDS, CEX-HPLC and SEC-HPLC assays for testing purity are stability indicating.

Overall, the stability of AVT02 AS has been adequately addressed according to ICH Q5C tripartite guideline. The proposed shelf-life of 24 months when stored at −70±10°C is supported by the provided data.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The FP (AVT02-DP) is a clear, colourless, sterile, preservative-free solution for subcutaneous injection containing 40 mg (AVT02-DP40) or 80 mg (AVT02-DP80) of adalimumab in 0.4 mL or 0.8 mL at a concentration of 100 mg/mL.

The FP is first filled into a pre-filled syringe (PFS), which includes syringe with a stopper, needle and needle cap. The PFS can further be assembled either to:

- 40 mg and 80 mg: Safety Device (SD) which consists of AVT02-DP PFS, fitted with a plunger rod, finger flanges and a needle safety device.
- 40 mg only: Autoinjector (AI) which consists of AVT02-DP PFS, together with two housing covers, and a cap remover sleeve that encloses the AVT02-DP PFS.

The list of excipients is included in section 6.1 of the SmPC and in paragraph 2..1 of this report.

Formulation development
The FP formulation was developed to generate a biosimilar to the reference product for subcutaneous administration capable of maintaining stability of quality attributes for the duration of the anticipated shelf life. The formulation was defined during early development (prior to shelf life determining studies and clinical studies) and has remained unchanged. All excipients in the formulation are of compendial quality and have not been changed during development, except for minor improvement in the quality standard of polysorbate 80. The choice of excipients has been justified.

Manufacturing process development
The manufacturing process development has mainly focused on the changes between the processes 1.0 and 1.1, and a tabulated summary of the changes between the two processes has been provided. Changes concern controlled-rate thawing of the AS, bioburden reduction filtration and sterile filtration as well as minor changes related to the devices used in filling and stoppering. Overall, no significant changes have been made to the manufacturing process throughout the product history. For the comparability confirmation (batches 1.0 and 1.1), comparative batch analysis data and stability data have been provided. According to the provided batch analysis and stability study results, the batches are comparable. It is unlikely that these presented changes affect the product quality.

The microbial safety of the FP is controlled by in-process bioburden and endotoxin tests within the release and during shelf-life.

Container closure system
The primary packaging components are glass syringe barrel and plunger stopper. The material of the glass syringe barrel is according to Ph. Eur. requirement hydrolytic glass type I (Ph.Eur 3.2.1) and the plunger stopper with Ph. Eur. requirement for rubber closures (Ph. Eur. 3.2.9). With regards to safety of the device components, including e.g., silicone, heavy metals, extractables and leachables, compliance of the PFS and PFP with the relevant Essential Requirements in Annex I of Directive 93/42/EEC was reviewed. Issues identified were satisfactorily addressed. Based on the presented information and assessment of the additional responses concerning safety of the device components, no further concerns remain. Sterilisation of the glass syringes is performed using Ethylene oxide (EtO). Ethylene oxide sterilisation method used by the supplier is justified. Stoppers and syringes are reported to be received sterile. Site of sterilisation is informed.

Specifications and method of analysis are listed for the device in section P.7.; release specification for both device types is provided and cover appearance, functional performance, and mechanism of action. Compatibility of the FP with syringe container closure systems has been established through stability studies. With regards to functional stability of both devices, the applicant has provided data and justification to support the functionality of the AI and the SD over the whole shelf-life. A summary of the shipping validation studies has been provided.

The safety and effectiveness of the auto-injector has been assessed in Human Factor studies which have been assessed in detail in the clinical assessment report.

2.4.3.2. Manufacture of the product and process controls

Manufacturers
The FP PFS is manufactured and released at Alvotech Hf Iceland. The site responsible for batch release of PFS and AI in the EU is Ivers-Lee CSM Germany.

Manufacturing process

The AVT02-DP PFS is manufactured by thawing, pooling and mixing of the formulated AVT02 AS, followed by filtration and aseptic filling into syringes. The AVT02-DP PFS is composed of the AS filled into syringes, each with a needle, needle-cap and stopper. The PFS is further assembled to auto-injector or safety device presentations. Necessary details concerning the manufacturing processes were provided.

It is indicated that more than one batch of AVT02 AS may be pooled to generate a single AVT02-DP PFS batch based on supply demand. Batch definition has been amended to include the maximum number of AVT02 AS batches which can be pooled to generate an AVT02-DP PFS batch.

Control of critical steps and intermediates
For process characterisation studies, the manufacturing process steps including thawing of the AS, pooling and mixing, bioburden reduction filtration, sterile filtration and filling/stoppering have been studied. Each manufacturing step has been assessed including parameters that may have a potential impact on the final product quality and process consistency. The ranges and criticality designation of each parameter based on the outcome of a characterisation risk assessment and characterisation studies were provided. The criticality assessment (i.e., the designation of parameters as CPPs/non-CPPs, as well as the setpoint, manufacturing operating range (MOR), proven acceptable range (PAR) and characterisation range (CR) were summarised. The designation of the criticality of process parameters is adequately addressed. The proposed controls and acceptance criteria also cover relevant points to achieve consistent quality in the manufacturing process of auto-injector (AI) and safety device (SD). Hold times were assigned from aseptic hold times supported by media fill studies and from development studies wherein the impact of these hold times for physicochemical stability was determined.

Manufacturing process validation
The formal validation of the AVT02-DP PFS manufacturing process has been performed at Alvotech, at full commercial scale as part of PPQ and included media fill validation and filters integrity studies. Further investigations were triggered for two of the PPQ batches because of detected out of specification (OOS) results in Purity test. The cause of the observed OOS was satisfactorily explained. Two additional batches were included in the process validation based on revised PPQ protocol to meet the protocol acceptance criteria for the number of qualification batches. To address the root cause and prevent similar incidents going forward, the specification for monomer purity for AS and FP was adjusted. Based on the provided results, the FP manufacturing process of the pre-filled syringe can be considered successfully validated. A summary of the results for process validation studies concerning assembly of the auto-injector and safety device were also provided and is deemed satisfactory. Filter validation studies are considered successfully performed as well.

2.4.3.3. Product specification

The release and shelf-life specifications for the 40 and 80 mg solution for injection in pre-filled syringe include tests and limits for general tests (clarity, colour, uniformity of dosage units, visible particles, pH, osmolality), tests for identity (peptide mapping), tests for quantity (protein concentration A_{280}, extractable volume), tests for biological activity (*in vitro* TNF-α neutralisation assay), purity and

impurity tests (non-reducing/reducing CE-SDS, SE-HPLC, CEX-HPLC), Polysorbate 80 (RP-UPLC-ELSD) as well as tests for safety (sterility, endotoxin, particulate matter).

The test items are identical for AS and FP, except for sterility, uniformity of dosage units, visible particles, extractable volume, osmolality and Polysorbate 80, which are only included in the FP specifications.

The proposed FP release and end of shelf-life specification acceptance criteria are considered acceptable. Release specifications for auto-injector (AI) and release and shelf-life specifications for the safety device (SD) were also provided. The specifications for auto-injector and for the safety device were presented and are acceptable.

Characterisation of impurities
No additional impurities are detected in the FP compared to the active substance. For discussion on impurities please refer to the Characterisation section. The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the FP specification. The information on the control of elemental impurities is satisfactory.

Also, in response to a Major Objection raised by the CHMP a risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods and method validation
The analytical methods used for the control of FP are largely the same as those used for AS. Analytical methods for Sterility and Polysorbate 80 are specific for the FP and have been validated to be used with the FP. The same reference standards are used for control of the AS and FP.

Batch data
Batch analysis data derived from several lots of AVT02 finished product manufactured throughout development were presented. These batches were used for non-clinical, clinical, and stability as well as analytical similarity studies. All batches except for two (as discussed previously) met the acceptance criteria in place at the time of release.

2.4.3.4. Stability of the product

A shelf life of 24 months at 5±3°C plus 2 weeks at room temperature (25°C) storage protected from light was claimed for the finished product.

Stability study results at long term conditions (5±3°C) for 3 batches up to 24 months, for 2 batches (commercial scale) up to 12 months, for 1 batch (commercial scale) up to 6 months and for 2 batches (commercial scale) up to 1 month, were provided. Stability specifications were met showing no significant trend in any tested parameter.

Stability study results at accelerated conditions (25±2°C) for 6 batches up to 6 months, for 2 batches up to 1 month and for 1 batch for 14 days, are provided. The results for peptide mapping, protein concentration, appearance (colour & clarity), pH, osmolality, endotoxin, sterility and polysorbate 80, were within specification limits. However, elevated temperature increases the amount HMW and acidic variants.

Stability study results at stressed conditions (40±2°C) for 7 batches up to 3 months and for 2 batches up to 1 month, are provided. The results for peptide mapping, protein concentration, appearance (colour & clarity), pH, osmolality, endotoxin, sterility and polysorbate 80, were within specification limits. However, the amount of HMW and acidic variants were increased but remained within specification.

As outlined in ICH Q5C tripartite guideline, primary data to support a requested storage period should be based on long-term, real-time, real-condition stability studies for at least three batches for which manufacture, and storage are representative of the manufacturing scale of production. The shelf-life assignment of AVT02-AI will be based on the long-term stability data available on the PFS. The assembly of PFS with the safety device (SD) or the autoinjector components is not anticipated to have a measurable impact on chemical and functional stability, and therefore the stability data taken from PFS is considered the primary product shelf-life assignment data. With regards to functional stability of both devices, satisfactory data, and justification to support the functionality of the AI and the SD over the whole shelf-life were provided.

Stability study results for the additional storage of 2 weeks at 25°C / 60% are provided for 3 batches. There is no significant upward or downward trend in any stability parameter, or any OOS results. Overall, the provided data support the claim of short-term temperature excursion outside the label storage conditions for 2 weeks.

Photostability studies were performed in accordance with ICH Q1B. Out of specification (OOS) results were detected in potency, charge heterogeneity (SEC-HPLC, %monomer), size variants (CE-SDS non-reducing, %monomer) and in heavy chain amounts (CE-SDS reducing, %monomer) when exposed to light. Thus, the product should be protected from light. Based on the results off the photostability study the cardboard secondary packaging is considered sufficient protection from light.

Container closure integrity test is conducted in accordance with Ph. Eur. 3.2.9 Self-sealing test and test results remained within the specification limits at all time-points.

Based on the overall data the proposed shelf-life of 24 months at long term conditions (5°C ± 3°C) for all presentations of the finished product is acceptable.

2.4.3.5. Biosimilarity

On the quality level, a comprehensive biosimilarity exercise has been performed following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012).

Comparative analysis has been performed using the AVT02 DP in a pre-filled syringe (AVT02-DP PFS) presentation with a 0.4 or 0.8 mL fill. A sufficient number of AVT02 DP lots, manufactured from independent AS batches, and of EU-Humira batches were included for comparability studies. US-Humira batches were also included in those studies. The clinical batch clinical AVT02 DP has been used in the comparability studies. AVT02 batches from an earlier process and the final process were included, trisulfide modification from the earlier process was remove in the final process.

Comparability between AS manufacturing processes have been demonstrated.

During the course of development of AVT02, multiple independent comparative analytical head-to-head (H2H) studies have been performed. From the provided testing plan it is understood that H2H assessment have been performed for all of the physicochemical and analytical methods. The applicant proposes to use a standard deviation (SD) approach as comparability ranges. The SD multipliers were chosen based on criticality ranking. Most of the comparability ranges were set at ±3SD; these were for CQAs ranked as high, moderate and low criticality. Tighter range (±2.5SD) was set for the CQAs with a highest risk. Comparability ranges are considered supportive of the overall similarity assessment. In addition, in most cases sufficient raw data has been provided to allow assessment of biosimilarity independently of statistical approach chosen. A summary table including critical evaluation of biosimilarity is presented in **Table 1**.

Table 1. Overall Summary of biosimilarity assessment between Hukyndra and Humira			
Molecular parameter	Attribute	Methods	Key findings
Primary structure	Amino acid sequence	Reducing peptide mapping (MS)	The amino acid sequence of AVT02 was confirmed to be identical to the sequence of Humira. The molecular mass of adalimumab in AVT02 and EU-Humira was confirmed to be highly similar. The amount of the C-terminal Lysine was larger for AVT02 (28.9-32.2%) compared to EU-Humira (18.8-25.0%). Amidation of the terminal proline was higher in AVT02 (2.6-3.3%) compared to EU-Humira (0.2-0.4%). These differences are not expected to have clinical impact. Slightly, non-significantly, lower levels of HT38 deamidation was observed for AVT02 (2.1-2.5%) when compared to EU-Humira (2.6-2.8%). In addition, oxidation levels of HT21 (Met256) and HTH42 (Met432) were higher in AVT02 (4.6-6.4% and 2.2-2.8%, respectively) than in EU-Humira (3.4-3.6% and 1.3-1.5%, respectively). The difference is considered clinically irrelevant. Difference in C-terminal Lysine and in Lysine glycation levels (slightly higher in AVT02 HC: 5.0-5.5 and LC: 1.8-2.3 than in EU-Humira HC:2.3-3-2 and LC: 1.0-1.1) were detected. These slight differences are not expected to have clinical impact. Overall, similarity in terms of primary structure was demonstrated.
	Molecular mass	LC-ESI-TOF-MS	
	N/C-terminal integrity	Peptide mapping LC-MS	
	Deamidation and oxidation		
	Glycation	Precise mass (reduced de-N-glycosylated) LC-MS	
Higher order structure	Secondary and tertiary structure	CD spectroscopy, Far/Near UV CD, FT-IR, DSC, Intrinsic fluorescence, Peptide mapping (LC-MS or HPLC)	Comparable secondary and tertiary structure is demonstrated. Highly similar molecular structure, no trisulfide linkages were detected in AVT02 (DS Process 1.1) and Humira. Similar, low levels of free thiols observed in AVT02 and Humira.
	Disulphide and trisulphide analysis	LC-MS	
	Free thiols	Ellman's reagent	
Content	Protein content	OD280	Highly similar protein content and extinction coefficient.
	Extinction coefficient	Amino acid analysis	
Aggregates and monomeric purity	Monomers, dimers, HMW species, higher order aggregates	SEC-HPLC	Amount of monomers measured via SEC-HPLC is high in both products (98.6-99.3% and 99.4-99.76% in AVT02 and EU-Humira, respectively). Slightly higher amounts of high molecular weight species (HMWs) are observed in AVT02 (0.7-1.3%) when compared to EU-Humira (0.29-0.5%). Differences do not have clinical significance. AUC was used as an orthogonal method to compare the levels of size variants and the data showed comparable amounts of monomers, and higher order oligomers. Differences are not considered clinically significant. SEC-MALS demonstrated similarity in monomers and dimers, however, a peak correlating with higher order aggregates was detected only for AVT02. Enriched SEC fractions were further analysed and confirmed that both AVT02 and Humira HMW1 mainly contains Adalimumab higher order aggregates and HMW2 fractions mainly contain Adalimumab dimer. The impact on potency was also studied confirming that the TNFα potency, ADCC activity and FcγRIIIa binding was similar for AVT02 and Humira for the dimer and the HOA. The data demonstrated that AVT02 and
		AUC	
		SEC-MALS	

			Humira HMWs (especially HMW1) had reduced potency and reduced effector functions. HMWs are controlled at DP release. These differences are not expected to have clinical impact.
Fragmentation and aglycosylation	IgG, HHL, total fragments, HC+ LC, HC, LC, deglycosylated heavy chain	CE-SDS (Reduced and Non-Reduced)	The level of intact IgG in non-reduced CE-SDS was slightly lower in AVT02 97.0-98.2% with total fragments of 1.8-3.0% compared to EU-Humira (97.8-98.8% and 1.0-2.7%, respectively). These very slight difference are not considered clinically significant. In the reduced CE-SDS HC+LC level in AVT02 (97.3%-98.4%) was slightly lower when compared to EU-Humira (98.2-99%), and the level of deglycosylated heavy chain (DHC) was slightly higher in AVT02 (1.7-1.9%) than in EU-Humira (1.0-1.3%). This minor max. 0.6% difference is not, however, expected to have clinical impact.
Glycan profile	Afucosylation and high mannose variants Galactosylation Sialyation	2-AB normal-phase HPLC	Slightly higher amount of galactosylated glycans is observed in AVT02, however the galactosylation levels are mostly overlapping and therefore AVT02 and EU-Humira can be considered similar in terms of galactosylation. The level of high mannose species was lower in AVT02 (3.4-4.2%) in comparison to EU-Humira (8.4-9.6%), whereas the level of afucosylated species (high mannoses not included) was slightly higher in AVT02 (2.3-2.7%) than in EU-Humira (1.2-1.5%). Consequently, the total level of afucosylated glycans was 6.0-6.7% in AVT02 in comparison to EU-Humira 10.4-11.7%.
Charged variants	Basic species, acidic species and main variants	CEX-HPLC (with and without CPB) cIEF Isolated fractions were further characterised via Peptide mapping (HPLC or LC-MS), CEX-HPLC, CEXHPLC+ CpB, sTNFα binding assayy, Inhibition of sTNFα binding activity, FcγRIIIa binding, C1q binding	AVT02 was confirmed to contain higher amount of acidic species (16-20%) than EU-Humira (13-17%). Higher levels of basic variants was observed in AVT02 (29-33%) than in EU-Humira batches (17-25%). Consequently, the amount of main species were 50-53% and 60-67% for AVT02 and EU-Humira, respectively. cIEF was used as an orthogonal method and similar data than with CEX-HPLC was observed. Predominant basic species corresponds to differences in C-terminal lysine. Other basic variants are caused by slightly higher levels of amidated proline variants as in AVT02. N-glycan analysis of fractions demonstrated that more galactosylated and sialyted glycans were present in AVT02 acidic fractions. Based on the characterisation results presented, it can be, however concluded that the differences observed in charge variant profiles are not expected to have clinical impact.
Particle analysis	Subvisible particles	MFI, DLS	Highly similar levels of sub-visible particles for AVT02 and EU-Humira.
Fab related properties	Potency	sTNFα neutralisation activity Cell viability assay Reverse signalling assay IL-8 assay	Similar binding to sTNFα and mTNFα was demonstrated. AVT02 neutralizes sTNFα in similar matter than EU-Humira, and subsequently inhibits TNFα induced cell death. In addition, apoptosis inhibition in intestinal epithelial cells (HCT11) was comparable. AVT02 and EU-Humira showed similar inhibition of IL-8 and IL-6 secretion in dose-dependent matter. Inhibition of adhesion E-Selectin, ICAM-1 and VCAM-1 expression by AVT02 and EU-Humira were

		Inhibition of adhesion molecule expression	comparable. Furthermore, AVT02 and EU-Humira blocked reverse signaling of TNFα in a similar way.
		Inhibition of apoptosis in intestinal epithelial cells	
	Binding to sTNFα and mTNFα	SPR	
		FACS	
Fc effector functions	Binding to FcγRIIIa (158F and V158), FcRn, FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIb, C1q	SPR	Similarity was demonstrated with FcγRIa, FcγRIIa, and FcγRIIb. Lower binding to FcγRIIIb was observed for AVT02 (82-108%) than for EU-Humira (102-117.9%). Also, as FcγRIIIb lacks robust signaling and it is found mainly in neutrophils and a sub-population of basophil, the importance of this difference with regards to MoA is not considered relevant. Classical ADCC assay was performed by primary PBMCs with low affinity F/F genotype. Even though ADCC activity of AVT02 batches (86-110%) fell within the comparability range 77-141%, a slight trend of lower ADCC activity was observed for AVT02 when compared to EU-Humira (91-122%). This trend was not, however observed in the cell-based ADCC reporter gene assay. Slightly lower trend of binding to FcγRIIIa (F158) supporting the lower ADCC activity could be seen for AVT02, however this was not detected with the high affinity V158 genotype. Based on the lower level of total afucosylated glycans present in AVT02 as compared to EU-Humira, a lower ADCC activity would be expected. No clear difference in relevant Fc receptor binding assays and only to a minor difference in the ADCC assay using PBMCs as effector cells. No differences were seen in the ADCC RGA. It is therefore considered unlikely that the difference seen in the ADCC PBMC assays would be clinically significant. However, to ensure to remain the similar with regards to ADCC activity, stringent control for total afucosylated glycans is set. Similar CDC activity and FcRn and C1q binding between AVT02 and EU-Humira is demonstrated.
		ELISA	
	Potency	ADCC PBMC (F/F) & (V/V)	
		ADCC RGA assay	
		CDC assay	
Other biological properties	Potency and binding	Inhibition of T cell proliferation in an MLR and induction of regulatory macrophages type II*	AVT02 showed similarity in their function to induce an increase in M2 macrophage differentiation and inhibiting T-cell proliferation.
Degradation profile	Low and high pH-, photolytic-, thermal-, oxidative-, and agitative degradation	CE-SDS nonreduced & reduced, SEC, CEX, peptide mapping LCMS, potency, DLS	Similarity in degradation studies was demonstrated.

Physicochemical properties

Primary structure

Primary structure has been studied with regards to amino acid sequence, peptide map (Lys-C/trypsin), molecular masses, disulphide bonds, and sulfhydryl analysis. The amino acid sequence of AVT02 was confirmed to be identical to the sequence of Humira. A sequence coverage of 100% of the HC and LC was achieved by LC-MS/MS peptide mapping using various types of proteases.

The molecular mass of adalimumab in AVT02 and EU-Humira was determined by high resolution LC ESI-TOF-MS, and confirmed to be highly similar with the theoretical values for the intact, reduced and de-N-glycosylated antibodies. Difference in C-terminal Lysine and in Lysine glycation levels (see table above) were detected. These slight differences are not expected to have clinical impact as these lysine residues were not located at complementarity-determining regions (CDRs) and therefore lack impact on Fc functions. Differences related to C-terminal lysine was observed also in peptide mapping profile.

Deamidations and oxidations were studied via LC-MS. Comparable levels of asparagine and glutamine deamidations were demonstrated for AVT02 and EU-Humira. It is however, noted that slightly, non-significantly, lower levels of HT38 deamidation was observed in AVT02 when compared to EU-Humira (see table above). In addition, oxidation levels of HT21 (Met256) and HTH42 (Met432) were higher in AVT02 than in EU-Humira (see table above). The difference is considered clinically irrelevant as no difference could be seen in overall FcRn binding or CDC activity for AVT02 and EU-Humira. Similar trend was observed also as part of thermal degradation studies (stressed conditions) via LC-MS, where calculated Met256 oxidation increase rate was slightly higher for AVT02 (+5.2) than for EU-Humira (+1.5). It seems that sAVT02's Met256 oxidates slightly more easily than EU-Humira's. However, as the thermal degradation studies did not indicate any difference in FcRn binding or CDC activity, the difference in Met256 due to extreme thermal stress is not considered significant from clinical point of view.

The analysis of the N- and C-terminal integrities of the light and heavy chains of AVT02 and Humira were evaluated by LC-MS analysis. The amount of the C-terminal Lysine was larger for AVT02 compared to EU-Humira (see table above). Such difference in C-terminal Lys is not considered clinically relevant. Furthermore, there are small differences in the levels of N-terminal pyroglutamic acid and C-terminal proline amidation. Amidation of the terminal proline was higher in AVT02 compared to EU-Humira (see table above). Considering the location of the proline in C-terminus of the heavy chain and having a similar charge profile to C-terminal Lysine, the difference in proline amidation is not expected to have clinical impact.

Higher order structure

Similar secondary and tertiary structure of AVT02 and EU-Humira was assessed by far- and near-UV circular dichroism (CD), Fourier-transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and intrinsic fluorescence. In intrinsic fluorescence studies, the fluorescence intensities varied slightly between AVT02 samples, however the maximal fluorescence intensity wavelength was similar for all batches of EU-Humira and AVT02. Additionally, the fluorescence curves were comparable between AVT02 and EU-Humira. Therefore, it can be concluded that the folding of the AVT02 and EU-Humira are similar.

Trisulfide peptides were estimated at 11.0% - 13.6% and 0.5% - 1.7% in the tested AVT02 batches produced by the earlier DS process 1.0. Trisulfides were however removed by a process change at the AS level (AVT02 DS process 1.1), and no trisulfide modifications were detected after that. Trisulfide modification was not detected in the Humira samples. This was also confirmed by the peptide mapping profile.

Overall, amount of free thiols is low in both AVT02 and EU-Humira. Quality range of 0.35-0.44 was set, and three batches of AVT02 were just over the quality range with values of 0.45, 0.47, and 0.46. The applicant's conclusion can be agreed upon, and this minor difference in free thiol content is not expected to be clinically meaningful.
In conclusion, no significant differences could be seen between AVT02 and Humira in any of the assays, therefore similarity with regard to higher order structures can be concluded.

Size heterogeneity
Amount of monomers measured via SEC-HPLC is high in both products (see table above). Slightly higher amounts of high molecular weight species (HMWs) are observed in AVT02 when compared to EU-Humira (see table above). In general, the HMW amounts can be considered low for both products. Additionally, AUC was used as an orthogonal method to compare the levels of size variants and the data showed comparable amounts of monomers, dimers and higher order oligomers. HMWs were further characterised with SEC-MALS demonstrating similarity in monomers and dimers, however, a peak correlating with higher order aggregates was detected only for AVT02. The applicant further characterised the SEC variant fractions via CE-SDS, LC-MS, and SEC-MALS utilizing heat stress samples where the HOA where enriched in both AVT02 and EU-Humira. It was and confirmed that both AVT02 and Humira HMW1 mainly contains Adalimumab higher order aggregates and HMW2 fractions mainly contain Adalimumab dimer. The impact on potency was also studied confirming that the TNFα potency, ADCC activity and FcγRIIIa binding was similar for AVT02 and Humira for the dimer and the HOA. The data demonstrated that AVT02 and Humira HMWs (especially HMW1) had reduced potency and reduced effector functions. HMWs are controlled at FP release. These differences are not expected to have clinical impact.

Size heterogeneity was evaluated also via CE-SDS under both reduced and un-reduced conditions. The level of intact IgG in non-reduced CE-SDS was slightly lower in AVT02 compared to EU-Humira (see table above). According to the applicant, the fragments were mainly due to Heavy-Heavy-Light Complexes (HHL), which were produced more by previous AS manufacturing process 1.0. In the newer AVT02 batches produced by the AS 1.1 process, the level of HHL complexes is clearly lower and in comparable levels to Humira. Nonetheless, these differences, are considered minor and do not imply clinical significance.

In the reduced CE-SDS HC+LC level in AVT02 was slightly lower when compared to EU-Humira (see table above), and the level of deglycosylated heavy chain (DHC) was slightly higher in AVT02 than in EU-Humira (see table above). This minor max. 0.6% difference is not, however expected to have clinical impact.

Glycan profile
N-glycan composition was compared by labelling the N-glycans with 2-AB and analyzing by normal-phase HPLC with fluorescence detection. Slightly higher amount of galactosylated glycans is observed in AVT02, however the galactosylation levels are mostly overlapping and therefore AVT02 and EU-Humira can be considered similar in terms of galactosylation.

The amount of sialyated glycans was greater in AVT02 in comparison to EU-Humira (see table above). Very low and similar levels of Neu5Ac and Neu5Gc were detected in AVT02 (<0.05% and 0.002%, respectively) compared to EU-Humira (<0.01% and <0.001%, respectively). It is justified by the applicant, that as no difference in Fc receptor function nor in clinical studies are observed, the difference in sialyated glycans is not considered great importance.

The main differences between AVT02 and EU-Humira were observed in the levels mannosylated and afucosylated glycans. The level of high mannose species (M5, M6, M7, M8, and M9) was lower in AVT02 (3.4-4.2%) in comparison to EU-Humira (8.4-9.6%), whereas the level of afucosylated species

(high mannoses not included) was slightly higher in AVT02 (2.3-2.7%) than in EU-Humira (1.2-1.5%). Consequently, the total level of afucosylated glycans was 6.0-6.7% in AVT02 in comparison to EU Humira 10.4-11.7%. According to the applicant, as no significant differences were noted in the overall ADCC activity and binding to FcγRIIIa or FcRn nor in the pharmacokinetic activities in the PK clinical trial, these differences are not expected to have clinical impact. The applicant has performed in addition effector glycan sensitivity studies for the FcγRIIIa F158 SPR, ADCC RGA and ADCC classical cell based PBMC (F/F). In summary, although a difference could be detected in the glycan profiles of AVT02 and EU Humira, this did not result in clear differences in relevant Fc receptor binding assays and only to a minor difference in the ADCC assay using PBMCs as effector cells. No differences were seen in the ADCC RGA assay. It is therefore considered unlikely that the difference seen in the ADCC PBMC assays would be clinically significant. However, as ADCC is considered as a likely mechanism of action for adalimumab in certain indications and a clear correlation between the level of total afucosylated glycans and high mannoses and ADCC activity can be observed, additional stringent specification have been set for total afucosylation to ensure the similarity of AVT02 to the reference medicinal product.

Charge variants

Distribution of charge variants was different for AVT02 than for EU-Humira. Charge variants were studied via CEX-HPLC and cIEF. CEX-HPLC was performed under two conditions: either with or without treatment of carboxypeptidase B (CPB) to remove C-terminal lysine residues. Without CPB treatment AVT02 was confirmed to contain higher amount of acidic species than EU-Humira (see table above). Higher levels of basic variants were observed in AVT02 than in EU-Humira batches (see table above). Consequently, the amount of main species were 50-53% and 60-67% for AVT02 and EU-Humira, respectively. After CPB digest the amount of basic variants was reduced, however still resulting slightly higher amounts when compared to EU-Humira. cIEF was used as an orthogonal method and similar data than with CEX-HPLC was observed. AVT02 contains slightly higher amount of acidic variants (21-29%) when compared to EU-Humira (20-23%). More basic variants were observed in AVT02 (30-32%) than in EU-Humira (21-24%) and less main variants in AVT02 (42-49%) than in EU-Humira (55-62%).

Additional characterisation was performed on charge variant CEX-HEPLC regions isolated from AVT02 (DP190002) and EU-Humira (93543XH05) batches. According to the applicant, the fractions were characterised using a combination of analytical techniques, including physicochemical assays to determine the structure, as well as potency and binding assays. As part of characterisation studies, a CPB treatment was performed to confirm that predominant basic species in AVT02 and EU Humira corresponds to differences in C-terminal lysine. Other basic variants are caused by amidated proline variants as slightly higher level of HL31-KG + proline amidation was observed via LC/MS analysis for AVT02 than in EU-Humira. Additionally, a peak fractionation study was conducted, including identification of the molecular variants present in each charge variant fraction. Based on the provided summary, it can be concluded that no new protein modifications were detected in AVT02 charge isoform assignments. Furthermore, N-glycan analysis of fractions demonstrated that more galactosylated and sialyted glycans were present in AVT02 acidic fractions, which could result the slight difference seen in acidic variants.

The charge variant fractions of AVT02 and Humira were also assessed for sTNFα binding, FcγRIIIa (V158) binding, C1q binding, and relative potency. Lowest potency was detected for acidic fraction. Otherwise, no significant differences are observed overall biological activity with the exception binding activity of the fractions to FcγRIIIa (V158). These were 97-115% and 122-144% for AVT02 and Humira, respectively. The applicant suspects that this could be due to lower level of afucosylated glycans in AVT02, which can be agreed. The fraction characterisation studies demonstrate that the main peak fractions of AVT02 and EU-Humira has similar binding affinity to FcγRIIIa 158V, thus indicating that unfractionated DP is much less affected. Based on the characterisation results

presented, it can be, however be concluded that the differences observed in charge variant profiles are not expected to have clinical impact.

Comparative stability studies

Forced degradation studies for AVT02 and EU-Humira was performed. The studies included low and high pH-, photolytic-, thermal-, oxidative-, and agitative degradation. The applicant has not performed comparative real-time real-condition stability studies for AVT02 and EU-Humira, which is, however not considered necessary for demonstration of biosimilarity.

Particle analysis

Subvisible particles analysis by MFI and DLS demonstrated highly similar levels of sub-visible particles for AVT02 and EU-Humira.

Biological properties

All biological characterisation results were briefly described and similarity expressed either by % of relative potency or % of relative binding. For receptor binding assays via SPR no Kd or Ka values have been provided, and only relative % values are included.

Fc related

Comparative ADCC assays (classical and a cell-based reporter assay), CDC assay, and binding of adalimumab to FcγRIIIa (F158 and V158), FcRn, FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIb and C1q were conducted. Similarity was demonstrated for FcγRIa, FcγRIIa, and FcγRIIb binding. Lower binding to FcγRIIIb was observed for AVT02 (82-108%) than for EU-Humira (102-117.9%), which can be also explained by the lower level of afucosylated glycans in AVT02. Also, as FcγRIIIb lacks robust signaling and it is found mainly in neutrophils and a sub-population of basophil, the importance of this difference with regards to MoA is not considered relevant.

