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EMA/322353/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gobivaz

International non-proprietary name: golimumab

Procedure No. EMEA/H/C/006560/0000

Note

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

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Table of contents

1. Background information on the procedure 7
1.1. Submission of the dossier 7
1.2. Legal basis, dossier content 8
1.3. Information on paediatric requirements 8
1.4. Information relating to orphan market exclusivity 9
1.4.1. Similarity 9
1.5. Scientific advice 9
1.6. Steps taken for the assessment of the product 9

2. Scientific discussion 11
2.1. About the product 11
2.2. Type of application and aspects on development 11
2.3. Quality aspects 12
2.3.1. Introduction 12
2.3.2. Active substance 13
2.3.3. Finished Medicinal Product 18
2.3.4. Discussion on chemical, pharmaceutical and biological aspects 28
2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects 28
2.3.6. Recommendations for future quality development 28
2.4. Non-clinical aspects 28
2.4.1. Introduction 28
2.4.2. Pharmacology 29
2.4.3. Pharmacokinetics 29
2.4.4. Toxicology 29
2.4.5. Ecotoxicity/environmental risk assessment 30
2.4.6. Discussion on non-clinical aspects 30
2.4.7. Conclusion on the non-clinical aspects 31
2.5. Clinical aspects 31
2.5.1. Introduction 31
2.5.2. Clinical pharmacology 33
2.5.3. Discussion on clinical pharmacology 40
2.5.4. Conclusions on clinical pharmacology 42
2.5.5. Clinical efficacy 42
2.5.6. Discussion on clinical efficacy 68
2.5.7. Conclusions on the clinical efficacy 71
2.5.8. Clinical safety 71
2.5.9. Discussion on clinical safety 95
2.5.10. Conclusions on the clinical safety 97
2.6. Risk Management Plan 98
2.6.1. Safety concerns 98
2.6.2. Pharmacovigilance plan 98
2.6.3. Risk minimisation measures 98
2.6.4. Conclusion 101
2.7. Pharmacovigilance 101

2.7.1. Pharmacovigilance system 101
2.7.2. Periodic Safety Update Reports submission requirements 101
2.8. Product information 101
2.8.1. User consultation 101
2.8.2. Additional monitoring 101

3. Biosimilarity assessment 101
3.1. Comparability exercise and indications claimed 101
3.2. Results supporting biosimilarity 103
3.3. Uncertainties and limitations about biosimilarity 104
3.4. Discussion on biosimilarity 104
3.5. Extrapolation of safety and efficacy 105
3.6. Additional considerations 106
3.7. Conclusions on biosimilarity and benefit risk balance 106

4. Recommendations 106

List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AI	Autoinjector
ALT	Alanine transferase
AR	Adverse reaction
AS	Ankylosing spondylitis
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC_{0-24}	Area under the serum concentration-time curve from time zero to 24 hours
AUC_{0-t}	Area under the serum concentration-time curve) after extrapolation from time t to time infinity
BMI	Body Mass Index
BLA	Biologics license application
BLQ	Below the limit of quantification
C_{max}	Maximum serum concentration
C_{trough}	Serum trough concentrations
CD	Crohn's disease
CDAI	Clinical Disease Activity Index
CDC	Complement dependent cytotoxicity
CI	Confidence interval
CL	Confidence Limit
CL/F	Apparent clearance
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common Terminology Criteria for adverse event(s)
CUHF	Comparative Use Human Factors
CV%	Coefficient of variation
DMEPA	Division of Medication Error Prevention and Analysis
DMSO	Dimethyl sulfoxide
DP	Drug Product
DS	Drug Substance
ECG	Electrocardiogram
ECL	Electrochemiluminescence
EMA	European Medicines Agency
EoS	End of study
EU	European Union
EULAR	European League Against Rheumatism
Fc	Crystallizable fragment
$t_{½}$	Elimination half-life
K_{el}	Elimination rate constant / Terminal elimination rate constant
Fab	Fragment antigen-binding
FACS	Fluorescence-activated Cell Sorting
FAS	Full Analysis Set

FDA	Food and Drug Administration
FIH	First in Human
GCP	Good Clinical Practice
GMR	Geometric Means Ratio
H2H	Head-to-head
HA	Health Authorities
HF	Human factor
HFI	Hereditary fructose intolerance
HV	Healthy volunteers
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG1κ	Immunoglobulin gamma 1 kappa
INN	International nonproprietary name
IP	Investigational product
IRS	Injection site reaction
i.v.	Intravenous
JP	Japan
LLOQ	Lower Level of Quantitation
LS	Least-squares
LTF	Liver function test
MAA	Marketing authorisation application
mAb	Monoclonal antibody
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor, and Welfare
MI	Multiple Imputation
MMRM	Mixed Efffects Model for Repeated Measures
MoA	Mechanism of action
MSD	Meso Scale Discovery
mTNF	Membrane tumour necrosis factor
MTX	Metotrexate
nAbs	Neutralising antibody / Neutralising ADA
NE	Not Evaluable
NOAEL	No observed adverse effect levels
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDE	Permissible daily exposure
PFS	Prefilled syringe
PFS-SD	Prefilled syringe with safety device
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PsA	Psoriatic arthritis
PT	Preferred term
Q4w	Every 4 weeks
RA	Rheumatoid arthritis
RMP	Reference medicinal product
SAE	Serious adverse event

SDAI	Simplified Disease Activity Index
SPEAD	Solid phase extraction and acid dissociation
SC, s.c.	Subcutaneous
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
T_{max}	Treatment-emergent adverse event
TA	Threshold analysis
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
tmTNF	Transmembrane tumour necrosis
TNF-α	Tumour necrosis factor-α
TRA	Tripropylamine
UC	Ulcerative colitis
ULN	Upper limit of normal
URRA	Use related risk analysis
US	United States of America
Vz/F	Volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Advanz Pharma Limited submitted on 11 October 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Gobivaz, 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 21 March 2024.

The applicant applied for the following indications:

Rheumatoid arthritis (RA)

Gobivaz, in combination with methotrexate (MTX), is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active, and progressive rheumatoid arthritis in adults not previously treated with MTX.

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

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Gobivaz in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

Psoriatic arthritis (PsA)

Gobivaz, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Golimumab 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.

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Gobivaz is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)

Gobivaz is indicated for the treatment of adults with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative colitis (UC)

Gobivaz 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Simponi, 50 mg, solution for injection; Simponi, 100 mg, solution for injection; Simponi 45mg/ 0.45ml, solution for injection.
- Marketing authorisation holder: Janssen Biologics B.V.
- Date of authorisation: 01-10-2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers: EU/1/09/546/001-004; EU/1/09/546/005-008; EU/1/09/546/009

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

- Product name, strength, pharmaceutical form: Simponi, 50 mg, solution for injection; Simponi, 100 mg, solution for injection
- Marketing authorisation holder: Janssen Biologics B.V.
- Date of authorisation: 01-10-2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers: EU/1/09/546/001-004; EU/1/09/546/005-008.

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

- Product name, strength, pharmaceutical form: Simponi, 50 mg, solution for injection
- Marketing authorisation holder: Janssen Biologics B.V.
- Date of authorisation: 01-10-2009
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/09/546/003-004.
- Bioavailability study numbers: AVT05-GL-P01, AVT05-GL-C01.

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 the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 April 2022	EMA/SA/0000078858	*Brigitte Schwarzer-Daum and Juha Kolehmainen*
26 January 2023	EMA/SA/0000119044	*Andrea Laslop and Juha Kolehmainen*

The applicant received scientific advice on the development of golimumab biosimilar (AVT05) for the treatment in the same indications as the reference product Simponi from the CHMP on 22/04/2022 (EMA/SA/0000078858). The scientific advice pertained to the following quality and clinical aspects:

- Analytical comparability exercise; release testing methods; master cell bank characterisation including control strategies for adventitious particles; batch release testing; requirement for animal studies; evidence to support auto-injector.
- Design of a PK study comparing the US- and EU-sourced reference product including study population, endpoints, statistical analysis plan; design of an efficacy, safety, and immunogenicity study to demonstrate comparability of AVT05 and the reference product including DAS-28 at 16 weeks as primary efficacy endpoint; clinical data extrapolation to all indications of the reference medicinal product.

The applicant received scientific advice on the development of golimumab biosimilar (AVT05) for the treatment in the same indications as the reference product Simponi from the CHMP on 26 January 2023 (EMA/SA/0000119044). The scientific advice pertained to the following quality and clinical aspects:

- Stability strategy for AVT05 pre-filled syringe, safety device, and autoinjector; batch release approach for AVT05 pre-filled syringe, safety device, and autoinjector; approach to validation of AVT05 autoinjector; proposal to develop a AVT05 45 mg/0.45 mL vial presentation instead of the Simponi 45 mg/0.45 mL pre-filled pen presentation.

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: Tomas Radimersky

The application was received by the EMA on	11 October 2024
The procedure started on	31 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 January 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 January 2025
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	03 February 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 April 2025
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	27 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 June 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	12 June 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 June 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2025
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	03 September 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 September 2025
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 Gobivaz on	18 September 2025

2. Scientific discussion

2.1. About the product

Gobivaz (company code: AVT05) contains the active substance golimumab, a human monoclonal antibody that binds with high affinity to both the soluble and transmembrane bioactive forms of human tumour necrosis factor alpha (TNF-α). By forming stable complexes with TNF-α, golimumab prevents its interaction with TNF receptors, thereby inhibiting downstream pro-inflammatory signalling. Golimumab belongs to the pharmacological class of TNF-α inhibitors.

2.2. Type of application and aspects on development

Gobivaz has been developed as a biosimilar to the reference medicinal product Simponi (golimumab), which received marketing authorisation in the European Union (EU) in October 2009.

The applicant is seeking approval for all authorised indications of Simponi, namely the treatment of rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, ulcerative colitis, and juvenile idiopathic arthritis. The proposed strengths (50 mg and 100 mg solution for injection) are identical to those of the reference product, with the exception of the paediatric strength (45 mg/0.45 ml solution for injection), which is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in children weighing less than 40 kg.

The applicant received an initial EMA scientific advice on 22 April 2022 (EMA/SA/0000078858) and a follow-up scientific advice on 26 January 2023 (EMA/SA/0000119044) (see also section 1.5.).

Quality

For the comparability approach to demonstrate safety, efficacy and quality of the at-scale finished product batches manufactured using MCB and WCB, the scientific advice EMA/SA/0000078858 has been followed, as applicable.

With regards to FP the advices have been generally followed.

For evaluation of the analytical similarity, the given advice EMA/SA/0000078858 has been mainly followed. The recommendations given in the EMA reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017) were followed, as applicable.

The applicant has addressed the similarity between AVT05 and the reference product, EU-Simponi in a comprehensive comparability exercise. Fab related biological activity and higher order structure were demonstrated to be similar between the products supporting similarity. Minor differences in α1,3-galactosylation, N-/C-terminal variants and sub-visible particles are highly unlikely to have clinically meaningful impact, thus, these differences do not preclude the similarity claim. The remaining uncertainties were appropriately addressed by extended characterisation and correlation analyses, as well as with relevant scientifically sound discussion.

Extended characterisation data indicates that differences in charge variants are associated with variants that have no relevant clinical impact. The differences observed in N-glycosylation profile were thoroughly discussed and conclusions were generally supported with results of the structure-function correlation analyses. The applicant justified that the identified minor differences in the Fc mediated effector activity observed for the batches produced so far would not have an impact on clinical performance. Sufficiently tight specification limits for high mannoses, total afucosylation and

afucosylation without high mannoses have been established to ensure that similarity is maintained between AVT05 and EU-Simponi in the future.

Overall, the analytical biosimilarity at the quality level has been appropriately demonstrated between Gobivaz and EU-Simponi. The panel of methods performed is satisfactory covering structural as well as biologicals quality attributes with the necessary level of depth.

The overall approach to demonstrate similarity of AVT05 to EU-Simponi is mainly in line with EMA/CHMP/BWP/247713/2012 and EMA/CHMP/138502/2017 guidance.

Non-clinical

The scientific advice given by CHMP (EMA/SA/0000078858) for non-clinical programme has been followed.

Clinical

The clinical development programme was designed to show similarity of the PK profile of AVT05 vs. EU-approved Simponi vs. US-licensed Simponi in healthy participants (a single dose study in healthy subjects including a subgroup of Japanese subjects [study AVT05-GL-P01]), and similarity of efficacy and safety (including immunogenicity) of AVT05 and EU approved Simponi in participants with rheumatoid arthritis (RA) (a comparative clinical study in patients with moderate to severe RA [study AVT05-GL-C01]). The clinical development programme is in accordance with the EMA's Guidelines on similar biological medicinal products (CHMP/437/04 Rev 1, October 2014) and on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1, December 2014). The clinical development programme is also largely in line with the received scientific advice.

2.3. Quality aspects

2.3.1. Introduction

Gobivaz has been developed as a proposed biosimilar to the reference product Simponi (golimumab). Gobivaz finished product (FP) is presented as solution for subcutaneous injection containing 50 mg/0.5 mL or 100 mg/1.0 mL of golimumab as active substance.

Other ingredients are: sorbitol, L-histidine, L-histidine monohydrochloride monohydrate, poloxamer 188, and water for injections.

The product is available in pre-filled pen (PFP) and pre-filled syringe (PFS):

50 mg solution for injection in PFP

0.5 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover in a pre-filled pen. Gobivaz is available in packs containing 1 pre-filled pen and multipacks containing 3 (3 packs of 1) pre-filled pens.

50 mg solution for injection in PFS

0.5 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover. Gobivaz is available in packs containing 1 pre-filled syringe and multipacks containing 3 (3 packs of 1) pre-filled syringes.

100 mg solution for injection in PFP

1 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover in a pre-filled pen. Gobivaz is available in packs containing 1 pre-filled pen and multipacks containing 3 (3 packs of 1) pre-filled pens.

100 mg solution for injection in PFS

1 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover. Gobivaz is available in packs containing 1 pre-filled syringe and multipacks containing 3 (3 packs of 1) pre-filled syringes.

2.3.2. Active substance

2.3.2.1. General information

Golimumab (INN, Company code: AVT05) is a recombinant human IgG1 tumor necrosis factor alpha (TNFα) antagonist monoclonal antibody of subtype κ, produced by murine hybridoma cell line (Sp2/0) with recombinant DNA technology. Golimumab forms high affinity, stable complexes with both the soluble and transmembrane forms of human TNFα, preventing the binding of TNFα to its receptors.

The golimumab molecule has two identical light (L) chains (approximately 23.5 kDa) and two heavy (H) chains (approximately 50.0 kDa), with a total molecular weight of approximately 147 kDa. Each light and heavy chain contains 3 complementary determining regions (CDR) in the N-terminal domains. Each light chain is covalently coupled through a disulfide bond at cysteine 215 to a heavy chain at cysteine 229. The two heavy chains are covalently coupled to each other through two inter-chain disulfide bonds at cysteines 235 and 238.

2.3.2.2. Manufacture, characterisation and process controls

The name, address and responsibility of all active substance manufacturers involved in the manufacturing, quality control and stability testing, as well as storage and testing of the master cell bank (MCB) and working cell bank (WCB) have been provided.

All active substance manufacturing sites are GMP compliant.

Description of manufacturing process and process controls

The active substance manufacturing process consists of upstream process and downstream process. The upstream process starts with inoculum and cell expansion steps started from thawed WCB. Cell culture production is performed in the perfusion mode which is continuous process. The cells from the thawed vial are expanded in a series of seed expansion steps from shake flasks to bag followed by single use bioreactor (SUB). The cells from SUB are transferred to production scale SUB and cultured in the perfusion mode. The material from the production bioreactor is harvested continuously as perfusate and collected in single use bags. These are immediately transferred to downstream processing.

The downstream process begins with the purification of perfusate using a series of purification steps. The downstream processing also includes effective orthogonal viral clearance steps, one virus inactivation step, and two virus removal steps along with chromatography steps which also contribute for viral clearance. The purified material is formulated, filtered, filled into AS containers, frozen and stored prior to further processing for FP manufacturing.

The number of freeze-thaw cycles of AS bulk, has been studied as part of manufacturing process characterisation. No reprocessing is foreseen in the manufacture of AVT05 AS. Overall, the

manufacturing process for AVT05 AS has been clearly defined and the purpose of each manufacturing step has been discussed in sufficient detail. The overall manufacturing process has been outlined in flow-diagrams and tables.

Critical process parameters (CPP) and in-process tests have been provided for each manufacturing step. Two types of in-process controls (IPCs) are defined, IPCs with an action limit (to assess the consistency of the process at less critical steps, their failure will result in a deviation and may affect the batch release) and IPCs with an acceptance criteria. The extent of IPC is considered generally comprehensive and in line with the requirements of ICH and EMA guidelines.

Additionally, AS process intermediate hold times are described. Details are provided in section S.2.5 Process validation and/or evaluation.

Control of materials

Materials used in the manufacture of AVT05 AS have been listed together with information on the quality and control of these materials. No materials of human or animal origin are used in the manufacture of AVT05 AS. Compendial grade material are used, where applicable. Specifications have been provided for all the non-compendial materials used in the manufacturing process. The non-compendial raw materials are tested for identity and they are required and verified to meet the specifications reported by the vendor on the Certificate of Analysis (CoA).

Composition of buffers and solutions used in the process was provided, as well as the qualitative composition of the used media and feeds.

The description of the preparation of the cell banking system was satisfactorily described. Characterisation of the cell banks is considered generally adequate. Viability test is performed as part of cell banks post-production recovery before release for characterisation.

Overall, the safety of materials used in the manufacturing of AVT05 is adequately presented. Compendial and non-compendial materials used in USP and DSP were listed. All materials used throughout the manufacturing process are animal component free (apart from the production cell line itself). Upon receipt, all raw material chemicals are tested for identity as a minimum and the certificates from the supplier are verified for conformity with the monograph or supplier specification.

Control of critical steps and intermediates

Overall, the presented process controls for manufacturing of AVT05 AS seem appropriate. In-process controls and in-process tests with their acceptance criteria (for IPCs) or action limits (for IPTs) applied in the manufacturing of AVT05 AS have been listed in CTD section S.2.4. IPCs with an action limit are used to assess consistency of the process at less critical set, failure will result to deviation. IPCs with acceptance criteria are numerical limits, ranges, or suitable measures for analytical procedure results. Failure of such control leads to deviation and/or OOS investigation. The justification for setting the IPCs/IPTs limits has been adequately discussed. Generally, the limits of these IPCs were defined based on development, manufacturing experience and process characterisation studies. The defined IPCs were tested in the process performance qualification (PPQ) studies. Criticality assessment report for critical quality attributes (CQAs) assignments has been provided, and the proposed CQAs are considered adequate.

Overall, the presented in-process controls and tests seem appropriate. IPC data was provided from several consecutive at-scale batches of AVT05-AS. Overall, the data indicate that the manufacturing process is capable of operating within defined parameters to generate product of the required quality.

Process validation and/or evaluation

Three stage process validation has been performed. First process characterisation and evaluation studies were performed to develop a robust manufacturing process for AVT05 AS. These are described and sufficiently discussed.

Subsequently, a formal validation of the AVT05-AS manufacturing process was conducted at full commercial scale as part of the PPQ. The PPQ program included the production of consecutive AS batches at commercial scale. Acceptance criteria applied during PPQ were based on data obtained during process development and characterisation.

Clear tables of the PPQ test results were provided including non-critical process parameters (non-CPP), CPPs, and IPCs. All consecutive PPQ batches were successfully processed through cell culture, harvest, and purification stages. CPP were maintained within established acceptable ranges. The final batch data was within specification for all batches. Continued process verification will be undertaken to ensure the process is under a state of control.

Impurity removal of process- and product- related residuals was studied at production scale for three PPQ batches. As a result, it was concluded that a clearance of process and product related impurities is successfully achieved in the downstream manufacturing process

Buffer- and product life time studies has been completed. Overall, the proposed approach is considered adequately justified. In conclusion, the conducted PPQ studies demonstrate that the AVT05 AS manufacturing process can consistently produce AVT05 AS that meet specifications.

Manufacturing process development

Risk assessments for assemblies or components used within the AVT05 manufacturing process were performed. Toxicological screening assessment was conducted to medium and high-risk components. Risk assessment reports for extractables and leachables are provided, and also data on toxicological screening assessment and leachable and/or extractable studies which are concluded acceptable. Summary of process characterisation (PC) studies was provided in section S.3.2.6 Manufacturing process development, and detailed study results for PC studies were provided as well.

Based on the outcome of the process characterisation study, the pCPPs were categorised as either CPPs or non-CPPs based on their impact on CQAs. Compatibility studies have been overall adequately performed and described.

The active substance manufacturing process has had minor updates throughout the AS manufacturing process development. Considering that the manufacturing process changes has been minor, no comparability exercise has been performed. However, the approach has been to demonstrate comparability throughout the AS manufacturing processes, and AS to FP conversion.

This includes: evaluation of the in-process data which represent process consistency during the upstream and downstream stages, evaluation of individual AS batch release data, and extended characterisation data for AVT05-FP (representative of AVT05-AS). The approach is generally considered acceptable for the full-scale manufacturing processes where only very minor changes have been introduced. This is acceptable.

Comparability of MCB and WCB originated batches

A WCB has been introduced during late manufacturing process development. the applicant conducted a comparability study between MCB and WCB originated batches. The comparability strategy was revised. Overall, the revised comparability strategy is considered appropriate.

In the revised comparability assessment, the quality ranges were derived from the data from the MCB batches, and the WCB batches were compared against those quality ranges. The appropriate statistical approach in line with the recommendations provided in the 'Reflection paper on statistical methodology

for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017) was selected for the comparability assessment and statistical simulation analysis justifying the statistical approach were added in the dossier.

Overall, the presented comprehensive comparability data seem to demonstrate sufficient comparability between MCB and WCB originated batches at most parts. All the observed differences were thoroughly justified and convincingly demonstrated that the differences will not have adverse impact on safety and efficacy of the product. The comparability of the stability trends of all the stability indicating parameters and forced degradation trends were also thoroughly discussed. Taking into account all provided data and discussions, it can be concluded that the comparability between AVT05 MCB and WCB batches was demonstrated.

Characterisation

AVT05 has been analysed using state-of-the-art methodology. Data on primary, secondary, and higher-order structures, post-translational modifications (e.g., glycoforms), biological and functional activity, purity, and immunochemical properties have been collected and evaluated. Overall, adequate panel of attributes and methods are included in the characterisation analysis.

Product-related impurities are controlled as part of batch release testing and have been evaluated as part of process performance qualification (3.2.S.2.5.1 Process validation and/or evaluation). Analytical methods used for testing has been listed. Furthermore, impurity clearance evaluation reports have been provided where impurity clearance capability of the AVT05 downstream AS manufacturing process is assessed. Based on manufacturing data, it was determined that the downstream process of AVT05 AS can control the process and product related impurities within the acceptable limits. The impact of product-related impurities on AVT05 biological activity, safety, and efficacy was appropriately discussed.

The assessment of N-nitrosamine impurities has been performed and it was concluded that the risk of nitrosamine contamination is negligible.

2.3.2.3. Specification

Active substance specification, including methods to evaluate appearance, clarity, colour, identity, potency, protein content, purity/impurities, bioburden, bacterial endotoxins, is presented. The test parameters proposed to be included in the AVT05 specification are considered relevant.

Compliance with the requirements of the Ph. Eur. monograph on Golimumab concentrated solution 3103, was adequately demonstrated for the mandatory methods. Additionally, Golimumab CRS was appropriately employed as part of method comparison studies and equivalency to in-house reference standard was demonstrated. Also, the golimumab BRP was appropriately bridged to the in-house reference for the potency assay.

Analytical procedures

AVT05 AS is tested using a combination of compendial and non-compendial methods. Compendial methods were adequately verified.

Overall, for non-compendial methods, method descriptions that include method details, operational parameters and system and sample acceptance criteria as well as data reporting details, have been provided for all methods. Method description including list of reagents and materials, as well as equipment that are used in the analytical methods were presented. Generally, non-compendial methods has been validated according to ICH Q2.

The applicant has adequately demonstrated that the methods comply with the assay as described in Ph. Eur. Golimumab concentrated solution monograph (01/2025:3103).

The analytical methods have been properly validated and the information provided is sufficient.

Batch analysis

Batch analysis data was provided for several AVT05 AS batches PPQ batches

All results provided comply with the proposed specifications, therefore it has been demonstrated that active substance of consistent quality is manufactured by the proposed manufacturing process.

Reference standards of materials

Overall, the reference standards used throughout the product development have been adequately described. The first research Standard used in the early analytical biosimilarity studies was an originator product, Simponi.

Currently, there are two qualified in-house reference materials for AVT05.

Following the interim reference material, the GMP in-house reference material and primary in-house reference materials were both prepared which has been used for the preparation of AVT05 clinical batch.

The GMP in-house reference material was qualified against the interim reference standard.

The protocol and acceptance criteria for the qualification of future WRS has been provided. Generally, the approach is considered adequate

The applicant has adequately demonstrated the compliance of the used reference standards with the ones required by the Ph. Eur. monograph**.**

Container closure system

AVT05 AS container closure system has been adequately described.

A schematic diagram of the container as well as specifications were provided in the dossier. Safety of the container closure system has been mainly evaluated by the supplier. Compatibility has been studied as part of AVT05 AS stability study program. It is understood that extractable study has been performed by the container closure supplier. According to the provided data covering the proposed AS shelf-life all results were below the respective reporting threshold.

2.3.2.4. Stability

Stability studies are carried out in representative AS primary container closure bags compared to the commercial primary packaging material for the active substance with the same interior product contact layer. Stability studies are performed at long-term storage conditions, at accelerated storage conditions, and stressed storage conditions.

The proposed stability study protocols are considered adequate and are carried in accordance with the current and relevant CHMP guidance.

The applicant will include at least one commercial batch (if manufactured) per year on long-term stability through the proposed testing period and the testing will be carried out as per the protocol summarised in the dossier. Separate post-approval stability protocol has been described.

Based on the stability data the proposed shelf-life for the active substance is supported by the real-time real-condition data of representative AS stability batches. The AS should be protected from light.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

AVT05 finished product is a sterile, preservative-free, practically free of visible particles, clear, colourless to slightly yellow solution for subcutaneous injection (sc) containing 50 mg of golimumab in 0.5 mL (AVT05-DP50) or 100 mg of golimumab as active substance in 1.0 mL (AVT05-DP100). Other ingredients are: sorbitol, L-histidine, L-histidine monohydrochloride monohydrate, poloxamer 188, and water for injections. Following assembly into SD (safety device) or AI (auto injector), the composition is unchanged.

50 mg dose presentation:

- Safety Device: fitted with a plunger rod, extended finger flange, and a needle safety device, forming the final product. The finished product is referred to as AVT05-SD50.
- Autoinjector: consists of a subassembly unit, housing cover, and cap remover sleeve that encloses the AVT05-DP50 PFS. The finished product is referred to as AVT05-AI50.

100 mg dose presentation:

- Safety Device: fitted with a plunger rod, extended finger flange, and a needle safety device, forming the final product. The finished product is referred to as AVT05-SD100.
- Autoinjector: consists of a subassembly unit, housing cover, and cap remover sleeve that encloses the AVT05-DP100 PFS. The finished product is referred to as AVT05-AI100.

Formulation development

The formulation was developed to generate a biosimilar to the reference product for subcutaneous administration. The formulation is qualitatively and quantitatively identical to the reference product formulation, with the exception of the surfactant used. The formulation development studies evaluated the effect of buffers, stabilizers, tonicity modifiers, surfactant. The selection process for Poloxamer 188 as a choice for surfactant, is adequately described and justified. Overall, the formulation development of AVT-05 FP has been adequately described, and the results of the studies are appropriately presented and summarised in the dossier.

Manufacturing process development

In summary, the manufacturing process development has been explained satisfactorily. Comparability between 50 mg and 100 mg presentations is adequately shown with quality attribute comparison, stability trends and forced degradation pathway studies. Extractable and leachable studies have been performed to evaluate the compatibility of the container closure with the finished product. In general, the suitability of the container closure system is shown and the proposed container closure system appears suitable for Gobivaz.

2.3.3.2. Manufacture of the product and process controls

Manufacturers

The name, address and responsibility of all finished product manufacturers involved in the manufacturing, quality control and stability testing, assembly and packaging, batch release have been provided. All sites involved in the manufacturing process of the finished product are GMP compliant.

Manufacturing process

The finished product manufacturing process is a standard process which comprises of AS thawing, bulk FP pooling and mixing, bioburden reduction filtration, sterile filtration, aseptic filling, and stoppering. Then, the syringes are visually inspected. Finally, all boxes with PFS are transferred to the warehouse. There are no reprocessing steps in the manufacture of AVT05 FPs.

A narrative description of the full manufacturing process was provided, accompanied by a table describing of each process step including process parameter with proposed proven acceptable range and criticality classification.

The shipping validation studies were conducted. Based on the available data, the proposed packing configuration it is confirmed that it does not have any impact on the packaging integrity, product quality, device functionality and product sterility.

The batch numbering system is explained for the PFS, SD and AI presentations in the dossier is sufficient detailed.

Process controls

In-process controls are presented separately for PFS, SD and AI. The manufacturing process is controlled using in-process controls (IPCs), which are used for critical parameters containing acceptance criteria/action limits. List of IPC methods performed during the manufacturing process of PFS and their respective acceptance criteria are defined in tabular form. Justifications of chosen critical in-process controls and process parameters are provided. The information provided is sufficient.