Classical ADCC assay was performed using primary PBMCs with low affinity F/F genotype. Even though ADCC activity of AVT02 batches (86-110%) fell within the comparability range 77-141%, a slight trend of lower ADCC activity was observed in AVT02 when compared to EU-Humira (91-122%). This trend was not, however observed in the cell-based ADCC reporter gene assay. SPR binding assay was employed to assess the binding affinity to FcγRIIIa (F158 and V158). Slightly lower trend of binding to FcγRIIIa (F158) supporting the lower ADCC activity could be seen for AVT02, however this was not detected with the high affinity V158 genotype.

In addition to classical ADCC assay, a RGA assay was employed to analyse the binding of adalimumab to FcγRIIIa and downstream signalling events in cell based assay. A stable Jurkat cell line expressing Fc□RIIIa was used to study the early steps of ADCC pathway. No significant differences were observed between AVT02 and EU-Humira. Similar CDC activity and FcRn and C1q binding between AVT02 and EU-Humira is demonstrated. AVT02 showed similarity in their function to induce an increase in M2 macrophage differentiation and inhibiting T-cell proliferation.

Fab related

Similar binding to sTNFα and mTNFα was demonstrated. AVT02 neutralizes sTNFα in similar matter as EU-Humira, and subsequently inhibits TNFα induced cell death. In addition, apoptosis inhibition in intestinal epithelial cells (HCT11) was comparable. AVT02 and EU-Humira showed similar inhibition of IL-8 and IL-6 secretion in dose-dependent matter. Inhibition of adhesion E-Selectin, ICAM-1 and VCAM-1 expression by AVT02 and EU-Humira were comparable. Furthermore, AVT02 and EU-Humira blocked reverse signaling of TNFα in a similar way.

Other biological properties

Induction of regulatory macrophages and subsequent T-cell anti-proliferation was investigate by studying inhibition of T cell proliferation in an MLR and induction of regulatory macrophages type II*. AVT02

showed similarity in their function to induce an increase in M2 macrophage differentiation and inhibiting T-cell proliferation.

Conclusion

In conclusion, the similarity between AVT02 and the reference product, EU-Humira has been addressed in a comprehensive comparability exercise. It is acknowledged that Libmyris is highly similar to Humira (EU) in physicochemical and biological properties. No clinically meaningful differences are expected between Libmyris and the reference product, as further supported by the results of the functional characterisation and the clinical studies.

Adventitious agents

AVT02 is expressed in well-described Chinese Hamster Ovary (CHO) cells, which are known to express retrovirus-like particles (RVLPs). The applicant determined the retroviral burden from cell culture supernatants. The calculated safety margin was considered sufficient.

The applicant has performed viral testing of the unprocessed bulk harvest material and presented the methods used in viral testing.

For viral clearance studies the applicant has chosen four model viruses, which was considered appropriate. These viruses included Xenotropic murine leukemia virus (MuLV), Pseudorabies (PRV), Reovirus 3 (Reo-3), and Minute virus of mice (MVM). The results of the viral clearance studies demonstrated that there are at least two orthogonal virus removal/inactivation steps which result in overall log reduction factors of over 10 for the tested model viruses. Both the mixed-mode chromatography and virus reduction filtration were effective in viral clearance. The applicant presented the inactivation results for low pH treatment for A-MuLV and PRV. The applicant has submitted virus validation reports to confirm that the viral clearance and inactivation studies performed result in a satisfactory outcome.

The applicant has also performed viral clearance studies to demonstrate the effectiveness of both fresh and aged chromatography resin for virus removal. The study with the aged resin demonstrates that the virus removal/inactivation capacity of the resins used in the AVT02 process is not impacted with the aged resin. Overall, it is agreed that the viral clearance/inactivation studies performed are sufficient.

The risk of microbial and mycoplasma contamination has, overall, been adequately addressed. The cell banks comply with the test for sterility and unprocessed bulk batches have been tested for bioburden and mycoplasma. Except for the cell banks, all raw materials and excipients used in the production process are of non-animal source. Consequently, no materials falling into the scope of the current Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy (TSE) agents via medicinal products (EMA/410/01 rev 3) are used in the manufacturing processes for AVT02.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled, and validated. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

A major objection was raised during the procedure relating to the lack of a risk evaluation on the

potential presence of nitrosamines impurities in the product. This major objection was satisfactorily resolved as the applicant provided the requested risk assessment and relevant documentation.

The similarity between Libmyris and the reference product, Humira-EU has been addressed in a comprehensive comparability exercise. The provided quality data support biosimilarity versus the EU reference medicinal product (Humira (EU)) at the quality level. In order to ensure that similarity remains at sufficient level with regards to ADCC activity, stringent controls for afucosylated glycan variants in AS release is applied.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendation for future quality development

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

- The applicant is recommended to revisit the acceptance limits for glycan structures once a certain number of batches of AS has been manufactured (REC).

–The applicant is recommended to validate the method for glycan structures at the release site and provide the respective data by end of November 2021 (REC).

2.5. Non-clinical aspects

2.5.1. Pharmacology

A battery of *in vitro* assays evaluating the similarity in functional activity of AVT02 and EU-Humira included assessment of Fab-related sTNFα neutralisation activity (inhibition of sTNFα induced activation of caspase 3 and 7), inhibition of sTNFα-induced apoptosis, inhibition of TNFα-induced IL-8 release from HT1080 cells, and induction of reverse signaling in Jurkat-mTNFα cells. Fc-related analyses included binding to FC-receptors and to C1q, ADCC assays (classical and reporter) and a CDC assay. Additional assays included analysis of induction of PBMC differentiation to CD68/CD206+ regulatory macrophages and inhibition of CD4+ T-cell proliferation. These studies are sufficient to cover all relevant modes of action of adalimumab and are in line with the EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). AVT02 batches representative of the proposed commercial process (manufacturing processes 1.0 and 1.1)-were used in head-to-head comparison of the pharmacological *in vitro* analyses.

All above mentioned *in vitro* comparability data were included under the M3.2.R.3, and no additional pharmacology data were presented under M4. To avoid repeating the provided data, functional comparability data are presented in the Quality Biosimilarity section. For the majority of the parameters analysed, similarity was demonstrated between AVT02 and EU-Humira.

No studies to evaluate secondary pharmacodynamics, safety pharmacology or pharmacodynamic drug interactions of AVT02 have been conducted in accordance with the EMA guidance for development of biosimilars.

2.5.2. Pharmacokinetics

One non-GLP study AVT02-PC-001 in Cynomolgus monkeys was conducted to investigate local tolerability and pharmacokinetics of AVT02 and EU-Humira. A single dose of adalimumab (8 mg/kg) was administered subcutaneously (s.c.) to 6 animals per treatment group. Plasma samples were collected up to 14 days post administration for PK analysis.

Two batches of AVT02 were included in the study, one from the early development process not representative of the drug product intended for marketing, and the other batch representative of the commercial product. This study was not designed to demonstrate the similarity in regards the PK or tolerability profiles and can be considered supportive only.

Electrochemiluminescence assay was fit for purpose to quantify adalimumab (AVT02 or EU-Humira) of 5 to 250 ng/mL in 5% cynomolgus monkey serum.

AVT02 showed comparable Tmax, a slightly reduced exposure and longer terminal half-life compared to EU-Humira (mean values). Overall, the data did not reveal significant differences between the AVT02 and EU-Humira in their PK profiles in cynomolgus monkeys.

No distribution, metabolism, excretion and pharmacokinetic drug interaction studies were conducted and are not required for a biosimilar.

2.5.3. Toxicology

No specific toxicology studies were conducted with AVT02. The toxicology of adalimumab is well known from the reference product. No new process or product related impurities were identified that would affect safety of AVT02 or require further toxicity testing.

The local tolerance investigations were included in the Cynomolgus monkey study investigating pharmacokinetics (AVT02-PC-001). The study was not designed to show similarity between AVT02 and EU-Humira. Nevertheless, the data indicated that there were no differences between AVT02 and Humira in injection site tolerability. Both adalimumabs triggered only mild reactions such as erythrema and edema in 1 out of 12 AVT02 group and 2 out of 6 in EU-Humira group cynomolgus monkeys.

2.5.4. Ecotoxicity/environmental risk assessment

The active substance of AVT02 (adalimumab) is a recombinant human monoclonal antibody, not expected to result in a significant risk to the environment. Furthermore, in the case of biosimilars, an environmental risk assessment is not needed, which is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

2.5.5. Discussion on non-clinical aspects

A stepwise development and the totality of the evidence approach was applied in line with recommendations from EMA scientific advice (EMA/CHMP/SAWP/859223/2018) and biosimilar guideline EMA/CHMP/BMWP/403543/2010) to demonstrate the biosimilarity between ATV02 and Humira. The

nonclinical dossier of AVT02 was very condensed. *In vitro* comparability data were included, and no additional pharmacology data were presented. In addition, nonclinical dossier included one supportive cynomolgus monkey study to assess pharmacokinetics and local tolerability.

The comparative side-by-side functional *in vitro* data are from 9 AVT02 and 9 EU-Humira batches. For establishment of quality target profile, altogether 28 EU-Humira batches were used, of which 5 - 23 batches were included in the cumulative comparative functional similarity assessments for calculating the % of relative potency or binding in comparison the reference standard. The functional analyses were done with AVT02 DP manufactured with processes 1.1 (commercial process) and 1.0.

The ATV02 development programme was carried out using state-of-the-art and orthogonal methods. These studies are sufficient to cover all relevant modes of action of adalimumab and are in line with the EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). The presented data were condensed but allowed drawing broad conclusions of the similarity between AVT02 and EU-Humira for the majority of functional parameters (see further the Quality/Biosimilarity). Some differences were noted, but these are not anticipated to have clinical impact. Nevertheless, the differences noted in such as in the charge variants (in total afucosylation species) triggered a need for further clarifications, including the sensitivity of FcγRIIIa and classical ADCC assays to detect differences (described under the Quality/biosimilarity sections). These questions were included in the Quality LoQ. The nonclinical PK and local tolerability study in Cynomolgus monkeys were conducted with process 1.1. AVT02 batch, and with an early development batch not representative of the commercial product. This study was not designed to demonstrate the similarity in PK or tolerability and is considered supportive. The pharmacokinetic and local tolerance profiles of AVT02 (commercial process 1.1 batch) and EU-Humira did not differ significantly.

2.5.6. Conclusion on the non-clinical aspects

No Major Objections were identified from the nonclinical data of AVT02. Similarity of AVT02 and EU-Humira in terms of functional, pharmacological activities was demonstrated adequately (refer to Quality/biosimilarity regarding the functional aspects rooting mainly to slight differences in the total afucosylation levels).

The proposed SmPC section 5.3 is identical to that of EU-Humira.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical studies were designed in accordance with the principles of International Council for Harmonisation Good Clinical Practice (GCP) and of the Declaration of Helsinki (2013) in keeping with local legal requirements. Some uncertainties concerning study conduct and proper monitoring arose during assessment of study AVT02-GL-301 and study AVT02-GL-101. In particular, doubts arose related to adherence to study protocol vis-à-vis exclusion criteria in study AVT02-GL-301 and related to study drug administration in study AVT02-GL-101. Upon request, acceptable GCP Training Certificates of the principal investigators were provided. The applicant also provided sufficient assurance of adequate training of the study personnel and adherence to study protocol. The study

conduct, monitoring and training of the personnel of studies AVT02-GL- 101 and AVT02-GL- 303 appear adequate. No further uncertainties regarding GCP compliance remain.

Tabular overview of clinical studies

Table 2 Tabular overview of clinical studies

Study Number	AVT02 DP Batch Number[a]	Main study objective	Study Design Study start/completion	Test product Dosage, regimen Route of administration	Number of subjects treated	Healthy subjects or diagnosis of patients	Duration of Treatment	Primary and main secondary endpoints
A. Similarity of AVT02 to EU- and US-Humira								
AVT02-GL-101	180004	PK similarity vs. EU- vs. US-Humira, PK similarity EU- vs. US-Humira	Multicenter, randomized, double-blind, parallel, 3-arm	AVT02 EU-Humira US-Humira 40 mg s.c.	390 (130|129|131/arm)	Healthy subjects	Single dose	C_{max}, AUC_{0-t}, AUC_{0-inf} Safety, immunogenicity
AVT02-GL-301	180004	Therapeutic equivalence of AVT02 to EU-Humira	Multicenter, randomized, double-blind, parallel, 2-arm, 2 stage, active control	Stage 1 AVT02 EU-Humira Stage 2 AVT02/AVT02 EU-Humira/AVT02 EU-Humira/Eu-Humira 80 mg s.c. (LD) followed by 40 mg s.c. EOW	Stage 1: 412 (205|207/arm) Stage 2: 392 (197|97|98)/arm)	Patients with chronic moderate to severe PsO	Repeat dose Stage 1 Week 0-16 Stage 2 Week 16-54	Efficacy: % change in PASI from BL to Week 16 % change in PASI from BL to Week 8, 12, 24, 32, 42, 50 PASI 50, PASI 75, PASI 90, and PASI 100 response rate at Weeks 16, 24, 50 Change from BL in QoL as measured by DLQI scores at Weeks 16, 24, 50 Safety, immunogenicity PK: C_{trough}
B. Validation of the autoinjector								
AVT02-GL-102	180004	PK similarity of AVT02 PFS and AI presentations	Multicenter, randomized, open label, parallel, 2-arm	AVT02-AI AVT02-PFS 40 mg s.c.	204 (100|104/arm)	Healthy subjects	Single dose	C_{max}, AUC_{0-t}, AUC_{0-inf} Safety, immunogenicity

Study Number	AVT02 DP Batch Number[a]	Main study objective	Study Design Study start/completion	Test product Dosage, regimen Route of administration	Number of subjects treated	Healthy subjects or diagnosis of patients	Duration of Treatment	Primary and main secondary endpoints
AVT02-GL-303[c]	Active period: 180004 Extension phase: DP190002	Real-life patient handling experience with an AI in patients with RA	Multicenter, open label, single arm, active period of 8 weeks, extension phase Week 9 to 56	Active period AVT02-AI Extension phase AVT02-PFS 40 mg s.c. EOW	107	Patients with active RA	Active period Week 0-8 Extension phase Week 9-56	Percentage of successful self-injections as reported in the questionnaires completed by the trial site personnel (OAT) and by the patients (PAT) AI handling events, ease of use, adequacy of the AI instructions for use, AI robustness Efficacy endpoints (ACR20/50/70 and DAS28 at Week 14, 24, 36, 56) Safety and immunogenicity PK: C_{trough}
Human factors summative study (Study AVT02 HF validation AI)	NA	Demonstration that intended users can use the AI safely and effectively	One-on-one, in-person interview sessions	Assessment of performance and function of the AVT02-AI and instructional labeling in a simulated-use setting	60, 15/arm	Adult Patients with RA Adolescent Patients with JIA Caregivers HCPs	60 min sessions	Demonstration that intended users can use the AI safely and effectively
C. Other completed studies: AVT02-GL-100								
AVT02-GL-100[b]	00001DP	Pilot, safety, tolerability, and PK study of AVT02 and EU-Humira	Randomized single-blind parallel 2-arm	AVT02 EU-Humira 40 mg s.c.	24; 12/arm	Healthy subjects	Single dose,	Safety, tolerability C_{max}, AUC_{0-t}, AUC_{0-inf}
D. Other ongoing studies: AVT02-GL-302								

Study Number	AVT02 DP Batch Number[a]	Main study objective	Study Design Study start/completion	Test product Dosage, regimen Route of administration	Number of subjects treated	Healthy subjects or diagnosis of patients	Duration of Treatment	Primary and main secondary endpoints
AVT02-GL-302[c]	DP200002	Compare PK, immunogenicity, efficacy and safety between patients receiving EU-Humira and patients undergoing repeated switches between EU-Humira and AVT02	Multicenter, double-blind, randomized, 2-arm, parallel group, active controlled, comparison study	AVT02-PFS EU-Humira	22 Mar 2021: 568 enrolled, 537 on study	PsO patients	Lead-in Period Week 1-12 (open label) Switching Module Week 12-28 (double blind) Extension Phase Week 28-50 (open label)	$AUC_{tau,\ 26\text{-}28}$ $C_{max,\ 26\text{-}28}$ Percent improvement in PASI from Week 1 to Week 28 Safety, immunogenicity

Note: All studies were conducted outside of the U.S.A. except the HF study

[a] A batch overview is provided in Module 2.7.1, Table 1. [b] Results of the pilot Study AVT02-GL-100 will not be part of the biosimilarity assessment as the AVT02 batch used in the study was manufactured by an earlier process and is not representative of the commercial batches. The CSR is available in Module 5.3.5.4. [c] Additional safety narratives for ongoing studies AVT02-GL-302 and AVT02-GL-303 are provided in Day 121 Safety Update for EMA.

ACR = American College of Rheumatology; AI = autoinjector; AUC_{0-t} = Area under the serum concentration time curve up to time t, where t is the last time point with concentrations above the lower limit of quantitation (LLOQ); AUC_{0-inf} = total AUC after extrapolation from time t to infinity, where t is the last time point with a concentration above LLOQ; $AUC_0 + C_{t/kel}$); C_{max} = maximum serum drug concentration; C_{trough} = serum through drug concentrations (= lowest serum drug concentration before the next dose is administered); DP = drug product; EOW = every other week; EU = Europe; HF = human factors; HPC = Healthcare Professional; JIA = juvenile idiopathic arthritis; LD = loading dose; NA = not applicable; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetics; PFS = prefilled syringe; PsO = plaque psoriasis; RA = rheumatoid arthritis; s.c. = subcutaneous; US = United States

2.6.2. Pharmacokinetics

Analytical methods

Bioanalytical methods used in the clinical studies for Hukydra adalimumab include determination of adalimumab concentrations in human serum by using Meso Scale Discovery (MSD) platform based on electrochemiluminescent (ECL) signal detection and immunogenicity testing including detection of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) also on ECL-MSD platforms.

MSD-ECL based method was used in PK studies to quantify AVT02 and adalimumab (EU-Humira and US-Humira) concentrations in healthy human serum (clinical studies AVT02-GL-101 and AVT02-GL-102) and in human serum samples from the patients with Plaque Psoriasis (PsO) (clinical study AVT02-GL-301). In this method, MSD plates were coated with the Fab fragment of a commercial monoclonal ant-adalimumab antibody (BioRad) used as a capture antigen. After blocking and washing steps the standards, quality controls and samples were added to the plate. After incubation and washing Sulfo-tagged detection antibody human anti-adalimumab was added and the ECL signal produced by Sulfo-tag was detected.

An ECL based method was utilised for the detection of ADAs against AVT02 and Humira in healthy and PsO human serum (clinical studies AVT02-GL-101, AVT02-GL-102 and AVT02-GL-301). A three-tiered approach comprising of screening, confirmation and titer was used. Both biotinylated and sulfo-tagged AVT02 preparations bind to anti-adalimumab antibodies. Resulting complexes were captured on streptavidin pre-coated ECL-specific microtiter plates and were detected via the emitted signal of the Sulfo-tag Polyclonal goat anti-AVT02 antibody and polyclonal goat anti-Humira antibody were used as positive controls.

An ECL assay for the detection of NAb against AVT02 and EU-Humira was performed using a competitive ligand binding assay format. In this method, biotinylated AVT02 was immobilised to streptavidin coated plates. The samples pre-treated with acid dissociation were added to plates. Sulfo-Tag-labeled TNFα bound to AVT02 and Sulfo-tag produced a chemiluminescent signal that was triggered when voltage was applied. Presence of NAb prevents binding of TNFα and results in decrease in chemiluminescent signal. The resulting signal is, thus, inversely proportional to the amount of NAb present in sample. Anti-adalimumab monoclonal antibody against Humira was used as positive control.

Pharmacokinetics

Three clinical PK studies are included in the dossier to support the current application:

- Clinical study AVT02-GL-101: This PK similarity study compared the PK of AVT02, EU-Humira and US-Humira after single s.c. administration of 40 mg adalimumab in healthy subjects.
- Clinical study AVT02-GL-102: In this study, PK of AVT02 was compared between pre-filled syringe (PFS) and autoinjector (AI) in healthy subjects.
- Clinical study AVT02-GL-301: In this study, steady-state PK of AVT02 after multiple administrations in patients with moderate-to-severe PsO was assessed.

Clinical PK similarity study in healthy subjects (AVT02-GL-101)

The study was conducted at 3 study sites in New Zealand (2 sites: 101 Christchurch Clinical Studies Trust Limited, Christchurch, 201 Auckland Clinical Studies, Auckland) and Australia (1 site: 301 Scientia Clinical Research Limited, New South Wales) between 20 March 2019 (first subject enrolled) and 27 Feb 2020 (last subject completed). The bioanalytical analyses at Nuvisan GmbH were performed between 31.10.2019 and 26.3.2020.

This study was a phase I, multicentre, randomised, double-blind, 3-arm, parallel, single-dose study in adult healthy subjects (13.3% Japanese). Enrollment was made in 2 parts. In part 1, at least 90 subjects (i.e., n = 30/group) were enrolled and before the part 2, an interim analysis of unblended data was made and the sample size for part 2 was calculated (to ensure power of at least 80%in the study).

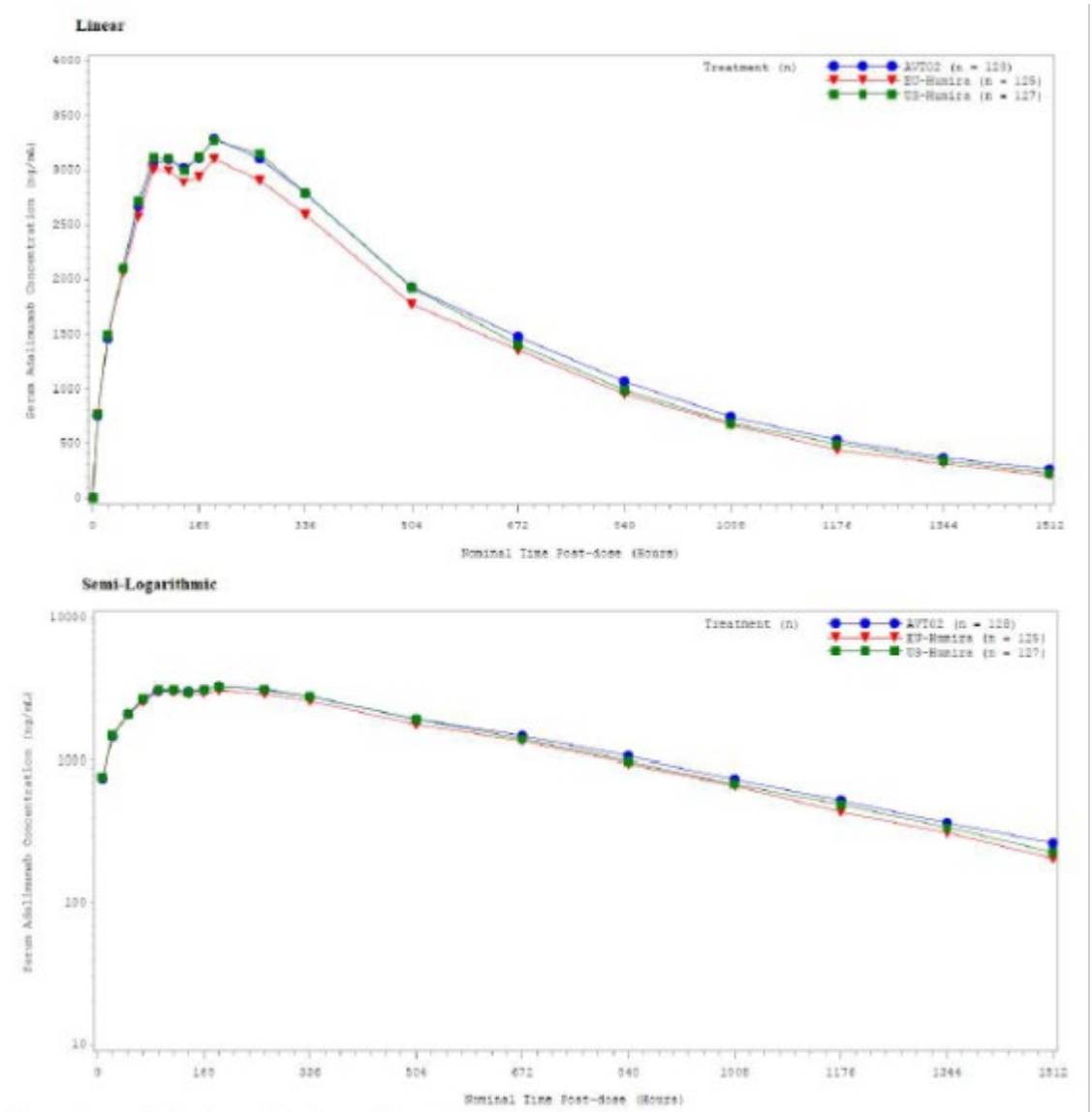
Subjects received a single 40 mg (0.4 ml) subcutaneous (s.c.) dose of either AVT02, EU-Humira, or US-Humira in a pre-filled syringe (PFS) in a fasted state (water was allowed). Blood samples were collected for measurement of serum concentrations of adalimumab from all subjects at the following time points: pre-dose (within 1 hour of dosing), post-dose: 8, 24, 48, 72, 96, 120, 144, 168, 192, 264, 336, 504, 672, 840, 1008, 1176, 1344, and 1512 hours (= 63 days i.e., 9 weeks). Immunogenicity samples were collected at pre-dose (30 min before dosing) and at post-dose: 9, 15, 29 and 64 days. 392 subjects were randomised, and 390 subjects were dosed (n = 130 to AVT02, n = 129 to EU-Humira and n = 131 to US-Humira). 384 subjects completed the study.

PK results

380 subjects (96.9%) were included in the PK population: 128 in the AVT02 group, 125 in the EU Humira group, and 127 in the US-Humira group.

Concentration-time profiles were similar following a single 40 mg s.c. dose of either AVT02, EU-Humira or US-Humira (**Figure 1**.

Figure 1 Mean serum concentration (ng/ml)-time (hours) profiles of adalimumab by treatment group on linear and semilogarithmic scale (PK population)



Notes: Lower limit of quantification = 7.5 ng/mL.
Concentrations reported as below the limit of quantification (<LLOQ) are set to zero for the calculation of summary statistics.
Mean concentration values of zero are excluded from printing on log concentration scale.

The geometric mean Cmax was similar across treatment groups for all 3 treatments (**Table 3**). The geometric mean AUC0-t and AUC0-inf were also comparable across the 3 treatment groups, with slightly higher geometric mean values observed for the AVT02 group compared with the EU-Humira group and US-Humira group for both parameters. Systemic elimination of adalimumab was consistent across the 3 treatment groups, with slow apparent total serum clearance and a long terminal half-life.

Table 3 Summary of serum PK parameters for adalimumab by treatment (PK population)

Treatment	Median (Range) T_{max} (h)	Geometric Mean (Geometric CV%) C_{max} (ng/mL)	AUC_{0-t} (h·ng/mL)	AUC_{0-inf} (h·ng/mL)	K_{el} (1/h)	$t_{1/2}$ (h)	CL/F (mL/h)	V_z/F (L)
AVT02 (N = 128)	192.0 (48-672)	3355 (41%)	2018000 (48%)	2159000 (53%)	0.00398 (107%)	174.1 (107%)	18.53 (53%)	4.654 (77%)
EU-Humira (N = 125)	168.0 (72-504)	3239 (38%)	1832000 (52%)	1971000 (52%)	0.00432 (95%)	160.6 (95%)	20.30 (52%)	4.702 (71%)
US-Humira (N = 127)	192.0 (24-506)	3365 (41%)	1954000 (51%)	2101000 (53%)	0.00416 (91%)	166.6 (91%)	19.04 (53%)	4.577 (60%)

AUC_{0-inf} = Area under the serum concentration-time curve from time zero (predose) extrapolated to infinity; AUC_{0-t} = Area under the serum concentration-time curve from time zero (predose) to the time of the last quantifiable concentration; CL/F = apparent total serum clearance; C_{max} = maximum serum concentration; CV% = coefficient of variation as a percent; K_{el} = terminal elimination rate constant; N = Total number of subjects in the relevant population; $t_{1/2}$ = apparent terminal half-life; T_{max} = time to C_{max}; V_z/F = apparent volume of distribution.

Lower limit of quantification was 7.5 ng/mL.

In the comparison of all combined data from parts 1 and 2 for the AVT02 group with the EU-Humira and US-Humira treatment groups, the 90% CI for the ratio of geometric means for the primary PK parameters of Cmax, AUC0-t, and AUC0-inf, based on the FC test analysis, were all contained within the pre-specified bioequivalence margins of 80% and 125%, thus demonstrating that systemic exposure after AVT02 administration is bioequivalent to exposure after both EU-Humira and US-Humira administration (**Table 4**).

Table 4 Overview of bioequivalence assessment of adalimumab primary PK parameters (PK population)

Parameter (unit)	Combined Geometric Mean Ratio (90% CI) [a] AVT02/EU-Humira	AVT02/US-Humira	EU-Humira/US-Humira
C_{max} (ng/mL)	1.0500 (0.96, 1.13)	1.0100 (0.93, 1.09)	0.9650 (0.89, 1.05)
AUC_{0-t} (ng·h/mL)	1.1000 (1.00, 1.23)	1.0300 (0.93, 1.15)	0.9350 (0.84, 1.04)
AUC_{0-inf} (ng·h/mL)	1.1098 (0.99, 1.24)	1.0400 (0.92, 1.16)	0.9350 (0.84, 1.05)

ANOVA = analysis of variance; AUC_{0-inf} = Area under the serum concentration-time curve from time zero (predose) extrapolated to infinity; AUC_{0-t} = Area under the serum concentration-time curve from time zero (predose) to the time of the last quantifiable concentration; CI = confidence intervals; C_{max} = maximum serum concentration; FC = Fisher's combination.

a. 90% CI*: FC method: p-values for Parts 1 and 2 data (P1 and P2) were recalculated using a range of limits (instead of 0.8 and 1.25) until the combined p-value* for the FC test equaled 0.05 – these final limits were the 90% CI for the Combined Geometric Mean Ratio

Results are based on an ANOVA model with treatment and randomization strata as a fixed effect. The data were logarithmically transformed prior to the analysis and then transformed back for the result presentation.

A sensitivity analysis of bioequivalence was performed on the combined final PK data using conventional methods (i.e., with no accounting for the 2 study parts). The results were supportive of the primary bioequivalence analysis. The 90% CIs of the geometric LS mean ratios for the 3 primary PK parameters were all contained within 80% and 125%. In the qualitative comparison of adalimumab primary PK parameters in the Japanese subgroup, no notable differences were observed between the treatment groups, and the geometric mean ratios in all cases fell within the predefined equivalence range for the study as a whole.

Due to the high frequency of ADA and NAb formation, relationships between immunogenicity and PK parameters could not be elucidated.

Clinical device study to compare PK of AVT02 when administered from PFS and from AI (AVT02-GL-102)

The study was performed at 2 study sites (i.e., Christchurch Clinical Studies Trust Ltd and Auckland Clinical Studies Ltd) in New Zealand, between 01 July 2019 (first subject enrolled) and 03 Dec 2019 (last subject completed). The PK bioanalytical analyses were performed by Nuvisan GmbH, Wegenerstrasse 13, Neu-Ulm, Germany. The immunogenicity bioanalytical analyses were made by BioAgilytix Europe GmbH, Hamburg, Germany.

This study was a phase I, multi-centre, randomised, open-label, 2-arm, parallel study in adult healthy subjects. The final protocol was dated 29 March 2019. Subjects received a single s.c. injection of 40 mg (0.4 ml) AVT02 on day 1, either via manually by a PFS or with an AI in the fasted state (water was allowed). The PK blood samples, and immunogenicity samples were collected at the same time points as in the pivotal PK study AVT02-GL-101 (see above). 204 subjects (N = 100 in PFS group and N = 104 in AI group; aged 18 to 55 years, BMI between 18.5 to 32.0 kg/m^2) were randomised and dosed and 197 subjects completed the study.

PK results

The PK population consisted of 198 subjects (N = 99 in PFS group and N = 99 in AI group).

In the comparison between treatment groups, the 90% CI for the ratio of geometric LS means for the primary PK parameters of C_{max}, AUC_{0-t}, and AUC_{0-inf} were all contained within the pre-specified bioequivalence margins of 80% and 125%, thus demonstrating that systemic exposure after AVT02-AI administration was bioequivalent to exposure after AVT02-PFS administration (**Table 5**).

Table 5 Bioequivalence assessment of adalimumab PK parameters (PK population)

			AVT02-AI/AVT02-PFS	
Parameter (unit)	Treatment	n	Ratio of Geometric Least Square Means (%)	90% CI of the Ratio
C_{max}	AVT02-AI	99	100.45	(92.18, 109.45)
(ng/mL)	AVT02-PFS	99		
AUC_{0-t}	AVT02-AI	99	107.31	(94.55, 121.79)
(ng·h/mL)	AVT02-PFS	99		
AUC_{0-inf}	AVT02-AI	97	107.22	(94.00, 122.30)
(ng·h/mL)	AVT02-PFS	95		

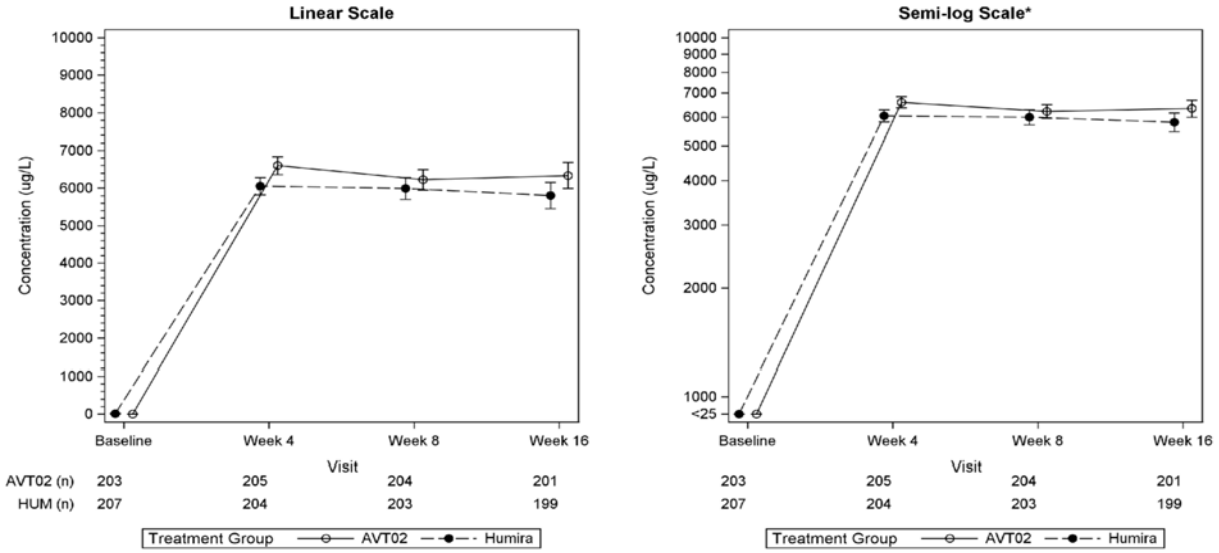
CI = confidence intervals; LS = least-squares; n = number of subjects in each category.
Results are based on an analysis of variance model with treatment as a fixed effect. The data were logarithmically transformed prior to the analysis then transformed back for the result presentation.

Clinical study in patients with moderate-to severe chronic plaque psoriasis (AVT02-GL-301)

The PK analysis set was the same as safety analysis set. The subject disposition was as follows: n = 205 AVT02 group, n = 207 EU-Humira group, n = 197 AVT02/AVT02 group, n = 97 EU-Humira/AVT02 group and n = 98 EU-Humira/EU-Humira group.

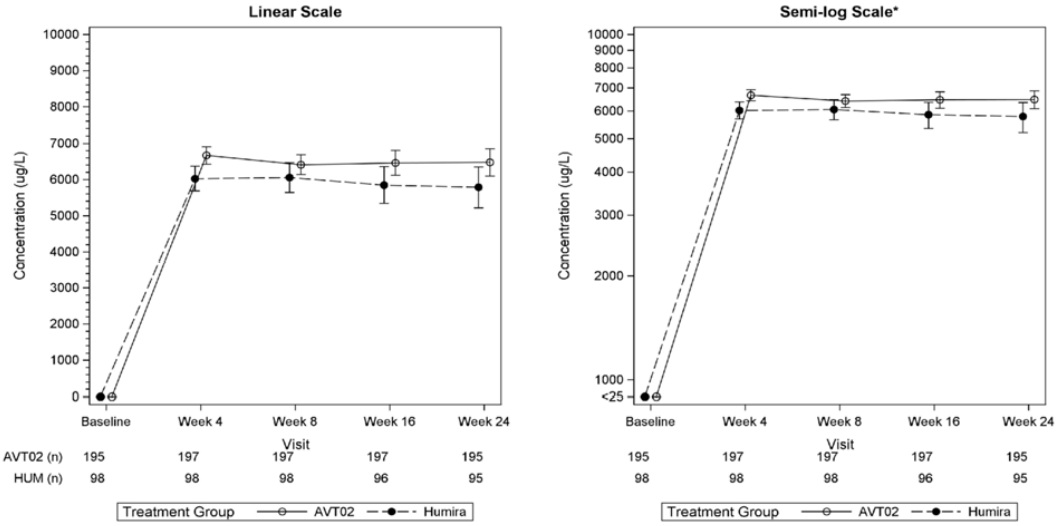
AVT02 concentrations were slightly above those of EU-Humira at all time points measured including those at steady-state **(Figures 2** and **3** and **Tables 6** and **7**); however, the total exposure was considered comparable.

Figure 2 Mean ± SE of serum trough concentrations (µg/l)-time (weeks) up to week 16 (safety analysis set)



*All baseline summary statistics are assigned a nominal value to enable plotting values of 0 on the log scale. Note: Only subjects who were treated with the same drug (AVT02 or Humira) are reported in this figure.
Abbreviations: HUM = Humira; n = number of subjects in the sample; ug/L = micrograms/liter Source: Figure 14.3.1.1

Figure 3 Mean ± SE of serum trough concentrations (µg/l)-time (weeks) up to week 24 (safety analysis set)



*In the semi-log plot, all baseline summary statistics are assigned a nominal value to enable plotting values of 0. Note: Only subjects who were treated with the same drug (AVT02 or Humira) are reported in this figure.
Abbreviations: HUM = Humira; n = number of subjects in the sample; ug/L =

Table 6 Serum trough concentrations over time up to week 16 (safety analysis)

	AVT02 Concentration (µg/L) (N = 205)							Humira Concentration (µg/L) (N = 207)						
Time Point	**n**	**Mean (SD)**	**Median**	**Min, Max**	**GEOM**	**Log_SD**	**CV%**	**n**	**Mean (SD)**	**Median**	**Min, Max**	**GEOM**	**Log_SD**	**CV%**
Baseline	203	1.3 (14.23)	0.0	0, 184	NA	NA	1069.6	207	11.1 (159.17)	0.0	0, 2290	NA	NA	1438.7
Week 4	205	6600.2 (3358.56)	6490.0	0, 15500	6220.38	0.55	50.9	204	6052.5 (3301.05)	5890.0	0, 17800	5388.78	0.83	54.5
Week 8	204	6224.1 (3927.25)	6300.0	0, 17500	4898.52	1.10	63.1	203	5989.2 (4157.68)	5450.0	0, 19900	4897.83	1.07	69.4
Week 16	201	6337.7 (4917.77)	6260.0	0, 24000	4897.45	1.23	77.6	199	5807.6 (4956.09)	5370.0	0, 19500	3978.90	1.57	85.3
ET	6	2083.3 (5103.10)	0.0	0, 12500	NA	NA	244.9	6	2148.3 (3082.37)	1120.0	0, 7920	3645.12	0.68	143.5

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug (Day 1) in Stage 1. Concentrations below the lower limit of quantitation (<LLOQ) measurable concentration were assigned a value of 0. CV% = (SD/Mean)*100. Two samples were not analyzable at BL in the AVT02 treatment group. Three subjects had adalimumab concentrations pre-dose; the reason for a detected adalimumab concentration in these samples is unknown. Calculations of GEOM and Log SD are based on non-zero values only. GEOM and Log SD are marked as NA when more than 50% of values for a given assessment are 0.
Abbreviations: CV = coefficient of variance; ET = early termination; GEOM = geometric mean; LLOQ = lower limit of quantitation; Log_SD = SD of log-transformed data; µg/L = microgram/liter; max = maximum; min = minimum; n = number of subjects in the sample; N = number of subjects; NA = not applicable; SD =standard deviation

Table 7 Serum trough concentrations over time through week 16 and week 24 (safety analysis)

	AVT02 Concentration (µg/L) (N = 197)							Humira Concentration (µg/L) (N = 98)						
Time Point	**n**	**Mean (SD)**	**Median**	**Min, Max**	**GEOM**	**Log_SD**	**CV%**	**n**	**Mean (SD)**	**Median**	**Min, Max**	**GEOM**	**Log_SD**	**CV%**
Baseline	195	1.4 (14.52)	0.0	0, 184	NA	NA	1048.2	98	0.0 (0.00)	0.0	0, 0	NA	NA	NA
Week 4	197	6666.9 (3340.16)	6550.0	0, 15500	6332.10	0.54	50.1	98	6025.2 (3377.38)	5890.0	0, 17800	4928.94	1.05	56.1
Week 8	197	6412.9 (3857.84)	6400.0	0, 17500	5430.35	0.92	60.2	98	6058.6 (4063.73)	5510.0	0, 15000	4636.28	1.15	67.1
Week 16	197	6460.0 (4890.48)	6360.0	0, 24000	5098.56	1.15	75.7	96	5848.5 (4998.19)	5640.0	0, 17500	4243.97	1.45	85.5
Week 24	195	6478.4 (5297.37)	6110.0	0, 20800	5146.95	1.30	81.8	95	5782.7 (5545.89)	5370.0	0, 25400	3734.95	1.82	95.9
ET	2	0.0 (0.00)	0.0	0, 0	NA	NA	NA	2	0.0 (0.00)	0.0	0, 0	NA	NA	NA

Note: Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug (Day 1) in Stage 1. Concentrations below the lower limit of quantitation (<LLOQ) measurable concentration were assigned a value of 0. CV% = (SD/Mean)*100. These data are related to PASI responders only. Two samples were not analyzable at BL in the AVT02 treatment group. Three subjects had adalimumab concentrations pre-dose; the reason for a detected adalimumab concentration in these samples is unknown. Calculations of GEOM and Log SD are based on non-zero values only. GEOM and Log SD are marked as NA when more than 50% of values for a given assessment are 0.
Abbreviations: CV = coefficient of variance; ET = early termination; GEOM = geometric mean; LLOQ = lower limit of quantitation; Log_SD = SD of log-transformed data; µg/L = microgram/liter; max = maximum; min = minimum; n = number of subjects in the sample; N = number of subjects; NA = not applicable; SD =standard deviation

2.6.3. Pharmacodynamics

Validated PD markers do not exist for the efficacy of TNF-α inhibitors and therefore, no pharmacodynamic data were evaluated in the Phase 1 bioequivalence studies in healthy subjects. Regarding the primary PD, a set of non-clinical *in vitro* studies have been performed. No studies on secondary PD have been provided, nor have they been required according to the EMA guideline (EMA/CHMP/BMWP/403543/2010).

2.6.4. Discussion on clinical pharmacology

Bioanalytics

Analysis of adalimumab in serum was performed and validated by Nuvisan GmgH, Neu-Ulm, Germany. Immunogenicity testing including detection of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) were performed by BioAgilytix GmbH, Hamburg, Germany. The bioanalytical methods used in the clinical studies for AVT02 have been validated according to the relevant guidelines. The CHMP requested that the applicant preforms further testing to provide long-term stability data, which will be submitted in post-authorisation phase; please see the list of recommendations in section 4.

Pharmacokinetics

Two clinical studies were performed, in which the PK of AVT02 was compared to that of EU-Humira and one in which also; the US-Humira was as a comparator product. The pivotal PK study (AVT02-GL-101) was performed in healthy subjects, in which adalimumab was administered 40 mg s.c. as a single dose in a PFS. The clinical study AVT02-GL-301 was performed in PsO patients, in which AVT02 and EU-Humira, after an 80 mg loading dose, were administered every other week in dose of 40 mg s.c. in a PFS. In addition, PK of AVT02 was evaluated in the device comparison study (AVT02-GL-102), in which adalimumab was administered in 40 mg s.c. single-dose using PFS or AI in healthy subjects. The applicant has two presentations of the test product. One has a nominal filling volume of 0.4 ml and another 0.8 ml. Both presentations contain adalimumab at a concentration of 100 mg/ml. In the clinical studies, the presentation 40 mg/0.4 ml has been used. For the 80 mg/0.8 ml presentation, there is no need for additional clinical data, as the pharmaceutical data submitted are acceptable.

Pivotal clinical PK study in healthy subjects (AVT02-GL-101)

The study design was satisfactory. A parallel design was acceptable considering the long half-life of adalimumab (approximately 2 weeks) and the potential influence of immunogenicity. The use of healthy subjects is agreed in line with the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. The treatment groups were similar in age, ethnicity and BMI in whole study. The 40 mg s.c. dose is the normally recommended and the use is endorsed.

The primary endpoints $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ were based on PK samples collected up to 9 weeks. The PK sampling period was not long enough for all subjects, because in the AVT02 group, eleven subjects', in the EU-Humira group five subjects' and in the US-Humira group nine subjects' $AUC_{0\text{-}inf}$ was > 20% of $AUC_{0\text{-}t}$ indicating that the sampling period for these subjects has been too short. The amount of the subjects with non-optimal concentration profiles can be considered comparable between studied groups and to have no big impact on the PK results. The all-above-mentioned subjects were included in the PK analyses.

The study included two parts with sample size re-estimation occurring after Part 1. An interim analysis for early bioequivalence was conducted as well. Sample size re-estimation and bioequivalence analysis have the potential for Type 1 error inflation. The applicant provided a response with a detailed rationale and references for the use of Fisher´s combination test and discuss the overall concept for multiplicity control of all variables that were considered in the formal interim analysis.

In addition, during evaluation of the data available for the interim analysis, one outlier subject was identified in the data and excluded from the statistical analysis as from the observed concentrations and the time to C_{max} at least part of the dose was given by the i.v. route (e.g., by tapping a s.c. vein). However, exclusion of data cannot be accepted for PK reasons alone. In addition, the outlier was removed from the analysis together with data from 5 randomly selected additional subjects (resulting in a total of 2 subjects from each treatment arm being excluded) in order to preserve the blind for the sponsor. This was not agreed. The applicant provided a response to this item, however, additional subjects from the part 1 were excluded from the final PK analysis due to incomplete sampling around C_{max} (2 subjects) and incomplete PK sampling (early withdrawal) (1 subject) and it was not clear why these subjects had not been also mentioned to be excluded at time of the interim analysis for the sample size re-estimation of the part 2. Upon CHMP's request the applicant provided clarifications regarding the lack of exclusion of additional three subjects. Considering the arguments provided and that the conducted sensitivity analyses with Fisher Combination test, with and without all excluded subjects, as well as the conventional method without the excluded subjects had no effect on the conclusion of bioequivalence, the issue is not further pursued.

The adalimumab concentration time profiles were quite flat and consequently, only three or four time points during the terminal log-linear phase were used in estimation of elimination rate constant.

The applicant provided results of the statistical analysis including also data of these 10 subjects excluded from the PK analysis. Both results (without and with data of these 10 subjects) were contained within the pre-defined bioequivalence margins of 80% and 125%. The results were consistent with the primary bioequivalence analysis conducted on the PK analyses set with the exclusion of the 10 subjects. In addition, the results of the sensitivity analysis supported the results of the primary bioequivalence analysis.

In conclusion, the justification of the applicant for the exclusion of these 10 subjects from the PK analysis is considered acceptable. The 90% CIs of the geometric LS mean ratios for the three primary PK parameters were all within 80% and 125%. In the AUC_{0-t} between AVT02 and EU-Humira, the lower limit of 90%CI was 1.00, which is considered acceptable. The sensitivity analysis supported the PK similarity between AVT02 and EU-Humira.

The 90% CIs of the geometric LS mean ratios for the 3 primary PK parameters were not all within 0.80 to 1.25 in Japanese subgroup. These comparisons can be considered qualitative only, because the study was not originally powered to conduct a formal statistical analysis in subgroup.

There has been mistakes in administration of adalimumab. In 4 subjects adalimumab was administered by an i.v. administration instead of s.c. administration. These subjects were excluded from the PK population and it can be considered adequate. However, the occurrence of i.v. administration raised uncertainties regarding proper training of the staff and adequate study conduct. The applicant was asked to explain in more detail how this misconduct could happen and provide assurance of appropriate qualification of the personnel involved in the study. On the basis of the provided data in the response, all efforts have been made to train the study personnel to conduct study properly and administer study drugs correctly.

The applicant has declared on what basis the needle angle was chosen to be 90º in the pilot study AVT02-GL-100 and at the beginning of the PK pivotal study AVT02-GL-101, although in the Humira PL the angle for the s.c. administration with PFS is 45º. In the response the applicant has clarified that the needle angle was erroneously stated to be 90º instead of 45º. The error was corrected by a non-substantial amendment. The changes included in this non-substantial protocol amendment were incorporated into protocol amendment 2 (protocol version 3.0 dated 6.5.2019). On the basis of the provided instruction materials for right administration before the study dosing, it can be maintained that all administrations were made correctly using 45º angle of needle.

Clinical device study to compare PK of AVT02 when administered from PFS and from AI (AVT02-GL-102)

The selected PK sampling schedule up to 9 weeks has been sufficient for a majority of the subjects (i.e., AUC0-t covered over 80% of AUC0-inf). There was however, 8 subjects in the AVT02-AI group and 4 subjects in the AVT02-PFS group, in which AUC0-inf was over 20% of AUC0-t demonstrating that the sampling period was too short. Ten of these 12 subjects have C_{last} concentration > 1000 ng/ml. In calculation of the elimination phase (kel and t1/2), generally only 3 time points were used (there were cases, where even 13 time points were used in calculation). The inter-subject variation in the AVT02 absorption phase and in the Cmax was lower than in the elimination phase (i.e., in AUCs, kel, t1/2, CL/F and Vz/F. The AVT02 PK profiles were very flat for many subjects.

All 90%CIs for AVT02-PFS to AVT02-AI ratios of primary PK parameters (i.e., Cmax, AUC0-t and AUC0-inf) were within the pre-specified acceptance window of 80% to 125% (including 100%). The bioequivalence between AVT02-AI and AVT02-PFS was demonstrated.

Clinical study in patients with moderate-to severe chronic plaque psoriasis (AVT02-GL-301)

The batch DP180004 for the test product (i.e., for AVT02) has been used in all clinical studies. The certificate of analysis for the test batch has been presented in Module 3. For test batches (i.e., EU Humira batches (i.e., batches 87387XH06, 95480XH04, 91433XH03, 06046XH05) the certificates of analyses have been provided, as requested. The mean trough concentrations have been slightly higher in the AVT02 group than in the EU-Humira group both on overall population (PK data up to week 16) and on PASI responders (PK data on PASI responders from 0 to week 24). The steady-state mean trough concentrations (5-7 µg/ml) are at the same level as reported in the clinical studies in psoriasis patients with original Humira (mean trough concentrations 5 µg/ml at steady-state, source: Humira SmPC). The variations (CV%) in the trough concentrations were large; however, quite same level between studied treatments. The differences in the median and geometric mean trough concentrations between AVT02 and EU-Humira were greater than in the mean values. Consequently, the applicant was asked to use geometric means of trough concentrations and perform a direct comparison of the trough concentrations between AVT02 group (n=205) and EU-Humira group (n=207) from week 0 to week 16 and between AVT02/AVT02 group vs EU-Humira/AVT02 group, AVT02/AVT02 group vs EU-Humira/EU-Humira group and EU-Humira/AVT02 group vs EU-Humira/EU-Humira group on PASI responders from week 0 to week 24, presenting point estimates and 90%CIs of the concentration ratios for all time points where the PK measurements were done. In the response, since the final study AVT02-GL-301 data were available, the applicant also presented the requested data up to week 54. The ratios of geometric means were generally higher in subjects treated with AVT02 compared to subjects treated with EU-Humira; however, almost all 90%CIs contain 1, indicating that there is no considerable difference between treatment groups. The differences in the C_{trough} concentrations can be considered not clinically meaningful.

No clinical studies in special populations and no *in vitro* or *in vivo* drug-drug interaction studies were conducted with the AVT02 and this is acceptable.

In the proposed AVT02 SmPC the PK text in Section "Pharmacokinetic properties" was taken from the Humira SmPC. As the AVT02 and Humira are considered to be biosimilar it is acceptable to use Humira SmPC text.

2.6.5. Conclusions on clinical pharmacology

The PK similarity between AVT02 and Humira has been demonstrated.

2.7. Clinical efficacy

Table 8 Tabular overview of comparative efficacy and safety and other studies conducted for development of AVT02

Study ID	No. of Study Centers Location(s)	Study Start Enrollment Status Date Total Enrollment / Enrollment Goal	Design Control Type	Study & Ctrl Drugs Presentation Dose, Route & Regimen	Study Objective	No. Subjects by Arm Entered/ Completed	Duration	Sex M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
AVT02-GL-301	20 Estonia Georgia Poland Ukraine	Feb 2019 24-week period Completed Dec 2019 Stage 2 ongoing as of Jul 2020. 412[1] / 400	Multicenter, double-blind, randomized, 2-arm, parallel group, equivalence design	AVT02-PFS EU-Humira 80 mg initial dose, followed by 40 mg EOW starting 1 week after initial dose s.c. injection	To compare efficacy, safety, and immuno-genicity of AVT02 and Humira	Stage 1 (randomized/ completed) AVT02 205/201 Humira 207/201 Stage 2 (randomized) AVT02/ AVT02 195 Humira/ Humira 96 Humira/ AVT02 96	Repeated dose (EOW) Last treatment: Week 48 Last efficacy evaluation: Week 50 EOS: Week 54	254 / 158 42.0 (18, 71)	Moderate to severe chronic PsO patients	Percent improvement in Psoriasis Area and Severity Index (PASI) from BL to Week 16
AVT02-GL-303	9 Georgia Ukraine	Oct 2019 8-week period Completed Mar 2020 Extension phase ongoing as of Jul 2020 107 / 100	Multicenter center, open-label, single arm	AVT02 40 mg, s.c. injection Active period (Week 0-8) AVT02 AI Extension phase (Week 9-56) AVT02-PFS	To estimate self-injection success rate in a real-life setting	Active period (enrolled/ completed) 107/106 Extension phase (included) 106	Repeated dose (EOW) EOS: Week 56	11 / 96 54.0 (29, 77)	Moderate to severe active rheumatoid arthritis patients	Injection success rate (Week 8)
AVT02 HF Validation AI	3 USA	Feb 2020 Completed Mar 2020 60/60	One-on-one, in-person interview sessions, 4 user groups (pts with RA, pts with JIA, HCP, Caregivers	AVT02-AI	to demonstrate that intended users can use the AI and instructional labeling safely and effectively	60 (15 subjects/ user group)	60 minutes	RA patients: 12/3 53 (30-68) JIA: 4/11 14 (12-17) HCPs: 1/14 37 (23-61) Caregivers: 4/11 50 (34-63)	15 pts with RA 15 patients with JIA 15 HCPs 15 Caregivers[2]	Safely and effectively use of AI

[1] number of patients receiving at least one dose of study medication. [2] caregivers, and HCPs help to treat RA and JIA
AI=autoinjector; BL=baseline; EOS=end of study; EOW=once every other week; HCP=Health Care Professional; HF=human factors; JIA=juvenile idiopathic arthritis; No.=number; PASI=Psoriasis Area and Severity Index; PFS=prefilled syringe; PsO=plaque psoriasis; RA=rheumatoid arthritis; s.c.=subcutaneous; Study ID=Study Identifier

2.7.1. Dose response studies and main clinical studies

No dose response studies were performed, and such studies are not deemed necessary in the biosimilarity setting.

2.7.2. Main study

AVT02-GL-301 (ALVOPAD PS)

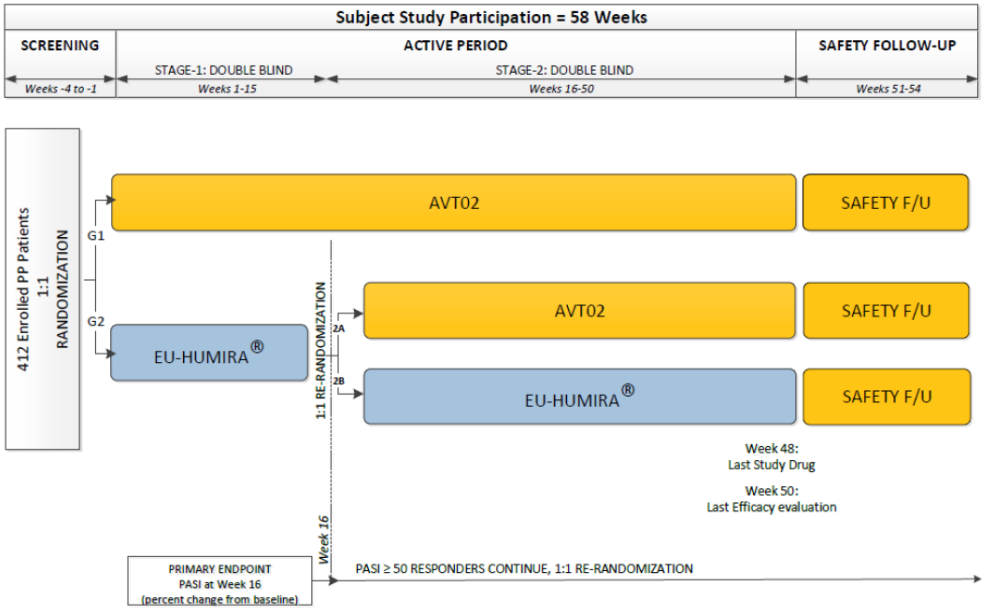
Title: A multicenter, double-blind, randomized, parallel-group, active control study to compare the efficacy, safety, and immunogenicity of AVT02 versus EU-Humira in patients with moderate-to-severe chronic plaque psoriasis (ALVOPAD PS).

Methods

Study AVT02-GL-301 is a 54-week study conducted in 2 stages: Stage 1 through Week 16 with a double-blind efficacy assessment and Stage 2 from week 16 through Week 50 with a double-blind, long-term efficacy and safety assessment, and follow-up for 4 weeks through Week 54. At Week 16, nonresponsive patients (less than 50% improvement in PASI) were withdrawn from the study. Responsive patients (at least PASI 50) began Stage 2 of the active period. At week 16, responders who were initially randomised in to receive Humira were re-randomised 1:1 into Groups 2A and 2B to receive either AVT02 (Group 2A) or Humira (Group 2B).

An overview of the study design of Study AVT02-GL-301 is presented in **Figure 4.**

Figure 4 Schematic study design of Study AVT02-GL-301



Source: CSR Study AVT02-GL-301, Figure 9.1
Note: 412 enrolled patients with plaque psoriasis (PP) received at least one dose of study medication
EU=Europe, F/U=follow up, G=group

Study Participants

The study was conducted at 20 study centres located in four countries: Estonia, Georgia, Poland and Ukraine.

Male or female patients aged 18 to 75 years of age with stable moderate to severe chronic plaque psoriasis for at least 2 months who had a previous failure, inadequate response, intolerance, or contraindication to at least 1 systemic antipsoriatic therapy (including, but not limited to, methotrexate, cyclosporine, psoralen plus ultraviolet light A (PUVA), and ultraviolet light B (UVB)) were eligible for the study.

Moderate to severe PsO was defined by an involved body surface area (BSA) ≥10% (Palm Method), ≥12 on the PASI, and static Physicians Global Assessments (sPGA) ≥3 (moderate) at Screening and at BL.

Subject were excluded if diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, other skin conditions (eg, eczema), or other systemic autoimmune disorder inflammatory disease at the time of the Screening Visit that could have interfered with evaluations of the effect of the study drug on psoriasis.

Previous use of not more than 1 prior biologics for treatment of PsO was allowed.

Prior use of any of the following medications within specified time periods or required use during the study was ground for exclusion:

a. Topical medications within 2 weeks of BL (Week 1).

b. PUVA phototherapy and/or UVB phototherapy within 4 weeks prior to the BL Visit.

c. Nonbiologic psoriasis systemic therapies (e.g., cyclosporine, methotrexate, and acitretin) within 4 weeks prior to the BL Visit.

d. Any prior or concomitant or biosimilar adalimumab therapy, either approved or investigational.

e. Any systemic steroid in the 4 weeks prior to BL.

Immunosuppressed patients (for any reason) were excluded.

A detailed listing of inclusion and exclusion criteria was provided in the CSR (M 5.3.5.1).

Only responsive subjects (subjects who achieved at least PASI 50) continued to Stage 2 of the study (beyond week 16).

Treatments

During Stage 1 (through Week 16):

Subjects in Group 1 received an initial loading dose of AVT02 80 mg (2 × 40 mg) administered s.c., followed by 40 mg given s.c. once every other week (EOW) starting 1 week after the loading dose and continued to receive AVT02 until Week 14. Subjects in Group 2 received an initial loading dose of Humira 80 mg (2 × 40 mg) administered s.c., followed by 40 mg given s.c. EOW starting 1 week after the loading dose and continued to receive Humira until Week 14.

At Week 16:

- Non-responsive subjects (less than 50% improvement in Psoriasis Area and Severity Index [PASI 50]) were withdrawn from the study.
- Responsive subjects (at least PASI 50) began Stage 2 (long-term efficacy and safety assessment) of the active period.

During Stage 2 (from Week 16 through Week 54):

- Responders who were initially randomised in Group 1 (AVT02) continued to receive AVT02 40 mg s.c. EOW from Week 16 through Week 48.
- Responders who were initially randomised in Group 2 (Humira) were re-randomised into Groups 2A and 2B, in a 1:1 ratio.
- Responders who were re-randomised into Group 2A started to receive AVT02 (40 mg EOW) from Week 16 through Week 48.

- Responders who were re-randomised into Group 2B continued to receive Humira (40 mg EOW) from Week 16 through Week 48.

Only the PFS presentation was used in study AVT02-GL-301. Injection sites were to be rotated between abdomen and thighs.

No rescue treatments were described.

Objectives

Primary Study Objective

The primary objective was to assess the equivalence by Psoriasis Area and Severity Index (PASI) of AVT02 to EU-approved Humira with regards to efficacy at Week 16 in subjects with moderate to severe chronic plaque psoriasis.

Equivalence was considered achieved if the 90% CI (as required by FDA)/95% CI (as required by EMA) lay within (-10%, 10%).

Secondary Study Objectives

- To compare the efficacy of AVT02 and Humira in subjects with moderate-to-severe chronic plaque psoriasis at week 8, 12, 16, 24, 32, 42, and 50.
- To compare steady-state pharmacokinetics (PK) of AVT02 and Humira.
- To compare the safety, tolerability, and immunogenicity of AVT02 and Humira at Weeks 16, 24, 32, 42, and 50.

The applicant states that there will be no formal comparisons between the treatment groups for Stage 2 (data after Week 24).

Exploratory Study Objectives

- To compare the efficacy of AVT02 and Humira in subjects with psoriatic arthritis (PsA) at Week 12.
- Change from Baseline (BL) in Routine Assessment of Patient Index Data 3 (RAPID3) at Week 12 (only for PsA).
- To assess ex-vivo immunogenicity by T-cell proliferation and cytokine production in a subset of subjects at Weeks 1, 8, and 16.

Outcomes/endpoints

Efficacy:

The primary efficacy endpoint was the percent improvement in PASI from BL to Week 16.

The secondary efficacy endpoints for the **Primary CSR** were:

- Percent improvement in PASI from BL to Weeks 8, 12, and 24.
- PASI 50, PASI 75, PASI 90, and PASI 100 response rate at Weeks 16 and 24.
- Number and percentage of subjects achieving static Physician's Global Assessments (sPGA) responses of clear (0) or almost clear (1) at Weeks 16 and 24.
- Change from BL in quality of life as measured by Dermatology Life Quality Index (DLQI) scores at Weeks 16 and 24.

The following exploratory efficacy endpoints were reported as part of the **Primary CSR**:

- The primary and secondary efficacy endpoints at Week 12 in subjects with PsA.
- Change from BL in Routine Assessment of Patient Index Data 3 (RAPID3) at Week 12 (only for PsA).