Process validation

The FP manufacturing process was validated by producing several consecutive commercial scale PPQ lots at the proposed commercial manufacturing site. All PPQ batches met in-process controls and acceptance criteria. The provided data demonstrates that when operating within the proposed ranges, the performance controls meet relevant quality criteria. PARs defined in the manufacturing process description are supported with appropriate data and are acceptable. It is indicated that continued process verification will be undertaken.

Overall, the AVT05-PFS, safety device and autoinjector (50 mg and 100 mg) FP manufacturing processes have been appropriately validated. All pre-determined acceptance criteria were satisfactorily met for all evaluated parameters, in-process controls and release tests.

Media fill studies are performed as per requirements set out by Eudralex Vol 4, Annex 1. The media fill validation data was provided in the MAA but is not assessed since it is considered to be covered by GMP. The timing of sterile filtration and filling process is justified.

The proposed process and hold times for commercial manufacturing process are clearly presented and summarised. Based on the provided results, the proposed process and hold times are considered adequately justified and validated and thus acceptable.

The filter validation studies included several tests. Acceptable results for these tests are provided.

2.3.3.3. Product specification

Specifications

Finished product specification includes testing for appearance, clarity, colour, identity, potency, protein content, purity/impurities, sterility, bacterial endotoxins.

In general, the proposed release and shelf-life specifications cover relevant tests and are considered acceptable.

There are no further product-related and process-related impurities in the finished product compared to those already discussed for the active substance. Risk assessment of nitrosamine impurities is provided and it is concluded that there is very low risk. Risk assessment for elemental impurities in accordance with ICH Q3D has been also provided.

As the formulation is performed at the level of the active substance and no degradation is expected during manufacture of the finished product, almost the same release acceptance criteria are proposed as for the active substance. This is acceptable.

Analytical procedures

The majority of analytical procedures used are the same as described in AS section, with additional methods. Compendial methods are based on respective Ph. Eur. monographs.

Relevant descriptions and verification data for all compendial methods are presented.

Non-compendial analytical methods for the finished product are mainly the same than those used for AS. In general, the validation of non-compendial analytical procedures has been done according to relevant guidelines. Validation reports are provided.

Batch analysis

The batch release of the AVT05 finished product comprises the batch release of the pre-assembled AVT05-FP PFS (Finished product in PFS) and the device-related functional batch release data of the post-assembled AVT05 PFS SD (PFS in Safety Device) and AVT05 PFS AI (PFS in Auto-Injector). The batch data is presented in tabular form per each presentation. All batches met the acceptance criteria of release in place at the time indicating adequate batch-to-batch consistency and controlled FP manufacturing process.

Reference standards

The reference standards used for stability testing and routine lot release testing of the FP are the same as those employed for the AS. For discussion on reference standards, please refer to section 3.1.2.3 of this AR (CTD section S.5).

Container closure system

AVT05-FP has two PFS single-use presentations (AVT05 50 mg/0.5 mL and AVT05 100 mg/1.0 mL) which use the same container closure system. The PFS can be assembled further to safety device or autoinjector.

The primary container closure for AVT05-FP PFS is a single-use, type I glass PFS (container) with a bonded needle and a rigid needle shield (RNS), and a plunger stopper. Specifications and CoA´s for syringes and plunger stoppers are provided. Specifications for syringe, plunger-stopper, and plungers with CoAs are provided. Components and suppliers for the secondary container closures SD and AI are listed. Specifications for the components are provided. The quality of the primary and secondary packaging components is stated to be of ISO, Ph. Eur. and USP quality. The Notified body opinions have been also provided. Overall, the provided data covering suitability of the CCS, confirmation of container closure integrity and stability tests indicates that the selected container closure system is in general appropriate and enables adequate protection from microbial contamination.

Stability of the product

The proposed shelf-life for AVT05 FP PFS/SD/AI finished product when stored at (2 °C – 8 °C) is 2 years with an additional storage at 25° for a maximum of 30 days at once and protected from light.

Stability data for PFS, from several batches, at long-term, accelerated and stressed conditions was provided.

Stability data for the safety device is available.

Out of fridge study was performed to confirm OOF storage shelf-life of up to 30 days at 25°C±2°C/60±5% RH within the shelf-life of the finished product. Taken together all current stability data, the proposed shelf-life concerning the PFS is acceptable.

Concerning stability data on safety device (and autoinjector, stability data as listed in tables P.8-2 and P.8-3, is provided. In summary, the provided data support the shelf-life concerning the functional properties for both devices and strengths.

Photodegradation study results for AVT05, EU-, and US-Simponi have been submitted. A post-approval stability protocol and stability commitment are provided.

Stability testing protocols for each batch are provided.

Based on the review of the available stability data a shelf life of 2 years when stored at (2 °C – 8 °C) is acceptable for the finished product. GOBIVAZ may be stored at temperatures up to a maximum of 25°C for a single period of up to 30 days, but not exceeding the original expiry date printed on the carton. The new expiry date must be written on the carton (up to 30 days from the date removed from the refrigerator). Once GOBIVAZ has been stored at room temperature, it should not be returned to refrigerated storage. GOBIVAZ must be discarded if not used within the 30 days of room temperature storage.

2.3.3.4. Biosimilarity

Gobivaz (AVT05) has been developed as a proposed biosimilar to Simponi (golimumab; EU/1/09/546/005 and EU/1/09/546/001, MAH Janssen Biologics B.V.). AVT05 FP has the same concentration (100 mg/mL) and formulation as Simponi, with the exception of containing poloxamer 188 instead of polysorbate 80. Two AVT05 FP presentations (100 mg/1.0 mL and 50 mg/0.5 mL) identical to Simponi presentations were developed.

The overall approach to demonstrate similarity of AVT05 to EU-Simponi is mainly in line with EMA/CHMP/BWP/247713/2012 and EMA/CHMP/138502/2017 guidance.

The QTPP was based on data from several EU-Simponi and US-Simponi batches (50 mg/0.5 mL and 100 mg/1.0 mL PFS combined). The same batches were included in the head-to-head (H2H) analytical comparability exercise, however, not all batches were analysed for each quality attribute (QA). The number of Simponi batches included in H2H analysis is considered sufficient for evaluating batch-to-batch variability of the reference product. Comparable quality of PFS 50 mg and 100 mg presentations of EU-Simponi or US-Simponi, as well as between EU-Simponi and US-Simponi was adequately demonstrated. However, data for EU-Simponi is considered pivotal for demonstrating analytical biosimilarity, whereas US-Simponi data is considered supportive.

A two-step risk-based approach was used to assess the criticality of the quality attributes. First, potential critical QAs (CQAs) were identified and assessed based on impact on biological activity, pharmacokinetics/pharmacodynamics (PK/PD), immunogenicity, and safety and uncertainty factor. Second, the criticality of CQAs was adjusted based on the criticality risk ranking step, considering the

presence and abundance of the QAs and the overall product specific knowledge. Quality attributes related to determination of primary structure, higher order structure, biological activity and physical attributes were not assessed as they are identified as obligatory CQAs. The risk assessment approach and classification of CQAs is considered acceptable.

Several AVT05 PFS batches, 50 mg/0.5 mL and 100 mg/1.0 mL manufactured were included in the comparability exercise, however, not all batches were tested for all QAs.

Comparability between 50 mg and 100 mg presentations has been adequately demonstrated, the applicant has provided a comprehensive comparability dataset, which demonstrates mainly comparable quality between MCB and WCB originated batches.

Numerous differences were observed in several QAs between AVT05 and EU-Simponi, and some, but not all of the differences were related to the age of the batches. Additionally, differences were more pronounced for younger than older AVT05 batches when compared to EU-Simponi. In line with the current guidance, EMA/CHMP/BWP/247713/2012, the relevance of the biosimilarity quality ranges should be discussed taking into account the age of the batches at the time of testing. To address this issue, the applicant re-analysed batches originating from WCB at an older age to ensure comparable age ranges for AVT05 and EU-Simponi. The revised analytical similarity data is presented as a standalone package "Comparative analytical similarity assessment 2" in the updated section 3.2.R.3.3, and the final conclusions made by the applicant are based on this dataset.

Altogether, the initially five separate H2H comparative analytical similarity studies were conducted during 2021-2024. Data from similarity studies has been presented in compiled form, which is generally acceptable.

Biosimilarity approach

To assess analytical similarity, either qualitative or quantitative comparison was performed for each of the tested quality attribute. Qualitative comparison was performed for QAs related to demonstration of primary and secondary structure which in principle is acceptable as it mostly relates to visual comparison. For the purpose of quantitative comparison, the similarity interval approach was chosen. A simulation was performed to estimate the probability of false positive and false negative conclusions on similarity. Additionally, the normality of the data was evaluated. For non-normally distributed data, potential differences were discussed separately for each QA.

A comprehensive set of state-of-the-art orthogonal methods was used. The extent of analytical tests is considered sufficient to cover all relevant quality attributes for the purpose of demonstration of analytical similarity.

Analytical methods used for biosimilarity evaluation have been sufficiently described. Validated methods used for AS batch release and for biosimilarity evaluation are described and assessed in AS section. Methods used only for comparative analytical similarity testing were appropriately qualified.

Analytical results

Biosimilarity data has been provided in summary tables. Analytical results have been presented separately for each individual AVT05 batch, and upon request also for EU-Simponi.

Quantitative data has been appropriately visualised using scatter plots and qualitative data using spectra/result images.

Table 1: Summary of the Gobivaz analytical similarity with Simponi			
Molecular parameter	**Attribute**	**Methods**	**Key findings, conclusions**
Primary structure	Peptide mapping, Amino acid sequencing	LC-MS/MS	Identical primary sequence with sequence coverage of 100%.
	Intact, reduced and de-N-glycosylated molecular mass	LC-MS	The major molecular masses are highly similar between the products.
Higher order structure	Secondary structure	Far-UV CD	Similar secondary and tertiary structures
		FT-IR	
		DSC	
	Tertiary structure	Near-UV CD	
	Disulfide/ trisulfide bonds	Non-reduced peptide mapping (LC-MS)	Similar intra- and inter-chain disulfide bonds. Sufficiently similar trisulfides.
	Free thiols	Ellman's reagent	Comparable low amount of free thiols.
Post-translational modifications	N-Glycosylation site occupancy	CE-SDS reduced	Similar very low level of non-glycosylated heavy chain
	N-Glycosylation	HPLC with Rapifluor labelling	Mainly comparable N-glycan profile. Total afucosylation slightly higher in AVT05 vs. EU-Simponi mainly due to high mannoses. Neutral complex afucosylated glycans lower and hybrid afucosylated glycans higher in AVT05, but sum of these species (i.e. afucosylation without high mannoses) is comparable between the products. Galactosylation lower and sialylation lower in AVT05. Differences in N-glycosylation were demonstrated not to have meaningful impact on Fc-mediated activities. Upon request, tight enough limits were set for high mannoses and afucosylated glycans in the AS release specification to ensure consistent quality and similarity of future AVT05 batches. Generally lower level of α1,3Gal in AVT05 is not expected to negatively impact the clinical performance.
	Sialic acid content	HPLC with DMB labelling	Sialic acid content (mainly NGNA) is slightly lower in AVT05, which does not preclude similarity.
	Oxidation (Met & Trp)	Peptide mapping (LC-MS)	Low level of Met and Trp oxidation in both products.
	Deamidation	Peptide mapping (LC-MS, LC-UV)	Deamidation equilibrium dynamics is time-dependent. Analysis of age-matched batches support similarity: Comparable HC N43 total deamidation. Deamidation of LC N93 (located in the CDR-L3) has demonstrated impact on potency. Similar LC N93 total deamidation. Similar total deamidation in all Fc sites.
	Isomerization of aspartic acid	Peptide mapping (LC-MS)	Similar low level of aspartate isomerization
	N/C-terminal integrity	Peptide mapping (LC-MS)	Higher C-terminal lysins in AVT05. Slightly lower N-terminal pyroglutamate (HC Q1) in AVT05.

			Trace amounts of LC E1 pyroglutamate in both products. The observed differences in the N-/C-terminus are highly unlikely to have clinical impact, and do not preclude similarity claim.
	Glycation	Reduced and de-N-glycosylated molecular mass (LC-MS)	Similar
Fab related functional activity	Potency	Inhibition of TNFα induced apoptosis in U937	Highly similar
	Soluble TNFα binding	SPR	
	Membrane bound TNFα binding	Cell-based assay (FACS)	
	Reverse signalling	Cell-based assay (FACS using Jurkat cell line)	
Fc related functional activity	FcRn binding	SPR	Similar
	FcγRIa binding	SPR	Slightly lower FcγRIa binding activity in AVT05, which is not considered clinically meaningful.
	FcγRIIa 131H binding	SPR	Similar
	FcγRIIIa 158V/158F binding	SPR	FcγRIIIa 158V and 158F binding slightly weaker in AVT05; however, within the QR of EU-Simponi
	C1q binding	SPR	Similar
	CDC	Cell based assay	Sufficiently similar
	ADCC 158V	Cell based (reporter) assay	Similar ADCC activity by RGA assay.
	ADCC PBMC V/V donor	Cell based assay	Primary ADCC activity with PMBCs (V/V) mainly similar between AVT05 and EU-Simponi with two AVT05 batches slightly above the QR. Similar ADCC (F/F) activity.
	ADCC PBMC F/F donor		
	Structure-function and correlation studies indicate, that these small differences do not have meaningful impact on Fc related functionalities, and thus do not preclude the similarity claim between AVT05 and EU-Simponi. Sufficient control for glycosylation is set in the AS specification to ensure consistent ADCC activity in the future.		
Physicochemical analyses	Protein content	OD280	AVT05 has higher protein content than EU-Simponi. Upon request, the limits for protein content were further tightened to ensure sufficient similarity in the future AVT05 batches. The theoretical extinction coefficient was experimentally confirmed.
	Charge variants	cIEF	Charge variant profiles are visually similar with no new peaks in AVT05.
		cIEF post CPB treatment	After removal of C-terminal lysines mainly similar charge variants. Minor differences in basic and acidic variants explained by clinically insignificant HC N43 deamidation and HC N-terminal glutamine.

	Differences in charge variants were demonstrated not to have meaningful clinical impact. Charge variants are considered similar between AVT05 and EU-Simponi.		
	Size variants	SEC-HPLC	HMW species slightly higher in AVT05, however, the level is low in both products raising no concern on similarity.
		SV-AUC	Similar level of monomer, dimer and higher order aggregates.
		SEC-MALS	Comparable main peak and dimer molecular weights.
		CE-SDS non-reduced	Fragment content slightly higher in AVT05. Difference is considered clinically insignificant, as potency/biological activity is similar.
		CE-SDS reduced	Similar HC and LC content, and amount of fragments.
	With regards size variants, AVT05 and EU-Simponi are considered sufficiently similar. Size variant characterisation with thermally stressed samples indicates that higher order aggregates (HOA) are similar between the products raising no concern.		
	Sub-visible particles	DLS	Similar polydispersity. Minor differences in Z-average, which are unlikely to be clinically meaningful.
Stability evaluation	Long-term Accelerated Stressed conditions	Deamidation by UPLC-UV, Potency by inhibition of TNFα induced apoptosis, Protein content by OD280, Size variants by SEC-HPLC, CE-SDS (nr/r), Charge variants by cIEF	Higher initial protein content and lower purity in AVT05. Stability trends mainly similar between the two products supporting the similarity claim.
Forced degradation	Thermal stress Photodegradation Low/high pH Oxidative stress (0.006% H_2O_2)	SEC-HPLC, CE-SDS (nr/r), cIEF with CPB, LC-MS (oxidation/ deamidation), Potency, TNFα binding, TNFα CFCA, FcRn binding	The main degradation pathways were similar between the products including aggregation, fragmentation, deamidation (HC N43 and LC N93), and oxidation (HC M261 and LC W94) reflected in changes of size and charge variants, decreased potency, and decreased binding to TNFα and FcRn.

Summary

Similarity has been adequately demonstrated between AVT05 and EU-Simponi for the physicochemical and biological properties (Table 1).

Thorough discussion and justification for individual differences and for a combination of all analytical differences observed between AVT05 and EU-Simponi were provided. Most of the concerns were adequately addressed, and the minor differences observed in various QAs were concluded clinically insignificant.

The correlation data of afucosylation vs. FcγRIIIa (V/F) binding vs. ADCC activity provides mainly sufficient evidence of similarity between AVT05 and EU-Simponi. The conclusions with regards to the correlation of different afucosylated glycan species and FcγRIIIa (V/F) binding remain unaffected raising no further concerns.

Tight enough limits are established for total afucosylation, high mannose and afucosylation without high mannose to ensure that Fc effector functions of the future commercial AVT05 batches remain

similar to EU-Simponi. The limits are acceptable. The limit for protein content was further tightened to ensure that future batches remain sufficiently similar to the reference product.

To maintain sufficient similarity of the future commercial AVT05 batches to EU-Simponi, limits for size variants were further tightened for AS and FP specifications.

Conclusions

The applicant has addressed the similarity between AVT05 and the reference product, EU-Simponi in a comprehensive comparability exercise. Fab related biological activity and higher order structure were demonstrated to be similar between the products supporting similarity.

Minor differences are highly unlikely to have clinically meaningful impact, thus, these differences do not preclude the similarity claim. The remaining uncertainties were appropriately addressed by extended characterisation and correlation analyses, as well as with relevant scientifically sound discussion.

Extended characterisation data indicates that differences in charge variants are associated with variants that have no relevant clinical impact. The differences observed in N-glycosylation profile were thoroughly discussed and conclusions were generally supported with results of the structure-function correlation analyses. The applicant justified that the identified minor differences in the Fc mediated effector activity observed for the batches produced so far would not have an impact on clinical performance. Sufficiently tight specification limits for high mannoses, total afucosylation and afucosylation without high mannoses have been established to ensure that similarity is maintained between AVT05 and EU-Simponi.

The specification limits for the quality attributes were tightened to ensure that future batches remain similar to the reference product.

Overall, the analytical biosimilarity at the quality level has been appropriately demonstrated between Gobivaz and EU-Simponi. The panel of methods performed is satisfactory covering structural as well as biologicals quality attributes with the necessary level of depth. From the quality perspective, Gobivaz is considered similar to EU-Simponi and is approvable as proposed biosimilar to Simponi.

2.3.3.5. Post approval change management protocol(s)

Not applicable.

2.3.3.6. Adventitious agents

The AVT05 manufacturing process is designed to have a controlled environment, single-use materials, and closed processing where applicable, thus preventing contamination by any adventitious agents during manufacturing.

Non-viral adventitious agents

TSE risk assessment

During the production of AVT05, no materials are used that are considered specified transmissible spongiform encephalopathy (TSE) or bovine spongiform encephalopathy (BSE) risk materials. No product contact materials from materials of animal origin are used. The Master Cell Bank, raw materials, Single Use Consumables, Primary packaging and other materials that are used to manufacture Gobivaz are of non-animal origin or conforms to the requirements as defined in the Guideline EMEA/410/01 "Note for guidance on minimizing the risk of transmitting animal spongiform

encephalopathy agents via human and veterinary medicinal products". On the basis of this information, it can be concluded that the risk of TSE contamination is highly unlikely.

Control of microbial, fungi and mycoplasma

All solid and liquid raw materials, the solutions and buffers, and all excipients are tested for endotoxins (Ph. Eur. 2.6.14). In addition, testing for bioburden (bacteria, fungi) as defined by Ph. Eur. 2.6.12 is performed on the purified water and water for injections. Both the MCB and WCB, as well as the post-production cell bank (PPCB), are tested for sterility and mycoplasma according to ICH Q5D.

Viral adventitious agents

Identification of raw materials of biological origin

To produce the MCB and WCB, only materials free of animal derived components were used. As recommended in Guidance ICH Q5A, three complementary approaches are used to control the potential viral contamination of the product: selecting and testing cell lines and other raw materials of animal origin for the absence of viruses that may be infectious and/or pathogenic for humans, testing the product at appropriate steps of production for the absence of contaminating infectious viruses and assessing the capacity of the production process to clear viruses.

Cell banking system

Results of the MCB, WCB, and PPCB testing are provided. Based on the provided information it could be concluded that there is no potential impact to the patients due to the presence of retroviruses.

Viral testing of unprocessed bulk

The unprocessed AVT05 bulk was tested for viral adventitious agents in representative AVT05 batches, and a summary of the results has been presented. The duration of the test for viral adventitious agents is justified and in line with the ICH Q5A guideline.

Virus clearance studies

Viral clearance was evaluated. The study involved qualified scale-down model (SDM) of the full-scale AVT05 process and measuring virus removal or inactivation capacity.

The viral inactivation and clearance capacity of the downstream process were confirmed by evaluating the inactivation and clearance rate of individual process steps. The choice of the used model viruses is adequately justified and relevant for this manufacturing process and cell culture type. Scale-down models of the commercial purification process were used in the viral clearance studies. The comparison of process parameters between scale-down model and commercial scale production was demonstrated.

The purification included several steps. Description and qualification data of methods used in the viral clearance studies including the suitability of these procedures to quantify the (model) virus particles were provided.

Summary of the viral inactivation and clearance capacity of the downstream process

The overall log reduction factors for the viruses investigated are presented. The overall cumulative reduction is considered safe and acceptable. Overall, the viral clearance studies were performed in accordance with ICH Q5A guideline and demonstrate adequate capacity of the production process to inactivate or remove viruses.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

In support of the MAA, the applicant provided well-structured quality dossier providing adequate data and information. All concerns identified during assessment have been appropriately addressed.

The applicant has addressed the overarching analytical biosimilarity MO raised at D120 regarding numerous differences observed between the proposed biosimilar and the reference product by reanalysis of AVT05 batches, by extended characterisation and correlation analyses, as well as with scientifically sound discussion. In conclusion, the differences were appropriately demonstrated not to have meaningful impact on clinical performance.

Overall, the analytical biosimilarity at the quality level has been appropriately demonstrated between Gobivaz and EU-Simponi. The panel of methods performed is satisfactory covering structural as well as biologicals quality attributes with the necessary level of depth. From the quality perspective, Gobivaz is considered similar to EU-Simponi and is approvable as a biosimilar to Simponi.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Gobivaz is considered acceptable when used in accordance with the conditions defined in the SmPC. The validation of the manufacturing process has been satisfactorily demonstrated ensuring the manufacturing process for Gobivaz is capable of consistent and robust performance. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. Adventitious agents safety including TSE have been sufficiently assured.

In conclusion, based on the review of the data provided, the marketing authorisation application for Gobivaz as a biosimlar to Simponi is considered approvable from the quality point of view.

2.3.6. Recommendations for future quality development

None.

2.4. Non-clinical aspects

2.4.1. Introduction

The demonstration of biosimilarity of AVT05 to EU-Simponi is based on the totality of evidence data of analytical, functional and clinical comparative studies to demonstrate the structural and functional similarity.

The *in vitro* biological activity studies are included in the quality dossier and therefore discussed in the Quality/Biosimilarity assessment.

No *in vivo* pharmacology, secondary pharmacodynamics, safety pharmacology, pharmacodynamic drug interactions, pharmacokinetics/toxicokinetics or toxicology studies have been conducted.

Relevant EU and ICH guidelines were followed in the development of a biosimilar medical product (Guideline on similar biological medicinal products (CHMP/437/04 Rev 1); Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/ 42832/2005 Rev 1) and ICH Topic S6 (R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH, 2011)).

The application concerns subcutaneous (SC) formulation of AVT05. Intravenous (IV) formulation has not been applied for AVT05 even if that is claimed in non-clinical documentation presented by the applicant.

Similar excipients to the reference product Simponi are used.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

AVT05 is a recombinant human immunoglobulin G1 kappa (IgG1κ) mAb that prevents the binding of tumour necrosis factor-α (TNF-α) to its receptors, thereby neutralising its activity. A comprehensive set of *in vitro* studies was conducted for analytical and functional characterisation and comparison of AVT05, EU-Simponi and US-Simponi to demonstrate the biosimilarity.

Full data from *in vitro* PD studies was included and discussed under the Quality dossier and evaluated under the Quality/Biosimilarity assessment. Therefore, the biosimilarity assessment is not repeated here. Please see Quality/Biosimilarity assessment for further details.

No *in vivo* pharmacodynamics studies are required for biosimilar medicinal products.

2.4.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies are required for biological medicinal products.

2.4.2.3. Safety pharmacology programme

Safety pharmacology studies are not required for similar biological medicinal products.

2.4.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies are required for similar biological medicinal products.

2.4.3. Pharmacokinetics

No non-clinical PK or TK studies are required for biosimilar medicinal products.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

No single-dose toxicity studies are required for biosimilar medicinal products.

2.4.4.2. Repeat dose toxicity

No repeat-dose toxicity studies are required for biosimilar medicinal products.

2.4.4.3. Genotoxicity

No genotoxicity studies are required for biosimilar medicinal products.

2.4.4.4. Carcinogenicity

No carcinogenicity studies are required for biosimilar medicinal products.

2.4.4.5. Reproductive and developmental toxicity

No developmental and reproductive toxicology studies are required for biosimilar medicinal products.

2.4.4.6. Toxicokinetic data

Not applicable for biosimilar medicinal products.

2.4.4.7. Local tolerance

No local tolerance studies are required for biosimilar medicinal products.

2.4.4.8. Other toxicity studies

Not applicable for biosimilar medicinal products.

2.4.5. Ecotoxicity/environmental risk assessment

An expert statement justifying the absence of ERA studies has been submitted by the applicant.

The active substance of Gobivaz is golimumab, a human IgG1κ monoclonal antibody. As golimumab is fully humanised protein, it is a naturally occurring substance. Therefore, in line with Guideline on the environmental risk assessment of medicinal products for human use - Revision 1 (EMEA/CHMP/SWP/4447/00 Rev. 1), Gobivaz falls into the group of medicinal products exempted from the conduct of environmental studies as it is unlikely to represent a significant risk to the environment.

2.4.6. Discussion on non-clinical aspects

Pharmacodynamics

The application concerned SC formulation of AVT05. IV formulation has not been applied for AVT05.

A comprehensive set of *in vitro* studies was conducted for analytical and functional characterisation and comparison of AVT05, EU-Simponi and US-Simponi to demonstrate the biosimilarity.

Full data from *in vitro* PD studies was included and discussed under the Quality dossier and evaluated under the Quality/Biosimilarity assessment (Please see Quality/Biosimilarity assessment for further details).

No separate *in vivo* pharmacodynamics, secondary pharmacodynamics studies, safety pharmacology or pharmacodynamic drug interaction studies were conducted with AVT05 and EU-Simponi and are not required in line with relevant EU guideline.

Pharmacokinetics

No non-clinical PK or TK studies have been conducted. This is in line with the EU guidelines for biological similar medicinal products.

Toxicology

No animal toxicity testing (*in vivo* comparison) is required for the biosimilar medicinal products in the EU (EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/05 Rev.1)).

ERA

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, it is agreed that golimumab is not expected to pose a risk to the environment and that ERA studies are not considered needed in line with the EMA guideline (EMEA/CHMP/SWP/4447/00 Rev 1).

2.4.7. Conclusion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. No stand-alone non-clinical data was submitted, and no major objections or other concerns were identified from the non-clinical data.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product Simponi.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2: Tabular overview of clinical studies

Study Number	Main Study Objective	Study Design	Test products: Dosage, Regimen, Route of administration	Number of Participants Treated	Participants	Duration of Treatment	Primary and Main Secondary Endpoints
AVT05-GL-P01	To demonstrate the PK similarity of AVT05 *versus* US-Simponi and EU-Simponi and the PK of EU-Simponi with US-Simponi.	Multi-center, randomised, parallel group treatment, double-blind, 3-arm	**50 mg/0.5 mL PFS** • AVT05 • Simponi (EU-approved and US-licensed)	336 (including 33 Japanese participants)	Healthy adults	Single dose, follow-up to Day 75	1°: $AUC_{(0\text{-}inf)}$ and C_{max} 2°: Further PK parameters, safety, tolerability, immunogenicity
AVT05-GL-C01	To demonstrate comparative efficacy of AVT05 *versus* EU-Simponi	Multi-center, randomised, parallel group treatment, double-blind, 2-arm, equivalence design. Participants were randomised to AVT05 or EU-Simponi and received study treatment through Week 12. At Week 16, responders who had been assigned AVT05 continued to take AVT05 and responders who had been assigned to EU-Simponi were re-randomised (1:1) to receive AVT05 or EU-Simponi. Participants received study treatment q4w through Week 48. Non-responders were withdrawn from study treatment at Week 16 and followed for efficacy, safety, and immunogenicity until Week 24.	**50 mg/0.5 mL PFS** • AVT05 • Simponi (EU-approved)	502 participants with RA AVT05 group: 251 participants; EU-Simponi group: 251 participants At Week 16, EU-Simponi/ AVT05 group: 112 participants and EU-Simponi/ EU-Simponi group: 113 participants. AVT05/ AVT05 group: 223 participants.	Adults with moderate to severe RA in presence of MTX	Repeat dose 50 mg s.c. q4w up to Week 48 and a safety follow up visit at Week 52	1°: DAS28-CRP at Week 16 2°: Further efficacy parameters (ACR20/50/70, individual components of ACR, SDAI, CDAI, CRP), PK parameters, safety, tolerability, immunogenicity

Abbreviations: ACR : American College of Rheumatology; AUC0-inf: area under the serum concentration-time curve from time zero extrapolated to infinity; CDAI: Clinical Disease Activity Index; C_{max}: maximum serum concentration; CRP : C-reactive protein; DAS28-CRP: Disease Activity Score-28 for Rheumatoid Arthritis with C-reactive protein; DP: drug product; MTX: methotrexate; PFS: prefilled syringe; PK: pharmacokinetics; q4w: every 4 weeks; RA: rheumatoid arthritis; s.c.: subcutaneous; SDAI : Simplified Disease Activity Index for Rheumatoid Arthritis

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Comparative PK data of AVT05 has been generated in one pivotal PK similarity study in healthy adult subjects (study AVT05-GL-P01) following a single SC injection. Additionally, steady-state PK characteristics after repeat SC administration has been evaluated in a phase 3 confirmatory study in adult patients with moderate to severe RA (study AVT05-GL-C01).