The following secondary efficacy endpoints will be reported as part of the **Final CSR**:

- The percent improvement in PASI from BL to Weeks 32, 42, and 50.
- PASI 50, PASI 75, PASI 90, and PASI 100 response rate at Week 50.
- Number and percentage of subjects achieving sPGA responses of clear (0) or almost clear (1) at Week 50
- Change from BL in quality of life as measured by DLQI scores at Week 50.

Pharmacokinetics:

The PK endpoint was to compare serum trough levels of AVT02 and Humira at steady-state.

Safety:

The safety variables evaluated were the frequency, type, and severity of adverse events (AEs) including adverse drug reactions; the frequency and severity of injection site reactions (ISRs); routine safety parameters, including laboratory safety, vital sign measurements, 12-lead electrocardiogram (ECG) results, chest X-ray, and physical examination findings.

Other:

Other evaluation criteria were the detection of anti-drug antibodies (ADA) to AVT02 or Humira at Weeks 4, 8, 16, 24, 32, 50, and Early Termination (ET)/ EoS Follow-up (Week 54). Ex-vivo immunogenicity was measured by T-cell proliferation and cytokine production in a subset of subjects at Weeks 1, 8, and 16. The results of the ex-vivo immunogenicity analyses are planned to be presented in a separate report.

Randomisation and blinding (masking)

At Stage 1: Patient randomisation was stratified by presence or absence of PsA, and by prior use of a biologic therapy for the treatment of PsO or PsA. Approximately 400 patients were to be randomly assigned to receive either AVT02 or Humira in a 1:1 ratio (approximately 200/arm).

At Stage 2 (Long-Term Efficacy and Safety Assessment): Responsive patients (patients who achieve at least PASI 50) who were taking Humira in Stage 1 were re-randomised into Groups AVT02 and Humira, in a 1:1 ratio at Week 16.

Subjects were assigned to study drug in accordance with the randomisation schedule generated using permuted block randomisation by an independent statistician.

Blinding of the study was achieved by the following measures:

- The EU-Humira and AVT02 syringes were masked by packaging that concealed the syringes during Stages 1 and 2 (double-blind treatment period) of the study.
- After the 24-week database lock, the Sponsor and the CRO will be partly unblinded, but the study remains double-blinded. In order to prevent accidental unblinding, dedicated blinded and unblinded teams were implemented within the Sponsor and CRO prior to the Week 24 database lock. The study still continues as a blinded study to the Investigator, subject, and dedicated Sponsor/CRO

representatives who are unaware of treatment assignment until study closure and final database lock.

Statistical methods

Analysis Populations

The Full Analysis Set (FAS), consistent with the intention-to-treat principle, is defined as all randomised subjects who received at least one dose of randomised study drug.

The Per-Protocol Set (PPS) is a subset of the FAS which includes subjects who have completed Stage 1 and do not have a protocol violation that would affect evaluation of the primary objective of the study. Protocol deviations should be collected by site and grouped into different categories. These deviations (major/minor) were reviewed and identified by the Sponsor before database lock.

The PPS is defined broadly as follows:

- Subject completes the 16-week Stage 1 with Week 16 PASI score reported
- Subject without the following major protocol deviations:
    - Receiving the wrong treatment according to the randomisation.
    - Missing baseline and/or week 16 PASI measures.
    - Noncompliance of inclusion/exclusion criteria.
    - Inappropriate PASI evaluation.
    - Receipt of certain protocol-prohibited medications.

The PPS is used for the sensitivity analysis of the primary endpoint. Summaries of subject demographics and baseline disease characteristics will also be presented for the PPS.

Primary Analysis

An analysis of covariance (ANCOVA) model to assess the efficacy of AVT02 compared with Humira at Week 16 will be used for the FAS set. The ANCOVA model includes percent improvement as response variable, treatment and 2 stratification factors as factors and baseline PASI score as covariate. This analysis provides standard error estimates for least squares means and their differences between group means adjusted for the factors and covariate. The two-sided 90%/95% CIs of the differences of least squares means between the AVT02 and Humira groups will be calculated. Equivalence is achieved if the 90% CI (as required by FDA)/95% CI (as required by EMA) lie within (-10%, 10%).

Missing percent improvement will be imputed using last observation carry-forward method (LOCF) for subjects with post-baseline assessment in Stage 1.

Sensitivity Analyses

To test the robustness of primary analysis, the following different sensitivity analyses of the primary endpoint will be performed.

- The primary analysis will be repeated using the PP set
- The primary analysis will be repeated with an additional random effects term for site.
- The primary analysis will be repeated using only completers at Week 16.
- Mixed effect Model Repeat Measurement (MMRM) analysis will be performed for the FAS set.

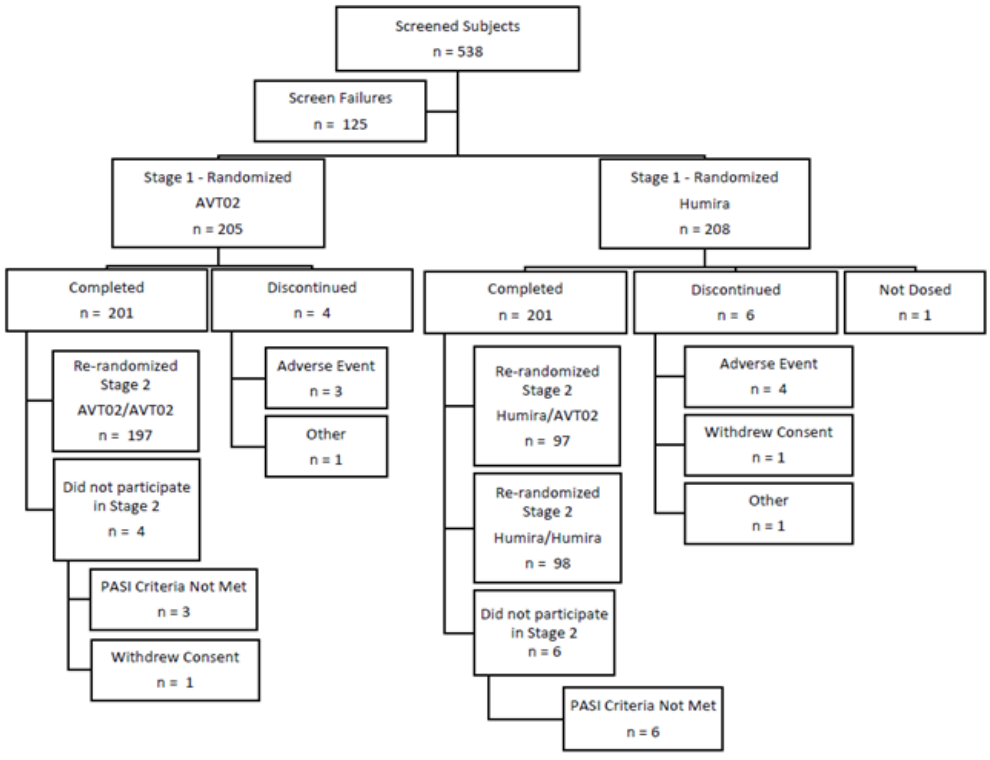
The MMRM analysis will include percent improvement from BL as response variable, treatment, 2 stratification factors, baseline PASI score, visit and visit time point-by-treatment interaction terms as explanatory variables. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, compound symmetry covariance structure will be used.

Results

Participant flow

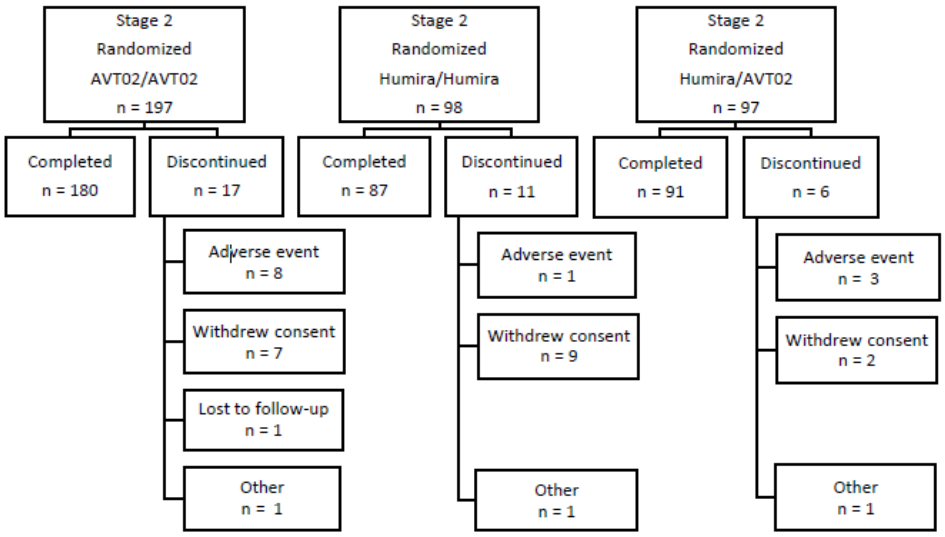
The numbers of subjects screened, randomised and treated in the different phases, as well as reasons for discontinuation, are presented in the flowcharts below.

Figure 5 Disposition of study subjects from re-randomisation through Week 54



Source: CSR Study AVT02-GL-301, Table 14.1.1.1 and Listing 16.2.1.2
n=number of subjects; PASI=Psoriasis Area and Severity Index

Figure 6 Disposition of study subjects from re-randomisation through Week 54



Baseline data

Baseline demographic and clinical characteristics are presented in **Tables 9 and 10.**

Table 9 Demographics and Baseline Characteristics – Full Analysis Set – Through Week 24

	AVT02 (N = 205)	**Humira (N = 207)**	**AVT02/AVT02 (N = 197)**	**Humira/AVT02 (N = 97)**	**Humira/Humira (N = 98)**	**Overall (N = 412)**
Age (years) at Informed Consent						
n	205	207	197	97	98	412
Mean (SD)	42.5 (12.39)	43.2 (13.24)	42.4 (12.26)	43.6 (13.40)	42.3 (13.03)	42.8 (12.81)
Median	42.0	43.0	42.0	43.0	42.0	42.0
Min, Max	20, 71	18, 70	20, 71	22, 69	18, 70	18, 71
Age group, n (%)						
<65 years	195 (95.1)	195 (94.2)	188 (95.4)	90 (92.8)	95 (96.9)	390 (94.7)
≥65 years	10 (4.9)	12 (5.8)	9 (4.6)	7 (7.2)	3 (3.1)	22 (5.3)
	AVT02 (N = 205)	**Humira (N = 207)**	**AVT02/AVT02 (N = 197)**	**Humira/AVT02 (N = 97)**	**Humira/Humira (N = 98)**	**Overall (N = 412)**
Gender, n (%)						
Male	125 (61.0)	129 (62.3)	122 (61.9)	56 (57.7)	67 (68.4)	254 (61.7)
Female	80 (39.0)	78 (37.7)	75 (38.1)	41 (42.3)	31 (31.6)	158 (38.3)
Ethnicity, n (%)						
Hispanic or Latino	2 (1.0)	2 (1.0)	2 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)
Not Hispanic or Latino	203 (99.0)	205 (99.0)	195 (99.0)	96 (99.0)	97 (99.0)	408 (99.0)
Race, n (%)						
White	205 (100.0)	207 (100.0)	197 (100.0)	97 (100.0)	98 (100.0)	412 (100.0)

Black or African American	0	0	0	0	0	0
Asian	0	0	0	0	0	0
Height (cm) at Screening						
n	205	207	197	97	98	412
Mean (SD)	172.87 (10.077)	172.90 (9.708)	173.00 (10.160)	172.20 (10.624)	174.09 (8.705)	172.88 (9.881)
Median	174.00	174.00	175.00	172.00	175.00	174.00
Min, Max	150.0, 195.0	147.0, 194.0	150.0, 195.0	147.0, 194.0	152.0, 190.0	147.0, 195.0
Weight (kg) at Screening						
n	205	207	197	97	98	412
Mean (SD)	85.81 (21.737)	84.62 (17.691)	85.41 (21.629)	83.10 (18.419)	85.71 (16.733)	85.21 (19.792)
Median	84.20	82.90	84.10	81.70	84.50	83.85
Min, Max	45.0, 204.1	43.1, 135.0	45.0, 204.1	43.1, 134.0	57.4, 135.0	43.1, 204.1
Country, n (%)						
Estonia	28 (13.7)	29 (14.0)	27 (13.7)	14 (14.4)	14 (14.3)	57 (13.8)
Georgia	31 (15.1)	29 (14.0)	30 (15.2)	12 (12.4)	15 (15.3)	60 (14.6)
Poland	123 (60.0)	126 (60.9)	117 (59.4)	59 (60.8)	58 (59.2)	249 (60.4)
Ukraine	23 (11.2)	23 (11.1)	23 (11.7)	12 (12.4)	11 (11.2)	46 (11.2)

Abbreviations: cm = centimeters; kg = kilograms; min = minimum; max = maximum; n = number of subjects in the sample; N = number of subjects; SD =standard deviation
Source: Table 14.1.3.1

Table 10 Clinical Baseline Characteristics – Full Analysis Set – Through Week 24

	AVT02 (N = 205)	**Humira (N = 207)**	**AVT02/AVT02 (N = 197)**	**Humira/AVT02 (N = 97)**	**Humira/Humira (N = 98)**	**Overall (N = 412)**
Psoriasis Area and Severity Index (PASI)						
n	205	207	197	97	98	412
Mean (SD)	23.17 (8.538)	22.98 (8.553)	22.79 (8.062)	22.74 (9.174)	23.10 (7.915)	23.08 (8.535)
Median	21.60	20.80	21.60	19.80	21.25	21.20
Min, Max	12.1, 55.9	12.0, 55.2	12.1, 51.0	12.1, 55.2	12.0, 46.0	12.0, 55.9
Static Physicians Global Assessment, (sPGA) n (%)						
Minimal	0	0	0	0	0	0
Mild	0	0	0	0	0	0
Moderate	112 (54.6)	119 (57.5)	108 (54.8)	60 (61.9)	51 (52.0)	231 (56.1)
Severe	76 (37.1)	73 (35.3)	74 (37.6)	29 (29.9)	40 (40.8)	149 (36.2)

Very Severe	17 (8.3)	15 (7.2)	15 (7.6)	8 (8.2)	7 (7.1)	32 (7.8)
Percentage of Body Surface Area Affected (%BSA)						
n	205	207	197	97	98	412
Mean (SD)	32.3 (17.84)	31.7 (17.88)	31.9 (17.65)	30.2 (18.03)	32.3 (16.51)	32.0 (17.84)
Median	28.0	26.0	28.0	25.0	28.0	28.0
Min, Max	10, 86	10, 84	10, 83	10, 84	11, 82	10, 86

	AVT02 (N = 205)	**Humira (N = 207)**	**AVT02/AVT02 (N = 197)**	**Humira/AVT02 (N = 97)**	**Humira/Humira (N = 98)**	**Overall (N = 412)**
Months from Diagnosis of Chronic Plaque Psoriasis to Informed Consent						
n	205	207	197	97	98	412
Mean (SD)	195.2 (131.43)	198.6 (130.23)	196.4 (131.80)	193.0 (128.78)	196.1 (127.20)	196.9 (130.68)
Median	183.0	183.0	183.0	184.0	172.5	183.0
Min, Max	6, 688	7, 593	6, 688	20, 593	20, 593	6, 688
Psoriatic Arthritis, (PsA) n (%)						
Presence	43 (21.0)	41 (19.8)	40 (20.3)	19 (19.6)	18 (18.4)	84 (20.4)
Absence	162 (79.0)	166 (80.2)	157 (79.7)	78 (80.4)	80 (81.6)	328 (79.6)
Months from Diagnosis of Psoriatic Arthritis to Informed Consent						
n	43	41	40	19	18	84
Mean (SD)	65.9 (62.68)	79.2 (67.68)	70.5 (62.60)	81.6 (74.56)	81.0 (66.63)	72.4 (65.12)
Median	45.0	62.0	58.0	64.0	57.0	56.5
Min, Max	0, 243	5, 276	0, 243	5, 276	9, 255	0, 276

Abbreviations: max = maximum; min = minimum; n = number of subjects in the sample; N = number of subjects; SD = standard deviation

Approximately half of subjects had at least 1 ongoing medical condition (100 AVT02 subjects [48.8%] and 110 Humira subjects [53.1%]). The most common ongoing medical condition SOC was vascular disorders (22.6%), and the most common preferred term was hypertension (20.9%).

Similar numbers of subjects used concomitant medications through Week 24; at initial randomisation 118 AVT02 subjects [57.6%] and 127 Humira subjects [61.4%] used any concomitant medication.

Numbers analysed

The Full Analysis Set (FAS), consistent with the intention-to-treat principle, was defined as all randomised subjects who received at least 1 dose of randomised study drug.

The Per-Protocol Set (PPS) was a subset of the FAS which included subjects who completed Stage 1 and did not have a protocol deviation that would affect evaluation of the primary objective of the study. The Safety Analysis Set included all subjects who received at least 1 dose of study drug, with treatment assignment based on actual treatment received.

Table 11 Subject Disposition – Analysis Sets – Enrolled Set

	AVT02 n (%)	Humira n (%)	AVT02/AVT02 n (%)	Humira/AVT02 n (%)	Humira/Humira n (%)	Overall n (%)
Subjects in Enrolled Set[1]						538
Subjects in Randomised Set[2]	205	208	197	97	98	413
Subjects in Safety Analysis Set[3]	205 (100.0)	207 (100.0)	197 (100.0)	97 (100.0)	98 (100.0)	412 (100.0)
Subjects in Full Analysis Set[4]	205 (100.0)	207 (100.0)	197 (100.0)	97 (100.0)	98 (100.0)	412 (100.0)
Subjects in Per-Protocol Set[5]	199 (97.1)	199 (96.1)	195 (99.0)	97 (100.0)	96 (98.0)	398 (96.6)

[1] Enrolled Set includes all subjects who gave informed consent.
[2] Randomised Set includes all randomised subjects.
[3] Safety Analysis Set includes all subject who received at least one dose of study drug, with treatment assignment based on actual treatment received.
[4] FAS, consistent with the intention-to-treat principle, is defined as all randomised subjects who received at least one dose of randomised study drug.
[5] PPS is a subset of the FAS which includes subjects who have completed the treatment Stage 1 and do not have a protocol deviation that would affect evaluation of the primary objective of the study.
Note: Percentages are based on the number of subjects in the FAS by treatment group. Abbreviations: n = number of subjects in the sample
Source: Table 14.1.1.2

Outcomes and estimation

Primary outcome

Percent improvement in Psoriasis Area and Severity Index

The ANCOVA analysis of the percent improvement in PASI from BL shows that AVT02 is within the predefined equivalence margin of ±10% for the 95% CI at Week 16 compared to Humira (**Table 12 and Table 13**). Mean actual PASI scores fell from 23.2 and 23.0 at baseline to 2.0 and 1.7 at week 16 (observed data) for AVT02 and Humira, respectively.

Table 12 Primary Analysis: Analysis of Covariance of Percent Improvement in Psoriasis Area and Severity Index from Baseline to Week 16 (Last Observation Carry-forward Data) – **Full Analysis Set** – Through Week 16

Time Point	AVT02 (N = 205)	Humira (N = 207)
Week 16 LOCF		
n	205	207
LS Mean (SE)	89.2 (1.61)	86.9 (1.65)
LS Mean Difference (SE) (AVT02 vs Humira)	2.3 (1.84)	
90% Confidence Interval	-0.76, 5.29	
95% Confidence Interval	-1.34, 5.88	

Notes: Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject received the first dose of study drug (Day 1) in Stage 1. The two-sided 90% and 95% confidence intervals of the differences of LS means between the AVT02 and Humira groups are from the ANCOVA model

including percent improvement as response variable, treatment and 2 stratification factors as factors and baseline PASI score as covariate. Missing percent improvement in PASI is imputed using LOCF method for subjects with post-BL assessment

Table 13 Primary Analysis: Analysis of Covariance of Percent Improvement in Psoriasis Area and Severity Index from Baseline to Week 16– **Per-Protocol Set** – Through Week 16

Time Point	**AVT02 (N = 199)**	**Humira (N = 199)**
Week 16		
n	199	199
LS Mean (SE)	90.9 (1.22)	90.6 (1.25)
LS Mean Difference (SE) (AVT02 vs Humira)	0.3 (1.39)	
90% Confidence Interval	-1.96, 2.62	
95% Confidence Interval	-2.40, 3.06	

Notes: BL is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject received the first dose of study drug (Day 1) in Stage 1. Observed Data: Missing percent improvement in PASI is not imputed. LOCF Data: Missing percent improvement in PASI is imputed using LOCF method for subjects with post-BL assessment
Abbreviations: BL = Baseline; LOCF = last observation carry-forward; LS mean = Least squares mean; n = number of subjects in the sample; N = number of subjects; SE = standard error

The following sensitivity analyses were performed to confirm the robustness of the results: ANCOVA analysis including site as a random effect, ANCOVA analysis in Week 16 completers in the FAS, and the MMRM analysis in the FAS and PPS for the percent improvement in PASI from BL to Week 16. The 95% CI: s was within ±10% for all sensitivity analyses.

Secondary outcome

Psoriasis Area and Severity Index

The mean difference in percent improvement in PASI from BL to Week 8 and 12 was within the predefined ±10% margin of clinical equivalence (**Table 14).**

Table 14 ANCOVA of Percent Improvement in Psoriasis Area and Severity Index from Baseline to Week 8 and 12 (Last Observation Carry-Forward Data) – Full Analysis Set – Through Week 16

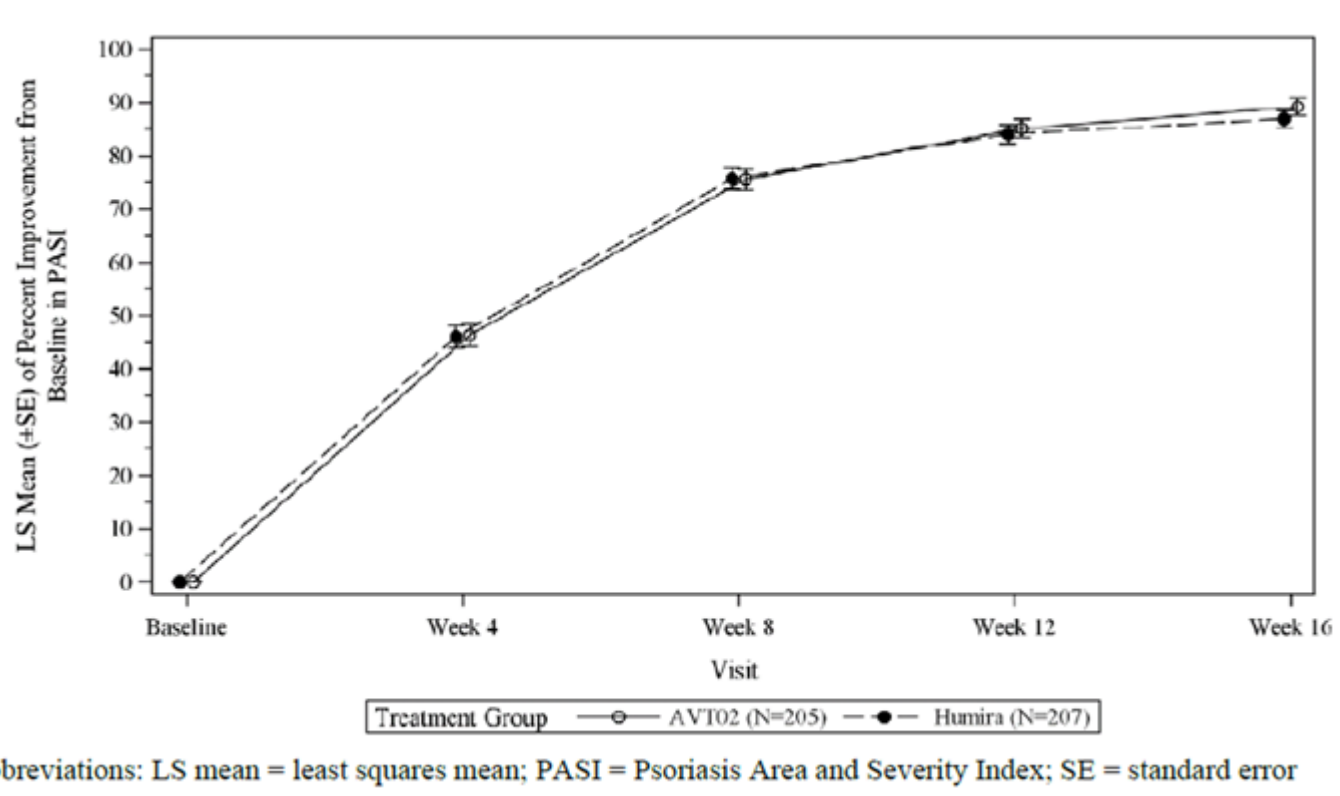
Time Point	**AVT02 (N = 205)**	**Humira (N = 207)**
Week 8 LOCF		
n	205	207
LS Mean (SE)	75.6 (1.95)	75.7 (2.00)
LS Mean Difference (SE) (AVT02 vs Humira)	-0.2 (2.22)	
90% Confidence Interval	-3.85, 3.49	
95% Confidence Interval	-4.55, 4.20	
Week 12 LOCF		
n	205	207
LS Mean (SE)	85.2 (1.73)	84.1 (1.77)

LS Mean Difference (SE) (AVT02 vs Humira)	1.1 (1.97)	
90% Confidence Interval	-2.15, 4.34	
95% Confidence Interval	-2.78, 4.96	

Abbreviations: LS mean = least squares mean; max = maximum; min = minimum; n = number of subjects in the sample; N = number of subjects; SD = standard deviation

The percent improvement from BL in PASI status at each time point showed similar levels of improvement in subjects randomised to AVT02 and Humira in both the LOCF analysis and the observed data analysis. Results from the LOCF analysis are presented graphically in **Figure 7**. The mean difference in percent improvement in PASI from BL to Week 8 was 0.2 (95% CI: -4.55 to 4.20) in the FAS LOCF analysis.

Figure 7 Least Squares Mean (±Standard Error) of Percent Improvement from Baseline in Psoriasis Area and Severity Index by Visit (Last Observation Carry-forward Data) - Full Analysis Set – Through Week 16



Abbreviations: LS mean = least squares mean; PASI = Psoriasis Area and Severity Index; SE = standard error

The PASI sores remained similar in all treatment arms also after re-randomisation and switching to AVT02 at week 16. Results up to week 50 are presented in **Table 15**.

Table 15 Percent Improvement from Baseline in Psoriasis Area and Severity Index by Visit – Full Analysis Set – Through Week 50

	Actual Value				Percent Change from Baseline			
Time Point	**n**	**Mean (SD)**	**Median**	**Min, Max**	**n**	**Mean (SD)**	**Median**	**Min, Max**
AVT02/AVT02 (N = 197)								
Baseline	197	22.79 (8.062)	21.60	12.1, 51.0				
Week 16	197	1.48 (2.711)	0.40	0.0, 20.9	197	93.64 (10.041)	98.25	48.3, 100.0
Week 24	194	1.47 (3.020)	0.00	0.0, 21.7	194	93.45 (12.906)	100.00	11.3, 100.0
Week 32	184	1.62 (3.398)	0.00	0.0, 21.7	184	92.43 (15.542)	100.00	20.0, 100.0
Week 42	182	1.76 (3.956)	0.00	0.0, 31.0	182	91.99 (16.502)	100.00	-8.7, 100.0
Week 50	181	1.82 (4.046)	0.10	0.0, 29.8	181	91.64 (17.792)	99.62	-6.4, 100.0
Humira/AVT02 (N = 97)								
Baseline	97	22.74 (9.174)	19.80	12.1, 55.2				
Week 16	97	1.04 (1.732)	0.30	0.0, 9.3	97	94.86 (8.870)	98.43	55.3, 100.0
Week 24	96	1.44 (2.387)	0.35	0.0, 11.4	96	92.83 (12.388)	98.51	40.8, 100.0
Week 32	92	1.76 (3.413)	0.50	0.0, 21.3	92	91.25 (17.909)	97.85	-19.7, 100.0

Week 42	91	1.70 (3.056)	0.00	0.0, 12.0	91	92.20 (14.844)	100.00	23.1, 100.0
Week 50	90	2.09 (3.504)	0.35	0.0, 14.4	90	90.75 (15.676)	98.85	21.5, 100.0
Humira/Humira (N = 98)								
Baseline	98	23.10 (7.915)	21.25	12.0, 46.0				
Week 16	98	1.46 (2.469)	0.30	0.0, 11.4	98	93.68 (9.773)	98.93	62.1, 100.0
Week 24	96	1.42 (2.565)	0.20	0.0, 13.4	96	93.18 (13.558)	99.13	5.3, 100.0
Week 32	91	1.55 (3.036)	0.00	0.0, 15.6	91	93.16 (12.989)	100.00	42.9, 100.0
Week 42	89	1.70 (3.240)	0.20	0.0, 20.8	89	92.97 (12.048)	99.23	35.1, 100.0
Week 50	87	2.17 (4.212)	0.00	0.0, 25.9	87	90.82 (16.598)	100.00	22.0, 100.0

Note: Three subjects (ie, AVT02: 3808012 and 3808013; Humira: 3808014) had non-zero results at BL. BL is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject received the first dose of study drug (Day 1) in Stage 1. Missing percent improvement in PASI is not imputed.
Abbreviations: BL = Baseline; max = maximum; min = minimum; n = number of subjects in the sample; N = number of subjects; SD = standard deviation

PASI 50, PASI 75, PASI 90, and PASI 100 response

The percentage of subjects achieving PASI 50, PASI 75, PASI 90, and PASI 100 was similar across treatment groups at each time point up to week 16 Table 14. At most, the difference in point estimate for PASI75 was 3.9% at week 8. The PASI 75 response at week 8 (FAS) was achieved for 125 (61.6%) subjects in the AVT02 treatment group and 133 (65.5%) subjects in the Humira treatment group.

Table 16 Percentage of Subject Achieving PASI 50, PASI 75, PASI 90, and PASI 100 Over Time. Full Analysis Set - Through Week 16

	AVT02 (N=205)			Humira (N=207)		
Visit	m	n	p	m	n	p
Week 4						
PASI 50	205	102	49.8	204	92	45.1
PASI 75	205	36	17.6	204	34	16.7
PASI 90	205	7	3.4	204	9	4.4
PASI 100	205	1	0.5	204	0	0
Week 8						
PASI 50	203	173	85.2	203	186	91.6
PASI 75	203	125	61.6	203	133	65.5
PASI 90	203	81	39.9	203	78	38.4
PASI 100	203	30	14.8	203	25	12.3
Week 12						
PASI 50	201	191	95.0	202	196	97.0
PASI 75	201	169	84.1	202	167	82.7
PASI 90	201	121	60.2	202	128	63.4
PASI 100	201	61	30.3	202	62	30.7
Week 16						
PASI 50	201	197	98.0	201	195	97.0
PASI 75	201	185	92.0	201	178	88.6
PASI 90	201	153	76.1	201	158	78.6
PASI 100	201	87	43.3	201	90	44.8

m=number of subjects in treatment group with assessment at both Baseline and the specified time point and is used as the denominator for percentage calculations; n=number of subjects achieving PASI 50, PASI 75, PASI 90 or PASI 100 at time point; p=percentage of subjects achieving PASI 50, PASI 75, PASI 90 or PASI 100.

In Stage 2 of the study, the response rates remained essentially similar between AVT02 and Humira treatment groups **(Table 17).**

Table 17 Percentage of Subject Achieving PASI 50, PASI 75, PASI 90, and PASI 100 Over Time Full Analysis Set - Through Week 50

	AVT02/AVT02 (N=197)			Humira/AVT02 (N=97)			Humira/Humira (N=98)		
Visit	m	n	p	m	n	p	m	n	p
Week 16									
PASI 50	197	196	99.5	97	97	100.0	98	98	100.0
PASI 75	197	185	93.9	97	90	92.8	98	88	89.8
PASI 90	197	153	77.7	97	81	83.5	98	77	78.6
PASI 100	197	86	43.7	97	46	47.4	98	44	44.9
Week 24									
PASI 50	194	190	97.9	96	94	97.9	96	95	99.0
PASI 75	194	182	93.8	96	87	90.6	96	88	91.7
PASI 90	194	157	80.9	96	76	79.2	96	77	80.2
PASI 100	194	99	51.0	96	43	44.8	96	47	49.0
Week 32									
PASI 50	184	177	96.2	92	89	96.7	91	87	95.6
PASI 75	184	165	89.7	92	85	92.4	91	82	90.1
PASI 90	184	149	81.0	92	69	75.0	91	75	82.4
PASI 100	184	102	55.4	92	41	44.6	91	46	50.5
Week 42									
PASI 50	182	173	95.1	91	89	97.8	89	88	98.9
PASI 75	182	166	91.2	91	79	86.8	89	80	89.9
PASI 90	182	143	78.6	91	70	76.9	89	69	77.5
PASI 100	182	96	52.7	91	48	52.7	89	42	47.2
Week 50									
PASI 50	181	174	96.1	90	87	96.7	87	83	95.4
PASI 75	181	163	90.1	90	78	86.7	87	78	89.7
PASI 90	181	143	79.0	90	64	71.1	87	63	72.4
PASI 100	181	90	49.7	90	43	47.8	87	45	51.7

m=number of subjects in treatment group with assessment at both Baseline and the specified time point and is used as the denominator for percentage calculations; n=number of subjects achieving PASI 50, PASI 75, PASI 90 or PASI 100 at time point; p=percentage of subjects achieving PASI 50, PASI 75, PASI 90 or PASI 100. Missing data not imputed.

%BSA and Physician's Global Assessments (sPGA)

The percentage (SD) of body surface area (%BSA) affected by psoriasis was 32.3 (17.84) and 31.7 (17.88) for AVT02 and Humira treatment arms respectively at baseline. At week 16 the corresponding percentages were 5.0 (11.22) and 3.7 (6.90). The results further slightly improved and remained similar between treatment arms up to week 24 and through week 50, being 3.2 (7.46), 2.9 (4.44) and 2.9 (4.83) at week 24 in the AVT02/AVT02, Humira/AVT02 and Humira/Humira groups, respectively.

The Physician's Global Assessments (sPGA) of plaque psoriasis was assessed on a scale of 0 to 5, with 0 indicating no psoriasis (clear of disease), 1 (almost clear), and 2 or higher scores indicating more severe disease. According to inclusion criteria, all subjects had involved body surface area (BSA) ≥10% and sPGA ≥ 3(moderate) at baseline. The percentage of subjects achieving clear (0) or almost clear (1) on the sPGA was comparable at each time point up to week 50 across treatment groups **(Table 18).**

Table 18 Percentage of Subject Achieving Static Physicians Global Assessment (sPGA) Responses of Clear (0) or Almost Clear (1) Over Time. Full Analysis Set - Through Week 50

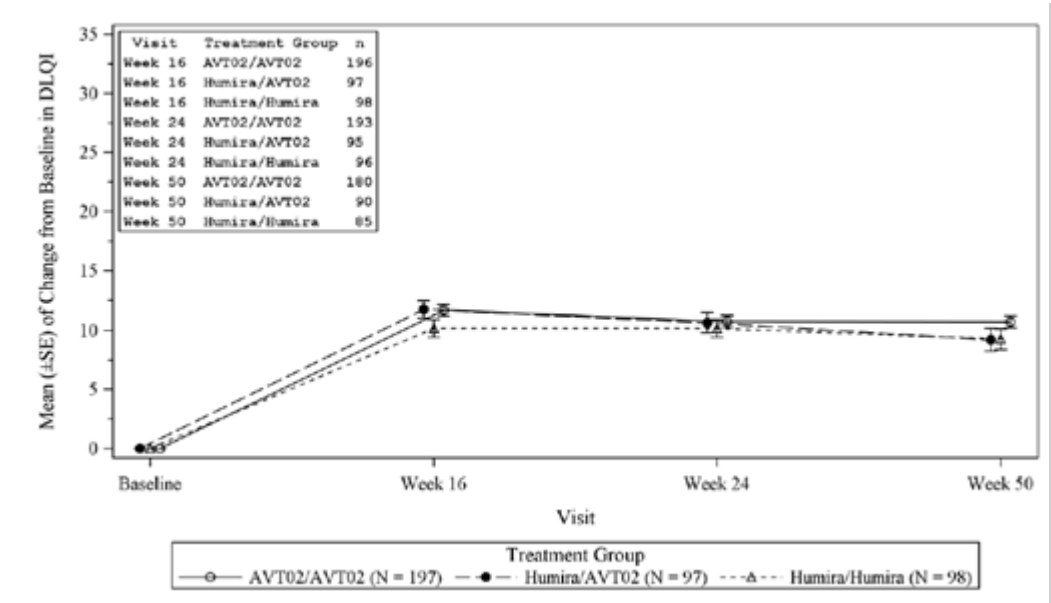
	AVT02 (N=205)			Humira (N=207)		
Visit	m	n	p	m	n	p
Week 4						
sPGA response is Clear (0) or Almost Clear (1)	205	36	17.6	204	43	21.1
Week 8						
sPGA response is Clear (0) or Almost Clear (1)	203	122	60.1	203	141	69.5
Week 12						
sPGA response is Clear (0) or Almost Clear (1)	201	162	80.6	202	162	80.2
Week 16						
sPGA response is Clear (0) or Almost Clear (1)	201	182	90.5	201	182	90.5

	AVT02/AVT02 (N=197)			Humira/AVT02 (N=97)			Humira/Humira (N=98)		
Visit	m	n	p	m	n	p	m	n	p
Week 16									
sPGA response is Clear (0) or Almost Clear (1)	197	182	92.4	97	94	96.9	98	88	89.8
Week 24									
sPGA response is Clear (0) or Almost Clear (1)	194	171	88.1	96	85	88.5	96	82	85.4
Week 32									
sPGA response is Clear (0) or Almost Clear (1)	184	156	84.8	92	78	84.8	91	75	82.4
Week 42									
sPGA response is Clear (0) or Almost Clear (1)	182	150	82.4	91	73	80.2	89	72	80.9
Week 50									
sPGA response is Clear (0) or Almost Clear (1)	181	153	84.5	90	70	77.8	87	67	77.0

Dermatology Life Quality Index (DLQI)

The change from BL in Dermatology Life Quality Index (DLQI) was similar across treatment groups at each time point through Week 16 and Week 50 **(Figure 8).**

Figure 8 Mean (±SE) of Change from Baseline in Dermatology Life Quality Index (DLQI) by Visit - Full Analysis Set - Through Week 50.

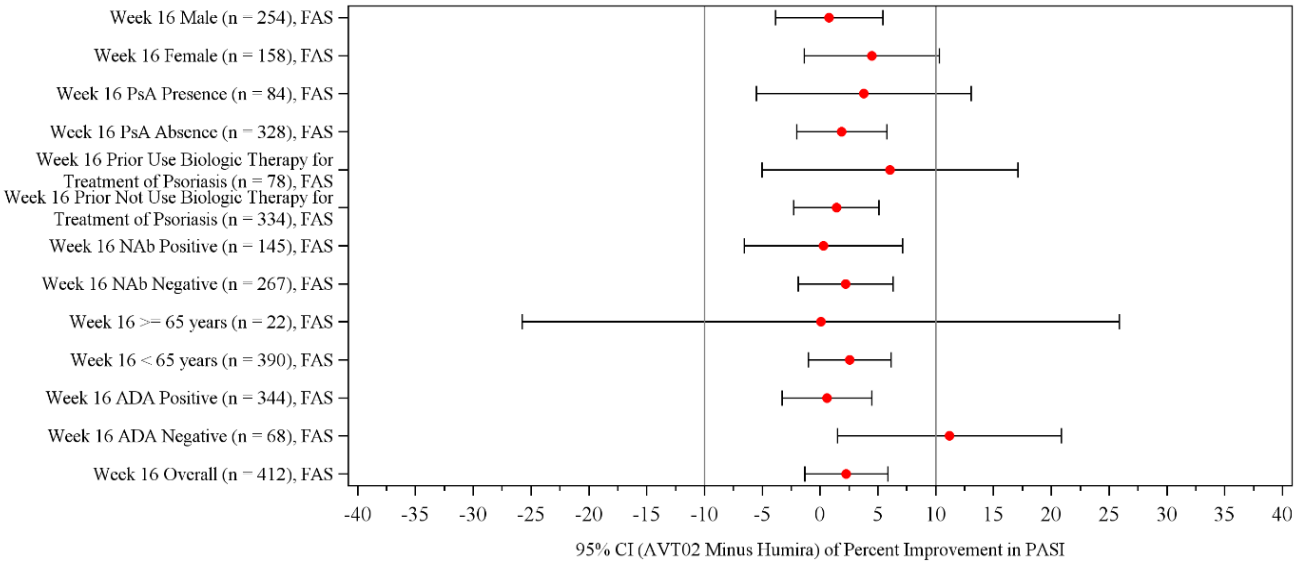


Ancillary analyses

PASI Subgroup Analysis

Subgroup analyses showed consistency between AVT02 and Humira treatment groups with respect to the primary endpoint in both the FAS and PPS in respect to gender, PsA, use of prior biologic therapy and age **(Figure 9**). The effect of ADA presence on efficacy is presented and discussed in section 4.8 of the clinical AR. While AVT02 showed significantly better efficacy than Humira among ADA negative subjects in the FAS population (LOCF analysis), the results were similar between groups in the per-protocol analysis set (PPS).

Figure 9 Forest Plot of 90% CI of Percent Improvement from Baseline in Psoriasis Area and Severity Index (PASI) at Week 16 (LOCF Data) Full Analysis Set - Through Week 16



Note: The two-sided 95% CI of the differences of least squares means between the AVT02 and Humira groups are from the ANCOVA model including percent improvement as response variable, treatment and 2 stratification factors as factors, and baseline PASI score as covariate.
LOCF data: Missing percent improvement in PASI is imputed using last LOCF for subjects with post-baseline assessment.
Abbreviations: CI = confidence interval; FAS = Full Analysis Set; LOCF = last observation carry-forward; n = number of subjects in the sample; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis

Summary of main efficacy results

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 biosimilarity assessment (see later sections).

Table 19 Summary of efficacy for trial AVT02-GL-301 – ALVOPAD-PS

Title: A Multicenter, Double-blind, Randomized, Parallel group, Active Control Study to Compare the Efficacy, Safety, and Immunogenicity of AVT02 Versus Humira® in Patients with Moderate-to-Severe Chronic Plaque Psoriasis (ALVOPAD PS)	
Study identifier	**Company Code:** AVT02-GL-301 **EudraCT Number:** 2017-003367-35 **ClinicalTrials.gov Number:** NCT03849404
Design	Multicentre, double-blind, randomised, parallel-group, active control, 2 stage study The active period comprised 2 stages, a core efficacy assessment (Stage 1) and a long term-efficacy and safety assessment (Stage 2). At Week 16, non-responsive patients (less than PASI 50* [50% improvement in PASI]) were withdrawn from the study. Responsive patients (at least PASI 50) began Stage 2 of the active period.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		50 weeks + 4-week safety follow-up not applicable not applicable
Hypothesis	Equivalence between AVT02 to EU-Humira in %-change from baseline in PASI at week 16 was considered achieved if the 90% CI lay within (-10%, 10%).		
Treatments groups	<u>Stage 1:</u> through Week 16 Dosing and dosing regimens for AVT02 and Humira were consistent with those provided in the Summary of Product Characteristics of Humira for treatment of moderate to severe PsO.		
	AVT02		Initial loading dose of AVT02 was 80 mg (2 x 40 mg) administered subcutaneously (s.c.), followed by 40 mg s.c. every other week (EOW) starting one week after the loading dose. Week 1-Week 16, N=205
	Humira		Initial loading dose of Humira was 80 mg (2 x 40 mg) administered s.c., followed by 40 mg s.c. EOW starting one week after the loading dose. Week 1-Week 16, N=207
	<u>Stage 2</u>: Week 16 through Week 54 (re-randomisation at Week 16) (Only patients with at least 50% PASI response to either AVT02 or Humira were eligible)		
	AVT02/AVT02 n= 197		Responders initially randomised to AVT02 continued to receive AVT02 40 mg s.c. EOW until week 48.
	Humira/AVT02 (Group 2A) n = 97		Responders initially randomised to EU-Humira were re-randomised 1:1 into two groups, Group 2A switched to AVT02 40 mg s.c. EOW until week 48 after re-randomisation.
	Humira/Humira (Group 2B) n = 98		Responders initially randomised to EU-Humira were re-randomised 1:1 into two groups, Group 2B continued to receive Humira 40 mg s.c. EOW until week 48 after re-randomisation.
Endpoints and definitions	Primary endpoint	% PASI	Percent improvement in PASI from baseline (BL) to Week 16
	Secondary endpoint	% PASI	Percent improvement in PASI from BL to Week 8, Week 12, Week 24, Week 32, Week 42, Week 50
Database lock	Primary CSR: 05-March-2020; CSR Final: 28-Aug-2020		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis** An analysis of covariance (ANCOVA) model to assess the efficacy of AVT02 versus Humira at Week 16 was used for the Full Analysis Set (FAS) using Last Observation Carried Forward (LOCF) imputation. The ANCOVA model includes percent improvement as response variable, treatment, and 2 stratification factors (presence or absence of PsA and prior use of biologic therapy for the treatment of PsO or PsA) as factors and baseline PASI score as covariate.		
Analysis population and time point description	Full Analysis Set (FAS). The FAS, consistent with the intention-to-treat principle, was defined as all randomised subjects who received at least 1 dose of randomised study drug.		

Descriptive statistics and estimate variability ***ANCOVA** of percent improvement in PASI from BL to Week 16 (FAS, LOCF Data)*	Treatment group Stage 1	AVT02	Humira
	Number of subjects	n=205	n=207
	% PASI W16 LS Mean (SE)	89.2 (1.61)	86.9 (1.65)
Effect estimate per comparison	Primary endpoint: % PASI Week 16	Comparison groups	AVT02 vs Humira
		LS Mean difference between groups (SE) (AVT02 vs. Humira)	2.3 (1.84)
		95% Confidence Interval (ANCOVA)	**-1.34, 5.88**
Analysis description	**Secondary analysis, Stage 1** The same methods used for the primary endpoint were used for mean percent improvement in PASI from BL to Weeks 8 and 12.		
Descriptive statistics and estimate variability ***ANCOVA of percent improvement in PASI from BL to Week 8 (FAS, LOCF Data)***	Treatment group Stage 1	AVT02 (N=205)	Humira (N=207)
	Number of subjects	n=205	n=207
	% PASI Week 8 (LOCF data) LS Mean (SE)	75.6 (1.95)	75.7 (2.00)
Effect estimate per comparison	Secondary endpoint: % PASI Week 8	Comparison groups	AVT02 vs Humira
		LS Mean difference between groups (SE)	-0.2 (2.22)
		95% Confidence Interval (ANCOVA)	**-4.55, 4.20**
Descriptive statistics and estimate variability ***ANCOVA of percent improvement in PASI from BL to Week 12 (FAS, LOCF Data)***	Treatment group Stage 1	AVT02 (N=205)	Humira (N=207
	Number of subjects	n=205	n=207
	% PASI Week 12 LS Mean (SE)	85.2 (1.73)	84.1 (1.77)
Effect estimate per comparison	Secondary endpoint: % PASI Week 12	Comparison groups	AVT02 vs Humira
		LS Mean difference between groups (SE)	1.1 (1.97)
		95% Confidence Interval (ANCOVA)	**-2.78, 4.96**
Analysis description	**Secondary analysis, Stage 2** There were no formal comparisons between the treatment groups for Stage 2 (Week 16-50) for Percent improvement in PASI from BL to specified time point.		
Analysis population and time point description	**Full Analysis Set (FAS) -** *for definition see primary analysis* **Result:** The mean percent PASI improvement from BL to each timepoint through Week 16 was comparable in the AVT02 and Humira groups in both the LOCF analysis (see below) and the observed data analysis (in the FAS (see CSR AVT02-GL-301). From Week 16 through Week 50 (Stage 2), the mean percent PASI improvement remained similar at each timepoint to those at Week 16 across the treatment groups.		

Descriptive statistics and estimate variability	Time Point	AVT02/AVT02		Humira/AVT02		Humira/Humira	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Percent improvement in PASI from BL to specified time point **(FAS, LOCF data)**	Week 16	197	93.64 (10.04)	97	94.86 (8.87)	98	93.68 (9.77)
	Week 24	194	93.45 (12.91)	96	92.83 (12.39)	96	93.18 (13.56)
	Week 32	184	92.43 (15.54)	92	91.25 (17.91)	91	93.16 (12.99)
	Week 42	182	91.99 (16.50)	91	92.20 (14.84)	89	92.97 (12.05)
	Week 50	181	91.64 (17.79)	90	90.75 (15.68)	87	90.82 (16.60)
Notes	Source: CSR AVT02-GL-301, Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject received the first dose of study drug (Day 1) in Stage 1. LOCF Data: Missing percent improvement in PASI is imputed using LOCF method for subjects with post-baseline assessment. Abbreviations: LOCF = last observation carry-forward; N = number of subjects in treatment group; PASI = Psoriasis Area and Severity Index; SD = standard deviation.						

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

Not applicable.

Clinical studies in special populations

No studies were performed in special populations and none are required in the biosimilar setting. The pivotal efficacy study AVT02-GL-301 included 22 subjects (5.3%) over the age of 65 years.

2.7.3. Supportive studyies

Study AVT02-GL-303 Study AVT02 HF validation AI

Real-life subject handling experience with the use of the autoinjector (AI) was studied in subjects with moderate to severe active RA who self-injected AVT02 s.c. in a single arm repeated dose study (AVT02-GL-303). After initial training, all 107 subjects were able to self-inject successfully, as recorded by the Observer Assessment Tool (OAT) and the Participant Assessment Tool (PAT), and no handling events were recorded. It was concluded that the AI device can be used and self-injected to deliver the medicinal product to the target population.

The applicant stated that the assessments that were used in the study are commonly used, standard measurements frequently seen in RA studies. However, no references were provided, and these OAT and PAT questionnaires are not familiar to the assessor. It seems that the tools used to assess usability in study AVT02-GL-303 were not optimal. The questionnaires do not provide any useful information regarding a possible need for amendment of the IFU.

However, the results obtained from this study support usability and combined with the results from the HF study, sufficient data was obtained also regarding details in the IFU.

A human factors summative study (AVT02 HF validation AI) was performed to determine if the autoinjector can be used safely and effectively without patterns of preventable use errors or difficulties that could result in serious harm to the intended users or patients. Adult Patients with RA (n = 15 (12 males and 3 female)), Adolescent Patients with JIA (n = 15), Caregivers (n = 15), and HCPs (n = 15)

performed simulated injections and performance was evaluated using a user task checklist. The study was representative of the intended population.

The task list followed the instructions of the IFU in a total of 1547 recordings, there were 163 use errors recorded. Five types of critical use errors were observed during the course of the study: Lifting up AI too early, failing to store AI in fridge, inappropriate disposal of AI, failing to correctly identify injection site, not correctly understanding the number of autoinjectors at a higher (loading) dose. The observed use errors were few and were not considered by the applicant to be further preventable through practicable means. The applicant confirmed that the sections on IFU, storage, handling and disposal in the SmPC and PL intended for the EU market are comparable with the Medication Guide and the Prescribing Information intended for the US market.

Overall, the study report provides evidence on safe AI usability. In the pivotal efficacy study AVT02-GL-301, the subject/caregiver were provided training on the s.c. administration of the study drug by PFS and on the disposal of the used syringe. As the IFU is adequate and no specific problems emerged during self-injection in study AVT02-GL-301, the lack of specific usability data for the PFS is acceptable.

2.7.4. Discussion on clinical efficacy

Design and conduct of clinical studies

To demonstrate the therapeutic equivalence in terms of efficacy and safety, including immunogenicity, the applicant conducted one pivotal randomised clinical trial (**Study AVT02-GL-301**) in patients with moderate to severe psoriasis (PsO).

The choice of patients with moderate to severe chronic plaque psoriasis as study population is acceptable as the concomitant immunosuppressive therapies that may interfere with treatment effects and immunogenicity are generally not used in psoriasis and established and sensitive outcome measures are available for psoriasis trials. In addition, the choice of the patient population was agreed in the EMA/CHMP scientific advice.

The proposed indications are the same indications as for EU-Humira. An extrapolation rational for indications held by the reference product, EU-Humira, was provided in Module 2.2 Introduction.

The dose and dosing regimen of EU-Humira and AVT02 used in the equivalence trial are in accordance with the Humira SmPC. The allowed and prohibited treatments are acceptable.

The inclusion/exclusion criteria are appropriate and in line with the Humira SmPC. The demographic characteristics and PsO characteristics were comparable between groups at baseline. The study objectives are adequate for an equivalence trial of a biosimilar candidate.

The 1-year duration is adequate to compare longer-term efficacy and safety, including immunogenicity as it is in line with the EMA guideline "Immunogenicity assessment of biotechnology-derived therapeutic proteins" (EMEA/CHMP/BMWP/14327/2006). In Stage 1 of the study (week 1-16), 413 subjects were randomised to receive either AVT02 or Humira 40 mg s.c. once every other week (EOW) starting 1 week after a loading dose of 80 mg. Only responsive subjects (at least PASI 50) continued beyond week 16. This approach is endorsed since it is stated in the Humira SmPC that treatment should not be continued beyond week 16 in non-responders. At week 16, subjects who initially received Humira were re-randomised to continue with either AVT02 or Humira, with the intention to clarify the interchangeability between the biosimilar and the originator. Hence, treatment was continued from week 16 up to week 48 in three parallel arms: Maintenance AVT02, Maintenance Humira and Switch AVT02.

The primary efficacy endpoint in Study AVT02-GL-301 was the percent improvement in PASI from BL to Week 16. As pointed out in the scientific advice (EMA/CHMP/SAWP/859223/2018), percent change in PASI is an acceptable primary endpoint. However, in equivalence trials, week 8 is considered to be the most appropriate timing of the primary efficacy endpoint in PsO, as a plateau in efficacy response is normally reached by week 12, rendering the sensitivity to detect differences at later stages insufficient. Hence, week 16 is not the optimal time point for the primary efficacy analysis. Therefore, the efficacy assessment will rely on the totality of data and week 8 in particular.

The secondary efficacy endpoints, including percent improvement in PASI at weeks 8, 12 and 24, the PASI 50, PASI 75, PASI 90, and PASI 100 response rates, the sPGA response and the DLQI score are adequate and in line with relevant guidelines. In respect to secondary efficacy assessment, only 'Percent improvement in PASI from BL to Week 8, 12' was assessed using the same methods as for the primary endpoint. The results of all other secondary endpoints have been analysed descriptively.

The equivalence margin for the primary endpoint was predefined as -10%, 10% with a 95% CI. This margin can be acceptable as an even broader margin has been approved in previous adalimumab applications.

During initial assessment, some concerns arose regarding proper conduct of the study. For example, three patients at site 3808 (Ukraine) had positive adalimumab concentrations at baseline combined with a very high proportion (20%) of patients had anti-adalimumab antibodies at baseline. The applicant provided sufficient assurance of appropriate study conduct, how principal investigators (PI) and study personnel were trained and how it was ensured that the staff had sufficient understanding of the principles of GCP and study procedures. Acceptable efforts have also been made to ensure that included subjects had no previous exposure of adalimumab.

Since there were only three subjects with non-zero adalimumab at baseline, and the subjects were not all in the same treatment arm, their impact on the outcome is negligible and additional analyses are not required for these subjects.

Efficacy data and additional analyses

205 subjects in the AVT02 arm and 207 subjects in the Humira arm initiated treatment. Demographic characteristics were similar across both treatment groups at screening. 22 subjects (5.3%) were ≥65 years. The BL disease characteristics were similar across the treatment groups. The mean baseline PASI score was 23.08. Most of the subjects (231 subjects, 56.1%) were rated as moderate on the sPGA, 7.8% were rated severe, while mild or moderate disease forms were not included per protocol.

Primary outcome

Both treatment arms showed significant improvement by week 16 (89.2% vs 86.9% in the LOCF FAS analysis and 90.9% vs 90.6% in the PPS analysis for AVT02 and Humira respectively). The percent improvement from BL in PASI status was in line with previous findings with adalimumab.

The 95% CI of the primary endpoint - mean difference in percent improvement in PASI from baseline to week 16 in the LOCF FAS - was within the predefined equivalence margin of ±10%. The 95% CI for all sensitivity analyses were within ±10%. Hence, the primary objective was met, and sensitivity analyses confirmed the robustness of the primary analysis.

As the dropout rate was low, and protocol deviations were rare, results from the LOCF FAS analysis were very similar to the observed data FAS results as well as the PPS results. Since the FAS is not always considered conservative in equivalence trials, the PPS analyses are an important addition.

Secondary outcome

The mean difference in percent improvement in PASI from baseline to Week 8 was 0.2 (95% CI: -4.55 to 4.20) in the FAS LOCF analysis. The 95% CI:s were within ±10% for all time points up to week 16. Since the differences between groups were very small at all time points and confidence intervals were narrow, no sensitivity analyses are requested for week 8, even if this would have been the preferred time point for primary analyses. It is concluded that similarity in PASI change from baseline was shown also at the most sensitive time points.

In the subset of patients continuing into Stage 2 of the study, the actual PASI scores and changes from baseline remained essentially similar between AVT02 and Humira treatment groups throughout the study, up to week 50.

Subgroup analyses at week 16 showed no significant difference with respect to the primary endpoint between AVT02 and Humira treatment groups when analysed by gender, PsA status, use of prior biologic therapy or age. While AVT02 showed significantly better efficacy than Humira among ADA negative subjects in the FAS LOCF analysis, the results were similar between groups in the observed data and in the per-protocol analysis set. Hence, this does not preclude a conclusion of similarity. The effect of ADA formation on efficacy is further discussed in section 3.3.8.

Through Week 16, the percentage of subjects achieving PASI 50, PASI 75, PASI 90, and PASI 100 at each time point was similar across treatment groups. At most, the difference in point estimate for PASI75 was 3.9% at week 8. The PASI 75 response was achieved for 125 (61.6%) subjects in the AVT02 treatment group and 133 (65.5%) subjects in the Humira treatment group at week 8 (FAS). This difference is considered negligible, since it is not seen consistently at other time points and in other PASI response outcome. In Stage 2 of the study, up to week 50, the response rates remained essentially similar between AVT02 and Humira treatment groups.

Through Week 50, the %BSA affected by psoriasis as well as the percentage of subjects achieving clear (0) or almost clear (1) on the sPGA was comparable at each time point across treatment groups. The change from BL in Dermatology Life Quality Index (DLQI) was similar across treatment groups at each time point through Week 16 and Week 50. Also, efficacy results in the subset of patients with PsA were compatible with similarity.

Overall, the results of the secondary efficacy endpoints support the results of the primary efficacy endpoints assessment.

2.7.5. Conclusions on the clinical efficacy

The design of the pivotal study to demonstrate therapeutic equivalence was adequate. Primary and secondary efficacy outcome were consistent and compatible with similarity principles.

2.8. Clinical safety

The safety profile of AVT02 has been investigated in two PK-studies conducted in healthy volunteers (AVT02-GL-101 and AVT02-GL-102 comparing PFS and AI), in one equivalence efficacy and safety study (AVT02-301), conducted in patients with moderate to severe PsA and in RA patients in an AI real-life handling study (AVT02-GL-303); see Table 3.3.1 for study descriptions.

For all clinical trials, safety analyses were performed on the safety population, which included all randomised subjects who received any amount of IP and was analysed according to the actual

treatment received, if this differed from that to which the subject was randomised. The Safety Population was used for the summaries of all safety data.

During the procedure, the applicant provided a safety update from the two still ongoing studies, AVT02-GL-302 and AVT02-GL-303. Safety data from first 8 weeks of the study AVT02-GL-303 were included in the applicant's initial submission. AVT02-GL-302 is a new study not included in initial submission (see the description in Table 3.3.1). The applicant's safety update report considers the narratives on any deaths, other TESAEs, AESIs with exclusion of ISRs and premature study discontinuation for safety grounds that occurred for the time periods that start from the first patient screened in study AVT02-GL-302 and from Week 9 in study AVT02-GL-303 until the data extraction point 22 Mar 2021 in both studies.

Patient exposure

In the clinical trials included in this application, safety of AVT02 was investigated in 334 adult healthy male and female subjects (single s.c. dose of 40 mg), in 302 (205 in Stage 1 plus 97 switching from Humira to AVT02 in Stage 2) adult patients with chronic plaque psoriasis (PsO, multiple s.c. doses through Week 48, initial dose of 80 mg followed by 40 mg EOW starting 1 week after the loading dose) and 107 patients with RA (multiple s.c. doses of 40 mg EOW through Week 54).

Phase III study AVT02-GL-301 in patients with PsO

Exposure, both in terms of mean duration and mean number of injections, was comparable in AVT02 and Humira groups through Week 16, from Week 16 through Week 50 (Stage 2), and from baseline through Week 50. The mean duration of treatment in subjects receiving AVT02/AVT02 was 31.3 weeks, 31.7 weeks in the Humira/AVT02 group, and 30.9 weeks in the Humira/Humira group, over which subjects received an average of 16 injections across the treatment groups.

Phase I study AVT02-GL-101 in healthy subjects

A total of 390 subjects received a single 40 mg s.c. dose of investigational product (IP). One subject randomised to the EU-Humira group had an IP dispensing error and received a single dose of AVT02 instead. Therefore, based on the actual treatment received, 130 subjects received AVT02, 129 subjects received EU-Humira, and 131 subjects received US-Humira. The study drug was administered according to the protocol in all other subjects.

Phase I study AVT02-GL-102 in healthy subjects

A total of 204 subjects (100 in the AVT02-PFS group and 104 in the AVT02-AI group) received a single 40 mg s.c. dose of AVT02. One subject in the AVT02-AI group had a major protocol deviation in IP compliance; this subject received an incomplete dose due to a technical issue with the AI device. The study drug was administered according to the protocol in all other subjects.

AI handling study AVT02-GL-303 in patients with RA

A total of 107 patients received 40 mg AVT02-AI every other week as a single dose via s.c. injection. Subjects were exposed to AVT02 for a mean of 56.6 days (range 55.6 to 57.7) with an average of 5 injections (1 investigator-led and 4 self-injections) over the course of the 8 weeks of the study. The mean (SD) cumulative dose administered was 198.1 (15.91) mg. Except for one patient, the complete volume of AVT02 was administered at every dose to every patient.

Adverse events

Phase III study AVT02-GL-301 in patients with PsO

Summary of adverse events

The AE profile in the first 16 weeks of the study was similar across treatment groups **(Table 20).** The AE profile from Week 16 through Week 24 of the study was also similar across treatment groups **(Table 21).** No deaths were reported in this study. Through Week 16, there were 2 subjects (1.0%) randomised to AVT02 who reported 3 TESAEs, 5 subjects (2.4%) randomised to Humira who reported 5 TESAEs. From Week 16 through Week 24, there were 4 subjects (2.0%) randomised to AVT02/AVT02 who reported 6 TESAEs.

In the AVT02 treatment group, 92 subjects (44.9%) reported a total of 192 TEAEs through Week 16. Of these, 44 subjects (21.5%) reported 84 events that were considered as treatment related TEAEs by the investigator. About one-third of subjects (61/205, 29.8%) reported the TEAEs were mild in nature.

Three subjects (1.5%) had a TEAE that led to ET from the study; of which 2 TEAEs were considered treatment-related by the investigator; none were deemed serious. Thirty-eight subjects (18.5%) reported 77 events that were considered TEAEs of special interest.

In the Humira treatment group, 91 subjects (44.0%) reported a total of 245 TEAEs through Week 16. Of these, 41 subjects (19.8%) reported 89 events that were assessed as treatment related TEAEs by the investigator. About one-fourth of subjects (51/207, 24.6%) reported the TEAEs were mild in nature. Three subjects (1.4%) reported 3 TEAEs that led to ET from the study; all 3 TEAEs were considered treatment-related by the investigator; none were deemed serious. Thirty-four subjects (16.4%) reported 76 events that were considered TEAEs of special interest.

Table 20 Adverse Events, Overview of Treatment-emergent Adverse Events – Safety Analysis Set – Through Week 16 (Study AVT02-GL-301)

	AVT02 (N=205)		Humira (N=207)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAE	92 (44.9)	192	91 (44.0)	245
Maximum Severity of TEAEs				
Mild	61 (29.8)	117	51 (24.6)	114
Moderate	27 (13.2)	37	37 (17.9)	52
Severe	4 (2.0)	5	3 (1.4)	3
Treatment-related TEAEs	44 (21.5)	84	41 (19.8)	89
TESAEs	2 (1.0)	3	5 (2.4)	5
Treatment-related TESAEs	1 (0.5)	1	0	0
TEAE Leading to ET	3 (1.5)	3	3 (1.4)	3
Treatment-related TEAE Leading to ET	2 (1.0)	2	3 (1.4)	3
TESAEs Leading to ET	0	0	0	0
Treatment-related TESAEs Leading to ET	0	0	0	0
TEAEs of Special Interest	38 (18.5)	77	34 (16.4)	76
Death	0	0	0	0

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 1 and before first dose of study drug of Stage 2. Subjects are counted only once at the maximum severity in the following order: severe, moderate, and mild. Events with unknown severity are counted as severe. Events with unknown relationship to study drug are counted as drug related.