Analytical methods

Quantification of golimumab concentration in human serum

MSD-ECL based immunocapture method was developed and validated for the quantification of golimumab (AVT05 and EU-Simponi) in both healthy individuals and those with RA. Method validation was conducted separately in healthy versus diseased serum with the main difference being MRD which was 1:10 for healthy serum and 1:30 for diseased serum. The comparability between the healthy and disease–state matrix was demonstrated in the validation of RA method, therefore calibration standard and QC samples were prepared in healthy volunteer serum in further validation tests and also in the AVT05-GL-C01 study with RA patients. Both methods demonstrated acceptable intra- and inter-run accuracy and precision. Specificity, selectivity and dilutional linearity were also found to be acceptable and no matrix interference nor hook effect was observed. In both studies, parallelism was tested with two study samples, both of which met the acceptance criteria and therefore no difference between spiked samples and real samples could be concluded. For HV serum, the long-term stability of AVT05 and Simponi-EU was demonstrated for 368 days at -20°C±5°C or at -75°C±15°C.

The analytical comparability of AVT05 and EU-Simponi in terms of precision, accuracy and selectivity was confirmed in healthy serum. However, demonstrating the analytical comparability of AVT05 and US-Simponi required two repeats of precision and accuracy runs. This is deemed acceptable, especially since the data from US-Simponi data serves only supportive evidence for biosimilarity demonstration. The appropriate analytical comparability of AVT05 batches used in method validation and clinical studies was successfully demonstrated. Overall, the assays used in the quantification of golimumab serum concentration were validated according to ICH M10 guideline and are considered acceptable.

The analysis of clinical samples was reliable within the given accuracy and precision ranges. The reasons for repeat analysis were acceptable and the required criteria for incurred method analysis was met.

Detection of Anti-Drug Antibodies in Human Serum

An ECL-based assay using affinity purified goat polyclonal antibodies against AVT05 as positive control was used for the detection of anti-drug antibodies. The assay was validated with AVT05, EU-Simponi and US-Simponi in healthy human serum and RA serum pre-study and in-run according to EMEA/CHMP/BMWP/14327/2006 Rev 1 Guideline on Immunogenicity assessment of therapeutic proteins. Same AVT05 batch was used in the validation and clinical studies. The assay was designed to allow 5% false positives in the screening stage and 1% in the confirmatory stage. No interference was observed in haemolysed or lipemic matrix and no Hook effect was observed up to 100 µg/ml. Methotrexate and the target, TNF-α, did not interfere with the assay. The drug tolerance was 10 µg/ml at 100 ng/ml ADA which is well above the drug concentrations in both clinical studies. Unfortunately, only short term stability at room temperature for 24 h and at 2-8 ºC for 20 days was demonstrated.

According to the applicant, stability of antibodies when stored at -60 to -80°C has been previously established for up to two years (Harlow and Lane, 1988 [12]; Michaut et al, 2014 [13]; Pihls et al, 2014 [14]). All samples were analysed within this time frame. The full validation report and bioanalytical reports for both clinical studies were provided.

Detection of neutralising antibodies in human serum

Detection of neutralising anti-drug antibodies was performed using a competitive ligand binding ECL assay. The assay format is a competitive/inverse format where samples without neutralising antibodies result in high signals and samples with high amounts of Nabs result in low signals. The assay was validated pre-study and in-run for the detection of NAbs against AVT05 and Simponi in serum of healthy participants as well as in serum of RA participant. The LPC1 (311 ng/ml) and LPC2 (500 ng/ml) positive control concentrations could not tolerate all three drugs at the concentration expected to be present in some of the study samples (10 µg/ml) in healthy matrix. All NAb samples (LPC2 = 500 ng/ml; LPC1 = 754 ng/ml; HPC = 5000 ng/ml) spiked with drug in matrix from RA patients could tolerate all tested drug concentrations (up to 20 µg/mL). No interference with MTX was observed in RA samples. No interference with the target, TNF-α, was observed in either matrix. Only short term stability at room temperature for 24 h and at 2-8 ºC for 20 days was demonstrated although the samples were stored up to 12 months. This can be accepted on the basis of the literature references. Full validation report and bioanalytical reports were provided.

PK similarity study in healthy adult subjects (study AVT05-GL-P01)

The study was a multicenter, randomised, double-blind, single-dose, parallel-group, 3-arm study. The study design is presented in Figure *1*. The study was conducted at 4 study sites in 3 countries: New Zealand (2 sites and 2 satellite sites), South Africa (1 site) and the United Kingdom (1 site) between 28 Dec 2022 and 03 Oct 2023. Two amendments were made to the study protocol before the start of the study. The amendment 4 was made after the study end (the 4th amendment was dated 01 Nov 2023). The only change in the 4th amendment related to the clinical PK was that the prespecified sensitivity PK similarity analysis using PK parameters adjusted by protein content was to be performed.

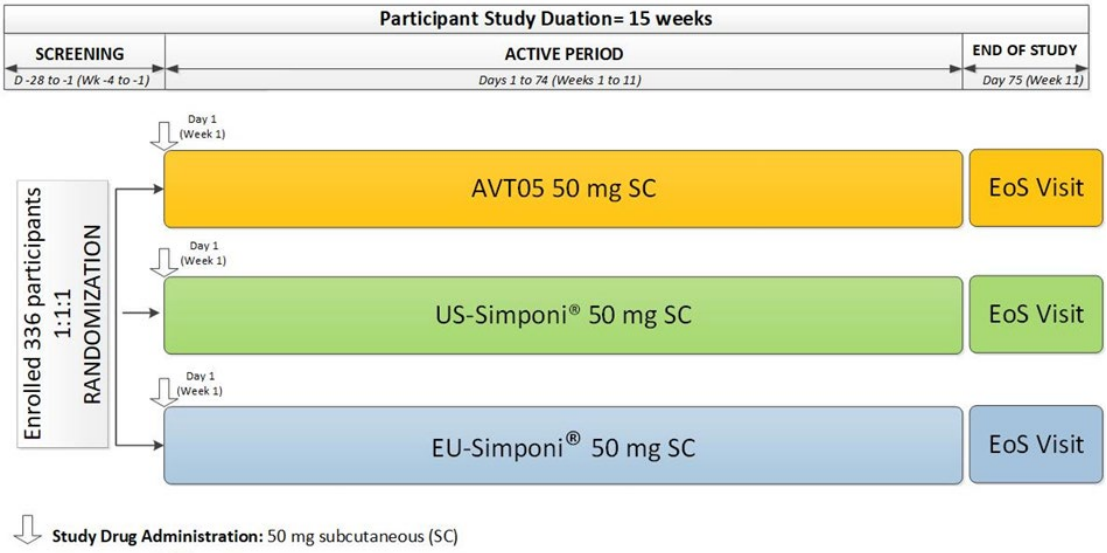


Figure 1: Schematic of study design (Study AVT05-GL-P01)

The primary objective was to demonstrate the PK similarity of AVT05 with US- and EU-Simponi and the PK of EU-Simponi with US-Simponi. Secondary objectives were to further characterise the PK and compare the safety, tolerability and immunogenicity of AVT05 with US-Simponi and EU-Simponi.

On Day 1, eligible participants were randomly assigned in a 1:1:1 ratio to receive a single dose of one of the following: AVT05 (Test product; T), US-licensed Simponi (Reference product; R), or EU-approved Simponi (Reference product; R). Randomisation was stratified by sex and by a three-level factor comprised of ethnicity and body weight at Day −1 as follows: Japanese, non-Japanese ≤80 kg, and non-Japanese >80 kg.

A total of 868 subjects consented to participate in the study, and 336 participants (115 in the AVT05 group, 111 in the EU-Simponi group, and 110 in the US-Simponi group) were enrolled and randomised; 33 participants (9.8%) were Japanese. Of the 336 randomised and dosed participants, 329 (97.9%) participants, including all 33 Japanese participants, completed the study up to Day 75. The primary reason for study discontinuation (4 of 7 participants) was withdrawal of consent.

Subjects received a single dose (50 mg/0.5 ml) SC in a supine or semi-supine position; the SC injection was administered in the abdomen (preferred site) or thigh (secondary site) of either AVT05, US-Simponi, or EU-Simponi on Day 1.

PK blood samples were collected at pre-dose, and at 8 h, 12 h, 24 h (=Day 2), 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 22, 29, 36, 43, 50, 57, 64, and 75 days after drug administration.

- The primary PK parameters: C_{max} and $AUC_{0\text{-}inf}$
- The secondary PK parameters:
  - Golimumab serum concentration-time profile following single-dose administration.
  - $AUC_{0\text{-}t}$, T_{max}, K_{el}, $t_{1/2}$, Vz/F, and CL/F.
  - Additional PK parameters:
    - R^2adj
    - $\%AUC_{extrap}$

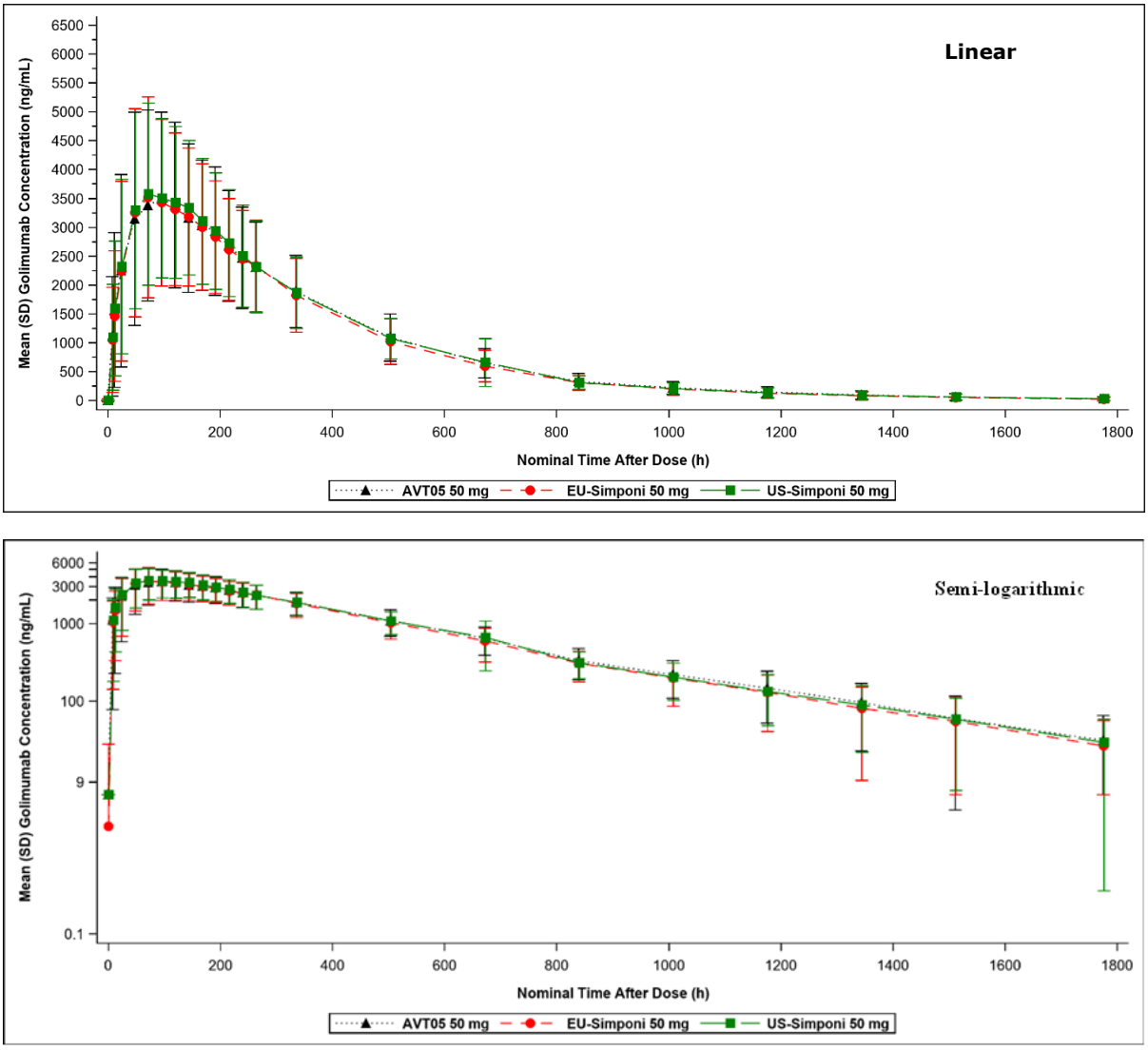
The ADA samples were collected at pre-dose, and at 9, 15, 29, 57, 64, and 75 days after drug administration.

PK similarity was assessed using the T to R ratio of the geometric least-squares (LS) means (T/R) and corresponding two-sided 90% CI for the primary PK parameters. The statistical model used to assess PK similarity was an analysis of covariance (ANCOVA) on the logarithmic scale (i.e., using natural log-transformed values of C_{max}, and $AUC_{0\text{-}inf}$) and included fixed effects for treatment, sex as factor and body weight at baseline as a continuous covariate. The primary analysis was conducted using the nominal protein content (50 mg) and nominal injection volume (0.5 mL). The analysis was repeated using the protein-adjusted parameters of C_{max} and $AUC_{0\text{-}inf}$ using the same ANCOVA model as performed on the non-adjusted PK parameters as a sensitivity analysis.

PK results

A total of 335 participants (99.7% of randomised participants) were included in the PK population. One participant was excluded before formal study unblinding, as the participant's PK profile suggested inadvertent vascular compromise during the SC administration procedure. In the PK population, the overall mean age of the participants was 28.6 years (age range, 18 to 54 years), and 57% were female and 43% were male. The overall mean weight of the participants was 67.40 kg, with 85.4% of participants weighing ≤80 kg. The mean BMI value was 23.98 kg/m^2. Of the 335 participants, the majority belonged to the following racial groups: Black or African American (37.3%), Caucasian/White (36.1%), and Asian (16.4%). The participants were predominantly of non-Japanese ethnicity (90.1%) and 9.9% were Japanese ethnicity.

In the PK population, following a single SC dose of 50 mg/0.5 mL, the mean serum golimumab concentration-time profiles for AVT05, EU-Simponi, and US-Simponi were comparable. All 3 profiles showed a slowly increasing absorption phase up to approximately 96 hours post-dose (Day 5), followed by a slowly declining phase (Figure *2*).



Abbreviations: SD: standard deviation. LLOQ: Lower limit of quantification (12.5 ng/mL). Serum concentrations below BLQ are set to 0.5 × LLOQ (12.5 ng/mL).

Figure 2: Mean (±SD) serum golimumab concentrations over time by treatment on linear and semi-logarithmic scales (Study AVT05-GL-P01, PK population)

The mean serum golimumab PK parameters in the AVT05 group were comparable with those in the EU-Simponi and US-Simponi (Table 3).

Table 3: Summary of serum golimumab PK parameters by treatment (Study AVT05-GL-P01, PK population)

Treatment	Median (Range)	Geometric Mean (Geometric CV%)						
	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-inf} (h·ng/mL)	AUC_{0-t} (h·ng/mL)	K_{el} (1/Day)	$t_{1/2}$ (h)	V_z/F (L)	CL/F (L/Day)
AVT05 (N = 114)	96.03 (24–334.18)	3453.8 (52%)	1423639 (38%)	1389335 (40%)	0.0757 (35.1%)	219.83 (35.1%)	11.14 (46.4%)	0.84 (37.7%)
EU-Simponi (N = 111)	95.75 (24–335.98)	3468.6 (50%)	1362263 (40%)	1344179 (40%)	0.0743 (29.9%)	223.80 (29.9%)	11.85 (43%)	0.88 (40.2%)
US-Simponi (N = 110)	96.00 (24–672)	3567.1 (51%)	1414744 (37%)	1399519 (37%)	0.0748 (33.3%)	222.45 (33.3%)	11.34 (46.2%)	0.85 (37%)

*AUC_{0-t}: Area under the concentration-curve from time zero to the last quantifiable concentration. AUC_{0inf}: Area under the concentration-curve from time zero extrapolated to infinite time. BLQ: below the limit of quantification; CL/F: Apparent Clearance. C_{max}: Maximum serum concentration. CV%: Coefficient of variation. Geometric CV%: calculated as gCV%: SQRT (Exp[s^2]-1) *100; where s is the standard deviation of the log-transformed values. K_{el}: Terminal elimination rate constant; PK: pharmacokinetics; $t_{1/2}$: Apparent terminal elimination half-life. T_{max}: Time of maximum serum concentration Vz/F: Apparent volume of distribution.*
N: Total number of participants in the relevant population. Serum concentrations that are BLQ will be designated a value of half LLOQ except for pre-dose that will be assigned zero.

The 90% CIs of the GMRs for both primary PK endpoints, C_{max} and AUC_{0-inf}, were contained within the prespecified margins of 80.00% and 125.00% for each of the 3 pairwise comparisons (i.e., AVT05 vs. US-Simponi, AVT05 vs. EU-Simponi, and EU-Simponi vs. US-Simponi (Table *4*).

Table 4: PK similarity assessment of primary serum golimumab PK parameters by treatment (Study AVT05-GL-P01, PK population)

		Test		Reference		Ratio of Geometric LS Means (%)	90% Confidence Interval for Ratio of LS Means	
Comparison (Test/Reference)	Parameter	n	Geometric LS Mean	n	Geometric LS Mean	Test/ Reference		
AVT05 50 mg / US-Simponi 50 mg	C_{max} (ng/mL)	114	3578.11	110	3661.66	97.72	**89.45**	**106.75**
	AUC_{0-inf} (h·ng/mL)	113	1455246.32	110	1438942.66	101.13	**94.35**	**108.40**
AVT05 50 mg / EU-Simponi 50 mg	C_{max} (ng/mL)	114	3578.11	111	3547.97	100.85	**92.33**	**110.15**
	AUC_{0-inf} (h·ng/mL)	113	1455246.32	110	1378869.21	105.54	**98.46**	**113.13**
EU-Simponi 50 mg / US-Simponi 50 mg	C_{max} (ng/mL)	111	3547.97	110	3661.66	96.90	**88.64**	**105.92**
	AUC_{0-inf} (h·ng/mL)	110	1378869.21	110	1438942.66	95.83	**89.36**	**102.76**

AUC_{0-inf}: Area under the concentration-curve from time zero extrapolated to infinite time; CL: Confidence Limit; C_{max}: Maximum serum concentration; LS: Least-Squares; n: Number of participants used in calculation.
The statistical model is an ANCOVA on the logarithmic scale (i.e., using natural log-transformed values of C_{max} and AUC_{0-inf}) and includes fixed effects for treatment, sex as factor and body weight at baseline as the continuous covariate. 90% confidence interval for ratio of LS mean is constructed from the one-sided lower 5% CL and one-sided upper 5% CL. PK similarity is determined if, for each pairwise comparison, the 90% confidence intervals for the ratios of geometric LS means are entirely contained with the PK similarity margin 80.00% to 125.00%.
*Values in **bold** text indicate that the PK similarity criteria were met.*

In the sensitivity analysis using protein-adjusted primary PK parameters all 90%CIs of the GMRs of C_{max} and AUC_{0-inf} were within the prespecified margins of 80.00%-125.00% for each of the 3 pairwise comparisons. In the PK similarity assessment performed for the AUC_{0-t} and protein-adjusted $AUC_{0-t,}$ the 90% CIs of the GMRs for the AUC_{0-t} were within the equivalence margin of 80.00%-125.00% in all treatment comparisons.

In the sub-group analyses based on randomisation strata (for the unadjusted and protein-adjusted exposure PK parameters) the 90% CIs of the GMRs of C_{max}, AUC_{0-t} and AUC_{0-inf} were within the prespecified margins of 80.00%-125.00% in the non-Japanese ≤ 80 kg for each of the 3 pairwise comparisons.

Clinical study in adult patients with moderate to severe RA (AVT05-GL-C01)

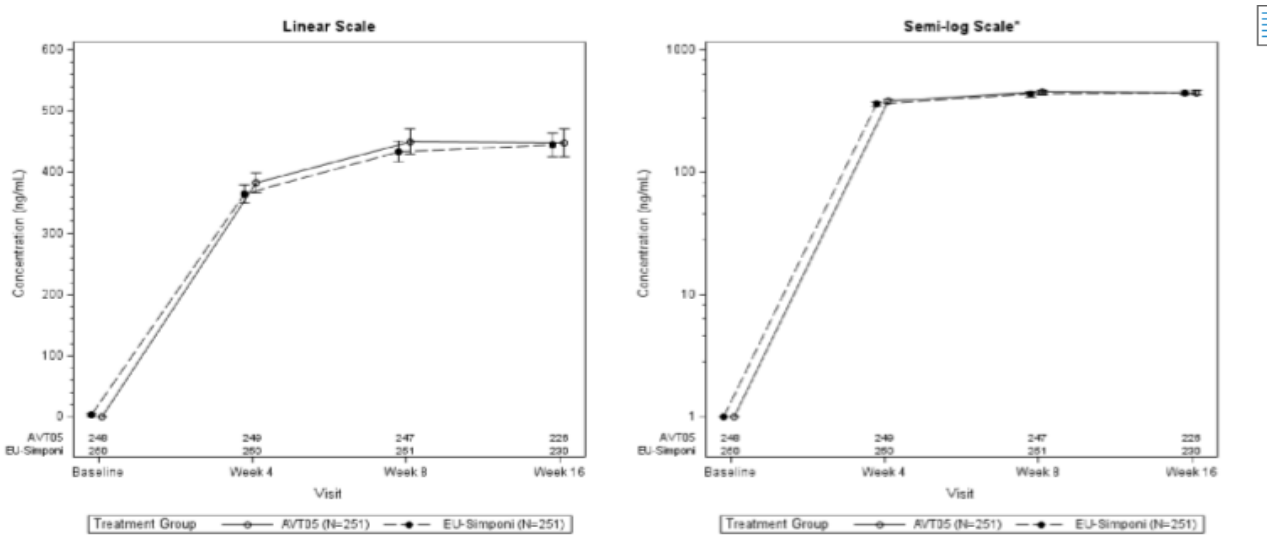
This study was a phase 3, multicenter, double-blind, randomised, parallel-group, active-control, 2-arm study to compare efficacy, safety, and immunogenicity between AVT05 and EU-Simponi in male and female participants with moderate to severe RA in presence of methotrexate.

The active period comprised 2 stages: On day 1, participants received AVT05 50 mg or EU-Simponi 50 mg SC every 4 weeks until week 12. At week 16, responders entered stage 2 and the responders who were initially randomised to receive AVT05 continued to receive AVT05 50 mg SC every 4 weeks until week 48 and the responders who were initially randomised to receive EU-Simponi were re-randomised and assigned in a 1:1 ratio to receive either AVT05 50 mg or EU-Simponi 50 mg SC every 4 weeks until week 48.

Comparison of steady-state PK of AVT05 and EU-Simponi was as a secondary objective. The blood samples for determination of serum trough concentrations of golimumab were collected at baseline, and after 4, 8, 16, and 24 weeks of drug administration.

PK results

Overall, mean serum trough PK concentration increased from Baseline to Week 4, with a further increase from Week 4 to Week 8, for both the AVT05 and EU-Simponi groups and then remained broadly stable at Week 16 (Figure *3* and Table *5*).



**All baseline summary statistics are assigned a nominal value to enable plotting values of 0 on the log scale.*

Figure 3: Mean (±SE) of serum trough PK concentrations vs time (safety analysis set- up to week 16)

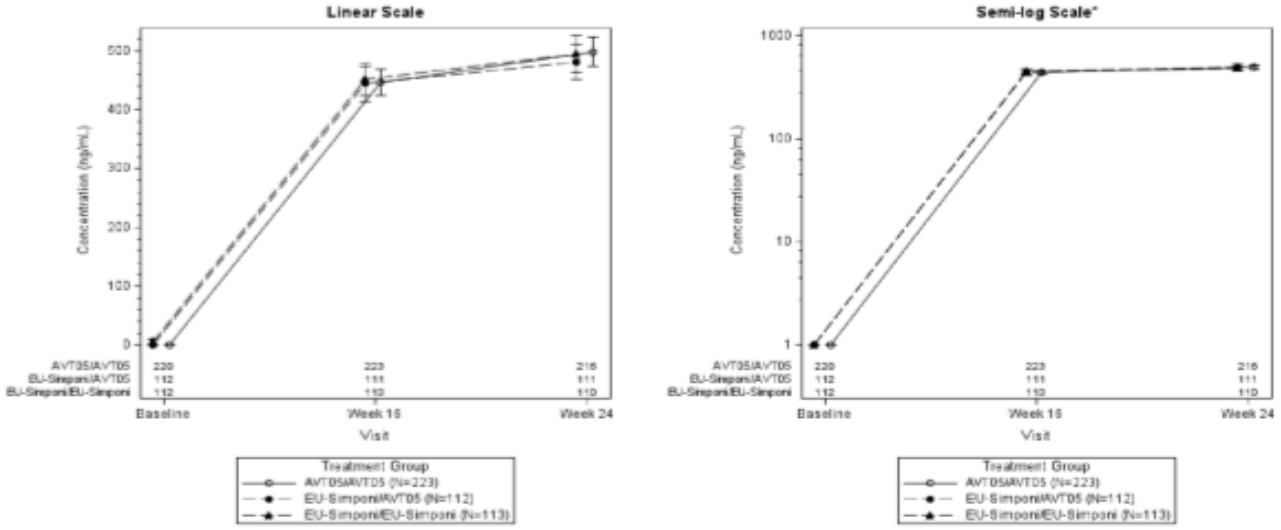
Table 5: Serum trough PK concentrations over time (Safety analysis set – up to Week 16)

	AVT05 Concentration (ng/mL) (N=251)						
Visit	**n**	**Mean (SD)**	**Median**	**Min, Max**	**CV%**	**GEOM**	**Log_SD**
Baseline	248	0.37 (4.164)	0.00	0.0, 49.6	1114.0	46.24	1.104
Week 4	249	382.57 (255.095)	348.00	18.8, 1440.0	66.7	297.80	2.189
Week 8	247	450.33 (318.794)	387.00	18.8, 1750.0	70.8	313.77	2.791
Week 16	226	448.10 (336.210)	400.50	18.8, 1750.0	75.0	294.98	3.053

	EU-Simponi Concentration (ng/mL) (N=251)						
Visit	**n**	**Mean (SD)**	**Median**	**Min, Max**	**CV%**	**GEOM**	**Log_SD**
Baseline	250	3.01 (41.857)	0.00	0.0, 655.0	1390.8	252.58	3.848
Week 4	250	364.21 (227.153)	316.50	18.8, 1120.0	62.4	284.82	2.219
Week 8	251	433.65 (273.013)	412.00	18.8, 1150.0	63.0	318.91	2.566
Week 16	230	444.98 (303.414)	404.00	18.8, 1430.0	68.2	307.93	2.855

*CV%: (SD/Mean) *100; GEOM: geometric mean; Log_SD: Standard Deviation (SD) of log-transformed data; NE: Not Evaluable.*
Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the patient receives the first dose of study drug (Day 1).
*Concentrations below the lower limit of quantification ('<LLOQ') measurable concentration are assigned a value of 0 for baseline values and a value of 0.5*LLOQ, where LLOQ:37.5 ng/mL, for post-baseline values.*

In the AVT05/AVT05, AVT05/EU-Simponi, and EU-Simponi/EU-Simponi groups, mean serum trough PK concentration increased from Baseline to Week 16 for all groups and increased again at Week 24 (Figure *4* and Table *6*).



Source: CSR AVT05-GL-C01 Figure 14.3.1.2, SE =standard error
**All baseline summary statistics are assigned a nominal value to enable plotting values of 0 on the log scale.*

Figure 4: Mean (±SE) of serum trough concentrations vs time – from week 16 to week 24 (study AVT05-GL-C01, safety analysis set)

Table 6: Serum trough PK concentrations over time (Safety analysis set – from Week 16 to Week 24)

	AVT05/AVT05 Concentration (ng/mL) (N=223)						
Visit	**n**	**Mean (SD)**	**Median**	**Min, Max**	**CV%**	**GEOM**	**Log_SD**
Baseline	220	0.23 (3.344)	0.00	0.0, 49.6	1483.2	49.60	NE
Week 16	223	445.98 (334.315)	400.00	18.8, 1750.0	75.0	295.70	3.013
Week 24	216	499.01 (366.531)	436.50	18.8, 1710.0	73.5	324.93	3.173
	AVT05/EU-Simponi Concentration (ng/mL) (N=112)						
Visit	**n**	**Mean (SD)**	**Median**	**Min, Max**	**CV%**	**GEOM**	**Log_SD**
Baseline	112	0.00 (0.000)	0.00	0.0, 0.0	NE	NE	NE
Week 16	111	444.68 (314.508)	401.00	18.8, 1430.0	70.7	307.16	2.825
Week 24	111	481.13 (312.716)	486.00	18.8, 1440.0	65.0	326.05	3.091
	EU-Simponi/EU-Simponi Concentration (ng/mL) (N=113)						
Visit	**n**	**Mean (SD)**	**Median**	**Min, Max**	**CV%**	**GEOM**	**Log_SD**
Baseline	112	5.85 (61.892)	0.00	0.0, 655.0	1058.3	655.00	NE
Week 16	113	451.46 (293.973)	429.00	18.8, 1280.0	65.1	315.28	2.866
Week 24	110	495.05 (321.790)	488.50	18.8, 1330.0	65.0	340.11	2.997

*CV%: (SD/Mean)*100; GEOM: geometric mean; Log_SD: Standard Deviation (SD) of log-transformed data; NE : Not Evaluable.*
Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the patient receives the first dose of study drug (Day 1).
*Concentrations below the lower limit of quantification ('<LLOQ') measurable concentration are assigned a value of 0 for baseline values and a value of 0.5*LLOQ, where LLOQ:37.5 ng/mL, for post-baseline values.*

2.5.2.2. Pharmacodynamics

Mechanism of action

Golimumab is a recombinant human IgG1κ monoclonal antibody (mAb) that prevents the binding of both forms of TNF-α (the soluble and transmembrane bioactive forms) to its receptors, thereby neutralising its activity.