Source: Table 12.2 in the AVT02-GL-301 final CSR

The AE profile from Week 16 through Week 54 of the study was similar across the AVT02/AVT02, Humira/AVT02, and Humira/Humira treatment groups although was slightly higher in the AVT02/AVT02 group (116 subjects [58.9%] reported 315 events) in comparison to other groups (Humira/AVT02: 46 subjects [47.4%] reported 153 events; Humira/Humira: 49 subjects [50.0%] reported 131 events) **(Table 21).** This difference was largely due to a slightly higher percentage of subjects in the AVT02/AVT02 group who reported ISRs and nasopharyngitis compared to other treatment groups. TEAEs reported by at least 5% of subjects in any treatment group from Week 16 through Week 54 of the study are presented in **Table 23**

The safety profile for treatment related TEAEs was comparable between treatment groups through Week 16 and from Week 16 through Week 54. Through Week 16, a similar percentage of subjects reported TEAEs that were considered treatment-related by the investigator (AVT02: 44 subjects [21.5%] reported 84 events; Humira: 41 subjects [19.8%] reported 89 events, respectively) (**Table 24**). From Week 16 through Week 54 of the study, 40 subjects [20.3%] reported 135 events that were considered as treatment related TEAEs by the investigator in the AVT02/AVT02 group compared to the Humira/AVT02 group in which 17 subjects [17.5%] reported 66 events and the Humira/Humira group in which 14.3 subjects (14.3%) reported 39 events **(Table 25)**. About one-third of subjects reported TEAEs that were

mild in nature across the treatment groups through Week 16 and from Week 16 through Week 54 of the study.

Table 21 Adverse Events, Overview of Treatment-emergent Adverse Events – Safety Analysis Set – from Week 16 through Week 54 (Study AVT02-GL-301)

	AVT02/AVT02 (N=197)		Humira/AVT02 (N=97)		Humira/Humira (N=98)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAE	116 (58.9)	315	46 (47.4)	153	49 (50.0)	131
Maximum Severity of TEAEs						
Mild	62 (31.5)	175	28 (28.9)	95	31 (31.6)	76
Moderate	50 (25.4)	79	18 (18.6)	28	18 (18.4)	34
Severe	4 (2.0)	5	0	0	0	0
Treatment-related TEAEs	40 (20.3)	135	17 (17.5)	66	14 (14.3)	39
Serious TEAEs	4 (2.0)	6	0	0	0	0
Treatment-related Serious TEAEs	1 (0.5)	1	0	0	0	0
TEAE Leading to Early Withdrawal	6 (3.0)	6	3 (3.1)	3	1 (1.0)	1
Treatment-related TEAE Leading to Early Withdrawal	4 (2.0)	4	3 (3.1)	3	1 (1.0)	1
Serious TEAE Leading to Early Withdrawal	0	0	0	0	0	0
Treatment-related Serious TEAE Leading to Early Withdrawal	0	0	0	0	0	0
TEAEs of Special Interest	45 (22.8)	137	17 (17.5)	64	13 (13.3)	37
Death	0	0	0	0	0	0

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 2. Subjects are counted only once at the maximum severity in the following order: severe, moderate, and mild. Events with unknown severity are counted as severe. Events with unknown relationship to study drug are counted as drug related.
Source: Table 12.3 in the AVT02-GL-301 final CSR

Through Week 16, the only TEAEs reported by more than 5% of subjects were ISR and nasopharyngitis (**Table 22)**. From Week 16 through Week 54, TEAEs reported by more than 5% of subjects were ISR, nasopharyngitis, pharyngitis, ALT increased and diarrhoea **(Table 23).**

Table 22 Adverse Events, Treatment-emergent Adverse Events (At Least 5% Subjects in Any Treatment Group) by Primary System Organ Class and Preferred Term – Safety Analysis Set – Through Week 16 (Study AVT02-GL-301)

System Organ Class Preferred Term	AVT02 (N=205)		Humira (N=207)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAEs	92 (44.9)	192	91 (44.0)	245
General disorders and administration site conditions	40 (19.5)	74	36 (17.4)	78
Injection site reaction	34 (16.6)	67	33 (15.9)	75
Infections and infestations	35 (17.1)	42	39 (18.8)	44
Nasopharyngitis	11 (5.4)	12	11 (5.3)	13

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 1 and before first dose of study drug of Stage 2. Subjects are counted once within a system organ class and once for each unique preferred term.

Source: Table 12.4 in the AVT02-GL-301 final CSR

Table 23 Adverse Events, Treatment-emergent Adverse Events (At Least 5% Subjects in Any Treatment Group) by Primary System Organ Class and Preferred Term – Safety Analysis Set – from Week 16 through Week 54 (Study AVT02-GL-301)

	AVT02/AVT02 (N=197)		Humira/AVT02 (N=97)		Humira/Humira (N=98)	
System Organ Class Preferred Term	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAEs	116 (58.9)	315	46 (47.4)	153	49 (50.0)	131
Gastrointestinal disorders	5 (2.5)	5	2 (2.1)	2	12 (12.2)	16
Diarrhoea	0	0	1 (1.0)	1	5 (5.1)	5
General disorders and administration site conditions	34 (17.3)	124	11 (11.3)	56	12 (12.2)	36
Injection site reaction	31 (15.7)	121	11 (11.3)	56	10 (10.2)	34
Infections and infestations	58 (29.4)	81	23 (23.7)	28	16 (16.3)	21
Nasopharyngitis	23 (11.7)	28	5 (5.2)	6	4 (4.1)	4
Pharyngitis	4 (2.0)	4	5 (5.2)	5	2 (2.0)	2
Investigations	29 (14.7)	44	12 (12.4)	25	16 (16.3)	21
Alanine aminotransferase increased	6 (3.0)	7	5 (5.2)	8	3 (3.1)	4

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 2. Subjects are counted once within a system organ class and once for each unique preferred term.

Source: Table 12.5 in the AVT02-GL-301 final CSR

Analysis of adverse events

Treatment-related TEAEs

Most TEAEs in this study were not considered treatment-related (**Table 20** and **Table 21).** ISR was the only treatment related TEAE reported by at least 5% subjects in any treatment group (**Table 24** and **Table 25**). Regarding TEAEs reported through Week 16, the investigator attributed the ISR in 4 subjects (AVT02) and 2 subjects (Humira) to the injection procedure not the study drug; therefore, these TEAEs were not considered treatment-related by the investigator; however, the Sponsor considers all ISRs to be treatment-related. Regarding TEAEs reported from Week 16 through Week 54, the investigator attributed the ISR in 3 subjects (AVT02/AVT02), 1 subject (Humira/AVT02), and 1 subject (Humira/Humira) to the injection procedure not the study drug; therefore, these TEAEs were not considered treatment-related by the investigator; however, the Sponsor considers all ISRs to be treatment-related.

Table 24 Adverse Events, Treatment-related Treatment-emergent Adverse Events (At Least 5% Subjects in Any Treatment Group) by Primary System Organ Class and Preferred Term – Safety Analysis Set – Through Week 16 (Study AVT02-GL-301)

	AVT02 (N=205)		Humira (N=207)	
System Organ Class Preferred Term	Subjects n (%)	Events n	Subjects n (%)	Events n
Any treatment-related TEAEs	44 (21.5)	84	41 (19.8)	89
General disorders and administration site conditions	30 (14.6)	62	31 (15.0)	69
Injection site reaction	30 (14.6)	62	31 (15.0)	69

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 1 and before first dose of study drug of Stage 2. Subjects are counted once within a system organ class and once for each unique preferred term.

Source: Table 12.6 in the AVT02-GL-301 final CSR

Table 25 Adverse Events, Treatment-related Treatment-emergent Adverse Events (At Least 5% Subjects in Any Treatment Group) by Primary System Organ Class and Preferred Term – Safety Analysis Set – from Week 16 through Week 54 (Study AVT02-GL-301)

	AVT02/AVT02 (N=197)		Humira/AVT02 (N=97)		Humira/Humira (N=98)	
System Organ Class Preferred Term	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any treatment-related TEAEs	40 (20.3)	135	17 (17.5)	66	14 (14.3)	39
General disorders and administration site conditions	28 (14.2)	116	10 (10.3)	51	9 (9.2)	32
Injection site reaction	28 (14.2)	116	10 (10.3)	51	9 (9.2)	32

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 2. Subjects are counted once within a system organ class and once for each unique preferred term.

Source: Table 12.7 in the AVT02-GL-301 final CSR

Adverse Events of Special Interest

Through Week 16, 38 subjects (18.5%) treated with AVT02 reported 77 events and 34 subjects (16.4%) treated with Humira reported 76 TEAEs of special interest were considered treatment-related by the investigator. The only TEAE of special interest reported by at least 5% in any treatment group was ISR,

which was reported by 34 subjects (16.6%) treated with AVT02 reported 67 events and 33 subjects (15.9%) treated with Humira reported 75 TEAEs (**Table 26**). Other TEAEs of special interest were Infections and infestations reported in 0.5% of subjects treated with AVT02 (PT: septic shock) and Investigations in 2.4% of subjects treated with AVT02 (PTs: ALT increased, blood bilirubin increased, and gamma-glutamyltransferase [GGT] increased [0.5% each], and AST increased, hepatic enzyme increased, and transaminase increased [1.0% each]). Other TEAEs of special interest were Investigations reported in 0.5% subjects (PT: ALT increased) treated with Humira.

From Week 16 through Week 24, slightly higher percentage of subjects reported TEAEs of special interest in the AVT02/AVT02 group compared to the Humira/AVT02 and Humira/Humira treatment groups caused largely by the higher number of ISRs compared to other treatment groups. 45 subjects (22.8%) treated with AVT02/AVT02 reported 137 events, 17 subjects (17.5%) treated with Humira/AVT02 reported 64 TEAEs, and 13 subjects (13.3%) treated with Humira/Humira reported 37 TEAEs **(Table 27).** The only TEAE of special interest reported by at least 5% in any treatment group was ISR, which was reported by 31 subjects (15.7%) treated with AVT02/AVT02 who reported 120 events, 10 subjects (10.3%) treated with Humira/AVT02 reported 54 events, and 10 subjects (10.2%) treated with Humira/Humira reported 34 TEAEs. Other TEAEs of special interest reported in 3.0% subjects treated with AVT02/AVT02 were Investigations (PT: ALT increased [0.5%] and Mycobacterium tuberculosis complex test positive [4.6%]), in subjects treated with Humira/AVT02 were Blood and lymphatic disorders, 1.0% (PT: leukopenia 1.0%) and Investigations, 4.1% (PTs: ALT increased [3.1%], AST increased [1.0%], and Mycobacterium tuberculosis complex test positive [1.0%]), and in subjects treated with Humira/Humira were Investigations, 1.0% (PTs: Mycobacterium tuberculosis complex test positive [1.0%]).

The only TEAE of special interest reported by >5% of subjects considered treatment-related was ISR **(Table 22 and Table 23)**. For those subjects with liver enzyme abnormalities, most had pre-existing conditions (e.g., obesity, fatty liver disease, increased cholesterolemia, and/or diabetes mellitus) which predisposed them to the possibility of such abnormalities.

Table 26 Adverse Events, Treatment-emergent Adverse Events of Special Interest by Primary System Organ Class and Preferred Term – Safety Analysis Set – Through Week 16 (Study AVT02-GL-301)

	AVT02 (N=205)		Humira (N=207)	
System Organ Class Preferred Term	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**
Any TEAEs of Special Interest	38 (18.5)	77	34 (16.4)	76
General disorders and administration site conditions	34 (16.6)	67	33 (15.9)	75
Injection site reaction	34 (16.6)	67	33 (15.9)	75
Infections and infestations	1 (0.5)	1	0	0
Septic shock	1 (0.5)	1	0	0
Investigations	5 (2.4)	9	1 (0.5)	1
Alanine aminotransferase increased	1 (0.5)	1	1 (0.5)	1
Aspartate aminotransferase increased	2 (1.0)	2	0	0
Blood bilirubin increased	1 (0.5)	1	0	0
Gamma-glutamyltransferase increased	1 (0.5)	1	0	0
Hepatic enzyme increased	2 (1.0)	2	0	0
Transaminases increased	2 (1.0)	2	0	0

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 1 and before first dose of study drug of Stage 2. Subjects are counted once within a system organ class and once for each unique preferred term.

Source: Table 12.8 in the AVT02-GL-301 final CSR

Table 27 Adverse Events, Treatment-emergent Adverse Events of Special Interest by Primary System Organ Class and Preferred Term – Safety Analysis Set – from Week 16 through Week 54 (Study AVT02-GL-301)

	AVT02/AVT02 (N=197)		Humira/AVT02 (N=97)		Humira/Humira (N=98)	
System Organ Class Preferred Term	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**
Any TEAEs of Special Interest	45 (22.8)	137	17 (17.5)	64	13 (13.3)	37
Blood and lymphatic system disorders	1 (0.5)	1	1 (1.0)	1	0	0
Leukopenia	1 (0.5)	1	1 (1.0)	1	0	0
General disorders and administration site conditions	31 (15.7)	120	10 (10.3)	54	10 (10.2)	34
Injection site reaction	31 (15.7)	120	10 (10.3)	54	10 (10.2)	34
Infections and infestations	2 (1.0)	2	0	0	0	0
Injection site infection	1 (0.5)	1	0	0	0	0
Meningitis meningococcal	1 (0.5)	1	0	0	0	0
Investigations	13 (6.6)	14	6 (6.2)	9	3 (3.1)	3
Alanine aminotransferase increased	1 (0.5)	1	4 (4.1)	5	1 (1.0)	1
Aspartate aminotransferase increased	3 (1.5)	3	1 (1.0)	1	0	0
Liver function test increased	1 (0.5)	1	0	0	0	0
Mycobacterium tuberculosis complex test positive	9 (4.6)	9	2 (2.1)	3	2 (2.0)	2

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 2. Subjects are counted once within a system organ class and once for each unique preferred term.

Source: Table 12.9 in the AVT02-GL-301 final CSR

Injection site reactions

ISR reported as TEAEs were similar across treatment groups through Week 16 **(Table 28).** All ISRs were mild in severity. From Week 16 through Week 54 of the study, there was a higher occurrence of ISRs in the AVT02/AVT02 group compared to the Humira/AVT02 and Humira/Humira treatment groups with a similar profile of ISR terms reported on the AE form between groups that was not clinically significant **(Table 29).** All ISRs were mild in nature except for 1 event of moderate severity reported by 1 subject in the AVT02/AVT02 group.

Generally, a similar profile of ISR terms were reported by a similar percentage of subjects across treatment groups both through Week 16 and from Week 16 through Week 54 of the study with no clinically significant differences.

Table 28 Injection Site Reactions Reported on AE Forms – Safety Analysis Set – Through Week 16 (Study AVT02-GL-301)

ISR Reported on AE forms	AVT02 (N=205)		Humira (N=207)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any Injection Site Reactions	34 (16.6)	67	33 (15.9)	75
Pain/tenderness	10 (4.9)	13	8 (3.9)	17
Erythema/redness	11 (5.4)	17	18 (8.7)	35
Induration/swelling	7 (3.4)	11	7 (3.4)	12
Pruritus/itching	12 (5.9)	27	12 (5.8)	29
Hematoma/ecchymosis/bruising	9 (4.4)	13	10 (4.8)	15
Other	0	0	0	0

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 1 and before first dose of study drug of Stage 2. All ISRs reported from the day of first dose through the day prior to the first dose of study drug in Stage 2 are reported in this summary.

Source: Table 12.11 in the AVT02-GL-301 final CSR

Table 29 Injection Site Reactions Reported on AE Forms – Safety Analysis Set – from Week 16 through Week 54 (Study AVT02-GL-301)

ISR Reported on AE forms	AVT02/AVT02 (N=197)		Humira/AVT02 (N=97)		Humira/Humira (N=98)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any Injection Site Reactions	31 (15.7)	122	10 (10.3)	54	10 (10.2)	34
Pain/tenderness	11 (5.6)	30	4 (4.1)	15	2 (2.0)	2
Erythema/redness	12 (6.1)	55	6 (6.2)	14	3 (3.1)	17
Induration/swelling	9 (4.6)	34	3 (3.1)	7	5 (5.1)	9
Pruritus/itching	13 (6.6)	61	6 (6.2)	31	7 (7.1)	27
Hematoma/ecchymosis/bruising	8 (4.1)	8	2 (2.1)	3	3 (3.1)	4
Other	0	0	0	0	0	0

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 2. All ISRs reported from the day of first dose of Stage 2 are reported in this summary.

Source: Table 12.12 in the AVT02-GL-301 final CSR

TEAEs based on presence of psoriatic arthritis

In the subset of subjects with psoriatic arthritis, the incidence of TEAEs was similar through Week 16 and from Week 16 through Week 54. The severity of TEAEs was similar across the treatment groups with about one-third of subjects reporting TEAEs which were mild in nature through Week 16 and 1 subject reporting 2 severe TEAEs (AVT02/AVT02; from Week 16 through Week 54).

Phase I study AVT02-GL-101 in healthy subjects

Overall, the safety profiles of AVT02, EU-Humira, and US-Humira were similar. 80.0% of subjects reported at least 1 TEAE during the study; the subject frequency of TEAEs was similar across treatment

groups. At least 1 treatment related TEAE was reported by 34.6% of subjects overall. Slightly more subjects in the AVT02 (34.6%) and EU-Humira (38.0%) groups reported at least 1 related TEAE compared with the US-Humira group (31.3%). The majority of subjects experienced TEAEs that were mild in severity (75.9%).

The most frequently reported AESIs across the 3 treatment groups were local administration site reactions. At least 1 local administration site reaction AESI was reported by 12.6% of subjects overall; the subject frequency of these events was comparable across treatment groups: 13.8% in the AVT02 group, 10.9% in the EU-Humira group, and 13.0% in the US-Humira group. The most frequently reported local administration site reaction AESI was injection site erythema (9.0% overall). The subject frequency of these events was higher in the AVT02 group (12.3%) compared with the EU-Humira (7.8%) and US-Humira (6.9%) groups. The majority of reported local administration site reaction AESIs were mild in severity (11.0% of subjects overall).

Phase I study AVT02-GL-102 in healthy subjects

Overall, the safety profiles of AVT02-PFS and AVT02-AI were similar. 84.8% of subjects reported at least 1 TEAE during the study; the frequency of TEAEs was similar between treatment groups. The majority of subjects experienced TEAEs that were mild in severity (82.8%).

At least 1 AESI was reported by 15.7% of subjects overall; the frequency of AESIs was comparable between treatment groups. The most frequently reported AESIs in both groups were local administration site reactions. The most frequently reported local administration site reaction was injection site erythema (9 subjects in the AVT02-PFS group and 12 subjects in the AVT02-AI group).

AI handling study AVT02-GL-303 in patients with RA

Twenty-three TEAEs were reported by 19 subjects (17.8%); 3 subjects (2.8%) each reported a treatment related TEAE; and 1 subject (0.9%) reported a TEAE of special interest (leukopenia) through Week 8 of the study. Through Week 8, the only TEAE reported by at least 2% of subjects were influenza (4.7%) and headache (2.8%. There were 68 reports of TEAE as of treatment Week 9 to the data extraction point. This included 5 AESIs and 3 TESAEs since treatment Week 9, which were either judged as not treatment-related or were consistent with the known safety profile of Humira. The majority of TEAEs were mild.

Pilot study AVT02-GL-100 in healthy subjects

Treatment-emergent AEs were experienced by 11 (91.7%) subjects in the AVT02 group compared with 10 (83.3%) in the EU-Humira group. The most frequently reported SOCs were infections and infestations (7 [58.3%] subjects in AVT02 group and 6 [50%] subjects in EU-Humira group) and nervous system disorders (4 [33.3%] subjects in each group). The most common TEAEs at the PT level were upper respiratory infection and headache. Upper respiratory tract infection was experienced by 5 (41.7%) subjects in the AVT02 group and 6 (50%) subjects in the EU-Humira group. Headache was experienced by 4 (33.3%) subjects in each group. No severe TEAEs were reported.

Study AVT02-GL-302 in patients with PsO

Of the 568 enrolled subjects, 536 were on treatment, and 35 had terminated the study early until the data extraction point, all of whom were being treated with Humira. There were 420 reports of TEAEs as of the data extraction point. Of those, 80 were AESIs comprising 70 ISRs, 2 liver enzyme elevations, 4 serious infections, 1 hypersensitivity reaction, 2 haematological disorders, and 1 malignancy. The majority of events were of mild severity (n = 311), with 100 events rated as moderate, 5 rated as severe, and 4 unclassified as of data extraction point. There were 6 serious TEAEs, all of which were judged to be not treatment-related (see Section 4.1.1). One was fatal (not treatment-related, because of carbon monoxide poisoning), 2 led to early discontinuation (COVID-19 infection, cancer of pancreas)

and 3 allowed continuation of the study (COVID-19 infection, pneumonia related to COVID-19 infection, and ulcer). In summary, the adverse events reported were consistent with the known safety profile of Humira. No new safety signals were identified.

Serious adverse events and deaths

Phase III study AVT02-GL-301 in patients with PsO

No deaths were reported in this study.

Through Week 16 serious TEAEs have been reported more frequently in Humira group (5 subjects [2.4%] reported 5 serious TEAEs) than in AVT02 group (2 subjects [1.0%] reported 3 serious TEAEs). No TESAE was reported in more than 1 subject in either treatment group. The TESAEs considered treatment-related by the sponsor were large intestinal polyp and salpingo-oophoritis in Humira group, and duodenal ulcer haemorrhage and septic shock + urosepsis in AVT02 group.

From Week 16 through Week 54 of the study, TESAEs were only reported by subjects in the AVT02/AVT02 treatment group. No TESAE was reported by more than 1 subject. Only 1 TESAE (meningitis meningococcal) was considered treatment-related by the investigator and sponsor. In addition, one report of pulmonary embolism was considered treatment-related by the sponsor.

All serious TEAEs reported during the study have been resolved. The narratives of all serious TEAEs have been provided. The applicant listed all serious TEAEs by primary SOC and PT, by relation to the study drug and by severity, in line with to the study protocol. However, the AEs have not been classified according to Common Terminology Criteria for Adverse Events, which would have been more informative.

One subject diagnosed with large intestinal polyp (in AVT02 group) was discontinued from the study at Week 16 as the Psoriasis Area and Severity Index criteria was not met. In addition, one subject diagnosed with salpingo-oophoritis (in Humira group) was discontinued from the study due to adnexa-uteri mass, which was considered unlikely to be related to Humira.

According to the applicant, no serious TEAEs reported in study AVT02-GL-301 led to early termination of the study.

Phase I Study AVT02-GL-101 in healthy subjects

No deaths or other serious TEAEs were reported in this study.

Phase I study AVT02-GL-102 in healthy subjects

No deaths were reported in this study. Three subjects (1.5% overall, 2 in AVT02-PFS group and 1 in the AVT02-AI group) reported a total of 4 SAEs during the study.

AI handling study AVT02-GL-303 in patients with RA

No deaths or other serious TEAEs were reported during the first 8 weeks. Three serious TEAEs were reported from Week 9 to the data extraction point of the applicant's safety update report: one (liver enzyme elevation) was judged to be treatment-related and the two other not treatment-related.

Laboratory findings

Phase III study AVT02-GL-301 in patients with PsO

<u>Tuberculosis testing</u>

One subject in Humira group had a positive QuantiFERON TB Gold Test at Screening but was randomised and received 3 injections (2 injections on Day 1 and 1 injection at Week 2); this subject was then discontinued from the study based on the Medical Monitor's decision. This was considered a critical protocol deviation. Eight subjects randomised to AVT02/AVT02 (3702025, 3808015, 3808024, 3808035, 4807001, 4808063, 9901006, and 9901016), 3 subjects randomised to Humira/AVT02 (3808019, 4802022, and 9904021), and 3 subjects randomised to Humira/Humira (3808005, 9904007, and 9904022) reported positive QuantiFERON TB Gold Tests through Week 54. All of those with positive tests were referred to a pulmonologist for further follow-up. Additionally, 2 subjects randomised to AVT02/AVT02 (9904008 and 9904018) reported a positive TB test as an AE where the associated test result data is missing or indeterminate. Subsequent chest X-rays were negative, and no TB lesion was concluded.

The percentage of subjects with a positive QuantiFERON TB Gold test result remained at <3.2% in all test groups throughout the study, except those subjects that terminated the study early. In patients that terminated the study early, patients with positive QuantiFERON TB Gold test result among the respective groups (AVT02, Humira, AVT02/AVT02, Humira/AVT02, Humira/Humira) were: 0 of 5 (0%), 0 of 7 (0%), 5 of 12 (41.7%), 2 of 5 (40.0%), and 1 of 7 (14.3%).

Laboratory values over time

No differences were observed between treatment groups in hematology, chemistry or urinalysis values during the study.

Most subjects had either a normal or CTCAE Grade 1 as the highest post-BL LFT result. An equal number of subjects in each treatment group had either a normal or CTCAE Grade 1 BL LFT result which became either a CTCAE Grade 2 or higher post-BL through Week 16. Ten of 197 subjects (%) randomised to AVT02 and 9 of 98 subjects (%) randomised to Humira reported a CTCAE Grade 2 or higher CK results post-BL.

Individual subject changes

No differences were observed in shifts between treatment groups in hematology, chemistry or urinalysis values during the study.

Studies AVT02-GL-101, AVT02-GL-102 and AVT02-GL-303

In the single-dose studies AVT02-GL-101 and AVT02-GL-102, results on the distributions of chemistry and hematology of healthy subjects were similar in AVT02, EU-Humira and US-Humira, as well as in AVT02-PFS and AVT02-AI treatment groups. No differences were observed between the treatment groups through the end of these studies.

In study AVT02-GL-303 in patients with RA, no unexpected changes in laboratory values were reported during the first phase of study through Week 8.

Vital Signs, Physical Examination Findings and Other Observations Related to Safety

Phase III study AVT02-GL-301 in patients with PsO

No differences were observed in vital signs, physical examinations and ECG findings during the study through Week 16 or Week 54. Across all treatment groups, most assessments had a mean change from baseline that was similar.

No differences were seen in physical examinations through Week 16 or Week 54.

No differences were seen in ECG findings through Week 16 or Week 54. Most ECG interpretations were normal or abnormal not clinically significant. Most assessments remained as they were assessed at Screening through Week 54; there were minimal changes.

Studies AVT02-GL-101, AVT02-GL-102 and AVT02-GL-303

In the single-dose studies AVT02-GL-101 and AVT02-GL-102, similar results on the vital signs, physical examinations and ECG findings of healthy subjects were observed in AVT02, EU-Humira and US-Humira, as well as in AVT02-PFS and AVT02-AI treatment groups through the end of these studies.

In the study AVT02-GL-303, AVT02 produced no changes in vital signs or ECG and no new differences in physical examinations were observed in patients with RA during the first phase of study through Week 8. Consistent with the RA, the X-ray of the hands/bone/wrists at baseline were almost all abnormal.

Safety in special populations

N/A

Immunological events

The immunogenic potential of AVT02 was analysed in healthy subjects after a single s.c. administration (studies AVT02-GL-101 and AVT02-GL-102) and in patients with moderate-to-severe PsO after multiple administration (study AVT02-GL-301). In addition, the applicant plans to submit immunogenicity data from the ongoing usability study AVT02-GL-303. Immunogenicity results from the pilot study with a qualitatively non-representative drug product (study AVT02-GL-100) are also briefly presented.

The drug tolerance of the ADA assay was reported to be at least 1000 ng/mL ADA detected at 62.5 µg/mL of AVT02 or at 61.89 µg/mL of Humira and at least 21 ng/mL ADA detected at 3.13 µg/mL of AVT02 or at 6.25 µg/mL of Humira.

NAb concentrations of at least 100 ng/ml were detected in the presence of 6 µg/ml AVT02.

Immunogenicity Results in patients with PsO (Study AVT02-GL-301)

Frequency of ADA and NAb

In Study AVT02-GL-301 the serum samples for the immunogenicity assessment (ADA and NAb) were collected at Week 1/Day 1 (predose), and predose at Weeks 4, 8, 16,24, 32 and 50 and on the follow-up visit at week 54.

Most subjects were ADA positive through Week 16 (AVT02: 88.8%; Humira: 90.8%) and through Week 54 (AVT02/AVT02: 93.4%; AVT02/Humira: 91.8%; Humira/Humira: 95.9%). Of these, most subjects were also positive for NAbs through Week 16 (AVT02: 66.3%; Humira: 73.4%) and through Week 54 (AVT02/AVT02: 84.3%; AVT02/Humira: 83.5%; Humira/Humira: 80.6%) **(Table 30** and **Table 31).**

Table 30 Confirmed Positive Antibody Frequency - Safety Analysis Set – Through Week 16

Results	**AVT02 (N=205) n (%)**	**Humira (N=207) n (%)**
Total Antibody Incidence[1]	m=205	m=207
Binding (ADA)	182 (88.8)	188 (90.8)
Neutralizing Antibodies	136 (66.3)	152 (73.4)
Baseline (Pre-existing Antibody Incidence)[2]	m=205	m=207
Binding (ADA)	42 (20.5)	39 (18.8)
Neutralizing Antibodies	6 (2.9)	5 (2.4)
Treatment-emergent ADA Incidence up to Week 16[3]	m1=163	m1=166
Binding (ADA)	140 (85.9)	149 (89.8)
Treatment-emergent NAb Incidence up to Week 16[3]	m2=199	m2=200
Neutralizing Antibodies	130 (65.3)	147 (73.5)

[1] Positive result at any visit in Stage 1.
[2] Baseline is defined as the last non-missing assessment prior to dose on the first dose day of Stage 1.
[3] Negative result or no result at Baseline and positive result post-dose up to Week 16.
Note: % = n/m, where m is the total number of subjects with ADA assessed at the specified time period. % = n/m1, where m1 is the number of subjects with ADA assessed post-dose of Stage 1. Subjects with ADA positive at Baseline are not included in m1. % = n/m2, where m2 is the number of subjects with ADA assessed post-dose of Stage 1. Subjects with NAb positive at Baseline are not included in m2.
Abbreviations: ADA = anti-drug antibody; n = number of subjects in the sample; N = number of subjects; NAb = neutralizing anti-drug antibody

Table 31 Confirmed Positive Antibody Frequency - Safety Analysis Set – from Week 16 Through Week 54

Results	AVT02/AVT02 (N=197) n (%)	Humira/AVT02 (N=97) n (%)	Humira/Humira (N=98) n (%)
Total Antibody Incidence[1]	m=197	m=97	m=98
Binding (ADA)	184 (93.4)	89 (91.8)	94 (95.9)
Neutralizing Antibodies	166 (84.3)	81 (83.5)	79 (80.6)
Antibody Incidence Before Week 16[2]	m=197	m=97	m=98
Binding (ADA)	174 (88.3)	87 (89.7)	91 (92.9)
Neutralizing Antibodies	129 (65.5)	73 (75.3)	68 (69.4)
Treatment-emergent Antibody Incidence[3]	m1=23	m1=10	m1=7
Binding (ADA)	10 (43.5)	2 (20.0)	3 (42.9)
Treatment-emergent Antibody Incidence[3]	m2=67	m2=22	m2=29
Neutralizing Antibodies	36 (53.7)	6 (27.3)	10 (34.5)

[1] Positive result at any visit.
[2] Positive result at any visit before Week 16.
[3] Negative result or no result at BL and at least one positive post dose through Week 54.
Note: % = n/m, where m is the total number of subjects with ADA assessed at the specified time period. % = n/m1, where m1 is the number of subjects with ADA assessed post-dose of Week 16. Subjects with ADA positive before Week 16 are not included in m1. % = n/m2, where m2 is the number of subjects with ADA assessed post-dose of Week 16. Subjects with NAb positive before Week 16 are not included in m2.
Abbreviations: ADA = anti-drug antibody; BL = Baseline; n = number of subjects in the sample; N = number of subjects; NAb = neutralizing anti-drug antibody

ADA titres

Descriptive statistics of ADA titres were presented by visit for all treatment arms from baseline to week 54 in Appendix tables to the CSR, Overall, ADA titers were similar between the treatment groups through Week 16, from Week 24 through Week 54, (compared with BL), and from BL through Week 54 (for subjects who were treated with the same drug, AVT02 or Humira) as indicated in **Figure 10** and **Figure 11.** The geometric means increased with the duration of the treatment and were comparable between the treatment groups, with maximal levels at Week 24.

Figure 10 Box Plot of Titers for Positive Anti-drug Antibody (ADA) Results by Visits Safety Analysis Set – Through Week 16 for AVT02-GLpdnt

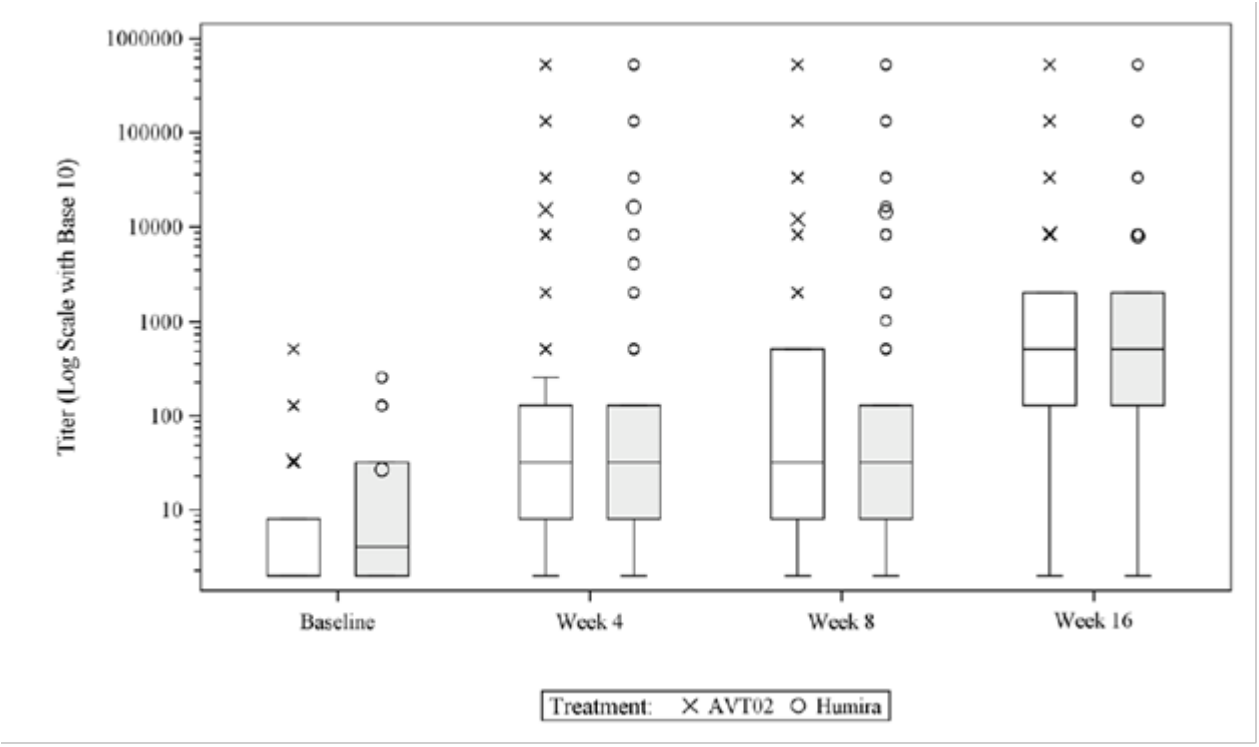
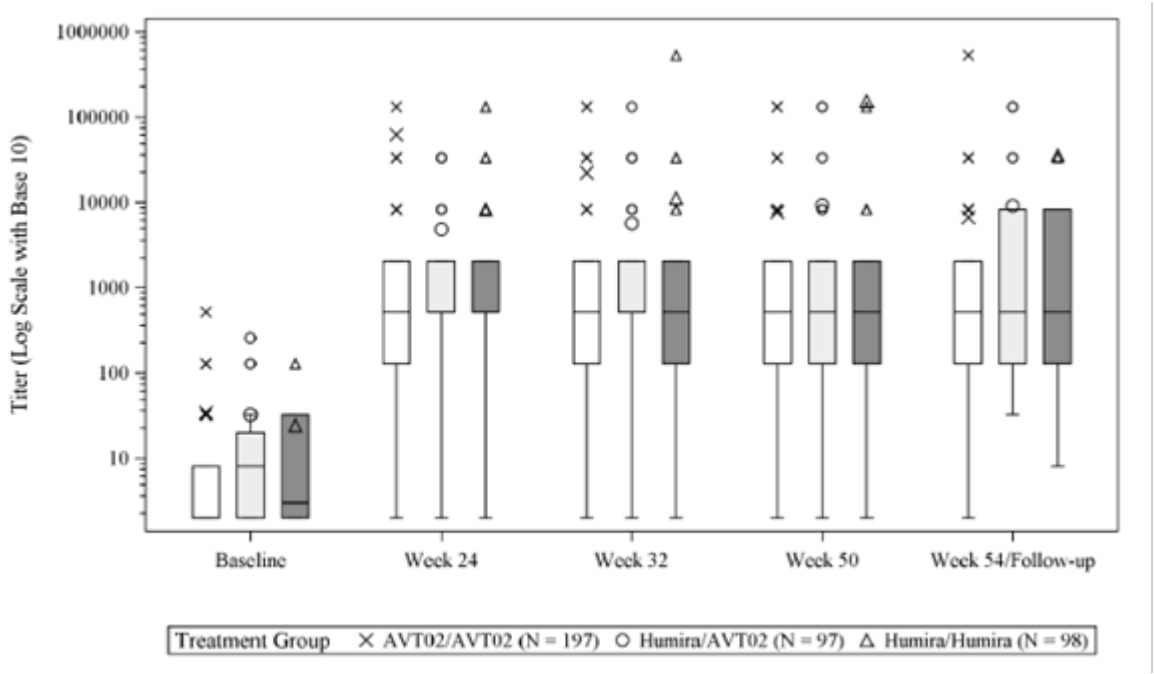


Figure 11 Box Plot of Titers for Positive Anti-drug Antibody (ADA) Results by Visits Safety Analysis Set – Through Week 54



Impact of ADA on PK

In the clinical study in PsO patients (AVT02-GL-301) mean serum trough levels of both AVT02 and EU-Humira were higher in those subjects that were ADA negative and lower in those subjects that were NAb positive (**Tables 32** and **33).**

Trough concentrations were comparable at steady-state between those subjects who were randomised to AVT02 and Humira or AVT02/AVT02 and Humira/Humira. There was no meaningful difference in the adalimumab serum trough concentrations when comparing subjects treated with AVT02 or Humira in subgroups without ADAs, with ADA, or with NAbs throughout the study period.

Of note, only overall post-dose ADA status was used in the tables below and not the actual visit-based ADA status, which makes it difficult to interpret results regarding impact of ADA status on PK.

Table 32 Mean (SD) serum trough concentrations (µg/l) over time by ADA/NAb status through week 16 (safety population)

	ADA negative*		ADA positive**		nAb positive**	
Time point	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
AVT02						
		N=23		**N=140**		**N=130**
Baseline	23	0.000 (0.0000)	139	0.000 (0.0000)	128	0.000 (0.0000)
Week 4	23	9437.391 (2825.0297)	140	6764.821 (2983.5607)	130	5756.992 (3019.7258)
Week 8	23	10898.696 (2620.5869)	139	5959.795 (3503.4925)	130	4687.968 (3246.0201)
Week 16	23	12870.000 (4059.4290)	136	5889.393 (4298.0846)	128	4117.816 (3579.9782)
ET			5	2500.000 (5590.1699)	5	0.000 (0.0000)
EU-Humira						
		N=19		**N=149**		**N=147**
Baseline	19	0.000 (0.0000)	149	0.000 (0.0000)	147	0.000 (0.0000)
Week 4	17	9525.882 (3231.8011)	148	6066.547 (2740.6532)	147	5341.756 (2932.0528)
Week 8	17	10693.529 (3437.8335)	147	5716.522 (3499.1060)	146	4653.964 (3380.6058)
Week 16	17	12583.529 (3399.3859)	143	5271.173 (4450.5754)	142	3925.617 (3827.8218)
ET			5	2578.000 (3239.0770)	4	682.500 (1365.0000)

Source: CSR AVT02-GL-301, Table 14.3.5.3.1

* Negative result or no result at both Baseline and post-dose up to Week 16

** Negative result or no result at Baseline and positive result post-dose up to Week 16

ADA = antidrug antibody; ET = early termination; n = number of patients with evaluable data; N = number of treated patients; nAb = neutralizing antibody; SD = standard deviation

Table 33 Mean (SD) serum trough concentrations (µg/l) over time by ADA/NAb status through week 16 and week 24 (safety population)

	ADA negative*		ADA positive**		nAb positive**	
Time point	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
AVT02/AVT02						
		N=18		**N=138**		**N=145**
Baseline	18	0.000 (0.0000)	137	0.000 (0.0000)	143	0.000 (0.0000)
Week 4	18	8775.556 (2823.0235)	138	7017.935 (3038.8058)	145	6221.441 (3190.5820)
Week 8	18	10681.667 (2874.8038)	138	6384.712 (3501.5234)	145	5462.688 (3413.0531)
Week 16	18	12675.556 (2824.6670)	138	6295.578 (4589.7675)	145	5005.812 (4264.2194)
Week 24	18	13612.778 (3869.9564)	138	6144.722 (4838.3168	143	4655.494 (4222.5939)
ET					2	0.000 (0.0000)
EU-Humira/EU-Humira						
		N=6		**N=76**		**N=71**
Baseline	6	0.000 (0.0000)	76	0.000 (0.0000)	71	0.000 (0.0000)
Week 4	6	9318.333 (4565.4898)	76	6072.750 (2965.0405)	71	5462.649 (3025.9215)
Week 8	6	9456.667 (2435.6738)	76	5859.455 (3640.9432)	71	4863.714 (3547.9376)
Week 16	6	11733.333 (2624.0097)	74	5551.681 (4713.2564)	69	4151.078 (4122.6374)
Week 24	6	13860.000 (6555.9134)	74	5201.751 (4875.3908)	68	3760.751 (4194.3933)
ET			1	0.000 (NA)	2	0.000 (0.0000)

Source: CSR AVT02-GL-301, Table 14.3.5.3.2

* Negative result or no result at both Baseline and post-dose up to Week 24

** Negative result or no result at Baseline and positive result post-dose up to Week 24

ADA = antidrug antibody; ET = early termination; n = number of patients with evaluable data; N = number of treated patients; NA = not applicable; nAb = neutralizing antibody; SD = standard deviation

Impact of ADA on efficacy

In ADA positive subjects, the mean percent improvement in PASI at week 16 was 90.8% vs 90.5%, in subjects randomised to AVT02 and Humira respectively. In ADA negative subjects, improvement in PASI was greater in the AVT02 group: 98.2% vs 81.5%, respectively (FAS, LOCF) **(Table 34).**

Table 34 Percent Improvement from Baseline in Psoriasis Area and Severity Index (PASI) by Visit and by Visit-based Anti-drug Antibody (ADA) Status (LOCF Data) Full Analysis Set – Through Week 16

Visit-based ADA Positive (LOCF Data)

	Actual Value				Percent Improvement from Baseline			
Time Point	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
AVT02 (N=205)								
Week 4	154	12.25 (7.076)	11.20	0.0, 34.3	154	46.89 (25.030)	44.68	-22.8, 100.0
Week 8	168	5.90 (6.916)	4.20	0.0, 57.0	168	75.44 (22.643)	80.94	-5.4, 100.0
Week 12	168	3.60 (6.397)	1.75	0.0, 56.5	168	85.69 (18.930)	91.35	-5.4, 100.0
Week 16	182	2.46 (5.869)	0.60	0.0, 54.4	182	90.77 (16.406)	97.60	-5.4, 100.0
Humira (N=207)								
Week 4	155	11.45 (6.251)	10.80	0.4, 33.4	155	49.15 (23.858)	48.94	-15.2, 97.8
Week 8	176	5.05 (5.085)	3.60	0.0, 26.6	176	77.58 (20.991)	83.09	0.0, 100.0
Week 12	176	3.04 (4.928)	1.20	0.0, 36.0	176	86.43 (19.978)	93.50	-20.0, 100.0
Week 16	187	2.12 (4.749)	0.40	0.0, 36.0	187	90.45 (19.259)	98.18	-20.0, 100.0

Visit-based ADA Negative (LOCF Data)

	Actual Value				Percent Improvement from Baseline			
Time Point	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
AVT02 (N=205)								
Week 4	51	10.33 (6.862)	9.60	1.0, 30.0	51	55.86 (23.034)	55.37	0.0, 94.3
Week 8	37	4.12 (5.729)	1.60	0.0, 21.0	37	82.95 (22.452)	94.07	17.1, 100.0
Week 12	37	2.09 (3.673)	0.60	0.0, 18.2	37	91.56 (14.699)	97.51	26.0, 100.0
Week 16	23	0.43 (0.738)	0.00	0.0, 3.0	23	98.20 (3.043)	100.00	87.8, 100.0
Humira (N=207)								
Week 4	52	11.71 (7.610)	11.10	0.7, 43.6	52	48.43 (24.282)	44.96	0.0, 95.7
Week 8	31	6.51 (9.339)	3.80	0.0, 43.6	31	74.32 (29.124)	78.06	0.0, 100.0
Week 12	31	4.85 (9.340)	1.20	0.0, 43.6	31	82.47 (29.165)	94.31	0.0, 100.0
Week 16	20	5.33 (11.464)	0.50	0.0, 43.6	20	81.48 (35.811)	96.82	0.0, 100.0

Percent improvement from baseline in PASI was comparable between AVT02 and Humira in both ADA positive and ADA negative subjects at all time points up to week 50 and also among patients who switched from Humira to AVT02. The slightly lower mean PASI improvement observed in the LOCF analyses, but not in the PPS, for ADA-negative subjects in the Humira treatment arm, could be explained by the impact of missing data on the small subject population and is not considered clinically meaningful.

Impact of ADA on safety

TEAES by Anti-drug Antibody Status

In Stage 1 of the study, through Week 16, a similar percentage of ADA positive subjects reported TEAEs in both treatment groups. Less ADA negative subjects reported TEAEs in the Humira group (18 subjects, 48.6%) than in the AVT02 group (11 subjects, 35.5%). However, this difference was not considered to be clinically significant, considering the low subject numbers. Severe TEAEs were only reported in subjects with ADA positive status in both treatment groups. There were no other notable clinically significant differences between groups. Through Week 16, 74 ADA positive subjects (44.0%) treated with AVT02, 18 ADA negative subjects (48.6%) treated with AVT02; 80 ADA positive subjects (45.5%) treated with Humira, and 11 ADA negative subjects (35.5%) treated with Humira reported TEAEs. TEAEs reported in ADA negative patients at frequencies ≥5% were the following (AVT02 vs Humira treatment group, respectively): injection site reaction (16.2%, 19.4%), nasopharyngitis (8.1%, 0%), upper respiratory tract infection (5.4%, 0%), pyrexia (0%, 6.5%) and tinea versicolor (5.4%, 0%). The differences in TEAEs reported in at least 5% of subjects in any treatment group between treatment groups was small, not considered related to ADA status, and not clinically significant.

Through Week 16, a similar percentage of treatment induced ADA subjects reported treatment-emergent adverse events (TEAEs) in both treatment groups. Less pre-existing ADA subjects reported TEAEs in the AVT02 group than in the Humira group. However, this difference was not considered to be clinically significant, considering the low subject numbers. Similar percentage of TEAEs were reported for pre-existing and treatment induced subjects within each treatment group. Severe TEAEs were only reported in subjects with treatment induced ADA status in both treatment groups. There were no other notable clinically significant differences between subjects with pre-existing and treatment induced groups.

From Week 16 through Week 54 of the study, a similar percentage of ADA positive subjects reported TEAEs across treatment groups. More ADA negative subjects reported TEAEs in the AVT02/AVT02 (18 subjects, 69.2%) group than in Humira/Humira (4 subjects, 28.6%) and Humira/AVT02 (8 subjects, 50.0%) groups. However, this difference was not considered clinically significant, considering the low subject numbers. Severe TEAEs were only reported in subjects with ADA positive status in the AVT02/AVT02 group. TEAEs reported in ADA negative patients at frequencies ≥5% and more often in more than one patient in groups receiving AVT02 were the following (AVT02/AVT02, Humira/AVT02, and Humira/Humira treatment group, respectively): injection site reaction (30.8%, 12.5%, 0%), nasopharyngitis (23.1%, 12.5%, 7.1%), and oral herpes (7.7%, 0%, 0%). The difference in ISRs and nasopharyngitis was not considered related to the ADA status, and not clinically significant.

From Week 16 through Week 54 of the study, a similar percentage of treatment induced ADA subjects reported TEAEs in Humira/AVT02 and Humira/Humira groups and was slightly higher in AVT02/AVT02 group. Less pre-existing ADA subjects reported TEAEs in the Humira/Humira group than in the AVT02/AVT02 and Humira/AVT02 groups. However, this difference was not considered clinically significant, considering the low subject numbers. Severe TEAEs were only reported in subjects with treatment induced ADA status in the AVT02/AVT02 group. There were no other notable clinically significant differences between subjects with pre-existing and treatment induced groups through the study.

Through Week 16 and through the study, differences in TEAEs were less than 5% of subjects in any treatment group by PT between treatment groups, for both pre-existing and treatment induced ADA subjects. The applicant concludes that based on presented results, the safety profile for subjects with pre-existing ADA and subjects with treatment induced ADA was similar between treatment groups through Week 16 and through the study.

Through Week 16 and through the study, differences in TEAEs were less than 5% of subjects in any treatment group by PT between treatment groups, for both pre-existing and treatment induced ADA subjects. The applicant concludes that based on presented results, the safety profile for subjects with pre-existing ADA and subjects with treatment induced ADA was similar between treatment groups through Week 16 and through the study.

TEAES by Neutralizing Anti-drug Antibody Status

A similar percentage of subjects reported TEAEs across treatment groups (39.7-45.6%) regardless of NAb status through Week 16 except slightly more NAb negative subjects reported TEAEs (47.2%) and those that were mild in nature (32.4%) in the AVT02 group. Through Week 16, 25 NAb positive subjects (39.7%) treated with AVT02, 67 NAb negative subjects (47.2%) treated with AVT02; 34 NAb positive subjects (41.5%) treated with Humira, and 57 NAb negative subjects (45.6%) treated with Humira reported TEAEs. TEAEs reported in NAb positive patients at frequencies ≥5% were the following (in AVT02 vs Humira treatment groups, respectively): injection site reaction (15.9%, 12.2%) and nasopharyngitis (1.6%, 7.3%). TEAEs reported in NAb negative patients at frequencies ≥5% were the following (AVT02 vs Humira treatment group, respectively): injection site reaction (16.9%, 18.4%) and nasopharyngitis (7.0%, 4.0%).

From Week 16 through Week 54 of the study, a similar percentage of NAb positive subjects reported TEAEs across treatment groups. In NAb negative subjects, the percentage of subjects reporting TEAEs was lower in the Humira/Humira group (65.6 %, 50.0% and 30.0% in AVT02/AVT02, Humira/AVT02 and Humira/Humira groups, respectively). However, this difference was not considered clinically significant, considering the low subject numbers (21, 9 and 6 NAb negative subjects in AVT02/AVT02, Humira/AVT02 and Humira/Humira groups, respectively). TEAEs reported in NAb negative patients at frequencies ≥5% and more often in more than one patient in groups receiving AVT02 were the following (AVT02/AVT02, Humira/AVT02, and Humira/Humira treatment group, respectively): injection site reaction (31.3%, 11.1%, 0%), nasopharyngitis (18.8%, 11.1%, 5.0%), oral herpes (6.3%, 0%, 0%), and dermatitis contact (6.3%, 0%, 5.0%).

Immunogenicity Results in healthy volunteers

The clinical studies in healthy subjects (i.e. clinical studies AVT02-GL-101, AVT02-GL-102 and [AVT02-GL-100]) are described in detail in Chapter 2.1.3. The clinical studies in patients (i.e. clinical studies AVT02-GL-301 and AVT02-GL-303) are described in detail in Chapter 3.3. Here, only the most important results related to the PK and immunogenicity are presented.

Study AVT02-GL-101

Study AVT02-GL-101 was designed to compare the PK of AVT02 with EU-Humira and US-Humira, following a single 40 mg SC injection in healthy adult volunteers. For safety and immunogenicity analyses a total of 390 subjects, randomised in a 1:1:1 ratio, were analysed.

The serum samples for the immunogenicity assessment (ADA and NAb) were collected at Day 1 (predose), and D9, D15, D29 and D64 post dose.

At baseline, the frequency of subjects who were positive for binding ADAs was 6.2% in the AVT02 group, 3.9% in the EU-Humira group and 5.3% in the US-Humira group. The incidence of ADA-positivity progressively increased over the duration of the study, with ADAs observed in >95% of subjects at Day 64 (**Table 35**).

At Day 64, the median ADA titer was 128 in both the AVT02 and EU-Humira groups **Table 36.**

Table 35 Summary of Antidrug Antibody frequency in healthy volunteers (Study AVT02-GL-101)

		Number of Subjects (%)				
		ADA Detection			NAb Detection	
Study Day	N	Sample not collected/analyzed	Negative	Positive	Negative	Positive
			AVT02			
Day 1 (predose)	130	0	122 (93.8%)	8 (6.2%)	8 (100%)	0
Day 9	130	1 (0.8%)	84 (64.6%)	45 (34.6%)	44 (95.7%)	2 (4.3%)
Day 15	130	0	41 (31.5%)	89 (68.5%)	88 (98.9%)	1 (1.1%)
Day 29	130	1 (0.8%)	24 (18.5%)	105 (80.8%)	90 (85.7%)	15 (14.3%)
Day 64/EOS	129	0	5 (3.9%)	124 (96.1%)	24 (19.4%)	100 (80.6%)
			EU-Humira			
Day 1 (predose)	129	0	124 (96.1%)	5 (3.9%)	5 (100%)	0
Day 9	129	0	53 (41.1%)	76 (58.9%)	71 (93.4%)	5 (6.6%)
Day 15	128	4 (3.1%)	24 (18.8%)	100 (78.1%)	97 (97.0%)	3 (3.0%)
Day 29	127	1 (0.8%)	18 (14.2%)	108 (85.0%)	96 (88.9%)	12 (11.1%)
Day 64/EOS	126	0	5 (4.0%)	121 (96.0%)	16 (13.1%)	106 (86.9%)
			US-Humira			
Day 1 (predose)	131	0	124 (94.7%)	7 (5.3%)	5 (71.4%)	2 (28.6%)
Day 9	131	0	89 (67.9%)	42 (32.1%)	40 (95.2%)	2 (4.8%)
Day 15	131	2 (1.5%)	42 (32.1%)	87 (66.4%)	85 (97.7%)	2 (2.3%)
Day 29	130	1 (0.8%)	24 (18.5%)	105 (80.8%)	88 (83.8%)	17 (16.2%)
Day 64/EOS	129	0	6 (4.7%)	123 (95.3%)	16 (13.0%)	107 (87.0%)

ADA = antidrug antibody; NAb = neutralizing antibody; EOS = End-of-study.
Notes: The NAb assay was only performed for samples positive for ADAs, except for 1 subject in the AVT02 group (Day 9 sample) and 1 subject in the EU-Humira group (EOS sample), whose ADA results were negative and NAb was performed (with negative NAb results).
Early termination samples were excluded from the data summary.
The denominator for the percent frequency of NAb detection is the total number of NAb results for the respective treatment and study day.

Table 36 Summary of Antidrug Antibody Titers in healthy volunteers (Study AVT02-GL-101)

Study Day	n	Mean	SD	Median	Minimum	Maximum
			AVT02			
Day 1 (predose)	8	1.0	0.00	1.0	1	1
Day 9	45	7.9	20.76	2.0	1	128
Day 15	89	32.7	70.50	8.0	1	512
Day 29	105	56.8	211.29	8.0	1	2048
Day 64/EOS	124	1039.1	3427.86	128.0	1	32768
			EU-Humira			
Day 1 (predose)	5	52.6	113.71	1.0	1	256
Day 9	76	121.7	938.76	4.0	1	8192
Day 15	100	217.1	1637.63	16.0	1	16384
Day 29	108	285.8	1636.39	32.0	1	16384
Day 64/EOS	121	1711.0	4425.09	128.0	1	32768
			US-Humira			
Day 1 (predose)	7	21.1	47.23	1.0	1	128
Day 9	42	3.5	5.10	2.0	1	32
Day 15	87	28.7	68.07	8.0	1	512
Day 29	105	69.9	184.17	16.0	1	1024
Day 64/EOS	123	1522.4	6302.29	256.0	1	65536

The applicant states that due to the high frequency of ADA and NAb formation, relationships between immunogenicity and PK parameters could not be elucidated.

It is acknowledged that formation of anti-drug antibodies (ADA) and NAb had a high frequency in study AVT02-GL-101 after a single-dose administration of 40 mg s.c. of either AVT02, EU-Humira or US-Humira. However, it is well known that development of antibodies causes increased clearance, lower drug concentrations and subsequent decreased exposure of adalimumab. Presence of NAb can affect the PK profile of adalimumab, especially the elimination phase. Thus, the applicant was asked to present box and whisker of plots of AUC_{0-t} (h·ng/mL), AUC_{0-inf} (h·ng/mL), C_{max} (ng/mL) by Treatment and NAb Status (Day 1-64) – Pharmacokinetic population. In the response, the applicant provided the asked data and it could be seen that presence of Nab affects adalimumab PK profile especially in the elimination phase of adalimumab. The impact of NAb presence on the PK parameters C_{max} is minor or negligible. The impact of NAb presence on the PK parameters AUC_{0-t} and AUC_{0-inf} is considerable. Comparisons of AVT02 vs EU-Humira vs US-Humira within the NAb positive and NAb negative subgroups showed no relevant differences between treatment groups.

Study AVT02-GL-102

At baseline (i.e. predose on Day 1), the frequency of subjects who were positive for binding ADAs were similar in the AVT02-PFS (12.0%) and AVT02-AI (15.4%) groups. Formation of ADAs progressively increased over the duration of the study, with a positive detection of binding ADAs observed in 100% (98 of 98) of subjects in the AVT02-PFS group and 97.0% (96 of 99) of subjects in the AVT02-AI group at Day 64 (i.e., EOS sample).

The frequency of subjects who tested positive for NAbs also increased over the duration of the study, at Day 64 85.7% of subjects in the AVT02-PFS group and 86.5% in the AVT02-AI group were NAb positive.

ADA titers increased from Day 1 to Day 64/EOS in both groups AVT02-AI and AVT02-PFS. Whereas the mean values of antidrug antibody titers were slightly higher in AVT02-PFS than in AVT02-AI, the median values were the same at Day 1, 9, 29 and 64/EOS. In addition, the maximum ADA titers were equal in both groups at Day 15, 29 and 64/EOS.

Due to the high frequency of ADA and NAb formation, relationships between immunogenicity and PK parameters could not be elucidated. See the comments regarding the impact of ADA on the PK parameters for study AVT02-GL-101. However, because the study was not a comparative study between AVT02 and EU-Humira, the issue is not further pursued.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to AEs

Phase III study AVT02-GL-301 in patients with PsO

Three subjects (1.5%) treated with AVT02 had 4 TEAEs and 2 subjects (1.0%) treated with Humira had 3 TEAEs which caused study drug discontinuation through Week 16 **(Table 37).**

Table 37 Treatment-emergent Adverse Events Leading to Study Drug Discontinuation by Primary System Organ Class and Preferred Term – Safety Analysis Set – Through Week 16 (Study AVT02-GL-301)

	AVT02 (N = 205)		Humira (N = 207)	
Primary System Organ Class/Preferred Term	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**
Any TEAEs Leading to ET	3 (1.5)	4	2 (1.0)	3
Blood and lymphatic system disorders	0	0	1 (0.5)	1
Thrombocytopenia	0	0	1 (0.5)	1
Investigations	2 (1.0)	2	0	0
Hepatic enzyme increased	1 (0.5)	1	0	0
White blood cell count increased	1 (0.5)	1	0	0
Reproductive system and breast disorders	0	0	1 (0.5)	1
Adnexa uteri mass	0	0	1 (0.5)	1
Skin and subcutaneous tissue disorders	2 (1.0)	2	1 (0.5)	1
Psoriasis	2 (1.0)	2	1 (0.5)	1

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 1 and before first dose of study drug of Stage 2. Subjects are counted once within a system organ class and once for each unique preferred term. Events with unknown relationship to study drug are counted as drug-related.

Source: Table 12.29 (Table 14.3.1.8.3) in the AVT02-GL-301 final CSR

Six subjects (3.0%) treated with AVT02/AVT02 had 6 TEAEs, 3 subjects (3.1%) treated with Humira/AVT02 had 3 TEAEs, and 1 subject (1.0%) treated with Humira/Humira had 1 TEAE which led to early withdrawal from the study from Week 16 through Week 54 **(Table 38).**

Table 38 Treatment-emergent Adverse Events Leading to Study Drug Discontinuation by Primary System Organ Class and Preferred Term – Safety Analysis Set – from Week 16 through Week 54 (Study AVT02-GL-301)

	AVT02/AVT02 (N=197)		Humira/AVT02 (N=97)		Humira/Humira (N=98)	
System Organ Class Preferred Term	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAEs Leading to Study Drug Discontinuation	6 (3.0)	6	3 (3.1)	3	1 (1.0)	1
Infections and infestations	1 (0.5)	1	0	0	0	0
Meningitis meningococcal	1 (0.5)	1	0	0	0	0
Investigations	5 (2.5)	5	2 (2.1)	2	1 (1.0)	1
Mycobacterium tuberculosis complex test positive	5 (2.5)	5	2 (2.1)	2	1 (1.0)	1
Skin and subcutaneous tissue disorders	0	0	1 (1.0)	1	0	0
Psoriasis	0	0	1 (1.0)	1	0	0

Note: N = Number of subjects treated in the Stage for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug of Stage 1 and before first dose of study drug of Stage 2. Subjects are counted once within a system organ class and once for each unique preferred term.

Source: Table 12.30 (Table 14.3.1.8.4) in the AVT02-GL-301 final CSR

Studies AVT02-GL-101, AVT02-GL-102 and AVT02-GL-303

No discontinuations due to AEs were reported in these studies.

Post marketing experience

N/A

2.8.1. Discussion on clinical safety

A total of 1,006 subjects were treated with AVT02 or Humira in one Phase III clinical study in patients with PsO, and in two Phase I single-dose studies in healthy subjects. Safety findings are reported for 594 healthy subjects and 412 PsO patients.

The applicant's clinical development programme included one pivotal Phase III confirmatory efficacy and safety study AVT02-GL-301 in patients with moderate to severe plaque psoriasis. For details on the study population, see section 3.3 of this AR. From the safety point of view, the objective of this study was to evaluate overall safety, including immunogenicity over 54 weeks. Duration of the study AVT02-GL-301 is considered long enough for safety assessment. However, data up to week 24 only was included in the applicant's initial submission. In order to enable full assessment of safety and biosimilarity, the pending long-term safety data up to 54 weeks was asked to be provided. The completed clinical study report with data up to week 54 was then submitted as response and has been assessed.

In addition to the pivotal biosimilarity study, safety data is also available from two Phase I single-dose studies in healthy volunteers: study AVT02-GL-101 (PK study for biosimilarity) and Study AVT02-GL-102 (PK study comparing AI and PFS). These studies have been completed and their final results are available at the time of this assessment. Overall, the safety results from these studies are considered supportive.

In the Phase III study AVT02-GL-301 in PsO patients, TEAEs were reported in 92 (44.9%) patients in the AVT02 treatment group and in 91 (44.0%) patients in the EU-Humira treatment group during Stage 1 through Week 16. The frequency of TEAEs was similar between treatment groups. The only TEAEs reported by more than 5% of subjects in any treatment group were injection site reaction (16.6% in AVT02 group, 15.9% in Humira group) and nasopharyngitis (5.4% in AVT02 group, 5.3% in Humira group).