High levels of TNF-α can be responsible for autoimmune inflammatory disease. TNF-α plays a crucial role in the pathogenesis of inflammatory diseases, such as RA, PsA, JIA, UC and AS.

Primary and secondary pharmacology

No separate *in vivo* pharmacodynamics studies were conducted with AVT05 and EU-Simponi. Validated PD markers do not exist for the efficacy of TNF-α inhibitors and therefore, no pharmacodynamic data were evaluated in the clinical studies.

2.5.3. Discussion on clinical pharmacology

The pharmacokinetics of AVT05 was investigated in two clinical studies (a pivotal PK study in healthy subjects including a subgroup of Japanese subjects [study AVT05-GL-P01] and a comparative clinical study in patients with moderate to severe RA [study AVT05-GL-C01]). In study AVT05-GL-P01, golimumab was administered as a single SC injection of 50 mg. In study AVT05-GL-C01, the dose was 50 mg every 4 weeks until week 12, and at week 16, responders entered stage 2 and received 50 mg SC every 4 weeks until week 48.

Bioanalytical methods

Validated ECL-based assays were used for determining golimumab concentrations, ADAs and NAbs in the clinical studies. Pre-study and in-run validations were mostly conducted according to current guidance. Only short term stability at room temperature for 24 h and at 2-8 ºC for 20 days was demonstrated for ADAs and NAbs. According to the applicant, stability of antibodies when stored at -60 to -80°C has been previously established for up to two years (Harlow and Lane, 1988; Michaut et al, 2014; Pihls et al, 2014). All samples were analysed within this time frame.

PK similarity study in healthy subjects (AVT05-GL-P01)

The study design and eligibility criteria were acceptable.

The demographic and baseline characteristics have been comparable across the treatment groups.

The CHMP has endorsed the selected dose of 50 mg SC injection, which is commonly used in most of the approved indications of golimumab (scientific advice).

All PFSs were weighted at pre-dose and post-dose and the administered injection volumes (ml) and actual protein contents administered (mg) were calculated. Based on the PFSs' weightings and calculations, the mean administered injection volumes of golimumab was slightly lower in the AVT05 group (0.517 ml) compared with the EU-Simponi (0.542 ml) and US-Simponi (0.532 ml) groups. The mean actual protein contents administered were in the AVT05 group 52.18 mg, in the EU-Simponi group 49.54 mg and in the US-Simponi group 50.38 mg. Consequently, the actual protein contents differed less than originally measured protein contents. In the documentation, the actual dose administered/ the injection volumes for two subjects in the EU-Simponi group have been reported to be 61.05 mg/0.67 ml and 154.95 mg/1.70 ml, respectively. In addition, the actual dose administered/the injection volume for another subject in the US-Simponi group have been reported to be 104.03 mg/1.10 ml. The applicant was asked to clarify the reason for the great actual doses/the injection volumes for those three subjects and discuss their effect on the clinical PK data. On the basis of the provided PK data in the response, it was concluded that the 3 participants have not received greater doses than anyone else and the reasons for the great actual doses/the injection volumes for those 3 subjects could have been a misread during the weighing process or a transcription error when transferring the data in CRF as suggested by the applicant. Hence, it was concluded that this had no impact on the clinical PK.

Only subjects without previous exposure to golimumab were to be included in the study, but a non-zero pre-dose concentration (266 ng/mL) was reported in one subject, which was not discussed by the applicant. However, as this was an isolated case, no impact on the study outcomes is expected. Almost all subjects' AUC0-t was more than 80% of the AUC0-inf, confirming that the PK sampling period was long enough. In the AVT05 group and in the US-Simponi group one subject had AUC0-t less than 80% of the AUC0-inf.

The overall PK profiles of AVT05, EU-Simponi and US-Simponi were very similar.

In the primary statistical analysis, the 90% CIs of the GMRs for the primary PK parameters, Cmax and AUC0-inf were within the equivalence margin of 80.00% and 125.00% (including 100%) for each of the 3 pairwise comparisons (i.e., AVT05 vs EU-Simponi, AVT05 vs US-Simponi and EU-Simponi vs US-Simponi) , thus demonstrating PK similarity between the test product AVT05 and the reference products, EU-Simponi and US-Simponi, as well as similarity between both reference products.

Also, the means of the secondary PK parameters (i.e., AUC0-t, t1/2, Kel, Vz/F and CL/F) and median Tmax were comparable between the study treatments.

In addition, a sensitivity analysis using protein-adjusted primary PK parameters was performed. Also in this analysis, all 90% CIs of the GMRs of Cmax and AUC0-inf, were within the prespecified margins of 80.00%-125.00% for each of the 3 pairwise comparisons.

The 90% CIs of the GMRS for the secondary PK parameter AUC0-t were also within the equivalence margins of 80.00-125.00% in all treatment comparisons.

The applicant performed additionally the subgroup analyses based on randomisation strata. These subgroup analyses were pre-specified in the SAP. In the non-Japanese ≤80 kg subgroup both unadjusted and protein-adjusted all 90% CIs of the GMRs of Cmax, AUC0-inf and AUC0-t, were within the prespecified margins of 80.00%-125.00% for each of the 3 pairwise comparisons. For the Japanese and Non-Japanese > 80 kg subgroups, the point estimates of the GMRs for the unadjusted and protein-adjusted exposure PK parameters were within the 80.00% to 125.00% margin, however, almost all 90%CIs for ratio of LSmeans of the exposure PK parameters were out of the bioequivalence range of 80.00% to 125.00%. The number of subjects in these two subgroups was small. In the Japanese subgroup, there were n=11/group and in the non-Japanese > 80 kg subgroup, n =18 in the AVT05 group and n = 16 in the EU-Simponi group and n = 14 in the US-Simponi group. Consequently, these subgroup analyses are probably underpowered for formal demonstration of PK similarity, and it is not any concern that the 90%CIs for the ratio of LSmeans of exposure PK parameters are not within the range of 80.00% to 125.00%, because in the primary PK analyses the PK biosimilarity has been demonstrated.

Thus, PK similarity between AVT05 and EU-Simponi and US-Simponi was demonstrated in the pivotal PK study AVT05-GL-P01.

Clinical study in adult patients with moderate to severe RA (AVT05-GL-C01)

The mean serum trough PK concentrations were similar level between AVT05 and EU-Simponi groups. The serum trough concentrations increased from baseline to week 8 for both groups. The serum trough concentrations were similar level at week 16 as at week 8. The interindividual variations in the serum trough concentrations at different weeks were great, however, at the same level between AVT05 and EU-Simponi groups.

The mean serum trough concentrations in the AVT05/AVT05, EU-Simponi/AVT05, and EU-Simponi/EU-Simponi groups were comparable from week 16 to week 24. The CV% of serum trough concentrations were large, however, at the same level in all studied treatment groups.

The serum trough concentrations data support the PK biosimilarity between AVT05 and EU-Simponi.

2.5.4. Conclusions on clinical pharmacology

The clinical PK data support the biosimilarity between AVT05 and EU-Simponi (and between AVT05 and US-Simponi).

2.5.5. Clinical efficacy

2.5.5.1. Dose response study

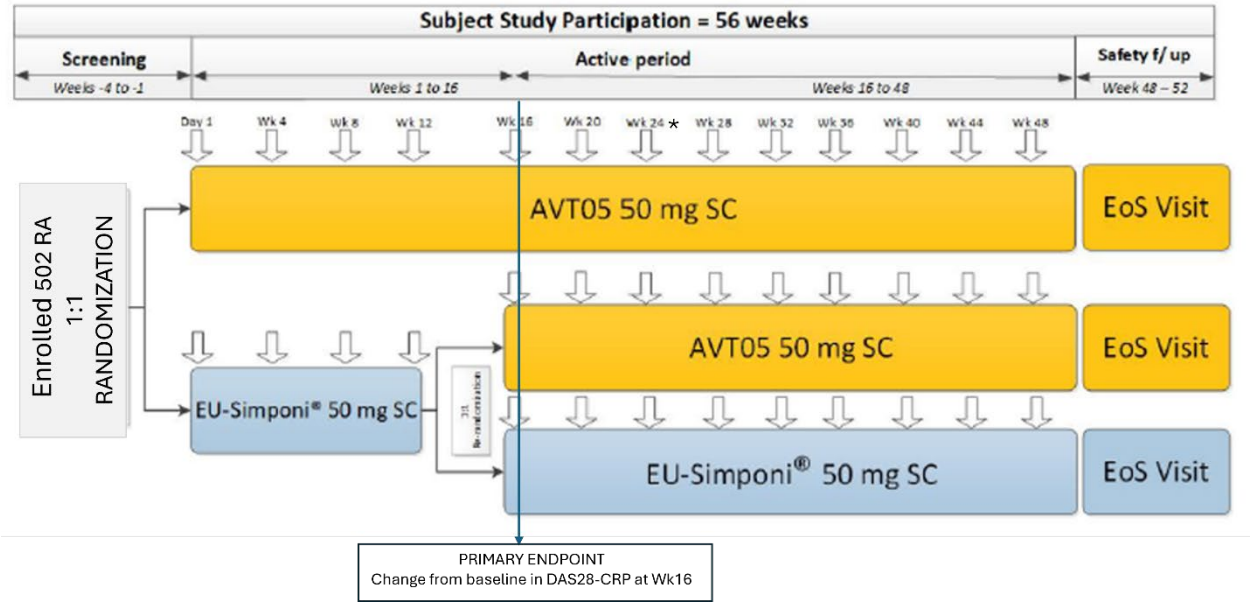
Not applicable.

2.5.5.2. Main study

Study AVT05-GL-C01

Methods

This was a multicenter, randomised, parallel group treatment, double-blind, 2-arm study to investigate the comparative efficacy, safety, and immunogenicity between subcutaneous AVT05 and EU Simponi in combination with methotrexate (MTX) in participants with moderate to severe RA.



DAS28-CRP: Disease Activity Score-28 for Rheumatoid Arthritis with C-reactive Protein; EoS: End of Study; EU-Simponi: EU- Simponi; f/up: Follow-up; IP: investigational product; RA: rheumatoid arthritis; S.C: subcutaneously; Wk: Week

Figure 5: Schematic Study Design of Study AVT05-GL-C01

- **Study participants**

Main inclusion criteria

- Male or female participants 18 to 75 years of age inclusive at the time of signing the ICF.
- Participants diagnosed with active RA according to American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 classification criteria for at least 4 months prior to Screening, and with a Clinical Disease Activity Index (CDAI) score >10.1 at Screening, who can give signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.
- Participants with moderately to severely active RA as defined by ≥6 swollen (out of 66) and ≥6 tender (out of 68) joint counts, C-reactive Protein (CRP) >1 mg/L, and who fulfill at least 1 of the following criteria at Screening:
    - Positive rheumatoid factor.
    - Positive anti-citrullinated peptide antibodies.
    - Evidence of 1 joint erosion on radiological assessment of the hands, wrist of the dominant hand, or feet at Screening.
- Participants must have taken MTX for ≥12 weeks, at a stable dose of ≥12.5 mg to 25 mg weekly in the last 4 weeks prior to Screening, and plan to remain on a stable dose throughout the study. Participants who are on a dose of MTX of ≥10 mg per week will be eligible if there is documented intolerance to further MTX dose escalation.

- Any concomitant non-steroidal anti-inflammatory drugs (NSAIDs) had to be stable for at least 2 weeks prior to Day 1.

Main exclusion criteria

Participants who met any one of the following criteria were ineligible for participation in the study:

- Prior treatment with biologicals or Janus kinase inhibitors that might have been used as disease-modifying antirheumatic drugs.
- Had any past or concurrent medical conditions that could have potentially increased the participant's risks or that could have interfered with the study evaluation, procedures, or study completion. Examples of these include medical history with evidence of clinically relevant pathology (e.g., uncontrolled diabetes, malignancies, or demyelinating disorders).
- RA with significant secondary involvement of any systemic organ (including, but not limited to vasculitis or pulmonary fibrosis) in the opinion of the Investigator.
- Major chronic inflammatory disease or connective tissue disease other than RA (e.g., gout, reactive arthritis, PsA, seronegative spondyloarthropathy, Lyme disease), or any active autoimmune disease (e.g., systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease, or any overlap syndrome) or diagnosis of juvenile idiopathic arthritis, and/or RA before the age of 16, or joint disease other than RA. Sjögren's syndrome secondary to RA was allowed if the diagnosis was clearly documented.

- **Treatments**

Stage 1: Participants received either AVT05 50 mg administered s.c on Day 1 followed by 50 mg every 4 weeks until Week 12 inclusive, or EU-Simponi 50 mg administered s.c on Day 1 followed by 50 mg every 4 weeks until Week 12 inclusive.

At Week 16:

- Non-responders (DAS28-CRP has decreased by ≤0.6 from baseline or disease activity DAS28-CRP >5.1) were withdrawn from study drug and followed for additional efficacy, safety, and immunogenicity assessments until Week 24.
- Responders (DAS28-CRP has decreased by >0.6 from baseline and disease activity DAS28-CRP ≤5.1) entered Stage 2 of the active period.

Stage 2: Responders who were initially randomised to receive AVT05 continued receiving AVT05 50 mg s.c every 4 weeks until Week 48.

Responders who were initially randomised to receive EU-Simponi were re-randomised in a 1:1 ratio to receive either:

- AVT05 50 mg administered s.c every 4 weeks until Week 48, or
- EU-Simponi 50 mg administered s.c every 4 weeks until Week 48.

All subjects were to remain on a stable dose of ≥12.5 mg to 25 mg MTX weekly. In case of documented intolerance to further MTX dose escalation a dose of MTX of ≥10 mg per week was acceptable.

- **Objectives**

The primary objective was to demonstrate comparative efficacy of AVT05 with EU-Simponi.

- **Outcomes/endpoints**

The primary efficacy endpoint was change from Baseline in DAS28-CRP up to Week 16.

Clinical similarity of the test product to the reference product was considered established if the 95% CI for least square mean difference in change from Baseline in DAS28-CRP up to Week 16 between test and reference groups was within the range [-0.6, 0.6].

The statistical justification of the margin was based on a meta-analysis of two placebo-controlled trials comparing golimumab+MTX vs. placebo+MTX in a comparable RA population (Table 7).

Table 7: Meta-analysis of RMP golimumab effect on DAS28 at Week 16

Reference	Variable	Placebo		Golimumab 50mg		Meta-analysis for difference of Golimumab - Placebo (95% CI)	Retention rate using a margin of [-0.6, 0.6]
		N	Mean (SD)	N	Mean (SD)		
Kay 2010[1]	CfB in DAS28-CRP*	35	-1.0 (1.00)	35	-2.0 (1.30)	-1.35 (-1.65, **-1.05**)	42.5%
Tanaka 2012[2]	CfB DAS28-ESR*	88	-0.43 (1.20)	86	-1.98 (1.25)		

* Since the minimum clinically meaningful difference of 0.6 is applicable for both DAS28-CRP and DAS28-ESR based on the EULAR criteria, both variables were used in the calculation.

[1] Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, Hsia EC, Han J, Wagner C, Xu Z, Visvanathan S, Rahman MU. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomised, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008 Apr;58(4):964-75. doi: 10.1002/art.23383. Erratum in: Arthritis Rheum. 2010 Nov;62(11):3518. PMID: 18383539.

[2] Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, et al; e patients with active rheumatoid arthritis: results of the GO-FORTH study. Ann Rheum Dis. 2012 Jun;71(6):817-24. doi: 10.1136/ard.2011.200317. Epub 2011 Nov 25. PMID: 22121129; PMCID: PMC3372319.

For the secondary endpoints, descriptive statistics of change and percent change from Baseline in DAS28-CRP and change from Baseline were provided by treatment group and study period for the FAS at Weeks 4, 8, 12, 16, and 24.

Change from Baseline in all individual ACR core components, SDAI, CDAI, and CRP were also summarised by treatment group and study period at the post-Baseline visits.

The percentages of participants achieving ACR 20, ACR 50 and ACR 70 at post-baseline visits were presented by treatment group and the difference in proportion between treatment group and associated 95% CI were provided for each study period based on the FAS. Data through the Week 24 database freeze is included in the clinical study report. Any participant with missing ACR20, ACR50 and ACR70 at any study week were treated as non-responders.

- **Sample size**

Approximately 400 evaluable participants were expected at Week 52 for safety assessments. Considering a 15% dropout rate during the entire study, approximately 472 participants needed to be randomly assigned at Baseline. Considering a non-evaluable rate of 5% up to Week 16, assuming a true difference of 0.1 and a standard deviation (SD) of 1.5 for change from Baseline in DAS28-CRP at Week 16, 448 participants would provide a power of 93.9% at a significance level of 0.025 (corresponding to a 95% CI) with a margin of [-0.6, 0.6].

- **Randomisation and blinding (masking)**

Randomisation was stratified by baseline DAS28-CRP score (≤5.1 and >5.1).

The study was blinded to participants, Investigators, and the Sponsor. Blinding was achieved using masking: a white semi-opaque blinding label applied to the syringe barrel which concealed syringe content and plunger stoppers during the storage, handling, and IP administration.

- **Statistical methods**

Planned analyses

The efficacy analyses were stated by the applicant to be done based on the Full Analysis Set (FAS), comprised of all randomised subjects who received at least 1 dose of study drug, and be consistent with intention-to-treat (ITT) principles. Actually, however, data for participants affected by specified intercurrent events were either not collected or were excluded from the analysis.

Analysis of the Primary Estimand

The primary endpoint was analysed based on the FAS according to randomised study treatment excluding participants' data at and after the occurrence of ICEs that can lead to attenuation of the difference between the treatment groups. The remaining data were analysed with a Mixed Model for Repeated Measures (MMRM) including treatment, visit, and treatment by visit interaction as fixed effects, and baseline DAS28-CRP as a continuous covariate. An unstructured covariance was used to model the within participant error and an adjustment to the degrees of freedom was made using the Kenward Roger's approximation. The LS mean estimates were provided for each treatment group for each study visit time points along with their SEs. The difference in LS means between the treatment groups and associated SE, 2-sided 95% CI (as required by the EMA) and 2-sided 90% CI (as required by the FDA) were provided for Week 16. If the 95% CI was completely contained within the clinical similarity margin of [-0.6, 0.6], comparative efficacy would have been demonstrated.

For the primary endpoint analysis, the missing data and data that were excluded due to ICEs were not imputed and were handled by MMRM under the assumption of MAR.

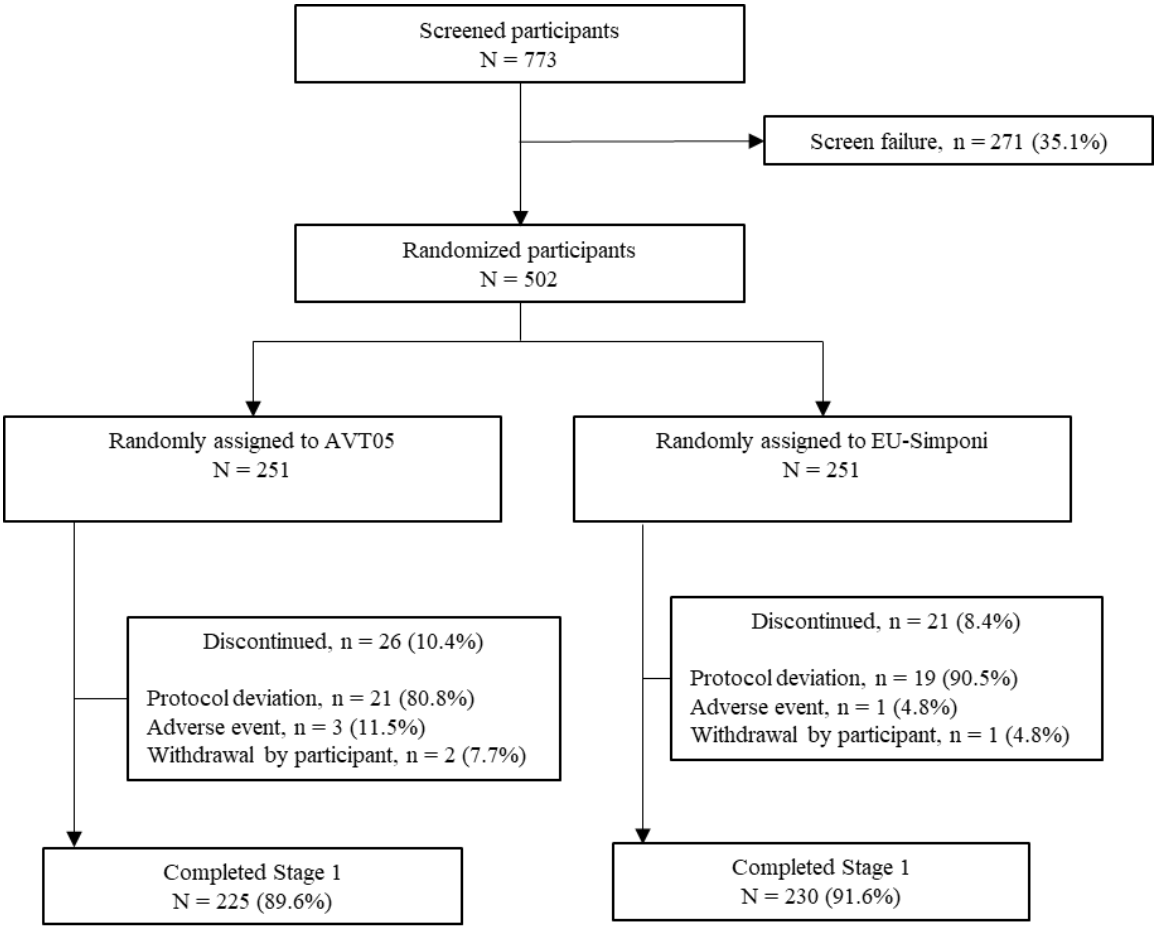
Planned subgroup analyses

Using the same MMRM as for the primary analysis, the 95% confidence intervals for the treatment difference in DAS28-CRP change from Baseline up to Week 16 were calculated separately for the subgroups defined below: Age group (<65 years, ≥65 years), Gender, Baseline DAS28-CRP score (≤ 5.1, >5.1) ADA status up to Week 16 (positive, negative), NAb status up to Week 16 (positive, negative).

Results

- **Participant flow**

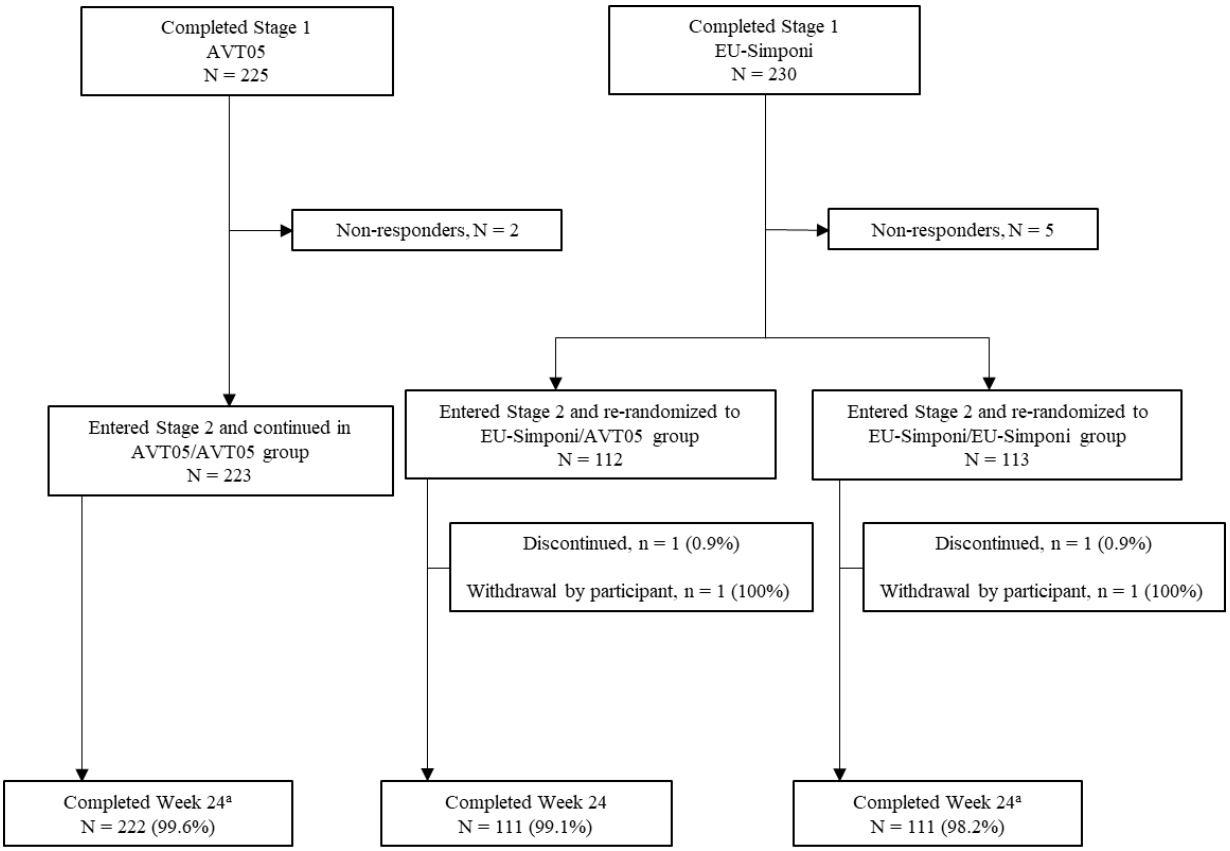
A total of 502 screened participants were randomly assigned to receive either AVT05 (251 participants) or EU-Simponi (251 participants).



Percentages are based on the number of participants in the FAS by treatment group.
Participants are counted only once in each row; however, a single participant may have more than 1 major or minor deviation reported across different categories.
This table includes protocol deviations reported during the screening process, prior to the first dose of IP.
Abbreviations: DAS28-CRP = Disease Activity Score-28 for Rheumatoid Arthritis with C-reactive Protein; FAS = Full Analysis Set; IP = investigational product.

Figure 6: Participant flow and Disposition of Participants in Study AVT05-GL-C01 up to Week 16

Of the 455 participants who completed Stage 1 (up to Week 16), 448 were responders and entered Stage 2. In total, there were 7 non-responders (2 [0.8%] participants in the AVT05 group and 5 [2.0%] participants in the EU-Simponi group) who did not enter Stage 2. A total of 444 participants completed up to Week 24.



[a] Participants who have not discontinued from the study or treatment, but without a Week 24 visit (n=2), are not included. One participant in the AVT05/AVT05 group did not attend the Week 24 visit due to an adverse event and 1 participant in the EU-Simponi/EU-Simponi group did not attend the Week 24 visit due to personal reasons.
Non-responders (DAS28-CRP at Week 16 decreased by ≤0.6 from Baseline or disease activity DAS28-CRP >5.1) were withdrawn from IP and followed for additional efficacy, safety, and immunogenicity assessments until Week 24.
In Stage 2, at Week 16, participants randomised to receive AVT05 50 mg SC continued to receive AVT05 50 mg SC every 4 weeks unless withdrawn. Participants randomised to EU-Simponi 50 mg SC were re-randomised in a 1:1 ratio to receive either AVT05 50 mg SC or EU-Simponi 50 mg SC every 4 weeks unless withdrawn.
Percentages for completed or discontinued are based on the number of participants in the stated analysis set by the treatment group.
Percentages for the primary reason for study discontinuation are based on participants who discontinued the study prior to Week 24.
EOS form could be completed later if the participant continued with safety follow-up.
Abbreviations: DAS28-CRP = Disease Activity Score-28 for Rheumatoid Arthritis with C-reactive Protein; EOS = End of Study; EU-Simponi = EU-approved Simponi®; SC = subcutaneous.

Figure 7: Participant flow and Disposition of Participants in Study AVT05-GL-C01 from Week 16 to Week 24

- **Recruitment**

Study Period:

Date of first participant screened: 30 Mar 2023

Date of first participant's first dose: 27Apr 2023

Date of last participant's Week 24 visit: 04 Mar 2024

Date of last participant's last visit – Week 52 (End of Study): Sept 2024

Reporting Period:

Date of database freeze for Week 24 analysis: 09 Apr 2024

Date of data cutoff: 04 Mar 2024

Initial database lock for final analysis: 29 Oct 2024. The study database was subsequently unlocked and re-locked on 20 Dec 2024 because discrepancies that required an update in the Clinical Trial Management System were identified, after reviewing the final protocol deviation log.

- **Conduct of the study**

Several protocol amendments were done after the start of recruitment but before unblinding of the results. Protocol amendments were clearly documented and justified by the applicant. All amendments were minor and not data driven.

The most common major protocol deviations observed up to Week 16 were related to invalid DAS28-CRP score at Baseline (39 [7.8%]) and study procedures (14 [2.8%]). Other major protocol deviations were very few. All deviations were balanced between treatment arms (Table *8*).

Table 8: Major Protocol Deviations (Full Analysis Set – Up to Week 16)

	AVT05 (N=251) n (%)	**EU-Simponi (N=251) n (%)**	**Overall (N=502) n (%)**
Participants Reporting Protocol Deviations	245 (97.6)	247 (98.4)	492 (98.0)
Major	37 (14.7)	33 (13.1)	70 (13.9)
Inclusion Criteria-Did not satisfy Entry Criteria	1 (0.4)	0	1 (0.2)
Incorrect Stratification	1 (0.4)	0	1 (0.2)
Invalid DAS28-CRP score at Baseline	20 (8.0)	19 (7.6)	39 (7.8)
Investigational Product-Wrong Treatment or Dose	5 (2.0)	4 (1.6)	9 (1.8)
Prohibited medication	1 (0.4)	0	1 (0.2)
Safety	0	1 (0.4)	1 (0.2)
Study Documentation	1 (0.4)	0	1 (0.2)
Study Procedures	6 (2.4)	8 (3.2)	14 (2.8)
Study Procedures-Dosing	1 (0.4)	0	1 (0.2)
Study Procedures-Lab Issues	1 (0.4)	2 (0.8)	3 (0.6)
Study Procedures-Randomisation	2 (0.8)	1 (0.4)	3 (0.6)
Subject Visits	4 (1.6)	1 (0.4)	5 (1.0)

Percentages are based on the number of participants in the Full Analysis Set by treatment group.
Participants are counted only once in each row; however, a single participant may have more than one major or minor deviation reported across different categories.
This table includes protocol deviations reported during the screening process, prior to first dose of study medication.

For 39 randomised participants at 11 sites the DAS28-CRP score, calculated at Baseline visit, was identified as invalid as it was calculated without Participant Assessment of Disease Activity VAS completion. These 39 participants were considered as non-evaluable for the primary endpoint analysis (due to an invalid Baseline DAS28-CRP score) and were therefore by protocol discontinued from the study.

- **Baseline data**

Table 9: Baseline Demographics (Full Analysis Set – Up to Week 16)

	AVT05 (N=251)	EU-Simponi (N=251)	Overall (N=502)
Age (years) at Informed Consent			
n	251	251	502
Mean (SD)	54.9 (10.99)	55.9 (11.12)	55.4 (11.06)
Median	56.0	57.0	57.0
Min, Max	23, 75	25, 75	23, 75
Age group, n (%)			
<65 years	201 (80.1)	186 (74.1)	387 (77.1)
≥65 years	50 (19.9)	65 (25.9)	115 (22.9)
Gender, n (%)			
Female	207 (82.5)	196 (78.1)	403 (80.3)
Male	44 (17.5)	55 (21.9)	99 (19.7)
Ethnicity, n (%)			
Hispanic or Latino	2 (0.8)	2 (0.8)	4 (0.8)
Not Hispanic or Latino	249 (99.2)	245 (97.6)	494 (98.4)
Not Reported	0	4 (1.6)	4 (0.8)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	250 (99.6)	251 (100.0)	501 (99.8)
Other	0	0	0
Multiple Race	1 (0.4)	0	1 (0.2)
Height (cm) at Screening			
n	251	251	502
Mean (SD)	165.75 (8.025)	165.86 (7.961)	165.80 (7.985)
Median	165.00	166.00	165.00
Min, Max	145.0, 188.0	148.0, 188.0	145.0, 188.0
Weight (kg) at Screening			
n	251	251	502
Mean (SD)	71.56 (13.200)	74.13 (12.619)	72.85 (12.964)
Median	69.60	74.00	71.90
Min, Max	50.0, 99.5	50.0, 101.0	50.0, 101.0
BMI (kg/m^2) at Screening			
n	251	251	502
Mean (SD)	25.96 (3.862)	26.86 (3.603)	26.41 (3.758)
Median	26.00	27.40	26.70
Min, Max	18.6, 32.0	18.7, 33.0	18.6, 33.0
Country, n (%)			
Bulgaria	6 (2.4)	11 (4.4)	17 (3.4)
Georgia	58 (23.1)	44 (17.5)	102 (20.3)
Poland	187 (74.5)	196 (78.1)	383 (76.3)

Min: minimum; Max: maximum; SD: Standard deviation.
Percentages are based on the number of participants in the Full Analysis Set by treatment group.
If more than one race category has been selected for a participant, these race categories are combined into a single category labeled "Multiple Race" in the summary table.

Table 10: Baseline Characteristics (Full Analysis Set – up to Week 16)

	AVT05 (N=251)	EU-Simponi (N=251)	Overall (N=502)
X-Ray Location			
Left Hand	162 (64.5)	163 (64.9)	325 (64.7)
Right Hand	195 (77.7)	198 (78.9)	393 (78.3)
Left Wrist	43 (17.1)	38 (15.1)	81 (16.1)
Right Wrist	50 (19.9)	48 (19.1)	98 (19.5)
Left Foot	29 (11.6)	35 (13.9)	64 (12.7)
Right Foot	29 (11.6)	43 (17.1)	72 (14.3)
Other	15 (6.0)	21 (8.4)	36 (7.2)
Swollen Joint Counts			
n	251	251	502
Mean (SD)	12.1 (5.51)	12.3 (5.26)	12.2 (5.38)
Median	10.0	11.0	11.0
Min, Max	3, 28	3, 26	3, 28
Tender Joint Counts			
n	251	251	502
Mean (SD)	15.3 (6.20)	15.1 (5.66)	15.2 (5.93)
Median	14.0	14.0	14.0
Min, Max	6, 28	6, 28	6, 28
C-Reactive Protein (CRP) (mg/L)			
n	251	251	502
Mean (SD)	13.60 (16.919)	11.26 (13.756)	12.43 (15.448)
Median	7.60	6.50	7.05
Min, Max	0.2, 90.3	0.3, 83.8	0.2, 90.3
DAS28-CRP Score at Baseline [1]			
n	231	232	463
Mean (SD)	5.86 (0.880)	5.81 (0.818)	5.84 (0.849)
Median	5.81	5.83	5.81
Min, Max	4.0, 8.1	3.8, 8.1	3.8, 8.1
DAS28-CRP Score Category at Baseline [1]			
≤5.1 n (%)	48 (19.1)	50 (19.9)	98 (19.5)
>5.1 n (%)	183 (72.9)	182 (72.5)	365 (72.7)
SDAI Score at Baseline			
n	243	250	493
Mean (SD)	42.97 (12.561)	42.90 (12.102)	42.93 (12.318)
Median	40.29	41.25	40.54
Min, Max	18.3, 72.5	18.6, 74.3	18.3, 74.3
CDAI Score at Baseline			
n	249	251	500
Mean (SD)	41.95 (12.584)	41.86 (11.919)	41.91 (12.243)
Median	39.00	39.50	39.50
Min, Max	18.0, 72.0	17.5, 72.5	17.5, 72.5
Months from Rheumatoid Arthritis Diagnosis to Informed Consent			
n	251	251	502
Mean (SD)	106.4 (84.35)	96.6 (83.80)	101.5 (84.13)
Median	87.0	76.0	82.0
Min, Max	6, 558	4, 508	4, 558
Covid-19 PCR Test			
Positive	0	0	0
Negative	249 (99.2)	249 (99.2)	498 (99.2)

ACR = American College of Rheumatology; CDAI: Clinical Disease Activity Index; DAS28-CRP = Disease Activity Score-28 using C-Reactive Protein; Min: minimum; Max: maximum; PCR = polymerase chain reaction; SD: Standard deviation SDAI = Simplified Disease Activity Index for Rheumatoid Arthritis.
Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the patient receives the first dose of study drug (Day 1).
Percentages are based on the number of participants in the Full Analysis Set by treatment group.

[1] *Subjects with an invalid assessment of disease activity visual analogue scale at baseline (n=39) are excluded from this summary.*

Demographic and disease characteristics from Week 16 to Week 24

Demographic characteristics were generally well balanced between groups in the FAS from Week 16 onward. Overall, the majority of participants were female (355 [79.2%]), White (447 [99.8%]), and not Hispanic or Latino (441 [98.4%]). The majority of participants were in the <65 years age group (344 [76.8%]) and the mean (SD) age at informed consent was 55.5 (11.03) years.

Overall, the majority of participants were in the >5.1 DAS28-CRP score category (353 [78.8%]), and the mean (SD) DAS28-CRP score at the Baseline was 5.83 (0.842). The mean (SD) swollen joint count was 12.1 (5.28) and the mean (SD) tender joint count was 15.0 (5.85). SDAI score ranged from 18.3 to 74.3 (mean [SD]: 42.54 [12.050]) and the CDAI score ranged from 18.0 to 72.5 (mean [SD]: 41.54 [11.990]).

- **Numbers analysed**

The number of participants who received injections up to week 16 is described in the Table 11.

Table 11: Drug Exposure and Compliance (Safety Analysis Set) – Up to Week 16

	AVT05 (N=251) n (%)	EU-Simponi (N=251) n (%)
Number of participants who received injections		
Baseline	251 (100.0)	251 (100.0)
Week 4	248 (98.8)	251 (100.0)
Week 8	239 (95.2)	240 (95.6)
Week 12	227 (90.4)	231 (92.0)

Overall, 44 (8.8%) participants had intercurrent events (ICEs) leading to the exclusion of data from the primary endpoint analysis. A majority of these ICEs were related to invalid DAS28-CRP score at Baseline, as described above in section "Conduct of the study".

Table 12: Intercurrent Events (ICEs) Leading to Exclusion of Data from the Primary Endpoint Analysis Full Analysis Set - Up to Week 16

Intercurrent Event	AVT05 (N=251) n (%)	EU-Simponi (N=251) n (%)
Patients with ICEs	25 (10.0)	19 (7.6)
Discontinuation from study drug prior to Week 16.	4 (1.6)	0
Prohibited concomitant medications prior to Week 16 that impact the primary endpoint.	0	0
Received treatment from incorrect treatment group prior to Week 16.	0	0
Protocol Deviations that Impact the Assessment of DAS28-CRP at Week 16.	0	0
Change in dose of concomitant medications prior to Week 16 that impact the primary endpoint.	1 (0.4)	0
Invalid baseline DAS28-CRP scores	20 (8.0)	19 (7.6)

- **Outcomes and estimation**

Primary endpoint

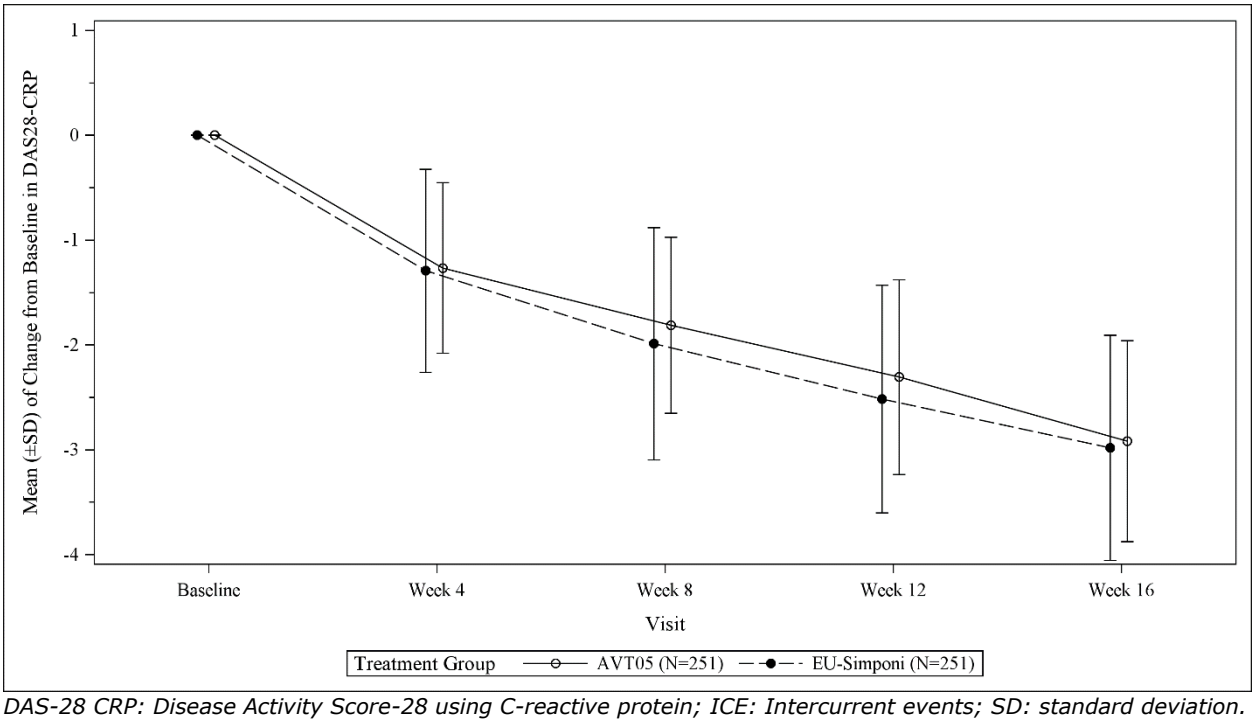
Table 13: Primary Analysis: Mixed Models for Repeated Measures (MMRM) of Change from Baseline in DAS28-CRP Score up to Week 16 Excluding Data Impacted by ICEs - Full Analysis Set - Up to Week 16

Time point	AVT05 (N=251)	EU-Simponi (N=251)
n	231	232
Week 16		
m	223	230
LS Mean (SE)	-2.89 (0.058)	-2.98 (0.058)
LS Mean Difference (SE) (AVT05 vs EU-Simponi)	0.09 (0.082)	
90% Confidence Interval	-0.05, 0.22	
95% Confidence Interval	-0.07, 0.25	

CI: Confidence Interval; DAS28-CRP: Disease Activity Score-28 using C-Reactive Protein; ICEs: Intercurrent events; LS: Least Squares; MMRM: SE: Standard Error
Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of study drug (Day 1).
Two-sided 90% and 95% CIs for the difference in least squares means between AVT05 and EU-Simponi groups are obtained from a MMRM including the treatment, visit, and treatment by visit interaction as fixed effects, and Baseline DAS28-CRP score as a continuous covariate.
An unstructured covariance structure is used to model the within participant error and an adjustment to the degrees of freedom is made using the Kenward Roger's approximation.
All missing data including actual missing DAS28-CRP and the data excluded due to ICEs are not imputed but are handled by MMRM under the assumption of missing at random (MAR).
n = number of participants with at least one non-missing change from Baseline in DAS28-CRP at Week 4, 8, 12 or 16.
m = number of participants with non-missing change from Baseline in DAS28-CRP at Week 16.
Clinical similarity of AVT05 and EU-Simponi will be established if the 95% and 90% CIs are contained within the respective equivalence margins of [-0.6, 0.6] for the EMA and [-0.6, 0.54] for the FDA.

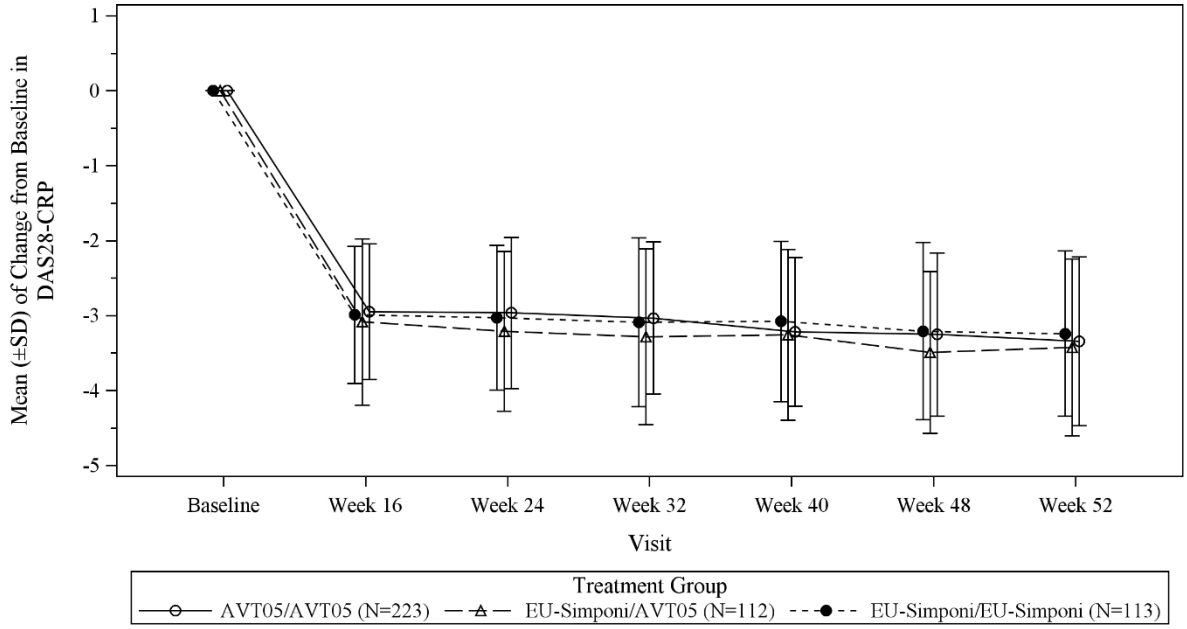
Secondary endpoints

Change from Baseline in DAS-28 CRP by visit



DAS-28 CRP: Disease Activity Score-28 using C-reactive protein; ICE: Intercurrent events; SD: standard deviation.
Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the patient receives the first dose of study drug (Day 1).
Patients with an invalid DAS28-CRP score at baseline (n=39) are excluded from this figure.

Figure 8: Mean (±SD) of Change from Baseline in DAS28-CRP Score by Visit Full Analysis Set Excluding Participants' Data at and after ICEs – Up to Week 16



DAS-28 CRP: Disease Activity Score-28 using C-reactive protein; SD: standard deviation.
Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of study drug (Day 1).
Participants with an invalid DAS28-CRP score at Baseline (n=39) are excluded from this figure.

Figure 9: Mean (SD) Change from Baseline in DAS-28 CRP by Visit (Full Analysis Set – From Week 16 to EoS)

Participants Achieving ACR20/50/70

Table 14: Percentage of Participants Achieving ACR20, ACR50 and ACR70 (Full Analysis Set – Up to Week 16)

Visit Treatment Parameter	m	n	p (%)	Difference (%) in Proportions (AVT05 vs EU-Simponi)	95% Confidence Interval
Week 4	-	-	-	-	-
AVT05 N=251	-	-	-	-	-
ACR20	240	113	47.1	4.8	-4.02, 13.64
ACR50	240	23	9.6	-0.6	-5.88, 4.72
ACR70	240	3	1.3	-0.8	-3.04, 1.47
EU-Simponi N=251	-	-	-	-	-
ACR20	246	104	42.3	-	-
ACR50	246	25	10.2	-	-
ACR70	246	5	2.0	-	-
Week 8	-	-	-	-	-
AVT05 N=251	-	-	-	-	-
ACR20	237	173	73.0	2.4	-5.65, 10.41
ACR50	237	68	28.7	4.6	-3.25, 12.47
ACR70	237	11	4.6	-3.1	-7.40, 1.17
EU-Simponi N=251	-	-	-	-	-
ACR20	245	173	70.6	-	-
ACR50	245	59	24.1	-	-
ACR70	245	19	7.8	-	-
Week 12	-	-	-	-	-
AVT05 N=251	-	-	-	-	-
ACR20	230	192	83.5	-1.1	-7.75, 5.61
ACR50	230	117	50.9	-0.2	-9.31, 8.90
ACR70	230	42	18.3	-1.5	-8.63, 5.66
EU-Simponi N=251	-	-	-	-	-
ACR20	233	197	84.5	-	-
ACR50	233	119	51.1	-	-
ACR70	233	46	19.7	-	-
Week 16	-	-	-	-	-
AVT05 N=251	-	-	-	-	-
ACR20	218	212	97.2	6.1	1.80, 10.39
ACR50	218	171	78.4	4.1	-3.78, 11.99
ACR70	218	88	40.4	-2.6	-11.72, 6.62
EU-Simponi N=251	-	-	-	-	-
ACR20	226	206	91.2	-	-

ACR50	226	168	74.3	-	-
ACR70	226	97	42.9	-	-

m = number of participants 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 participants achieving ACR20, ACR50 or ACR70 at time point; p = percentage of participants achieving ACR20, ACR50 or ACR70.
Participants with an invalid DAS28-CRP score at Baseline (n=39) are excluded from this table.
Abbreviations: ACR = American College of Rheumatology; DAS28-CRP = Disease Activity Score-28 using C-Reactive Protein; EU-Simponi = EU-approved Simponi.

Table 15: Percentage of Participants Achieving ACR20, ACR50, and ACR70 (Full Analysis Set – From Week 16 to EoS)

Visit Treatment Parameter	m	n	p (%)	Difference (%) in Proportions (Comparison)	95% Confidence Interval
Week 16	-	-	-	-	-
AVT05/AVT05 N=223 [1]	-	-	-	[1] versus [3]	-
ACR20	215	212	98.6	5.0	0.14, 9.79
ACR50	215	171	79.5	-0.5	-9.68, 8.75
ACR70	215	88	40.9	-2.7	-14.07, 8.66
EU-Simponi/AVT05 N=112 [2]	-	-	-	[1] versus [2]	-
ACR20	110	102	92.7	5.9	0.78, 10.98
ACR50	110	80	72.7	6.8	-3.11, 16.72
ACR70	110	49	44.5	-3.6	-14.99, 7.76
EU-Simponi/EU-Simponi N=113 [3]	-	-	-	[2] versus [3]	-
ACR20	110	103	93.6	-0.9	-7.57, 5.75
ACR50	110	88	80.0	-7.3	-18.46, 3.91
ACR70	110	48	43.6	0.9	-12.21, 14.03
Week 24	-	-	-	-	-
AVT05/AVT05 N=223 [1]	-	-	-	[1] versus [3]	-
ACR20	214	203	94.9	-0.5	-5.46, 4.43
ACR50	214	161	75.2	-2.5	-12.29, 7.20
ACR70	214	105	49.1	0.9	-10.64, 12.48
EU-Simponi/AVT05 N=112 [2]	-	-	-	[1] versus [2]	-
ACR20	108	104	96.3	-1.4	-6.07, 3.19
ACR50	108	84	77.8	-2.5	-12.29, 7.20
ACR70	108	48	44.4	4.6	-6.90, 16.14
EU-Simponi/EU-Simponi N=113 [3]	-	-	-	[2] versus [3]	-
ACR20	108	103	95.4	0.9	-4.40, 6.25
ACR50	108	84	77.8	0.0	-11.09, 11.09
ACR70	108	52	48.1	-3.7	-16.99, 9.59
Week 32	-	-	-	-	-
AVT05/AVT05 N=223 [1]	-	-	-	[1] versus [3]	-

ACR20	213	202	94.8	2.5	-3.39, 8.45
ACR50	213	172	80.8	-2.9	-11.77, 5.96
ACR70	213	94	44.1	-6.8	-18.53, 4.87
EU-Simponi/AVT05 N=112 [2]	-	-	-	[1] versus [2]	-
ACR20	106	98	92.5	2.4	-3.46, 8.22
ACR50	106	81	76.4	4.3	-5.33, 14.00
ACR70	106	52	49.1	-4.9	-16.55, 6.70
EU-Simponi/EU-Simponi N=113 [3]	-	-	-	[2] versus [3]	-
ACR20	104	96	92.3	0.1	-7.03, 7.32
ACR50	104	87	83.7	-7.2	-18.00, 3.52
ACR70	104	53	51.0	-1.9	-15.43, 11.62
Week 40	-	-	-	-	-
AVT05/AVT05 N=223 [1]	-	-	-	[1] versus [3]	-
ACR20	213	204	95.8	3.5	-2.32, 9.26
ACR50	213	165	77.5	1.5	-8.44, 11.45
ACR70	213	121	56.8	5.8	-5.84, 17.53
EU-Simponi/AVT05 N=112 [2]	-	-	-	[1] versus [2]	-
ACR20	104	98	94.2	1.5	-3.69, 6.78
ACR50	104	79	76.0	1.5	-8.44, 11.45
ACR70	104	58	55.8	1.0	-10.60, 12.67
EU-Simponi/EU-Simponi N=113 [3]	-	-	-	[2] versus [3]	-
ACR20	104	96	92.3	1.9	-4.88, 8.73
ACR50	104	79	76.0	0.0	-11.61, 11.61
ACR70	104	53	51.0	4.8	-8.74, 18.35
Week 48	-	-	-	-	-
AVT05/AVT05 N=223 [1]	-	-	-	[1] versus [3]	-
ACR20	209	197	94.3	3.3	-3.18, 9.69
ACR50	209	172	82.3	2.3	-7.10, 11.69
ACR70	209	122	58.4	-0.6	-12.36, 11.10
EU-Simponi/AVT05 N=112 [2]	-	-	-	[1] versus [2]	-
ACR20	105	101	96.2	-1.9	-6.76, 2.90
ACR50	105	86	81.9	0.4	-8.61, 9.39
ACR70	105	61	58.1	0.3	-11.29, 11.84
EU-Simponi/EU-Simponi N=113 [3]	-	-	-	[2] versus [3]	-
ACR20	100	91	91.0	5.2	-1.51, 11.89
ACR50	100	80	80.0	1.9	-8.85, 12.66
ACR70	100	59	59.0	-0.9	-14.40, 12.59
Week 52	-	-	-	-	-

AVT05/AVT05 N=223 [1]	-	-	-	[1] versus [3]	-
ACR20	207	198	95.7	3.6	-2.38, 9.53
ACR50	207	171	82.6	3.4	-6.05, 12.85
ACR70	207	135	65.2	-0.1	-11.45, 11.19
EU-Simponi/AVT05 N=112 [2]	-	-	-	[1] versus [2]	-
ACR20	102	97	95.1	0.6	-4.47, 5.58
ACR50	102	83	81.4	1.2	-7.92, 10.39
ACR70	102	63	61.8	3.5	-7.99, 14.90
EU-Simponi/EU-Simponi N=113 [3]	-	-	-	[2] versus [3]	-
ACR20	101	93	92.1	3.0	-3.71, 9.75
ACR50	101	80	79.2	2.2	-8.78, 13.11
ACR70	101	66	65.3	-3.6	-16.81, 9.65

m = number of participants 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 participants achieving ACR20, ACR50 or ACR70 at time point; p = percentage of participants achieving ACR20, ACR50 or ACR70.
Abbreviations: ACR = American College of Rheumatology; EU-Simponi = EU-approved Simponi.

Participant's Assessment of Disease Activity

Table 16: Change from Baseline in Participant Visual Analogue Scale Disease Activity (Full Analysis Set – Up to Week 16)

Time Point	**AVT05 (N=251)**		**EU-Simponi (N=251)**	
	Actual Value	**Change from Baseline**	**Actual Value**	**Change from Baseline**
Baseline	-	-	-	-
N	245	-	249	-
Mean (SD)	7.221 (1.7270)	-	6.941 (1.8347)	-
Median	7.470	-	7.120	-
Min, Max	0.02, 9.95	-	0.05, 9.98	-
Week 4	-	-	-	-
N	244	244	249	249
Mean (SD)	5.372 (2.2409)	-1.856 (2.1542)	5.477 (2.0161)	-1.464 (2.0142)
Median	5.570	-1.690	5.710	-1.420
Min, Max	0.03, 9.93	-8.21, 6.12	0.06, 9.69	-7.35, 4.69
Week 8	-	-	-	-
N	241	241	248	248
Mean (SD)	4.536 (2.1436)	-2.694 (2.3378)	4.422 (2.1204)	-2.522 (2.5731)
Median	4.630	-2.750	4.475	-2.720
Min, Max	0.03, 9.45	-8.28, 5.56	0.04, 8.95	-9.61, 6.23
Week 12	-	-	-	-
N	232	232	237	237

Mean (SD)	3.658 (2.3671)	-3.550 (2.5984)	3.494 (2.2139)	-3.424 (2.7375)
Median	3.390	-3.750	3.310	-3.810
Min, Max	0.04, 9.87	-9.83, 4.65	0.00, 8.96	-9.68, 5.57
Week 16	-	-	-	-
N	221	221	229	229
Mean (SD)	2.443 (1.7742)	-4.744 (2.2270)	2.418 (1.9527)	-4.482 (2.7084)
Median	2.090	-5.170	1.960	-5.020
Min, Max	0.05, 10.00	-9.85, 1.44	0.00, 9.01	-9.81, 6.10

Baseline is defined as the last non-missing value (either scheduled, unscheduled, or repeated) before the participant received the first dose of IP (Day 1).
Abbreviations: EU-Simponi = EU-approved Simponi; IP = investigational product; Max = maximum; Min = minimum; SD = standard deviation.