During Stage 2 of the study AVT02-GL-301 from Week 16 through Week 54, 58.9% of subjects on AVT02/AVT02, 47.4% of subjects on Humira/AVT02, and 50.0% of subjects on Humira/Humira, respectively, reported at least 1 TEAE. This difference between groups was largely due to a slightly higher percentage of subjects in the AVT02/AVT02 group who reported ISRs and nasopharyngitis compared to other treatment groups. The only TEAEs reported by more than 5% of subjects in any treatment group and more often in groups that received AVT02 were injection site reaction and nasopharyngitis. 15.7% of subjects on AVT02/AVT02, 11.3% of subjects on Humira/AVT02, and 10.3% of subjects on Humira/Humira reported injection site reactions. Nasopharyngitis were reported by 11.7% of subjects on AVT02/AVT02, 5.2% of subjects on Humira/AVT02, and 4.1% of subjects on Humira/Humira.

Adverse events of special interest were reported by similar percentage of patients in AVT02 and Humira treatment groups during study AVT02-GL-301. From Week 16 through Week 54 of the study, a slightly higher percentage of subjects reported TEAEs of special interest in the AVT02/AVT02 group (22.8%) compared to the Humira/AVT02 (17.5%) and Humira/Humira (13.3%) treatment groups caused largely by the higher number of ISRs compared to other treatment groups. No clinically significant differences are seen between treatment groups with regard to TEAEs of special interest.

A discrepancy was identified between different documents regarding the number of psoriasis events by treatment arms reported in study AVT02-GL-301, which lead to study drug discontinuation. Thus, the applicant was requested to clarify this discrepancy and correct accordingly the information. In the response, the applicant clarified the noted discrepancy and provided the narrative for the 4th psoriasis (worsening) event occurred in one subject treated with AVT02, which lead to study drug discontinuation. The issue was resolved.

Another discrepancy was identified between different documents regarding the number events of Mycobacterium tuberculosis complex test positive in AVT02/AVT02. The applicant clarified these discrepancies; the narrative for subject 4808063 with positive QuantiFERON Mycobacterium tuberculosis complex (TB+) test event was included in the Final CSR. Narratives for subjects 9904008 and 9904018 as well as Listing 16.2.8.4 QuantiFERON-TB Gold Test of the CSR were corrected to reflect the TB indeterminate status at Week 24. For subject 9904008 at EOS Visit the QuantiFERON-TB Gold Test was negative. For subject 9904018 the QuantiFERON-TB Gold Test was repeated, and the results was the same, indeterminate. In addition, Chest X-ray were performed, and no signs of tuberculosis were detected. The issue was resolved.

In addition, there was a concern regarding the causality assessment of events of Mycobacterium tuberculosis complex test positive reported in AVT02-GL-301, which lead to study drug discontinuation.

As all these are TEAEs of special interest, the applicant was asked to clarify this. In the response, the applicant justified that the causality assessment was performed by each of the Investigators independently based on their best medical knowledge, evaluation of the nature and case of each event, the main non-drug causes of the reported events, but taking into account also the prevalence of tuberculosis that is high in some countries in which Study AVT02-GL-301 was conducted. Some of the narratives were updated in the Final CSR. The causality assessment performed by the Investigator was changed in respect to the number of events of Mycobacterium tuberculosis complex test positive reported which led to study drug discontinuation. In summary, the final conclusion was that the 3 events in AVT02/AVT02 group, 2 events in Humira/AVT02 group and one event in Humira/Humira group were

reported as treatment-related by the Investigator. Based on the applicant's response, this issue is not further pursued.

From Week 16 through Week 54, serious TEAEs were reported in the AVT02/AVT02 group only. Of these, one (meningitis meningococcal) was considered related to the study drug by the investigator and sponsor, and one (pulmonary embolism) by the sponsor only. No serious TEAEs were reported by more than subject or led to early termination during the study AVT02-GL-301.

In the subset of patients with psoriatic arthritis, the incidence of TEAEs was comparable in study AVT02-GL-301.

Taken together, the number and pattern of TEAEs and proportion of patients reporting them were in general comparable in AVT02 and Humira groups in the pivotal safety study AVT02-GL-301. The adverse event profile in study AVT02-GL-301 appears in line with expectations from historical data for Humira and its previously approved biosimilars.

The number and pattern of adverse events in the single-dose studies AVT02-GL-101 and AVT02-GL-102 appear supportive of the preliminary conclusions based on the safety data currently available from the pivotal safety study AVT02-GL-301.

No notable differences or trends in laboratory parameters or marked differences in vital sign measurements, ECG, physical examination results, tuberculosis assessment or in local site pain assessment between treatment groups were seen in studies AVT02-GL-301, AVT02-GL-101 and AVT02-GL-102.

Discussion on immunogenicity

The immunogenic potential of AVT02 was analysed in healthy subjects after a single s.c. administration (studies AVT02-GL-101 and AVT02-GL-102) and in patients with moderate-to-severe PsO after multiple administrations (study AVT02-GL-301).

The sampling time points, and study designs were suitable for adequate immunogenicity detection in all studies. The drug tolerance of the ADA assay was sufficient to analyse 96% of the samples correctly and the differences in drug tolerance between Libmyris and Humira was shown to be negligible. Therefore, potentially undetected ADAs among patients with drug concentrations above the drug tolerance level of the ADA assay are not abundant and are not expected to affect conclusions regarding similarity between the products.

In the pivotal study on therapeutic equivalence in PsO patients (AVT02-GL-301), most subjects in both treatment arms (up to 96%) were positive for ADAs over the presented 54-week period. No clinically significant difference in ADA incidence between AVT02 and Humira was apparent by week 16. Throughout the study, the timing of ADA formation and the ADA titers were similar between the treatment groups. The geometric means increase with the duration of the treatment and were comparable between the treatment groups, with maximal levels at Week 24.

A high proportion of patients were ADA positive at baseline; 20.5% and 18.8% in the AVT02 and Humira arms respectively. High baseline frequencies of ADA were also found among healthy volunteers in Study AVT02-GL-101 (6.2% in the AVT02 group, 3.9% in the EU-Humira group) and Study AVT02-GL-102 (12% in the PFS arm and 15.4% in the AI arm). This finding is confusing, considering that healthy volunteers should have no prior exposure to TNF-alfa inhibitors and that any use of prior or concomitant or biosimilar adalimumab therapy, either approved or investigational, was an exclusion criterion in all studies. After the responses to LoQ, the ADA-method is considered acceptable. The reasons for high frequency of pre-dose concentrations remain unclear. However, the frequency of pre-existing ADAs was similar in both groups. In addition, the applicant demonstrated that no meaningful difference in efficacy or safety was seen between treatment groups in subjects with pre-existing or treatment induced ADA.

Moreover, the overall frequency of subjects with detected ADA despite no previous use of adalimumab is comparable to that observed in other clinical studies with Humira biosimilars. Hence, this issue is not pursued further.

There was a somewhat lower incidence of NAb with AVT02 compared to Humira by week 16 (total cumulative incidence by week 16: 66.3% and 73.4% for AVT02 and Humira respectively). According to the EMA Guideline on similar biological medicinal products containing monoclonal antibodies, a lower immunogenicity for the biosimilar does not preclude biosimilarity. Therefore, the difference in detected NAbs is acceptable, as no meaningful difference in safety or efficacy was detected.

A trend for lower drug concentrations was seen in the Humira group, especially among NAb positive subjects. The results are difficult to interpret since only overall post-dose ADA status was used and not the actual visit-based ADA/NAb status. The applicant was asked to re-analyse the impact of ADA and NAb status on the serum trough concentrations using visit-based ADA and including all three treatment arms (serum trough concentrations trough Week 24 were not presented for "the switchers" EU-Humira/AVT02 group). The applicant was also required to present the serum through concentrations for NAbs-negative PsO subjects, through Week 16 of study AVT02-GL-301, as these have not been found in the dossier. The applicant provided the requested data (additionally up to week 54). The impact of ADA and NAb on the serum trough concentration has been considerable. Generally, within ADA and NAb subgroups, there has been no difference between treatment arms in adalimumab serum trough concentrations throughout the study period for all treatment groups. Efficacy, in terms of the mean percent improvement in PASI at weeks 8, 12 and 16 was similar between treatment arms in ADA positive as well as in ADA negative subjects. The percent improvement from baseline in PASI status at each timepoint was similar for subjects with pre-existing ADA status compared to subjects with treatment induced ADA. No meaningful difference in efficacy or safety was seen between treatment groups in subjects with pre-existing or treatment induced ADA.

A great majority of patients developed ADA. However, no anaphylaxis or other serious hypersensitivity reactions were seen.

A similar percentage of ADA/NAb positive subjects reported TEAEs across treatment groups during the study. Among those who were tested ADA negative, more subjects reported TEAEs in AVT02 treatment groups. 18 ADA negative subjects (48.6%) in AVT02 group and 11 ADA negative subjects (35.5%) in Humira group reported TEAEs through Week 16. From Week 16 through Week 54 of the study, the amount of ADA negative subjects reporting TEAEs were 18 (69.2%), 8 (50.0%), and 4 (28.6%) in AVT02/AVT02, Humira/AVT02 and Humira/Humira groups, respectively. Of NAb negative subjects, 21 (65.6%) in AVT02/AVT02, 9 (50.0%) in Humira/AVT02, and 6 (30.0%) in Humira/Humira reported TEAEs from Week 16 through Week 54 of the study.

Although greater percentage of those who were ADA/NAb negative reported TEAEs in AVT02/AVT02 group, it should be noted that the numbers of those ADA/NAb negative subjects were low. In conclusion, the difference seen in TEAE reporting between treatment groups is not considered clinically significant.

The formation of ADAs and NAbs had a high frequency in study AVT02-GL-101 after a single-dose administration of 40 mg s.c. of either AVT02, EU-Humira or US-Humira, overall, with ADA titers slightly lower in AVT02 group as compared to EU-Humira and US-Humira groups. Most of the subjects became ADA positive through Day 64 EOS, i.e., 96.1% in AVT02 group, 96.0% in EU-Humira group and 95.3% in US-Humira group, respectively.

The frequency of subjects with positive NAb increased through Day 64 EOS. At Day 64 the percentage of subjects with positive NAb were high in each treatment group: 80.6% in AVT02 group, 86.9% in EU-Humira and 87.0% in US-Humira group, respectively.

It is well known that development of antibodies causes increased clearance, lower drug concentrations and subsequent decreased exposure of adalimumab. Presence of NAb can affect the PK profile of adalimumab, especially the elimination phase. Thus, the applicant was asked to present box and whisker of plots of AUC_{0-t} (h·ng/mL), AUC_{0-inf} (h·ng/mL), C_{max} (ng/mL) by Treatment and NAb Status (Day 1-64) – Pharmacokinetic population. In the response, the applicant provided the asked data, and it could be seen that presence of Nab affects PK profile of adalimumab especially in the elimination phase. The impact of NAb presence on the PK parameters C_{max} is minor or negligible. The impact of NAb presence on the PK parameters AUC_{0-t} and AUC_{0-inf} is considerable. Comparisons of AVT02 vs EU-Humira vs US-Humira within the NAb positive and NAb negative subgroups showed no relevant differences between treatment groups.

In study AVT02-GL-102, most of the subjects became ADA positive through Day 64 EOS, i.e., 97% in AVT02-AI group and 100% in AVT02-PFS group, respectively. The frequency of subjects with positive NAb increased through Day 64 EOS. At Day 64 the percentage of subjects with positive NAb were 86.5% in AVT02-AI group and 85.7% in AVT02-PFS group, respectively.

2.8.2. Conclusions on the clinical safety

From the safety point of view, no major concerns regarding similarity have emerged based on the data presented by the applicant. The number of subjects is sufficient for comparing the safety profile of the biosimilar candidate AVT02 and reference medicinal product Humira and studying the safety of a biosimilar product for up to one year is adequate. Broadly, the number, severity and type of TEAEs, SAEs, AEs of special interest, treatment discontinuations due to AEs, and laboratory findings were comparable between AVT02 and Humira and mirroring the safety profile as described in the SmPC of Humira.

Most subjects in all treatment arms (up to 96%) became positive for ADAs over the presented 54-week period. No clinically significant difference in ADA incidence or titres between AVT02 and Humira was apparent in the submitted data. A trend for lower drug concentrations was seen in the Humira group, especially among NAb positive subjects. Among NAb negative patients, more subjects reported TEAEs of mild severity in the AVT02 treatment arm. The difference in detected NAbs and drug concentrations is acceptable, as no meaningful differences in safety were detected.

2.9. Risk Management Plan

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infections	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Section 4.4 of the SmPC states that patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

	risk for developing infections. Patients must therefore be monitored closely for infections, before, during and after treatment with adalimumab. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period. It also warns that treatment with adalimumab should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. Patients who develop a new infection while undergoing treatment with adalimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of adalimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of adalimumab in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications. Section 4.4 of the SmPC also states that, for patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected, and administration of adalimumab should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections. In order to warn patients about this risk, corresponding text is also present in the package leaflet.	

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: restricted medical prescription. Additional risk minimisation measures: Patient reminder card.	
Tuberculosis (TB)	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. According to section 4.4 of the SmPC, before initiation of therapy with adalimumab, all patients must be evaluated for both active or inactive ("latent") TB infection. This evaluation should include a detailed medical assessment of patient history of TB or possible previous exposure to people with active TB and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. If active TB is diagnosed, adalimumab therapy must not be initiated. If latent TB is suspected, a physician with expertise in the treatment of TB should be consulted. In addition, appropriate treatment must be started with anti-TB prophylaxis treatment before the initiation of adalimumab, and in accordance with local recommendations. Use of anti-TB prophylaxis treatment should also be considered before the initiation of adalimumab in patients with several or significant risk factors for TB despite a negative test for TB and in patients with a past history of latent or	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	active TB in whom an adequate course of treatment cannot be confirmed. Patients should be instructed to seek medical advice if signs/symptoms suggestive of a TB infection (e.g. persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with adalimumab. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: Patient reminder card.	
Malignancies	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. There is a warning in section 4.4 of the SmPC stating that all patients, and in particular patients with a medical history of extensive immunosuppressant therapy or Ps 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. In addition, there is a warning in section 4.4 of the SmPC stating that caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking. Section 4.4 of the SmPC also states that 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	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. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: Patient reminder card.	
Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis)	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. According to section 4.4 of the SmPC, prescribers should exercise caution in considering the use of adalimumab in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of adalimumab should be considered if any of these disorders develop. In addition, neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of adalimumab therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: Patient reminder card.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
BCG disease following live BCG vaccination in infants with *in utero* exposure to adalimumab	Routine risk minimisation measures: SmPC sections 4.4 and 4.6. In order to inform patients of this risk, corresponding text is also present in the package leaflet. According to section 4.4 of the SmPC, administration of live vaccines (e.g. BCG vaccine) to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: Patient reminder card.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Progressive Multifocal Leukoencephalopathy (PML)	Routine risk minimisation measures: Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	Routine risk minimisation measures: Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Adenocarcinoma of colon in UC patients	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.4. In order to inform patients of this risk, corresponding text is also present in the package leaflet. There is a warning in section 4.4 of the SmPC stating that all patients with UC who are at increased risk for dysplasia or colon carcinoma (e.g. 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. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: None.	reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Patients with Immune Compromised conditions	Routine risk minimisation measures: SmPC section 4.4. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	Routine risk minimisation measures: Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		None.
Episodic treatment in psoriasis (Ps), ulcerative colitis (UC) and juvenile idiopathic arthritis (JIA)	Routine risk minimisation measures: Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Long-term safety information in the treatment of children with uveitis	Routine risk minimisation measures: Section 4.2. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Section 4.2 of the SmPC states that it is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	Routine risk minimisation measures: Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

2.9.1. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.10. Pharmacovigilance

2.10.1. Pharmacovigilance system

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

2.10.2. 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.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.11.2. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing statutory and additional information (see below) has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: website including the SmPC, Annex II, package leaflet (statutory information), and administration videos of the instructions for use (additional information).

2.11.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Libmyris (adalimumab) is included in the additional monitoring list as a 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 following indications, identical to the indications in the label of EU-approved Humira, are applied for:

- Rheumatoid arthritis (RA)

- Juvenile idiopathic arthritis (JIA) including polyarticular juvenile idiopathic arthritis (PJIA) and enthesitis-related arthritis (ERA)
- Ankylosing spondylitis (AS) and axial spondyloarthritis without radiographic evidence of AS
- Psoriatic arthritis (PsA)
- Psoriasis
- Paediatric plaque psoriasis
- Hidradenitis suppurativa (HS)
- Crohn's disease (CD)
- Paediatric Crohn's disease
- Ulcerative colitis (UC)
- Paediatric ulcerative colitis
- Uveitis (UV)
- Paediatric uveitis

Summary of quality comparability data

On the quality level, a comprehensive biosimilarity exercise has been performed following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012).

Comparative analysis has been performed using the AVT02 DP in a pre-filled syringe (AVT02-DP PFS) presentation with a 0.4mL fill or 0.8mL fill. Total of 9 AVT02 DP batches manufactured from 9 independent DS batches, 28 EU-Humira batches, and 11 US-Humira have been included for the comparability studies. One clinical AVT02 DP (DP180004) has been used in the comparability studies. During the course of development of AVT02, five separate comparative analytical head-to-head (H2H) studies have been performed. A SD approach was chosen to set comparability ranges, and the SD multipliers were chosen based on criticality ranking. Most of the comparability ranges were set at ± 3SD; these were for CQAs ranked as high, moderate and low criticality. Tighter range (± 2.5SD) was set for the CQAs with a highest risk. Comparability ranges are considered supportive of the overall similarity assessment. In addition, in most cases sufficient raw data has been provided to allow assessment of biosimilarity independently of statistical approach chosen.

Analytical comparability studies included primary, secondary and higher order structures, post translational modifications (charge variants and glycan profiles), purity and impurities, quantity, biological activity of Fab and Fc related functions, and comparative stability studies.

Summary of non-clinical comparability data

Comparability at *in vitro* functional level was assessed by head-to-head assays including evaluation of TNF neutralisation and Fc-effector functions using cell-based assays (TNF neutralisation, ADCC, CDC) and ligand binding assays using both SPR and ECL-ELISA methodology. These are the same as stated in the summary of quality comparability data.

One pharmacokinetics and local tolerability study was conducted in cynomolgus monkeys.

The nonclinical development plan is in agreement with EMA guidelines for biosimilar products.

Summary of clinical comparability data

Comparability of AVT02 to EU-Humira in terms of PK, safety and immunogenicity was assessed in one randomised, double-blind single dose study in 390 healthy volunteers (AVT02-GL-101). Comparability of clinical efficacy, safety, immunogenicity was assessed in one randomised double-blind multiple dose study in 412 patients with plaque psoriasis (PsO) (AVT02-GL-301).

In addition, one single arm, multiple dose study (AVT02-GL-303) was performed in 107 patients with rheumatoid arthritis (RA) for device development of the autoinjector. Comparability between the autoinjector and the PFS was assessed in one randomised single dose study in 207 healthy volunteers (AVT02-GL-102).

The development plan was in agreement with EMA guidelines on development of biosimilar products.

3.2. Results supporting biosimilarity

Quality data

Similarity between AVT02 and EU-Humira has been demonstrated for the following physico-chemical and biological properties:

- Primary and higher order structure (with some minor exceptions)
- Content and extractable volume
- Size heterogeneity (with some exceptions)
- Glycosylation (with the exception of afucosylated glycans)
- Binding to soluble and transmembrane TNFα and neutralisation of TNFα
- Reverse signaling activity
- Binding to following Fc-receptors (FcγRIIb, FcγRI and FcRn)
- Binding to C1q and CDC activity
- ADCC activity (minor differences are observed)
- Inhibition of TNFα-induced apoptosis, IL-8 release, inhibition of expression of adhesion molecules
- Induction of regulatory macrophages and subsequent T-cell anti-proliferation
- Stability under stressed conditions and forced degradation

Non-clinical data

The functional similarity was demonstrated in *in vitro* assays relevant for the mode of action of adalimumab (see above Quality data in regards of the assay battery). No such differences between AVT02 and EU-Humira were noted that would have implications to clinical efficacy or safety.

There were no significant differences in the pharmacokinetic profiles and local tolerance of AVT02 and EU-Humira in cynomolgus monkeys.

Clinical data

Pharmacokinetics

In the comparison of all combined data from parts 1 and 2 (pivotal PK study AVT02-GL-101) for the AVT02 group with the EU-Humira and US-Humira treatment groups, the 90% CIs of the geometric LS

mean ratios for the three primary PK parameters (i.e. C_{max}, AUC_{0-t} and $AUC0-_{inf}$) were all within 80% and 125%. In the AUC_{0-t} between AVT02 and EU-Humira, the lower limit of the 90%CI was 1.00, which is acceptable. The sensitivity analysis supported the PK similarity between AVT02 and EU-Humira.

In the confirmatory clinical study (AVT02-GL-301) in PsO patients, the mean trough concentrations were quite comparable although slightly higher in the AVT02 group than in the EU-Humira group both in overall population (PK data up to week 16) and in PASI responders (PK data on PASI responders from up to week 54).

Efficacy

In study AVT02-GL-301, in the FAS LOCF ANCOVA analysis, the LS mean difference (SE) between treatment arms in percent improvement in PASI from baseline to week 16 was 0.4 (1.39). Mean actual PASI scores fell from 23.2 and 23.0 at baseline to 2.0 and 1.7 at week 16 (observed data) for AVT02 and Humira, respectively. The 95% CI of the primary efficacy endpoint was within the predefined equivalence margin of ±10%. The 95% CI for all sensitivity analyses were also within ±10%. Hence, the primary objective was met and sensitivity analyses confirmed the robustness of the primary analysis. Similarity in PASI change from baseline was shown also at the most sensitive time points, week 8 and week 12. The mean difference in percent improvement in PASI from BL to Week 8 was 0.2 (95% CI: -4.55 to 4.20).

Subgroup analyses at week 16 showed no significant difference with respect to the primary endpoint between AVT02 and Humira treatment groups when analysed by gender, PsA status, use of prior biologic therapy, ADA status or age.

Results from all secondary efficacy endpoints (PASI 50, PASI 75, PASI 90, and PASI 100, sPGA, DLQI) were supportive of similarity up to week 50.

Safety

In the pivotal Phase III safety study AVT02-GL-301 in PsO patients, TEAEs were reported in 92 (44.9%) patients in the AVT02 treatment group and in 91 (44.0%) patients in the EU-Humira treatment group during Stage 1 through Week 16. The only TEAEs reported by more than 5% of subjects in any treatment group were injection site reaction and nasopharyngitis. During Stage 2 from Week 16 through Week 54, 58.9% of subjects on AVT02/AVT02, 47.4% of subjects on Humira/AVT02, and 50.0% of subjects on Humira/Humira, respectively, reported at least 1 TEAE. This difference between groups was largely due to a slightly higher percentage of subjects in the AVT02/AVT02 group who reported injection site reactions and nasopharyngitis compared to other treatment groups. Adverse events of special interest were reported by similar percentage of patients in all treatment groups during the study. In the subset of patients with psoriatic arthritis, the incidence of TEAEs was comparable in study AVT02-GL-301.

Taken together, the number and pattern of TEAEs and proportion of patients reporting them were in general comparable in AVT02 and Humira groups during the study AVT02-GL-301. No major differences in frequency or pattern of TESAEs, TEAEs leading to discontinuation of study drug or AESIs were seen between treatment groups.

The safety results from the Phase I single-dose studies in healthy subjects are considered supportive of the pivotal safety data.

Immunogenicity

No clinically significant difference between AVT02 and Humira in ADA incidence or ADA titre was apparent throughout the 54-week study in the pivotal Phase III trial (AVT02-GL-301).

In the pivotal PK study (AVT02-GL-101) the ADA and NAb frequencies and ADA titres were similar between AVT02 and EU-Humira at Day 64 (EOS). Most of the subjects became ADA positive through Day 64 EOS, i.e. 96.1% in AVT02 group, 96.0% in EU-Humira group and 95.3% in US-Humira group, respectively.

3.3. Uncertainties and limitations about biosimilarity

Quality data

None

Non-clinical data

Refer to above Quality *in vitro* functionality data.

Clinical data

Pharmacokinetics

None

Efficacy

None

Safety

None

Immunogenicity

None

3.4. Discussion on biosimilarity

Libmyris has been developed as a biosimilar to the reference product Humira. In this application only the 100mg/ml strength has been used in clinical studies and this is the only strength applied for in two vial sizes; 0.4ml and 0.8ml. Humira is available also in 50mg/ml strength.

The development plan to show similarity between AVT02 and Humira was adequate and in agreement with EMA guidelines on development of biosimilar products.

Quality aspects

Overall, a comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012) has been performed. The comparability exercise is mostly based on comparison of analytical characterisation data collected during the years of drug development. For most quality attributes high similarity has been demonstrated.

Slightly higher amounts of HMWs are observed in AVT02 (0.7-1.3%) when compared to EU-Humira (0.29-0.5%). HMWs were further characterised with SEC-MALS and a peak correlating with higher order aggregates was detected only for AVT02. As requested at D120, the applicant further characterised the SEC variant fractions via CE-SDS, LC-MS, and SEC-MALS utilizing heat stress samples where the HOA where enriched in both AVT02 and EU-Humira. However, due to assay limitations, no solid conclusion on the HMW1 was derived from CE-SDS (R & NR) nor LC-MS studies. Enriched SEC fractions were further analysed by SEC-MALS and confirmed that AVT02 and Humira HMW1 mainly contains Adalimumab higher order aggregates and HMW2 fractions mainly contain Adalimumab dimer. The impact on potency was also studied confirming that the TNFα potency, ADCC activity and FcγRIIIa binding was similar for AVT02 and Humira for the dimer and the HOA. The data demonstrated that AVT02 and Humira HMWs (especially HMW1) had reduced potency and reduced effector functions. Considering that the HMWs are controlled at DS and DP release with tight enough acceptance criteria (<2% and <2.5%, respectively), and that overall, the HMWs are detected in very low levels in AVT02 batches, the applicant's conclusion can be agreed. The minor difference in HMW species is not expected to have clinical impact.

A lower level of afucosylated glycans, including high mannose glycans is observed in AVT02 batches. Although a difference could be detected in the glycan profiles of AVT02 and EU Humira, this did not result in clear differences in relevant Fc receptor binding assays and resulted only in a minor difference in the ADCC assay using PBMCs as effector cells. No differences were seen in the ADCC RGA assay. It is therefore considered unlikely that the difference seen in the ADCC PBMC assays would be clinically significant. However, as ADCC is considered as a likely mechanism of action for adalimumab in certain indications and a clear correlation between the level of total afucosylated glycans and high mannoses and ADCC activity can be observed, stringent specifications for total afucosylation, high mannoses, and afucosylated glycans (-high mannoses) is considered necessary. At D195 responses the applicant agreed to include an additional specification for total afucosylated glycans. It was also agreed to set dual DS testing via two different methods (Rapifluor and 2AB labelling) for total afucosylated glycans. Until further experience has been gained with the Rapifluor method and an acceptance limit for Rapifluor total afulcosylation is justified in a way that it will ensure that AVT02 will maintain an ADCC activity similar to EU Humira.

The acceptance limits for glycan structures should be reconsidered once 30 batches has been manufactured. The 2AB labelling method should be validated at the release site within a time period proposed by the applicant. See the list of recommendations.

Nonclinical aspects

A stepwise development and the totality of the evidence approach was applied in line with recommendations from EMA scientific advice and biosimilar guideline (EMA/CHMP/BMWP/403543/2010) to demonstrate the biosimilarity between ATV02 and Humira. All *in vitro* comparability data were (included under the M3.2.R.3) are assessed in the Quality section in order to avoid repeating the data. The data allowed drawing broad conclusions of the similarity between AVT02 and EU-Humira for the majority of functional parameters.

In addition, nonclinical dossier included one cynomolgus monkey study to assess pharmacokinetics and local tolerability. This study was not designed to demonstrate the similarity in PK or tolerability and is considered supportive. The pharmacokinetic and local tolerance profiles of AVT02) and EU-Humira did not differ significantly.

Clinical aspects

Biosimilarity has been formally demonstrated between AVT02 and EU-Humira and US-Humira in the pivotal PK study (AVT02-GL-101) using healthy subjects as in the primary PK parameters C_{max}, AUC_{0-t} and AUC_{0-inf}, the 90%CI for the ratio of test-to-reference/comparator fell within the acceptance range of 80.00-125.00%. The sensitivity analyses support biosimilarity. Additional support for similarity in terms of PK between AVT02 and EU-Humira was obtained in the clinical study in PsO patients (AVT02-GL-301). In this study, the mean C_{trough} concentrations were quite comparable although slightly higher with AVT02 than with EU-Humira. The trend for lower drug concentrations in the Humira group was seen especially among NAb positive subjects but this did not lead to meaningful differences in efficacy or safety.

The results showing similarity in efficacy seem robust and from the safety point of view, no major concerns regarding similarity have emerged based on the data presented in the applicant's initial submission. The safety data from the study AVT02-GL-301 indicated in general similar incidence and pattern of TEAEs, TESAEs, AESIs between the AVT02 and Humira treatment groups. No new or unexpected safety findings were thus far evident.

More ADA/NAb negative subjects reported adverse events in treatment groups receiving AVT02 than in those receiving Humira. However, these differences are not considered clinically significant, considering also the low numbers of ADA/NAb negative subjects in this study.

3.5. Extrapolation of safety and efficacy

All indications granted for the originator EU approved Humira are applied for Libmyris (AVT02). These include rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), active enthesitis-related arthritis, axial spondyloarthritis (ankylosing spondylitis [AS], and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis (PsA), adult and paediatric plaque psoriasis (Ps), adult and paediatric Crohn's disease (CD), ulcerative colitis (UC), adult and adolescent hidradenitis suppurativa (HS), adult and paediatric non-infectious uveitis (UV).

As referenced by the applicant, the MoA of adalimumab therapy is primarily based on both inhibition of pro-inflammatory effects such as apoptosis, cell proliferation and cytokine secretion, and stimulation of anti-inflammatory effects through reverse signalling. Although the MoA of adalimumab is not completely elucidated, it is well accepted that adalimumab acts as a TNFα antagonist by binding to and neutralising soluble TNFα (sTNFα) and tmTNFα.

Neutralisation of sTNFα is a common mechanism across the non-IBD indications (RA, JIA, AS, PsA, Ps, HS, and UV), and the primary mechanism by which adalimumab particularly exerts its effect.

In addition to neutralisation of sTNFα, tmTNFα binding is considered to play a key role in treatment of the IBD indications (CD and UC).

Other mechanisms that could contribute to the biological activity of adalimumab include Fc-mediated binding which could induce ADCC, CDC and regulatory macrophage activation although the balance of evidence suggests that ADCC and CDC do not play a major role.

In comprehensive *in vitro* analyses, the similarity was demonstrated for the majority of functional parameters relevant for the mode of actions of adalimumab, supporting extrapolation of efficacy to all indications.

Results for primary PK parameters AUC_{0-inf}, AUC_{0-last} and C_{max} support the conclusion of biosimilarity of AVT02 to EU-Humira.

Extrapolation of the results to all indications approved for the originator is supported as similarity has been shown by the following *in vitro* tests: Inhibition of TNFα-induced IL-8 and IL-6 secretion, Inhibition of TNFα-induced expression of adhesion molecules on HUVEC cells (demonstrate MoA valid across all therapeutic indications of adalimumab); inhibition of apoptosis of intestinal epithelial cells and induction of regulatory macrophages by MLR (sustain MoA valid in IBD). Similarity has also been shown in PK, efficacy, safety and immunogenicity.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, biosimilarity of Libmyris to EU-approved Humira has been established. The benefit/risk balance is positive and comparable to the reference product.

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 Libmyris is favourable in the following indications:

Rheumatoid arthritis

Libmyris in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

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

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

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Libmyris 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 DMARD. Libmyris 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). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Libmyris 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).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

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

Axial spondyloarthritis without radiographic evidence of AS

Libmyris 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 (NSAIDs).

Psoriatic arthritis

Libmyris is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous DMARD 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

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

Paediatric plaque psoriasis

Libmyris 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)

Libmyris 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).

Crohn’s disease

Libmyris is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients

who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Libmyris is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

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

Paediatric ulcerative colitis

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

Uveitis

Libmyris 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

Libmyris 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.

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

An updated RMP should be submitted:

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

Additional risk minimisation measures

The Patient Reminder Cards (adult and paediatric) contain the following key elements:

- infections, including tuberculosis
- cancer
- nervous system problems
- vaccinations.

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

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that adalimumab is not a new active substance as it is a constituent of a medicinal product previously authorised within the European Union. Adalimumab is contained in the marketing authorisation Humira, which was authorised in the European Union on 08 September 2003.