Simplified Disease Activity Index

Table 17: Change from Baseline in Simplified Disease Activity Index for Rheumatoid Arthritis (SDAI) Scores (Full Analysis Set - Up to Week 16)

Time Point	AVT05 (N=251)		EU-Simponi (N=251)	
	Actual Value	**Change from Baseline**	**Actual Value**	**Change from Baseline**
Baseline	-	-	-	-
n	243		250	-
Mean (SD)	42.97 (12.561)		42.90 (12.102)	-
Median	40.29		41.25	-
Min, Max	18.3, 72.5		18.6, 74.3	-
Week 4	-	-	-	-
n	232	229	224	224
Mean (SD)	29.03 (13.577)	-14.56 (10.291)	30.82 (12.735)	-12.34 (9.999)
Median	25.71	-12.54	28.66	-10.43
Min, Max	5.6, 71.2	-51.0, 10.9	7.1, 70.3	-55.3, 30.4
Week 8	-	-	-	-
n	208	205	193	193
Mean (SD)	22.94 (11.890)	-21.51 (10.777)	22.89 (11.601)	-20.75 (12.158)
Median	19.66	-20.22	20.07	-19.27
Min, Max	4.1, 64.1	-53.6, 4.6	4.0, 60.9	-64.0, 26.4
Week 12	-	-	-	-
n	165	163	149	149
Mean (SD)	18.95 (10.149)	-27.01 (11.997)	17.37 (9.016)	-26.54 (12.275)
Median	16.13	-26.32	15.15	-24.61
Min, Max	4.6, 56.2	-58.3, -1.5	5.1, 58.6	-59.5, 6.4
Week 16	-	-	-	-
n	106	105	110	110
Mean (SD)	13.71 (10.602)	-31.69 (13.481)	13.05 (8.332)	-30.29 (12.781)

Time Point	AVT05 (N=251)		EU-Simponi (N=251)	
	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Median	11.22	-30.46	11.22	-28.23
Min, Max	3.1, 94.1	-64.8, 26.8	3.1, 46.5	-60.6,3.3

Max: maximum; Min: minimum; SDAI: Simplified Disease Activity Index; SD: Standard deviation.
Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant received the first dose of IP (Day 1).

Clinical Disease Activity Index

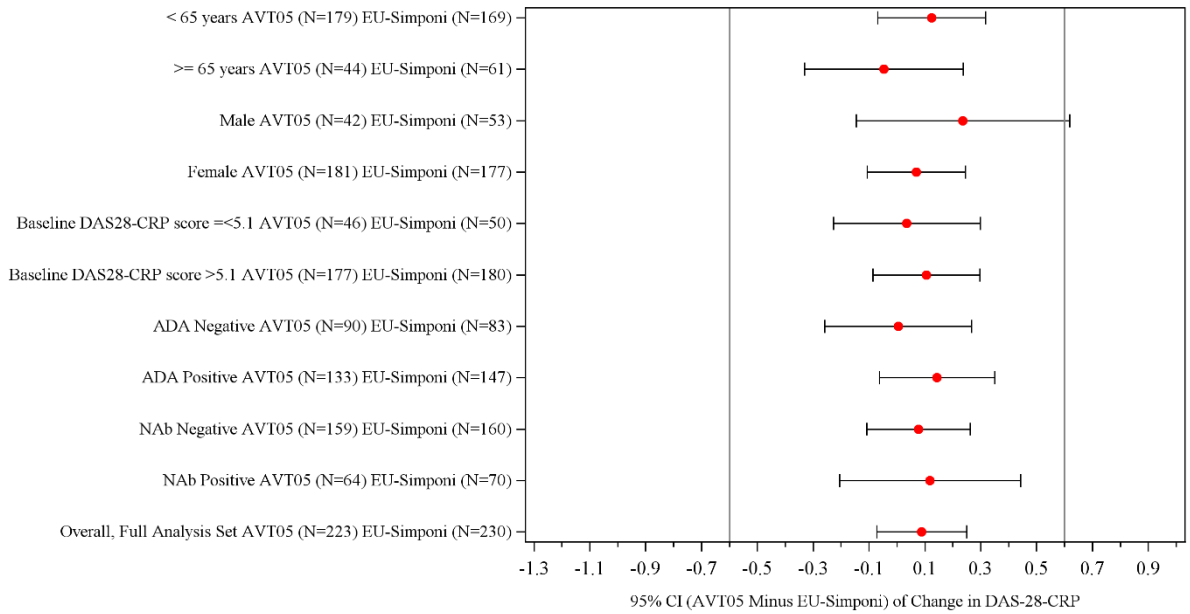
Table 18: Change from Baseline in Simplified Disease Activity Index for Rheumatoid Arthritis (SDAI) Scores (Full Analysis Set - Up to Week 16)

Time Point	AVT05 (N=251)		EU-Simponi (N=251)	
	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline	-	-	-	-
n	249		251	-
Mean (SD)	41.95 (12.584)		41.86 (11.919)	-
Median	39.00		39.50	-
Min, Max	18.0, 72.0		17.5, 72.5	-
Week 4	-	-	-	-
n	236	234	225	225
Mean (SD)	28.56 (13.615)	-14.06 (10.194)	30.17 (12.591)	-11.92 (10.064)
Median	25.00	-12.00	28.00	-10.00
Min, Max	5.5, 70.0	-54.5, 10.5	6.5, 70.0	-55.5, 30.0
Week 8	-	-	-	-
n	211	209	193	193
Mean (SD)	21.95 (11.500)	-21.14 (10.735)	22.07 (11.168)	-20.39 (11.891)
Median	19.00	-19.50	19.50	-19.00
Min, Max	4.5, 64.0	-51.5, 4.5	3.5, 60.5	-63.0, 26.0
Week 12	-	-	-	-
n	168	166	149	149
Mean (SD)	18.08 (9.682)	-26.64 (11.971)	16.39 (8.610)	-26.24 (12.077)
Median	15.50	-25.25	14.50	-24.00
Min, Max	4.5, 56.0	-58.5, -2.0	4.5, 58.0	-60.0, 6.0
Week 16	-	-	-	-
n	109	107	110	110
Mean (SD)	12.53 (8.632)	-31.54 (13.007)	12.20 (7.500)	-29.87 (12.390)
Median	10.00	-30.00	11.00	-27.50
Min, Max	3.0, 75.5	-64.5, 17.0	2.5, 39.5	-60.5, 0.5

CDAI: Clinical Disease Activity Index; Max: maximum; Min: minimum; SD: Standard deviation.
Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of study drug (Day 1).

- **Ancillary analyses**

Subgroup analyses



CI: Confidence Interval; DAS28-CRP: Disease Activity Score-28 using C-Reactive Protein; ICEs: Intercurrent events. Two-sided 95% CIs for the difference in least squares means between AVT05 and EU-Simponi groups are obtained from MMRM including the treatment, visit, and treatment by visit interaction as fixed effects, and Baseline DAS28-CRP score as a continuous covariate. An unstructured covariance structure is used to model the within participant error and an adjustment to the degrees of freedom is made using the Kenward Roger's approximation.
N = number of participants with non-missing change from Baseline in DAS28-CRP at Week 16.

Figure 10: Forest Plot of 95% CI of Change from Baseline in Disease Activity Score-28 using C-Reactive Protein (DAS28-CRP) Score at Week 16 Excluding Data Impacted by ICEs (Full Analysis Set – Up to Week 16)

Table 19: Mixed Models for Repeated Measures (MMRM) of Change from Baseline in DAS28-CRP Score up to Week 16 Excluding Data Impacted by ICEs by Anti-drug Antibody (ADA) Status (Positive, Negative)

ADA Positive

Time Point	AVT05 (N=138)	EU-Simponi (N=147)
n	*138*	*147*
Week 16		
m	*133*	*147*
LS Mean (SE)	*-2.86 (0.076)*	*-3.00 (0.072)*
LS Mean Difference (SE) (AVT05 vs EU-Simponi)	*0.14 (0.105)*	
90% Confidence Interval	*-0.03, 0.32*	
95% Confidence Interval	*-0.06, 0.35*	

ADA Negative

Time Point	AVT05 (N=93)	EU-Simponi (N=85)
n	*93*	*85*
Week 16		
m	*90*	*83*
LS Mean (SE)	*-2.95 (0.092)*	*-2.95 (0.096)*
LS Mean Difference (SE) (AVT05 vs EU-Simponi)	*0.00 (0.133)*	
90% Confidence Interval	*-0.22, 0.22*	
95% Confidence Interval	*-0.26, 0.27*	

ICEs = Intercurrent events; CI = Confidence Interval; LS = Least Squares; SE = Standard Error; DAS28-CRP = Disease Activity Score-28 using C-Reactive Protein.
Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the patient receives the first dose of study drug (Day 1).
Two-sided 90% and 95% CIs for the difference in least squares means between AVT05 and EU-Simponi groups are obtained from a MMRM including the treatment, visit, and treatment by visit interaction as fixed effects, and baseline DAS28-CRP score as a continuous covariate.
An unstructured covariance structure is used to model the within patient error and an adjustment to the degrees of freedom is made using the Kenward Roger's approximation.
All missing data including actual missing DAS28-CRP and the data excluded due to ICEs are not imputed but are handled by MMRM under the assumption of missing at random (MAR).
n = number of patients with at least one non-missing change from baseline in DAS28-CRP at Week 4, 8, 12 or 16.
m = number of patients with non-missing change from baseline in DAS28-CRP at Week 16.
ADA Positive if any positive ADA result observed before Week 16 dose; ADA Negative otherwise

- **Summary of main efficacy results**

The following table summarises 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 biosimilarity assessment (see later sections).

Table 20: Summary of efficacy for trial AVT05-GL-C01

Title: A Multicenter, Randomised, Parallel Group Treatment, Double-Blind, 2-arm Study to Investigate the Comparative Efficacy, Safety, and Immunogenicity Between Subcutaneous AVT05 and EU-approved Simponi in Combination with Methotrexate in Subjects with Moderate to Severe Rheumatoid Arthritis (ALVOFLEX)		
Study identifiers	Protocol Number: AVT05-GL-C01 EudraCT number: 2022-001825-63	
Design	Study AVT05-GL-C01 was a multicenter, double-blind, parallel-group, active-control, 2-arm randomised clinical study to compare the efficacy, safety, and immunogenicity between AVT05 and EU-approved Simponi (EU-Simponi) in combination with methotrexate in participants with moderate-to-severe rheumatoid arthritis. The study comprised 2 stages. Stage 1 started after 1:1 randomisation (Day 1) and lasted until Week 16. During Stage 1, participants received the investigational product every 4 weeks until Week 12, inclusive. At Week 16, responders entered Stage 2; non-responders were withdrawn from the study treatment and followed for efficacy, safety, and immunogenicity assessments until Week 24. At the initiation of Stage 2, responders who had been assigned AVT05 in Stage 1 continued to take AVT05 and responders who had been assigned to EU-Simponi were re-randomised (1:1) to receive AVT05 or EU-Simponi. In Stage 2, participants received the investigational product every 4 weeks until Week 48 (inclusive).	
	Duration of main phase:	48 weeks
Hypothesis	**Null Hypothesis**	**Alternative Hypothesis**
	For the EMA	
	H_{01}: $Mean_{AVT05}$ - $Mean_{EU\text{-}Simponi}$ ≤-0.6 or $Mean_{AVT05}$ - $Mean_{EU\text{-}Simponi}$ ≥0.6	H_{11}: -0.6< $Mean_{AVT05}$ - $Mean_{EU\ Simponi}$ <0.6
Notes	*DAS28-CRP = Disease Activity Score-28 for Rheumatoid Arthritis with C-reactive Protein; EMA = European Medicines Agency; EU-Simponi = EU-approved Simponi®; FDA = Food and Drug Administration.* *Note: $Mean_{AVT05}$ and $Mean_{EU\text{-}Simponi}$ denote the mean of the changes from Baseline in DAS28 CRP up to Week 16 in the AVT05 and EU-Simponi group, respectively.*	
Treatment groups	**AVT05**	AVT05 50 mg administered s.c. on Day 1 followed by 50 mg every 4 weeks until Week 12 N=251
	EU-Simponi	EU-Simponi 50 mg administered s.c. on Day 1 followed by 50 mg every 4 weeks until Week 12 N=251
	AVT05/AVT05 (At Week 16, participants who were initially randomised to receive AVT05 continued to receive AVT05)	AVT05 50 mg administered s.c. every 4 weeks until Week 24 N=223
	EU-Simponi/AVT05 (At Week 16, participants who were initially randomised to receive EU-Simponi were re-randomised to receive AVT05)	AVT05 50 mg administered s.c. every 4 weeks until Week 24 N=112
	EU-Simponi/EU-Simponi (At Week 16, participants who were initially randomised to receive EU-Simponi continued to receive EU-Simponi)	EU-Simponi 50 mg administered s.c. on Day 1 followed by 50 mg every 4 weeks until Week 24: N=113
Endpoints	**Endpoints**	**Description**

	Primary endpoint	Change from Baseline in DAS28-CRP at Week 16	The DAS28-CRP score is a composite measure derived from the tender joint count (28-joint assessment), swollen joint count (28 joint assessment), CRP level, and the participant's assessment of disease activity. The difference in LS means in DAS28-CRP between the treatment groups and the associated SE, 2-sided 95% CI (as required by the EMA) and 2-sided 90% CI (as required by the FDA) were analysed for Week 16 only. If the 95% CI was completely contained within the equivalence margin of [-0.6, 0.6] for the EMA, or if the 90% CI was completely contained within the equivalence margin of [-0.6, 0.54] for the FDA, comparative efficacy was demonstrated, respectively.
	Secondary endpoints	Change from Baseline in DAS28-CRP at Weeks 4, 8, 12, 24, 32, 40, 48, and 52.	Descriptive statistics of change from Baseline in DAS28-CRP were analysed by treatment group and study period for the full analysis set (FAS) at Weeks 4, 8, 12, 16, and 24.
		Percentage of participants achieving ACR20/50/70 at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 52 in comparison to Baseline	The percentages of participants achieving ACR 20, ACR 50, and ACR 70 at post-baseline visits were presented by treatment group and the difference in proportion between treatment group and associated 95% CI were analysed for each study period based on the FAS.
		Percent change in DAS28-CRP from Baseline at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 52.	Descriptive statistics of percent change from Baseline in DAS28-CRP were analysed by treatment group and study period for the FAS at Weeks 4, 8, 12, 16, and 24.
		Change from Baseline in all individual ACR core components (swollen joint count, tender joint count, Participant's Assessment of Pain, Participant's Assessment of Disease Activity, Physician's Assessment of Disease Activity, Participant's Assessment of Activity Level), SDAI, CDAI, and CRP at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 52.	Change from Baseline in all individual ACR core components, SDAI, CDAI, and CRP were also summarised and analysed by treatment group and study period at the post-Baseline visits.
Database freeze	09 Apr 2024		
Notes	*ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; FAS: Full analysis set; SDAI: Simplified Disease Activity Index for Rheumatoid Arthritis.*		
Results and Analyses			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Change from Baseline in DAS28-CRP at Week 16. Population: FAS Timepoint: Week 16		
	Treatment group	**AVT05**	**EU-Simponi**
		n=231	n=232

Descriptive statistics and estimate variability	Number of participants	m=223	m=230
	The LS mean change in DAS28-CRP from Baseline to Week 16	-2.89	-2.98
	Standard error	0.058	0.058
Effect estimates per comparison	The primary endpoint of change from baseline in DAS28-CRP score up to Week 16 was analysed using a mixed effects model for repeated measures (MMRM) including the treatment, visit, and treatment by visit interaction as fixed effects, and Baseline DAS28-CRP score as a continuous covariate.	**Comparison groups**	**AVT05 vs EU-Simponi**
		LS Mean Difference	0.09
		Standard Error	0.082
		90% Confidence Interval	-0.05, 0.22
		95% Confidence Interval	-0.07, 0.25
Notes	*CI: Confidence Interval; DAS28-CRP: Disease Activity Score-28 using C-Reactive Protein; ICEs: Intercurrent events; LS: Least Squares; MMRM: mixed effects model for repeated measures; SE: Standard Error* *Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of study drug (Day 1).* *Two-sided 90% and 95% CIs for the difference in least squares means between AVT05 and EU-Simponi groups are obtained from a MMRM including the treatment, visit, and treatment by visit interaction as fixed effects, and Baseline DAS28-CRP score as a continuous covariate.* *An unstructured covariance structure is used to model the within participant error and an adjustment to the degrees of freedom is made using the Kenward Roger's approximation.* *All missing data including actual missing DAS28-CRP and the data excluded due to ICEs are not imputed but are handled by MMRM under the assumption of missing at random (MAR).* *n = number of participants with at least one non-missing change from Baseline in DAS28-CRP at Week 4, 8, 12 or 16.* *m = number of participants with non-missing change from Baseline in DAS28-CRP at Week 16.* *Clinical similarity of AVT05 and EU-Simponi will be established if the 95% and 90% CIs are contained within the respective equivalence margins of [-0.6, 0.6] for the EMA and [-0.6, 0.54] for the FDA.*		
Analysis description	**Secondary Analyses**		
Analysis population and time point description	The secondary endpoint was change from Baseline in DAS28-CRP at Weeks 4, 8, 12, and 16. Population: FAS Timepoint: Up to Week 16		

Descriptive statistics and estimate variability	**Treatment group**	**AVT05**	**EU-Simponi**
	Number of subjects		
	Week 4	n=231	n=232
	Week 8	n=228	n=231
	Week 12	n=227	n=231
	Week 16	n=224	n=230
	Mean change from Baseline in DAS28-CRP (SE), by Visit		
	Week 4	-1.27 (0.815)	-1.29 (0.967)
	Week 8	-1.81 (0.838)	-1.99 (1.107)
	Week 12	-2.31 (0.930)	-2.52 (1.086)

	Week 16	-2.92 (0.958)	-2.98 (1.075)
Notes	*DAS28-CRP: Disease Activity Score-28 using C-Reactive Protein; Min: minimum; Max: maximum; SD: Standard deviation.* *Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of study drug (Day 1).* *Participants with an invalid DAS28-CRP score at Baseline (n=39) are excluded from this table.*		
Analysis population and time point description	The secondary endpoint was percent change in DAS28-CRP at Weeks 4, 8, 12, 16. Population: FAS Timepoint: Up to Week 16		
Descriptive statistics and estimate variability	**Treatment group**	**AVT05**	**EU-Simponi**
	Number of subjects		
	Week 4	n=231	N=232
	Week 8	n=228	N=231
	Week 12	n=227	N=231
	Week 16	n=224	N=230
	Mean percent change from Baseline in DAS28-CRP (SE), by visit		
	Week 4	-21.61 (13.764)	-22.02 (16.214)
	Week 8	-30.91 (13.388)	-33.92 (17.554)
	Week 12	-39.31 (14.877)	-43.09 (16.619)
	Week 16	-49.51 (13.293)	-50.88 (15.216)
Notes	. *DAS28-CRP: Disease Activity Score-28 using C-Reactive Protein; Min: minimum; Max: maximum; SD: Standard deviation.* *Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of study drug (Day 1).* *Participants with an invalid DAS28-CRP score at Baseline (n=39) are excluded from this table.*		
Analysis population and time point description	The secondary endpoint was percentage of participants achieving ACR20/50/70 at Weeks 4, 8, 12, 16, in comparison to Baseline Population: FAS Timepoint: Up to Week 16		

Descriptive statistics and estimate variability	**Visit** **Treatment** Parameter	**m**	**n**	**p (%)**	**Difference (%) in Proportions (AVT05 vs EU-Simponi)**	**95% Confidence Interval**
	Week 4					
	AVT05 N=251					
	ACR20	240	113	47.1	4.8	-4.02, 13.64
	ACR50	240	23	9.6	-0.6	-5.88, 4.72
	ACR70	240	3	1.3	-0.8	-3.04, 1.47
	EU-Simponi N=251	-	-	-	-	-
	ACR20	246	104	42.3	-	-
	ACR50	246	25	10.2	-	-
	ACR70	246	5	2.0	-	-
	Week 8	-	-	-	-	-
	AVT05 N=251	-	-	-	-	-

	ACR20	237	173	73.0	2.4	-5.65, 10.41
	ACR50	237	68	28.7	4.6	-3.25, 12.47
	ACR70	237	11	4.6	-3.1	-7.40, 1.17
	EU-Simponi N=251	-	-	-	-	-
	ACR20	245	173	70.6	-	-
	ACR50	245	59	24.1	-	-
	ACR70	245	19	7.8	-	-
	Week 12	-	-	-	-	-
	AVT05 N=251	-	-	-	-	-
	ACR20	230	192	83.5	-1.1	-7.75, 5.61
	ACR50	230	117	50.9	-0.2	-9.31, 8.90
	ACR70	230	42	18.3	-1.5	-8.63, 5.66
	EU-Simponi N=251	-	-	-	-	-
	ACR20	233	197	84.5	-	-
	ACR50	233	119	51.1	-	-
	ACR70	233	46	19.7	-	-
	Week 16	-	-	-	-	-
	AVT05 N=251	-	-	-	-	-
	ACR20	218	212	97.2	6.1	1.80, 10.39
	ACR50	218	171	78.4	4.1	-3.78, 11.99
	ACR70	218	88	40.4	-2.6	-11.72, 6.62
	EU-Simponi N=251	-	-	-	-	-
	ACR20	226	206	91.2	-	-
	ACR50	226	168	74.3	-	-
	ACR70	226	97	42.9	-	-
Notes	*m = number of participants 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 participants achieving ACR20, ACR50 or ACR70 at time point;* *p = percentage of participants achieving ACR20, ACR50 or ACR70.* *The ACR20/50/70 is a composite measure based on a 20%/50%/70% improvement in both of the number of tender and swollen joints and 3 of 5 criteria: Physician Assessment of Disease Activity, Participant Assessment of Disease Activity, Participant's Assessment of Activity Level, a pain scale, and CRP. ACR scores were calculated using the CRP value obtained at the corresponding visit.* *Participants with an invalid DAS28-CRP score at Baseline (n=39) are excluded from this table.*					

CSR#1: clinical study report #1 with data up to Week 24.
Final CSR: Final CSR will have the complete data up to Week 52 and be submitted during dossier review (D121 response).

2.5.5.3. Clinical studies in special populations

Not applicable.

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.5.5.6. Supportive study(ies)

Usability of the PFS and AI

The usability of the AVT05 delivery devices, PFS SD and AI, has been demonstrated by comparing the proposed devices and their uses with the existing, already marketed delivery devices. The applicant has performed failure modes and effects analyses (uFMEA) to identify the hazards, hazardous situations and potential harms associated with the use of AVT05 drug product during normal and abnormal use (including foreseeable misuse). In addition, the applicant conducted a threshold analysis to compare the user interfaces to identify and assess the potential impact of any differences that would affect task performance and user safety.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme comprised one phase III study (Study AVT05-GL-C01), a multicenter, randomised, double-blind, 2-arm study to investigate the comparative efficacy, safety, and immunogenicity between subcutaneous AVT05 and EU- Simponi in combination with methotrexate (MTX) in participants with moderate to severe rheumatoid arthritis (RA).

The design and objectives of the study are adequate for the similarity setting and in line with the EMA guideline on similar biological medicinal products (CHMP/437/04 Rev 1). Patients with moderate to severe active RA and an inadequate response to MTX are considered an appropriate population. Similar disease characteristics have been used as inclusion criteria in previous marketing authorisation applications for the RA indication.

Participants received either AVT05 50 mg s.c or EU-Simponi 50 mg s.c. The posology and dosing regimen is in line with the approved RA dosing regimen for Simponi. At Week 16, participants were evaluated for responder/non-responder status using DAS28-CRP. Responders were defined as having DAS28-CRP decreased by >0.6 from Baseline and disease activity DAS28-CRP ≤5.1. Non-responders were withdrawn from the investigational product (IP) and followed until Week 24. Responders in the AVT05 arm continued with the same treatment up to week 52, responders to EU-Simponi were re-randomised to receive either AVT05 or EU-Simponi.

The 52 weeks follow-up for responders is in line with the scientific advice received and the EMA Guideline on clinical investigation of medicinal products for the treatment of RA (CPMP/EWP/556/95 Rev. 2). The methods for efficacy assessment are validated, broadly used in RA studies, and also in agreement with the EMA Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis (CPMP/EWP/556/95 Rev. 2).

The primary efficacy endpoint was change from Baseline in DAS28-CRP up to Week 16. According to the EULAR response criteria, a change of 0.6 in DAS28-CRP score is considered to be the minimum clinically meaningful difference. Therefore, an equivalence margin of [-0.6, 0.6] was used. DAS28-CRP is a validated and commonly used disease activity score in RA trials. Being a continuous variable, DAS28-CRP is well suited to detect small differences, and the chosen equivalence margin is clinically justified and commonly used in similar trials.

By performing a meta-analysis across two published placebo-controlled trials of the RMP golimumab

(Kay 2010; Tanaka 2012), the equivalence margin was justified on statistical grounds: demonstrating equivalent efficacy using a margin of [-0.6, 0.6] would ensure that AVT05 has an absolute efficacy that corresponds to at least 40% of the efficacy of Simponi.

Treatment difference in mean DAS28-CRP at Week 16 was estimated using a conventional mixed-effects model repeated measures (MMRM) model fitted on a dataset that essentially reflects patients who were treated per protocol without deviations that might impact the primary outcome.

Efficacy data and additional analyses

Results

A total of 502 screened participants were randomly assigned to receive either AVT05 (251 participants) or EU-Simponi (251 participants). Randomisation was stratified by baseline DAS28-CRP score (≤5.1 and >5.1).

Of the 455 participants who completed Stage 1 (up to Week 16), 448 were responders and entered Stage 2. In total, there were only 7 non-responders (2 [0.8%] participants in the AVT05 group and 5 [2.0%] at week 16, when response was defined as having DAS28-CRP decreased by >0.6 from Baseline and disease activity DAS28-CRP ≤5.1.

The most common reason for discontinuation before W16 was protocol deviation. The most common major protocol deviation was related to invalid DAS28-CRP score at Baseline. Baseline DAS28-CRP score was deemed invalid by the sponsor in 39 participants from 11 sites.

According to the protocol, a subject was to be permanently discontinued from the study drug in case of a protocol deviation that may affect the primary endpoint analyses. Hence, while this statement could have been interpreted differently (e.g. clinical events that invalidate any subsequent measurements), the applicant's decision to withdraw these patients from treatment can be understood in light of the protocol text. From a scientific assessment perspective, alternative methods of analysis of data from the 39 patients with invalid baseline DAS28-CRP would have been preferable. However, as the invalid scores were evenly distributed between the study arms (20 (8.0%) and 19 (7.6%) patients in the AVT05 and EU-Simponi groups, respectively) the issue is not expected to have an impact on the outcome of the study and recalculation of DAS28-CRP results is not required: given that the affected patients were withdrawn from the study, the limited additional data could not change the results. As these irregularities were spread over 11 sites, no single site stands out as less competent or compliant with the protocol. These deviations did not have any impact on the clinical efficacy results of the study.

Otherwise, there were few intercurrent events or missing data, the results are statistically robust in this regard, and there is no apparent need for further sensitivity analyses.

Efficacy data and additional analyses:

The mean change in DAS28-CRP from Baseline to Week 16 was similar for the AVT05 and EU-Simponi groups (-2.89 [0.058] and -2.98 [0.058], respectively). The 95% CI for the mean difference was completely contained within the equivalence margin of [-0.6, 0.6]. Thus, the primary objective of the study was achieved.

The 95% confidence intervals for the assessed subgroups (by age, baseline DAS28-CRP score (≤5.1, >5.1), ADA Nab status and sex) were contained within the equivalence margin except for the subgroup of males for whom the confidence interval only marginally exceeded the equivalence boundaries. In conclusion, no important effects of demographic or disease characteristics were seen on the comparison between AVT05 and EU-Simponi.

No meaningful difference was seen between AVT05 and EU-Simponi up to week 16 in any of the secondary efficacy endpoints, nor between the three treatment arms (including patients who switched

from Simponi to AVT05) during Period 2 up to week 52. The outcome of all secondary efficacy endpoints are consistent and support similarity.

During assessment it was noticed that the initially reported ACR response rates in AVT05-GL-C01 were incorrect due to an issue in data collection. Upon the CHMP's request, the applicant identified the root cause to be a failure to use consistent units in the data collection system. The 1174 values affected by this issue were corrected programmatically by hard coding. Based on the corrected numbers, the ACR response rates are similar between treatment arms.

Given the unexpectedly high response rate in both treatment groups in this study (even after the correction discussed above, >90% achieved ACR20 at week 16 as compared to 60% achieving ACR20 at week 24 during treatment with the reference product in the GO-FORWARD study[1]) the applicant was requested to discuss the constancy assumption in relation to the historical studies. The applicant listed potential factors to explain this difference including improvements in the management of RA with early intervention, optimised use of the concomitant medication and better control of comorbidities, leading to less irreversible damage hence making the current population more responsive to effective therapeutical interventions. The applicant also provided data to show that improvements in therapeutic responses in contemporary clinical studies compared to historical studies conducted > 10 years ago can be observed across several therapeutic indications and in several other biosimilars. As no further uncertainties concerning the validity of the data remained, the proposed explanation was not further questioned.

The mean DAS28-CRP change from baseline was similar in ADA positive and ADA negative subjects with no meaningful difference between treatment arms throughout the study. To conclude, ADA formation does not seem to affect efficacy even though a significant effect of ADA on drug concentrations was seen (see section 2.5.8.7.).

GCP issues

Several issues regarding data handling arose during assessment.

a) Baseline DAS28-CRP score was deemed invalid by the sponsor in 39 participants from 11 sites. The patient assessment of global health status VAS (mm) was needed to calculate individual DAS28-CRP. For some patients, the actually collected item represented patient's global disease activity VAS from SDAI or CDAI instead of that from DAS28. In some instances, DAS28-CRP was calculated using rater's assessment instead of patient's assessment of global health. While these patients were excluded and this issue does not affect the conclusions on efficacy, the irregularities in data collection may reflect poor instructions on protocol requirements or lack of understanding by the site personnel or issues in the technical set-up. As these irregularities were spread over 11 sites, no single site stands out as less competent or compliant with the protocol. It rather reflects a lack of oversight by the sponsor.

b) The initially reported ACR response rates in AVT05-GL-C01 were incorrect: For some participants, 0-100 VAS was used while for others 0-10 VAS was used. More importantly, the scale was changed within participants from 0-100 to 0-10 during the study leading to inflated improvements. This issue was not noticed by the applicant. Upon request of the CHMP, the applicant identified the root cause to be a failure to use consistent units in the data collection system, whereafter the 1174 values affected by this issue were corrected programmatically by

[1] Keystone E, Genovese MC, Klareskog L et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Randomized Controlled Trial Ann Rheum Dis. 2010 Jun;69(6):1129-35.

hard coding. Based on the corrected numbers, the conclusions on clinical similarity remain unchanged.

c) Initially, there was an error in the formula used for calculation of the DAS28-CRP when using W15 CRP values. This error was noticed during assessment and corrected by the applicant upon CHMP's request. Re-examination of the data confirmed that the inaccurate values were not used to determine the responder/non-responder status and therefore, did not affect the outcome.

All issues were eventually resolved and the irregularities concerning data handling [high number of invalid baseline DAS-CRP values, wrong formula for DAS-CRP at Week 16 (with CRP at Week 15), programming error compromising ACR outcome] did not affect conclusions on clinical similarity.

Usability of the PFS and AI

The applicant has adequately identified the possible risks related to the use of the devices and compared the required user tasks, physical attributes and labeling (including IFU) of AVT05 devices with those of Simponi/AVT02 delivery devices. The IFU of the PFS and AI are considered adequately validated.

2.5.7. Conclusions on the clinical efficacy

Results from the clinical study in patients with RA support biosimilarity of AVT-05 with EU-Simponi.

2.5.8. Clinical safety

The safety of AVT05 was evaluated in two clinical studies, the Phase 1 study (AVT05-GL-P01) and the pivotal Phase 3 study (AVT05-GL-C01).

Safety analyses in the two clinical studies included treatment-emergent adverse events (TEAEs), which included all TEAEs, serious TEAEs, TEAEs leading to death, TEAEs leading to discontinuation of study treatment or withdrawal from the study, all TEAEs by severity, and treatment-related TEAEs. Attention was paid to treatment emergent AEs of special interest (TEAESIs), encompassing all relevant warnings and precautions from the Simponi product information, as well as injection site reactions (ISRs). In addition, routine laboratory safety parameters, vital sign and physical examination measurements, 12-lead electrocardiogram (ECG) results, and QuantiFERON Tuberculosis (TB) Gold test were analysed. The immunogenicity assessments included the detection of ADAs and nAbs to golimumab and their impact on safety and tolerability.

In the Phase 1 study, AEs were monitored throughout the study until the follow-up visit at day 75. The severity of the AEs was assessed by the investigator and assigned to the following categories:

- Mild: An AE that is easily tolerated by the participant, causes minimal discomfort, and does not interfere with everyday activities.
- Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- Severe: An AE that prevents normal everyday activities; treatment or other intervention usually needed.

In addition, clinically significant abnormalities in protocol-specified laboratory parameters were graded for severity according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and were recorded as AEs.

ISRs in the Phase 1 study were evaluated by the clinical staff at protocol-specified time points (on day 1 pre-dose and post-dose, on days 2, 3, 5, 9, 29 and on day 75 at EOS visit) and specific reactions of pain, tenderness, erythema/redness, and induration/swelling were graded for severity. Each ISR was categorised using the FDA Toxicity Grading Scale: Grade 0 (absent), Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), and Grade 4 (potentially life-threatening). If an injection site reaction was observed, it was to be characterised and documented as an AE and AESI by a physician.

In the Phase 3 study, AEs were monitored throughout the study and safety assessments were performed every 4 weeks during the site visits until the follow-up visit at week 52. The assessment of severity was made according to CTCAE v5.0 (Grades 1 to 5). If grading did not exist for a specific AE, the severity was assigned to the categories mild, moderate, or severe.

ISRs in the Phase 3 study were assessed by the investigator at day 1 (15 and 30 minutes, 1h, 2h and 4h post-dose) and 2 hours after each study drug administration thereafter, i.e. every 4 weeks until week 48. Any findings (e.g., pain/tenderness, erythema/redness, swelling/induration, pruritus/itching, hematoma/ecchymosis/bruising) were categorised by FDA Toxicity Grade and at least Grade 1 ISRs were to be reported as AEs. Grade 4 ISRs were to be reported as AESIs.

In both clinical studies, safety analysis was carried out using the safety population, which was defined as all randomised participants who received at least one dose of the study treatment, with treatment assignment based on the actual treatment received.

2.5.8.1. Patient exposure

In the Phase 1 study, 115 healthy adult participants received a single 50 mg/0.5 mL s.c. dose of AVT05, 111 participants received EU-Simponi, and 110 participants received US-Simponi.

The patient exposures in the Phase 3 study up to week 16 are shown in Table 21 and from week 16 to week 24 in Table 22.

Table 21: Drug Exposure Up to Week 16 (Last Dose Received at Week 12) (Study AVT05-GL-C01, Safety Analysis Set) (Study AVT05-GL-C01, Safety Analysis Set)

	AVT05 (N=251) n (%)	**EU-Simponi (N=251) n (%)**
Number of participants who received injections		
Baseline	251 (100.0)	251 (100.0)
Week 4	248 (98.8)	251 (100.0)
Week 8	239 (95.2)	240 (95.6)
Week 12	227 (90.4)	231 (92.0)

Table 22: Drug Exposure From Week 16 to Week EoS (Last Dose Received at Week 48) (Study AVT05-GL-C01, Safety Analysis Set)

	AVT05/AVT05 (N=223) n (%)	EU-Simponi/ AVT05 (N=112) n (%)	EU-Simponi/ EU-Simponi (N=113) n (%)
Number of participants who received injections			
Week 16	223 (100.0)	112 (100.0)	113 (100.0)
Week 20	217 (97.3)	110 (98.2)	110 (97.3)
Week 24	220 (98.7)	109 (97.3)	111 (98.2)
Week 28	222 (99.6)	106 (94.6)	108 (95.6)
Week 32	219 (98.2)	107 (95.5)	107 (94.7)
Week 36	220 (98.7)	106 (94.6)	109 (96.5)
Week 40	219 (98.2)	105 (93.8)	103 (91.2)
Week 44	219 (98.2)	107 (95.5)	105 (92.9)
Week 48	216 (96.9)	107 (95.5)	104 (92.0)

2.5.8.2. Adverse events

Phase 1 study (AVT05-GL-P01)

An overview of the TEAEs in the Phase 1 study is provided in Table *23*. The common TEAEs, i.e. TEAEs occurring in ≥1% of subjects is provided in Table *24*.

Table 23: Overview of TEAEs (Study AVT05-GL-P01, Safety Population)

Category	Statistic	AVT05 (N=115)	EU-Simponi (N=111)	US-Simponi (N=110)	Overall (N=336)
All Participants					
	N	**115**	**111**	**110**	**336**
At least one TEAE	n (%) E	76 (66.1) 163	75 (67.6) 162	75 (68.2) 189	226 (67.3) 514
At least one IP-related TEAE	n (%) E	32 (27.8) 43	40 (36.0) 53	33 (30.0) 45	105 (31.3) 141
At least one TEAE of special interest	n (%) E	7 (6.1) 8	12 (10.8) 17	7 (6.4) 9	26 (7.7) 34
At least one IP-related TEAE of special interest	n (%) E	6 (5.2) 6	12 (10.8) 14	7 (6.4) 8	25 (7.4) 28
At least one TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	10 (8.7) 12	11 (9.9) 12	9 (8.2) 10	30 (8.9) 34
At least one IP-related TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	2 (1.7) 3	4 (3.6) 5	5 (4.5) 5	11 (3.3) 13
At least one local administration site reaction	n (%) E	7 (6.1) 8	12 (10.8) 17	6 (5.5) 7	25 (7.4) 32
At least one serious TEAE	n (%) E	1 (0.9) 1	1 (0.9) 1	0	2 (0.6) 2
At least one serious IP-related TEAE	n (%) E	-	-	-	-
Any TEAE leading to death	n (%)	-	-	-	-
Any TEAE leading to discontinuation from the study	n (%)	-	-	-	-
At least one TEAE by severity[a]					
Mild	n (%)	70 (60.9)	71 (64.0)	71 (64.5)	212 (63.1)
Moderate	n (%)	15 (13.0)	11 (9.9)	14 (12.7)	40 (11.9)
Severe	n (%)	1 (0.9)	1 (0.9)	2 (1.8)	4 (1.2)
At least one IP-related TEAE by severity[a]					
Mild	n (%)	30 (26.1)	35 (31.5)	32 (29.1)	97 (28.9)
Moderate	n (%)	3 (2.6)	5 (4.5)	3 (2.7)	11 (3.3)
Severe	n (%)	0	0	1 (0.9)	1 (0.3)
At least one TEAE of special interest by severity[a]					
Mild	n (%)	7 (6.1)	12 (10.8)	6 (5.5)	25 (7.4)

Moderate	n (%)	0	0	0	0
Severe	n (%)	0	0	1 (0.9)	1 (0.3)
At least one IP-related TEAE of special interest by severity					
Mild	n (%)	6 (5.2)	12 (10.8)	6 (5.5)	24 (7.1)
Moderate	n (%)	-	-	-	-
Severe	n (%)	-	-	1 (0.9)	1 (0.3)
At least one local administration site reaction by severity					
Mild	n (%)	7 (6.1)	12 (10.8)	6 (5.5)	25 (7.4)
Moderate	n (%)	-	-	-	-
Severe	n (%)	-	-	-	-

AE: adverse event; CTCAE: Common Terminology Criteria for AE; IP: Investigational product; n: Number of participants with at least one TEAE in each category (participants with multiple events in each category are counted only once in each category); N: Total number of participants in the relevant population; E: Number of TEAEs in each category; TEAE: treatment-emergent AE; %: Percentage of participants in each category calculated relative to the total number of participants in the relevant population.
A TEAE is defined as any AE which commenced or worsen in severity on or after the start of IP administration. A related TEAE is defined as any TEAE reported as related to study drug and included events with a missing relationship. A serious TEAE is defined as any TEAE for which 'Serious event' is indicated as 'Yes'. A TEAE of special interest is defined as any AE considered to be of special interest per protocol. A local administration site reaction is defined as any AE for which the high-level group term is coded to 'Administration site reactions' and considered to be of special interest per protocol. AEs with missing severity were classified as 'severe'.
a For the summary of TEAEs by severity, participants could appear in each category. Participants are only counted once in each severity category

Four participants experienced severe TEAEs, 1 in the AVT05 group (syncope), 1 in the EU-Simponi group (vomiting) and 2 in the US-Simponi group (rash macular and hemorrhoids).

Table 24: Incidence of TEAEs Occurring in ≥1% of Participants in Any treatment Group by SOC and PT (AVT05-GL-P01, Safety Population)

System Organ Class Preferred Term	Statistic	AVT05 (N=115)	EU-Simponi (N=111)	US-Simponi (N=110)	Overall (N=336)
At least one TEAE	n (%) E	76 (66.1) 163	75 (67.6) 162	75 (68.2) 189	226 (67.3) 514
Infections and infestations	n (%) E	25 (21.7) 34	33 (29.7) 39	37 (33.6) 43	95 (28.3) 116
Upper respiratory tract infection	n (%) E	9 (7.8) 11	13 (11.7) 13	14 (12.7) 15	36 (10.7) 39
Influenza	n (%) E	6 (5.2) 6	5 (4.5) 6	7 (6.4) 7	18 (5.4) 19
COVID-19	n (%) E	5 (4.3) 5	4 (3.6) 4	5 (4.5) 5	14 (4.2) 14
Gastroenteritis	n (%) E	2 (1.7) 2	2 (1.8) 2	2 (1.8) 2	6 (1.8) 6
Nasopharyngitis	n (%) E	2 (1.7) 2	2 (1.8) 2	1 (0.9) 1	5 (1.5) 5
Urinary tract infection	n (%) E	2 (1.7) 2	-	2 (1.8) 2	4 (1.2) 4
Rhinitis	n (%) E	-	2 (1.8) 2	1 (0.9) 1	3 (0.9) 3
Viral upper respiratory tract infection	n (%) E	2 (1.7) 2	-	1 (0.9) 1	3 (0.9) 3
Nervous system disorders	n (%) E	23 (20.0) 27	18 (16.2) 19	26 (23.6) 34	67 (19.9) 80
Headache	n (%) E	20 (17.4) 23	13 (11.7) 14	20 (18.2) 26	53 (15.8) 63
Dizziness	n (%) E	1 (0.9) 1	3 (2.7) 3	1 (0.9) 1	5 (1.5) 5
Migraine	n (%) E	-	1 (0.9) 1	3 (2.7) 3	4 (1.2) 4
General disorders and administration site conditions	n (%) E	18 (15.7) 23	24 (21.6) 33	19 (17.3) 21	61 (18.2) 77
Influenza like illness	n (%) E	5 (4.3) 6	4 (3.6) 4	7 (6.4) 7	16 (4.8) 17
Injection site erythema	n (%) E	5 (4.3) 5	5 (4.5) 5	4 (3.6) 4	14 (4.2) 14
Vessel puncture site bruise	n (%) E	3 (2.6) 3	5 (4.5) 6	5 (4.5) 5	13 (3.9) 14
Injection site pain	n (%) E	2 (1.7) 2	6 (5.4) 9	2 (1.8) 2	10 (3.0) 13
Fatigue	n (%) E	-	4 (3.6) 4	-	4 (1.2) 4
Catheter site related reaction	n (%) E	2 (1.7) 2	-	-	2 (0.6) 2
Injection site bruising	n (%) E	-	2 (1.8) 2	-	2 (0.6) 2
Gastrointestinal disorders	n (%) E	16 (13.9) 18	12 (10.8) 15	14 (12.7) 14	42 (12.5) 47
Nausea	n (%) E	4 (3.5) 4	6 (5.4) 6	1 (0.9) 1	11 (3.3) 11
Abdominal pain	n (%) E	1 (0.9) 1	4 (3.6) 4	2 (1.8) 2	7 (2.1) 7

System Organ Class Preferred Term	Statistic	AVT05 (N=115)	EU-Simponi (N=111)	US-Simponi (N=110)	Overall (N=336)
Diarrhoea	n (%) E	1 (0.9) 1	2 (1.8) 2	4 (3.6) 4	7 (2.1) 7
Toothache	n (%) E	3 (2.6) 3	-	1 (0.9) 1	4 (1.2) 4
Dyspepsia	n (%) E	2 (1.7) 2	-	-	2 (0.6) 2
Musculoskeletal and connective tissue disorders	n (%) E	8 (7.0) 10	10 (9.0) 12	10 (9.1) 11	28 (8.3) 33
Back pain	n (%) E	2 (1.7) 2	5 (4.5) 5	3 (2.7) 3	10 (3.0) 10
Arthralgia	n (%) E	2 (1.7) 2	1 (0.9) 1	3 (2.7) 3	6 (1.8) 6
Pain in extremity	n (%) E	3 (2.6) 3	1 (0.9) 1	2 (1.8) 2	6 (1.8) 6
Respiratory, thoracic and mediastinal disorders	n (%) E	12 (10.4) 12	5 (4.5) 7	11 (10.0) 12	28 (8.3) 31
Oropharyngeal pain	n (%) E	5 (4.3) 5	3 (2.7) 3	3 (2.7) 3	11 (3.3) 11
Cough	n (%) E	3 (2.6) 3	1 (0.9) 1	1 (0.9) 1	5 (1.5) 5
Nasal congestion	n (%) E	-	1 (0.9) 1	3 (2.7) 3	4 (1.2) 4
Rhinorrhoea	n (%) E	2 (1.7) 2	-	-	2 (0.6) 2
Throat irritation	n (%) E	-	-	2 (1.8) 2	2 (0.6) 2
Investigations	n (%) E	10 (8.7) 10	10 (9.0) 10	7 (6.4) 8	27 (8.0) 28
Blood creatine phosphokinase increased	n (%) E	7 (6.1) 7	5 (4.5) 5	3 (2.7) 3	15 (4.5) 15
Mycobacterium tuberculosis complex test positive	n (%) E	1 (0.9) 1	4 (3.6) 4	3 (2.7) 3	8 (2.4) 8
Injury, poisoning and procedural complications	n (%) E	7 (6.1) 9	5 (4.5) 5	9 (8.2) 12	21 (6.3) 26
Ligament sprain	n (%) E	2 (1.7) 2	2 (1.8) 2	2 (1.8) 2	6 (1.8) 6
Contusion	n (%) E	1 (0.9) 1	2 (1.8) 2	2 (1.8) 2	5 (1.5) 5
Skin laceration	n (%) E	2 (1.7) 3	-	1 (0.9) 1	3 (0.9) 4
Muscle strain	n (%) E	-	-	2 (1.8) 2	2 (0.6) 2
Thermal burn	n (%) E	-	-	2 (1.8) 2	2 (0.6) 2
Skin and subcutaneous tissue disorders	n (%) E	4 (3.5) 4	3 (2.7) 4	10 (9.1) 11	17 (5.1) 19
Dermatitis contact	n (%) E	1 (0.9) 1	1 (0.9) 1	5 (4.5) 6	7 (2.1) 8
Rash	n (%) E	1 (0.9) 1	2 (1.8) 2	2 (1.8) 2	5 (1.5) 5
Blood and lymphatic system disorders	n (%) E	2 (1.7) 3	5 (4.5) 6	7 (6.4) 7	14 (4.2) 16
Neutropenia	n (%) E	2 (1.7) 3	5 (4.5) 6	6 (5.5) 6	13 (3.9) 15
Reproductive system and breast disorders	n (%) E	4 (3.5) 4	4 (3.6) 5	5 (4.5) 5	13 (3.9) 14
Dysmenorrhoea	n (%) E	3 (2.6) 3	3 (2.7) 3	3 (2.7) 3	9 (2.7) 9
Cardiac disorders	n (%) E	1 (0.9) 1	2 (1.8) 2	3 (2.7) 3	6 (1.8) 6
Tachycardia	n (%) E	-	2 (1.8) 2	1 (0.9) 1	3 (0.9) 3
Palpitations	n (%) E	-	-	2 (1.8) 2	2 (0.6) 2

AE: adverse event; E: Number of TEAEs in each category; IP: Investigational product; MedDRA: Medical Dictionary for Regulatory Activities; n: Number of participants with at least one TEAE in each category (participants with multiple events in each category are counted only once in each category); N: Total number of participants in the relevant population; TEAE: treatment-emergent AE; %: Percentage of participants in each category calculated relative to the total number of participants in the relevant population.
A TEAE is defined as any AE which commenced or worsened in severity on or after the start of IP administration. AEs were coded using MedDRA Version 25.1.

Related TEAEs, i.e. TEAEs that were considered to have at least a reasonable possibility to be caused by the study drug, are summarised in Table *25*.

Table 25: Incidence of related TEAEs Occurring in ≥5% of Participants in Any Treatment Group (AVT05-GL-P01; Safety Population)

System Organ Class Preferred Term	Statistic	AVT05 (N=115)	Eu-Simponi (N=111)	US-Simponi (N=110)	Overall (N=336)
At least one IP-related TEAE	n (%) E	32 (27.8) 43	40 (36.0) 53	33 (30.0) 45	105 (31.3) 141
General disorders and administration site conditions	n (%) E	8 (7.0) 10	15 (13.5) 18	12 (10.9) 13	35 (10.4) 41
Injection site pain	n (%) E	2 (1.7) 2	6 (5.4) 7	2 (1.8) 2	10 (3.0) 11
Infections and infestations	n (%) E	10 (8.7) 12	13 (11.7) 14	11 (10.0) 11	34 (10.1) 37
Influenza	n (%) E	6 (5.2) 6	4 (3.6) 5	6 (5.5) 6	16 (4.8) 17
Nervous system disorders	n (%) E	8 (7.0) 8	6 (5.4) 6	3 (2.7) 4	17 (5.1) 18
Headache	n (%) E	8 (7.0) 8	5 (4.5) 5	3 (2.7) 4	16 (4.8) 17

AE: adverse event; E: number of TEAEs in each category; IP: Investigational product; n: number of participants with at least one TEAE in each category; N: total number of participants in the relevant population; TEAE: treatment-emergent AE; %: percentage of participants in each category calculated relative to the total number of participants in the relevant population.

Phase 3 study (AVT05-GL-C01)

An overview of the TEAEs is presented in Table *26* and common TEAEs in Table *27*.

An overview of the TEAEs from week 16 to EoS is presented in Table 28 and common TEAEs in Table 29.

Table 26: Overview of TEAEs Up to Week 16 (Study AVT05-GL-C01, Safety Analysis Set)

	AVT05 (N= 251)		EU-Simponi (N= 251)	
	Patients n (%)	Events n	Patients n (%)	Events n
Any TEAE	96 (38.2)	192	99 (39.4)	177
Maximum Severity of TEAEs				
Grade 1 – Mild	52 (20.7)	134	53 (21.1)	113
Grade 2 – Moderate	40 (15.9)	53	43 (17.1)	60
Grade 3 – Severe	4 (1.6)	5	2 (0.8)	3
Grade 4 – Potentially Life-threatening	0	0	0	0
Grade 5 – Death	0	0	1 (0.4)	1
Treatment-Related TEAEs	19 (7.6)	33	28 (11.2)	49
Serious TEAEs	4 (1.6)	4	2 (0.8)	2
Treatment-Related Serious TEAEs	1 (0.4)	1	1 (0.4)	1
TEAE leading to discontinuation from study treatment phase	4 (1.6)	4	1 (0.4)	2
Treatment-related TEAE leading to discontinuation from study treatment phase	1 (0.4)	1	1 (0.4)	2
TEAE leading to early termination from study	4 (1.6)	4	1 (0.4)	1
Treatment-related TEAE leading to early termination from study	1 (0.4)	1	1 (0.4)	1
Serious TEAE leading to early termination from study	4 (1.6)	4	1 (0.4)	1
Treatment-related serious TEAE leading to early termination from study	1 (0.4)	1	1 (0.4)	1
TEAEs of special interest	47 (18.7)	65	38 (15.1)	53

N: number of patients treated in the relevant safety analysis set and is used as the denominator for percentage calculations; n: number and % of patients with events starting on or after the first dose of study drug (Day 1) but before the Week 16 dose.
All events are included for those subjects that did not continue into Stage 2, including any reported beyond Week 16. Patients are counted only once at the maximum severity in the following order: Grade 5, 4, 3, 2 and 1 (mild). Events with unknown severity are counted as severe. Patient is presented only once in the respective patient count by highest relationship. Events with unknown relationship to study drug are counted as drug-related.

Table 27: TEAEs Reported in ≥1% of Patients in Any Group by SOC and PT up to 16 Weeks (Study AVT05-GL-C01, Safety Analysis Set)

System Organ Class Preferred Term	AVT05 (N=251) Patients n (%)	Events n	EU-Simponi (N=251) Patients n (%)	Events n
Any Reported	96 (38.2)	193	105 (41.8)	184
Infections and infestations	53 (21.1)	66	56 (22.3)	66
Urinary tract infection	10 (4.0)	12	20 (8.0)	20
Upper respiratory tract infection	9 (3.6)	9	10 (4.0)	10
Nasopharyngitis	11 (4.4)	12	7 (2.8)	7
Bacteriuria	6 (2.4)	7	1 (0.4)	1
Pharyngitis	1 (0.4)	1	5 (2.0)	5
Bronchitis	2 (0.8)	2	3 (1.2)	3
COVID-19	3 (1.2)	3	2 (0.8)	2
Influenza	3 (1.2)	3	2 (0.8)	2
Sinusitis	3 (1.2)	3	2 (0.8)	2
Oral herpes	1 (0.4)	1	3 (1.2)	3
Investigations	25 (10.0)	67	24 (9.6)	50
Alanine aminotransferase increased	9 (3.6)	11	6 (2.4)	7
Aspartate aminotransferase increased	8 (3.2)	9	3 (1.2)	5
Blood creatine phosphokinase increased	5 (2.0)	5	4 (1.6)	4
White blood cells urine positive	5 (2.0)	5	2 (0.8)	2
Blood cholesterol increased	4 (1.6)	5	2 (0.8)	2
Crystal urine present	5 (2.0)	6	1 (0.4)	1
Urinary sediment present	3 (1.2)	4	1 (0.4)	1
Bilirubin urine present	4 (1.6)	4	0	0
Gamma-glutamyl transferase increased	1 (0.4)	1	3 (1.2)	3
Neutrophil count decreased	0	0	3 (1.2)	3
Metabolism and Nutrition Disorders	9 (3.6)	10	11 (4.4)	12
General disorders and administration site conditions	4 (1.6)	4	10 (4.0)	13
Injection site reaction	1 (0.4)	1	8 (3.2)	10
Blood and lymphatic system disorders	7 (2.8)	10	4 (1.6)	5
Anemia	3 (1.2)	3	3 (1.2)	3
Injury, poisoning and procedural complications	4 (1.6)	4	7 (2.8)	8
Vascular disorders	5 (2.0)	6	5 (2.0)	5
Hypertension	5 (2.0)	5	5 (2.0)	5
Musculoskeletal and connective tissue disorders	5 (2.0)	5	3 (1.2)	3
Renal and urinary disorders	4 (1.6)	5	3 (1.2)	3
Gastrointestinal disorders	4 (1.6)	4	3 (1.2)	3
Skin and subcutaneous tissue disorders	3 (1.2)	3	2 (0.8)	2
Respiratory, thoracic and mediastinal disorders	0	0	5 (2.0)	5

IP: investigational product; MedDRA: Medical Dictionary of Regulatory Activities; N: Number of patients treated in the relevant Safety Analysis Set and was used as the denominator for percentage calculations; TEAE: treatment-emergent adverse event.
n (%) is the number and percentage of patients with events starting on or after the first dose of IP (Day 1) but before the Week 16 dose. Patients are counted once within a system organ class and once for each unique preferred term. Adverse events are coded using MedDRA version 27.1.

Table 28: Overview of TEAEs From Week 16 to EoS (Study AVT05 GL-C01, Safety Analysis Set)

	AVT05/ AVT05 (N=223)		EU-Simponi/ AVT05 (N=112)		EU-Simponi/ EU-Simponi (N=113)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Any TEAE	114 (51.1)	207	65 (58.0)	130	65 (57.5)	170
Maximum Severity of TEAEs						
Grade 1 - Mild	42 (18.8)	97	24 (21.4)	63	23 (20.4)	91
Grade 2 - Moderate	61 (27.4)	96	35 (31.3)	61	33 (29.2)	62
Grade 3 - Severe	11 (4.9)	14	6 (5.4)	6	8 (7.1)	15
Grade 4 - Potentially Life-threatening	0	0	0	0	1 (0.9)	2
Grade 5 - Death	0	0	0	0	0	0
Treatment-Related TEAEs	15 (6.7)	21	12 (10.7)	16	18 (15.9)	30
Serious TEAEs	6 (2.7)	6	2 (1.8)	2	7 (6.2)	9
Treatment-Related Serious TEAEs	0	0	0	0	1 (0.9)	1
TEAE Leading to Discontinuation from Study Treatment Phase	2 (0.9)	2	2 (1.8)	2	5 (4.4)	6
Treatment-Related TEAE Leading to Discontinuation from Study Treatment Phase	0	0	2 (1.8)	2	1 (0.9)	1
TEAE Leading to Early Termination from Study	3 (1.3)	3	2 (1.8)	2	5 (4.4)	5
Treatment-Related TEAE Leading to Early Termination from Study	0	0	2 (1.8)	2	1 (0.9)	1
Serious TEAE Leading to Early Termination from Study	1 (0.4)	1	0	0	2 (1.8)	2
Treatment-Related Serious TEAE Leading to Early Termination from Study	0	0	0	0	0	0
TEAEs of Special Interest	57 (25.6)	77	36 (32.1)	47	32 (28.3)	38

N: number of patients treated in the relevant safety analysis set and is used as the denominator for percentage calculations.
n (%) represents number and % of patients with events starting on or after the Week 16 dose but through End of Study. Patients are counted only once at the maximum severity in the following order: Grade 5, 4, 3, 2 and 1 (mild). Events with unknown severity are counted as severe. Patient is presented only once in the respective patient count by highest relationship. Events with unknown relationship to study drug are counted as drug-related.WW

Table 29: TEAEs Reported in ≥1% of Patients in Any Group by SOC and PT From Week 16 to EoS (Study AVT05-GL-C01, Safety Analysis Set)

System Organ Class Preferred Term	AVT05/ AVT05 (N=223)		EU-Simponi/ AVT05 (N=112)		EU-Simponi/ EU-Simponi (N=113)	
	Participants n (%)	Events n	Participants n (%)	Events n	Participants n (%)	Events n
Any reported	114 (51.1)	207	65 (58.0)	130	65 (57.5)	170
Infections and infestations	67 (30.0)	76	41 (36.6)	55	38 (33.6)	55
Upper respiratory tract infection	16 (7.2)	17	11 (9.8)	11	9 (8.0)	10
Urinary tract infection	15 (6.7)	15	6 (5.4)	6	10 (8.8)	11
Nasopharyngitis	9 (4.0)	9	6 (5.4)	7	4 (3.5)	5
Influenza	6 (2.7)	6	3 (2.7)	3	2 (1.8)	2
Pharyngitis	3 (1.3)	3	2 (1.8)	3	4 (3.5)	4
Bronchitis	6 (2.7)	6	1 (0.9)	1	1 (0.9)	1
Oral herpes	1 (0.4)	1	3 (2.7)	3	3 (2.7)	3
Pneumonia	1 (0.4)	2	0	0	4 (3.5)	4
Laryngitis	1 (0.4)	1	2 (1.8)	2	1 (0.9)	1
Sinusitis	1 (0.4)	1	3 (2.7)	3	0	0
Pulpitis dental	0	0	2 (1.8)	3	0	0
Rhinitis	0	0	0	0	2 (1.8)	2
Investigations	23 (10.3)	40	13 (11.6)	18	13 (11.5)	32

System Organ Class Preferred Term	AVT05/ AVT05 (N=223)		EU-Simponi/ AVT05 (N=112)		EU-Simponi/ EU-Simponi (N=113)	
	Participants n (%)	Events n	Participants n (%)	Events n	Participants n (%)	Events n
Alanine aminotransferase increased	5 (2.2)	5	7 (6.3)	7	1 (0.9)	1
Blood cholesterol increased	5 (2.2)	8	2 (1.8)	2	1 (0.9)	1
Aspartate aminotransferase increased	4 (1.8)	4	4 (3.6)	4	0	0
Blood glucose increased	1 (0.4)	1	0	0	3 (2.7)	3
White blood cells urine positive	1 (0.4)	1	0	0	3 (2.7)	3
Blood creatine phosphokinase increased	1 (0.4)	1	0	0	2 (1.8)	2
Hepatic enzyme increased	3 (1.3)	3	0	0	0	0
Lymphocyte count decreased	0	0	1 (0.9)	1	2 (1.8)	2
Neutrophil count increased	0	0	0	0	2 (1.8)	2
Musculoskeletal and connective tissue disorders	11 (4.9)	15	4 (3.6)	4	9 (8.0)	13
Rheumatoid arthritis1	5 (2.2)	6	0	0	1 (0.9)	1
Arthralgia	3 (1.3)	3	0	0	2 (1.8)	2
Back pain	0	0	0	0	2 (1.8)	2
Metabolism and nutrition disorders	8 (3.6)	8	6 (5.4)	8	8 (7.1)	17
Hypercholesterolemia	4 (1.8)	4	1 (0.9)	1	1 (0.9)	1
Hyperlipidemia	1 (0.4)	1	2 (1.8)	2	0	0
Nervous system disorders	8 (3.6)	9	8 (7.1)	8	5 (4.4)	5
Headache	2 (0.9)	2	4 (3.6)	4	1 (0.9)	1
Sciatica	3 (1.3)	3	1 (0.9)	1	3 (2.7)	3
Vascular disorders	8 (3.6)	8	4 (3.6)	6	4 (3.5)	4
Hypertension	6 (2.7)	6	2 (1.8)	3	4 (3.5)	4
Renal and urinary disorders	7 (3.1)	8	2 (1.8)	2	5 (4.4)	7
Cystitis noninfective	3 (1.3)	4	0	0	0	0
Renal cyst	0	0	0	0	3 (2.7)	3
Skin and subcutaneous tissue disorders	8 (3.6)	9	3 (2.7)	3	3 (2.7)	3
Gastrointestinal disorders	4 (1.8)	5	2 (1.8)	3	6 (5.3)	9
Respiratory, thoracic and mediastinal disorders	6 (2.7)	9	3 (2.7)	3	3 (2.7)	3
Blood and lymphatic system disorders	4 (1.8)	4	2 (1.8)	2	3 (2.7)	5
Anemia	2 (0.9)	2	1 (0.9)	1	2 (1.8)	3
Hepatobiliary disorders	3 (1.3)	3	2 (1.8)	3	3 (2.7)	3
Cholelithiasis	1 (0.4)	1	0	0	2 (1.8)	2
Injury, poisoning and procedural complications	2 (0.9)	2	4 (3.6)	4	2 (1.8)	2
Reproductive system and breast disorders	2 (0.9)	2	2 (1.8)	3	3 (2.7)	3
Benign prostatic hyperplasia	0	0	0	0	2 (1.8)	2
General disorders and administration site conditions	0	0	4 (3.6)	4	3 (2.7)	3
Asthenia	0	0	2 (1.8)	2	1 (0.9)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1	1 (0.9)	1	3 (2.7)	4

EU-Simponi: EU-approved Simponi; MedDRA: Medical Dictionary of Regulatory Activities; TEAE: treatment-emergent adverse event.

N is the number of patients treated in the relevant Safety Analysis Set and was used as the denominator for percentage calculations. n (%) is the number and percentage of patients with events starting on or after the Week 16 dose through End of Study. Participants are counted once within a system organ class and once for each unique preferred term. Adverse events are coded using MedDRA version 27.1.d[1] Verbatim terms for the AVT05/AVT05 group: "exacerbation of rheumatoid arthritis" in 1 participant; "exacerbation rheumatoid arthritis" in 1 participant; "RA exacerbation" and "exacerbation of RA" in 1 participant; "worsening of rheumatoid arthritis" in 1 participant; and "RA worsening" in 1 participant. Verbatim terms for the EU-Simponi/EU-Simponi group: "exacerbation rheumatoid arthritis" in 1 participant. d

Related TEAEs up to week 16 are summarised in Table 30 and from week 16 to week 24 in Table 31.

Table 30: Related TEAEs occurring in ≥ 1% of Patients in any Treatment Group up to Week 16 (AVT05-GL-C01, Safety Analysis Set)

System Organ Class Preferred Term	AVT05 (N=251)		EU-Simponi (N=251)	
	Patients n (%)	Events n	Patients n (%)	Events n
Any Reported	19 (7.6)	33	28 (11.2)	49
INFECTIONS AND INFESTATIONS	7 (2.8)	8	15 (6.0)	18
Bronchitis	0	0	3 (1.2)	3
Pharyngitis	0	0	3 (1.2)	3
Upper respiratory tract infection	0	0	3 (1.2)	3
INVESTIGATIONS	6 (2.4)	12	8 (3.2)	16
Alanine aminotransferase increased	3 (1.2)	5	2 (0.8)	2
Aspartate aminotransferase increased	4 (1.6)	5	1 (0.4)	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.8)	2	7 (2.8)	10
Injection site reaction	1 (0.4)	1	6 (2.4)	8

N: Number of patients treated in the relevant Safety Analysis Set and is used as the denominator for percentage calculations; n (%) represents number and % of patients with events starting on or after the first dose of study drug (Day 1) but before the Week 16 dose; TEAEs: Treatment-Emergent Adverse Events.
Patients are counted once within a system organ class and once for each unique preferred term. Patient is presented only once in the respective patient count by highest relationship. Events with unknown relationship to study drug are counted as drug related. See TEAE definition in SAP. Adverse events are coded using MedDRA version 26.0.

Table 31: Related TEAEs occurring in ≥ 1% of Patients in any Treatment Group from Week 16 to EoS (AVT05-GL-C01, Safety Analysis Set)

System Organ Class Preferred Term	AVT05/ AVT05 (N=223)		EU-Simponi/ AVT05 (N=112)		EU-Simponi/ EU-Simponi (N=113)	
	Participants n (%)	Events n	Participants n (%)	Events n	Participants n (%)	Events n
Any reported	15 (6.7)	21	12 (10.7)	16	18 (15.9)	30
Infections and infestations	9 (4.0)	9	6 (5.4)	6	12 (10.6)	17
Nasopharyngitis	3 (1.3)	3	1 (0.9)	1	3 (2.7)	4
Pharyngitis	1 (0.4)	1	1 (0.9)	1	2 (1.8)	2
Upper respiratory tract infection	1 (0.4)	1	1 (0.9)	1	2 (1.8)	2
Oral herpes	0	0	1 (0.9)	1	2 (1.8)	2
Urinary tract infection	1 (0.4)	1	0	0	2 (1.8)	2
Investigations	2 (0.9)	5	3 (2.7)	5	4 (3.5)	10
Alanine aminotransferase increased	1 (0.4)	1	2 (1.8)	2	0	0
Aspartate aminotransferase increased	1 (0.4)	1	2 (1.8)	2	0	0
White blood cells urine positive	0	0	0	0	2 (1.8)	2
Skin and subcutaneous tissue disorders	1 (0.4)	1	2 (1.8)	2	0	0

EU-Simponi: EU-approved Simponi; IP: investigational product; MedDRA: Medical Dictionary of Regulatory Activities; PT: preferred term; SOC: system organ class; TEAEs: Treatment-Emergent Adverse Events.
N is the number of participants treated in the relevant Safety Analysis Set and was used as the denominator for percentage calculations. n (%) is the number and percentage of participants with events starting on or after the Week 16 dose through End of Study. Participants are counted once within a SOC and once for each unique PT. Participants are presented only once in the respective participant count by highest relationship. Events with unknown relationship to IP are counted as IP-related. See TEAE definition in SAP. Adverse events are coded using MedDRA version 27.1.dd

2.5.8.3. Serious adverse event/deaths/other significant events

Serious adverse event

Phase 1 study (AVT05-GL-P01)

Two serious TEAEs were reported; one participant in the AVT05 group (PT: abortion induced) and one participant in the EU-Simponi group (PT: abortion spontaneous). The events were not considered to be related to the study drug.

Phase 3 study (AVT05-GL-C01)

Up to week 16, serious TEAEs were reported for 4 (1.6%) patients in the AVT05 group and 2 (0.8%) patients in the EU-Simponi group (Table *32*.). All serious TEAEs had an outcome of recovered/resolved, except for infectious pleural effusion (severity: Grade 3; outcome: recovered/resolved with sequelae) and the metastatic neoplasm (severity: Grade 5; outcome: fatal).

Table 32: Serious TEAEs up to Week 16 (AVT05-GL-C01, Safety Analysis Set)

System Organ Class Preferred Term	AVT05 (N=251) Patients n (%)	 Events n	EU-Simponi (N=251) Patients n (%)	 Events n
Any Reported	4 (1.6)	4	2 (0.8)	2
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.4)	1	1 (0.4)	1
Benign Neoplasm of Thyroid Gland	1 (0.4)	1	0	0
Metastatic Neoplasm	0	0	1 (0.4)	1
Renal And Urinary Disorders	1 (0.4)	1	1 (0.4)	1
Nephrotic Syndrome	1 (0.4)	1	0	0
Renal Colic	0	0	1 (0.4)	1
Infections And Infestations	1 (0.4)	1	0	0
Infectious Pleural Effusion	1 (0.4)	1	0	0
Nervous System Disorders	1 (0.4)	1	0	0
Meningitis noninfective	1 (0.4)	1	0	0

N: Number of patients treated in the relevant Safety Analysis Set and is used as the denominator for percentage calculations; n (%) represents number and % of patients with events starting on or after the first dose of study drug (Day 1) but before the Week 16 dose; TEAEs: Treatment-Emergent Adverse Events.
Patients are counted once within a system organ class and once for each unique preferred term. See TEAE definition in SAP. Adverse events are coded using MedDRA version 26.0.

From week 16 to EoS, serious TEAEs were reported for 6 (2.7%) patients in the AVT05/AVT05 group, 2 (1.8%) patients in the EU-Simponi/AVT05 group, and 7 (6.2%) patients in the EU-Simponi/EU-Simponi group (Table *33*).

All serious TEAEs had an outcome of recovered/resolved, except for pneumonia (1 [0.4%] patient in the AVT05/AVT05 group and 1 [0.9%] patient in the EU-Simponi/EU-Simponi group), which had an outcome of recovered/resolved with sequalae, and breast cancer (1 [0.4%] patient in the AVT05/AVT05 group, which had an outcome of recovering/resolving.

Table 33: Serious TEAEs from Week 16 to EoS (AVT05-GL-C01, Safety Analysis Set)

	AVT05/ AVT05 (N=223)		EU-Simponi/ AVT05 (N=112)		EU-Simponi/ EU-Simponi (N=113)	
System Organ Class Preferred Term	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Any Reported	6 (2.7)	6	2 (1.8)	2	7 (6.2)	9
INFECTIONS AND INFESTATIONS	1 (0.4)	1	1 (0.9)	1	2 (1.8)	2
Pneumonia	1 (0.4)	1	0	0	2 (1.8)	2
Laryngitis	0	0	1 (0.9)	1	0	0
GASTROINTESTINAL DISORDERS	0	0	1 (0.9)	1	2 (1.8)	2
Gastritis	0	0	1 (0.9)	1	0	0
Inguinal hernia	0	0	0	0	1 (0.9)	1
Umbilical hernia	0	0	0	0	1 (0.9)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.4)	1	0	0	2 (1.8)	2
Rheumatoid arthritis	1 (0.4)	1	0	0	1 (0.9)	1
Back pain	0	0	0	0	1 (0.9)	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.4)	1	0	0	1 (0.9)	1
Breast cancer	1 (0.4)	1	0	0	0	0
Endometrial adenocarcinoma	0	0	0	0	1 (0.9)	1
METABOLISM AND NUTRITION DISORDERS	0	0	0	0	1 (0.9)	2
Hyponatraemia	0	0	0	0	1 (0.9)	2
CARDIAC DISORDERS	1 (0.4)	1	0	0	0	0
Chronic coronary syndrome	1 (0.4)	1	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.4)	1	0	0	0	0
Tibia fracture	1 (0.4)	1	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.4)	1	0	0	0	0
Rheumatoid arthritis-associated interstitial lung disease	1 (0.4)	1	0	0	0	0

N: Number of patients treated in the relevant Safety Analysis Set and is used as the denominator for percentage calculations.
n (%) represents number and % of patients with events starting on or after the Week 16 dose through End of Study; TEAEs: Treatment-Emergent Adverse Events. Patients are counted once within a system organ class and once for each unique preferred term. See TEAE definition in SAP. Adverse events are coded using MedDRA version 27.1.

Deaths

There were no deaths in the phase 1 study.

One death was reported in the phase 3 study in the EU-Simponi group. The patient had a Grade 5 TEAE of metastatic neoplasm that started on day 92, with a fatal outcome on day 117. As the role of the study drug in exacerbation of the disease could not be ruled out, the event was considered related to the study treatment.

Other significant events

Phase 1 study (AVT05-GL-P01)

No adverse event of special interests (AESIs) of serious infections, malignancies, autoimmune disorders, demyelinating disorders, or congestive heart failure were reported during the study. In addition to the local administration site reactions shown in Table *34*, the remaining AESIs were rash macular (1 participant) and vulvovaginal candidiasis (1 participant), both occurring in the US-Simponi group.

Table 34: Incidence of AESIs of Local Administration Site Reaction by Maximum Severity (AVT05-GL-P01, Safety Population)

System Organ Class Preferred Term	Severity	Statistic	AVT05 (N=115)	EU-Simponi (N=111)	US-Simponi (N=110)	Overall (N=336)
At least one local administration site reaction	Mild	n (%)	7 (6.1)	12 (10.8)	6 (5.5)	25 (7.4)
	Moderate	n (%)	-	-	-	-
	Severe	n (%)	-	-	-	-
General disorders and administration site conditions	Mild	n (%)	7 (6.1)	12 (10.8)	6 (5.5)	25 (7.4)
Injection site erythema	Mild	n (%)	5 (4.3)	5 (4.5)	4 (3.6)	14 (4.2)
Injection site pain	Mild	n (%)	2 (1.7)	6 (5.4)	2 (1.8)	10 (3.0)
Injection site pruritus	Mild	n (%)	1 (0.9)	1 (0.9)	1 (0.9)	3 (0.9)
Injection site bruising	Mild	n (%)	-	2 (1.8)	-	2 (0.6)

AE: adverse event; IP: Investigational product; MedDRA: Medical Dictionary for Regulatory Activities; n: Number of participants with at least one TEAE in each category (participants with multiple events in each category are counted only once in each category); N: Total number of participants in the relevant population; %: Percentage of participants in each category calculated relative to the total number of participants in the relevant population.
A local administration site reaction is defined as any AE for which the high-level group term is coded to 'Administration site reactions' and considered to be of special interest per protocol. AEs with missing severity were classified as 'severe'. AEs were coded using MedDRA Version 25.1.

Local injection site reactions

In separate ISR evaluations made by the clinical staff at protocol-specified time points, 21 (6.3%) of participants experienced at least 1 local ISR: 6 (5.2%) in the AVT05 group, 9 (8.1%) in the EU-Simponi group, and 6 (5.5%) in the US-Simponi group. All reported ISRs were categorised as Grade 1 to 2 in severity.

Phase 3 study (AVT05-GL-C01)

Up to Week 16, treatment-emergent AESIs were reported for 48 (19.1%) patients in the AVT05 group and 38 (15.1%) patients in the EU-Simponi group (Table *35*.).

Table 35: Treatment emergent AESIs Reported in ≥1% of Patients in Any Group up to Week 16 (AVT05-GL-C01, Safety Analysis Set*)*

System Organ Class Preferred Term	AVT05 (N=251)		EU-Simponi (N=251)	
	Patients n (%)	Events n	Patients n (%)	Events n
Any Reported	48 (19.1)	65	38 (15.1)	53
Infections and Infestations	32 (12.7)	36	25 (10.0)	27
Upper Respiratory Tract Infection	9 (3.6)	9	10 (4.0)	10
Nasopharyngitis	11 (4.4)	12	5 (2.0)	5
Pharyngitis	1 (0.4)	1	5 (2.0)	5
Sinusitis	3 (1.2)	3	2 (0.8)	2
Investigations	13 (5.2)	22	9 (3.6)	18
Alanine Aminotransferase Increased	9 (3.6)	11	6 (2.4)	7
Aspartate Aminotransferase Increased	8 (3.2)	9	3 (1.2)	5
Gamma-Glutamyltransferase Increased	0	0	3 (1.2)	3
Vascular Disorders	4 (1.6)	4	3 (1.2)	3
Hypertension	4 (1.6)	4	3 (1.2)	3

N: Number of patients treated in the relevant Safety Analysis Set and is used as the denominator for percentage calculations; n (%) represents number and % of patients with events starting on or after the first dose of study drug (Day 1) but before the Week 16 dose.
Patients are counted once within a system organ class and once for each unique preferred term. See TEAE definition in SAP. TEAEs: Treatment-Emergent Adverse Events. Adverse events are coded using MedDRA version 27.1.

From Week 16 to EoS, treatment-emergent AESIs were reported for 57 (25.6%) patients in the AVT05/AVT05 group, 36 (32.1%) patients in the EU-Simponi/AVT05 group, and 32 (28.3%) patients in the EU-Simponi/ EU-Simponi group (Table *36*).

Table 36: Treatment emergent AESIs Reported in ≥1% of Patients in Any Group from Week 16 to EoS (AVT05-GL-C01, Safety Analysis Set)

	AVT05/ AVT05 (N=223)		EU-Simponi/ AVT05 (N=112)		EU-Simponi/ EU-Simponi (N=113)	
System Organ Class Preferred Term	**Participants n (%)**	**Events n**	**Participants n (%)**	**Events n**	**Participants n (%)**	**Events n**
Any reported	57 (25.6)	77	36 (32.1)	47	32 (28.3)	38
Infections and infestations	40 (17.9)	47	26 (23.2)	28	25 (22.1)	30
Upper respiratory tract infection	16 (7.2)	17	11 (9.8)	11	9 (8.0)	10
Nasopharyngitis	8 (3.6)	8	3 (2.7)	4	4 (3.5)	5
Influenza	5 (2.2)	5	3 (2.7)	3	2 (1.8)	2
Pharyngitis	3 (1.3)	3	2 (1.8)	3	4 (3.5)	4
Bronchitis	5 (2.2)	5	1 (0.9)	1	1 (0.9)	1
Pneumonia	1 (0.4)	2	0	0	3 (2.7)	3
Sinusitis	1 (0.4)	1	3 (2.7)	3	0	0
Investigations	12 (5.4)	18	8 (7.1)	12	2 (1.8)	2
Alanine aminotransferase increased	5 (2.2)	5	7 (6.3)	7	1 (0.9)	1
Aspartate aminotransferase increased	4 (1.8)	4	4 (3.6)	4	0	0
Hepatic enzyme increased	3 (1.3)	3	0	0	0	0
Vascular disorders	6 (2.7)	6	2 (1.8)	3	3 (2.7)	3
Hypertension	6 (2.7)	6	2 (1.8)	3	3 (2.7)	3
Respiratory, thoracic and mediastinal disorders	2 (0.9)	2	2 (1.8)	2	1 (0.9)	1

N: Number of patients treated in the relevant Safety Analysis Set and is used as the denominator for percentage calculations.
n (%) represents number and % of patients with events starting on or after the Week 16 dose through End of Study; TEAEs: Treatment-Emergent Adverse Events. Patients are counted once within a system organ class and once for each unique preferred term. See TEAE definition in SAP. Adverse events are coded using MedDRA version 27.1.

Local injection site reactions

By week 16, ISRs were reported for 1 (0.4%) patient (1 event: ISR) in the AVT05 group and 10 (4.0%) patients (12 events: 10 ISRs, 1 contusion, and 1 injection site hematoma) in the EU-Simponi group. All events were of Grade 1 severity.

From week 16 to EoS, any ISR was reported for 2 (1.8%) patients (2 events: upper respiratory tract infection [Grade 1] and myositis [Grade 2]) in the EU-Simponi/AVT05 group and for 1 (0.9%) patient (1 event: ISR [Grade 1]) in the EU-Simponi/EU-Simponi group.

2.5.8.4. Laboratory findings

Phase 1 study (AVT05-GL-P01)

There were no apparent changes in mean values for hematology, coagulation, clinical chemistry values over time, and no differences between study groups. No abnormal clinically significant findings in urinalysis parameters were observed at any visit.

In total, 30 (8.9%) participants experienced TEAEs of Grade ≥3 laboratory abnormalities, and 11 (3.3%) had study drug-related Grade ≥3 laboratory abnormalities, mostly neutropenia. The percentages of participants who reported these abnormalities were comparable across the treatment groups.

There were no clinically meaningful changes in mean values for vital signs or ECG parameters from baseline over the course of the study and no meaningful differences across treatment groups.

One participant in the AVT05 group, 4 in the EU-Simponi group and 3 in the US-Simponi group tested positive for *M. tuberculosis* in the QuantiFERON test at their EOS visit, although all had tested negative at screening. The events were considered not related to the IP, as the positive QuantiFERON result in absence of active disease reflects TB infection [latent TB] indicating exposure to TB, and it was considered that such exposure was unrelated to the IP. All the participants were asymptomatic, their physical examination and other laboratory results were normal.

Phase 3 study (AVT05-GL-C01)

There were no apparent differences across the treatment groups in hematology, coagulation, clinical chemistry, liver function or urinalysis parameters in terms of abnormal laboratory results up to week 16 or from week 16 to EoS. Up to week 16, a similar decrease in the mean CRP values was observed in AVT05 and EU-Simponi groups. From Week 16 to EoS, CRP values decreased, and creatine kinase values increased over time in all treatment groups.

Vital signs parameters were comparable between AVT05 and EU-Simponi groups up to week 16 and between the study groups from week 16 to EoS, and generally stable over time.

The laboratory-related TEAEs occurring in ≥1% of patients up to week 16 is shown in Table 29 and from week 16 to 24 in Table 31.

ECGs were evaluated at baseline, at week 24 and at week 52. From baseline to EoS, a shift from normal to abnormal clinically significant overall interpretation was reported for 1 patient in the AVT05/AVT05 group. No TEAEs related to ECG parameters were reported.

At baseline, all participants had a negative QuantiFERON-TB Gold Test except for 1 patient in the AVT05/AVT05 group. The patient was formerly diagnosed with TB infection and active disease was ruled out after appropriate testing (treated according to local recommendations and screened at the discretion of the investigator). At Week 52, 4 (1.9%) participants in the AVT05/AVT05 group and 1 (1.0%) participant in the EU Simponi/EU Simponi group had a positive QuantiFERON-TB Gold Test result.

There were no TEAEs related to TB testing up to week 16. From week 16 to EoS, the following TEAEs related to TB testing were reported:

- *Mycobacterium tuberculosis* complex test positive (1 event) in 1 (0.9%) participant in the EU-Simponi/AVT05 group. According to the applicant, this was a false positive reported as an AE.
- Latent TB (1 event) in 1 (0.4%) participant in the AVT05/AVT05 group and (1 event) in 1 (0.9%) participant in the EU-Simponi/EU-Simponi group. The participant in the EU-Simponi/EU-Simponi group was early terminated from the study. TB disease was ruled out.
- TB (1 event) in 1 (0.9%) participant in the EU-Simponi/AVT05 group.

The TEAE of latent TB in the AVT05/AVT05 group was of Grade 1 severity. Other TEAEs were of Grade 2 severity.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable for biosimilars.

2.5.8.6. Safety in special populations

Not applicable for biosimilars.

2.5.8.7. Immunological events

Frequencies and titres of ADAs and Nabs

The immunogenicity of AVT05 was analysed in healthy participants after a single s.c. administration in Study AVT05-GL-P01 and in patients with moderate to severe rheumatoid arthritis in combination with Methotrexate after multiple administration in Study AVT05-GL-C01.

Study AVT05-GL-P01

The frequency of ADAs and NAbs development progressively increased over the duration of the study, with the highest positivity rates seen at Day 75 (EoS visit).

Table 37: Summary of Detection of ADAs and nAbs by treatment (Study AVT05-GL-P01, Immunogenicity Population)

Treatment Group	Statistics	Day 1 Predose	Day 9	Day 15	Day 29	Day 57	Day 64	EoS /Day 75	Any Positive
Antidrug Antibody Positivity									
AVT05 (N=115)	n (%)	9 (7.8)	13 (11.3)	12 (10.4)	36 (31.3)	74 (64.3)	79 (68.7)	84 (73.0)	87 (75.7)
EU-Simponi (N=111)	n (%)	4 (3.6)	14 (12.6)	17 (15.3)	38 (34.2)	77 (69.4)	78 (70.3)	89 (80.2)	92 (82.9)
US-Simponi (N=110)	n (%)	4 (3.6)	25 (22.7)	21 (19.1)	31 (28.2)	63 (57.3)	70 (63.6)	81 (73.6)	89 (80.9)
Neutralising Antibody Positivity									
AVT05 (N=115)	n (%)	0	1 (0.9)	1 (0.9)	7 (6.1)	42 (36.5)	54 (47.0)	50 (43.5)	66 (57.4)
EU-Simponi (N=111)	n (%)	0	5 (4.5)	6 (5.4)	13 (11.7)	42 (37.8)	49 (44.1)	59 (53.2)	68 (61.3)
US-Simponi (N=110)	n (%)	0	6 (5.5)	5 (4.5)	12 (10.9)	44 (40.0)	42 (38.2)	49 (44.5)	61 (55.5)

ADA: anti-drug antibody; EOS: end of study; nAb: neutralising antibody; N: total number of participants in the relevant population; n: number of participants with an assessment available at the relevant point; %: percentage of participants in each category calculated relative to the total number of participants in the relevant population. For Nab positivity rates, percentage of participants at each timepoint who are positive to Nab divided by total number of participants with any ADA-positive result are presented.

The median ADA titres were generally low and with a similar progression between study arms.

Study AVT05-GL-C01

Up to Week 16, the overall incidences of ADAs was 63.3% vs. 58.6%, respectively in the EU-Simponi and in the AVT05 groups. The treatment-emergent ADA incidence was 57.8% vs.52.7%, respectively.

Table 38: Confirmed Positive Antibody Incidence– Up to Week 16 (Study AVT05-GL-P01, Safety Analysis Set)

Results	AVT05 (N=251) n (%)	EU-Simponi (N=251) n (%)
Total Antibody Incidence [1]	m=251	m=251
Binding (ADA)[A]	147 (58.6)	159 (63.3)
Neutralising Antibodies (nAb)[B]	68 (46.3)	76 (47.8)
Baseline (Pre-existing Antibody Incidence) [2]	m=249	m=251
Binding (ADA)[A]	31 (12.4)	33 (13.1)
Neutralising Antibodies (nAb)[B]	2 (6.5)	1 (3.0)
Treatment-emergent ADA Incidence up to Week 16 [3]	m1=220	m1=218
Binding (ADA)[C]	116 (52.7)	126 (57.8)
Treatment-emergent nAb Incidence up to Week 16 [3]	m2=116	m2=126
Neutralising Antibodies (nAb)[D]	54 (46.6)	60 (47.6)

[1] Positive result at any visit before Week 16 dose.
[2] Baseline is defined as the last non-missing assessment prior to first dose (Day 1).
[3] Negative result or no result at Baseline and positive result post-dose but before Week 16 dose.
[A] %: n/m, where m is the total number of patients with ADA assessed in the specified time period.
[B] %: n/ADA+, where ADA+ is the total number of patients with positive ADA status in the specified time period.
[C] %: n/m1, where m1 is the number of patients with ADA assessed post-dose up to Week 16 dose. Patients with ADA positive at Baseline are not included in m1.
[D] %: n/m2, where m2 is the number of patients with treatment-emergent ADA Incidence up to Week 16 dose. Patients with ADA / nAb positive at Baseline are not included in m2.

From Week 16 up to Week 24, the treatment-emergent ADA incidence was 14.8% vs. 20.0% vs. 15.9%, respectively in the AVT05/AVT05 group, in the EU-Simponi/AVT05 group, and in the EU-Simponi/EU-Simponi group.

Table 39: Confirmed Positive Antibody Incidence– From Week 16 to Week 24 (Study AVT05-GL-P01, Safety Analysis Set)

Results	AVT05/AVT05 (N=223) n (%)	EU-Simponi/AVT05 (N=112) n (%)	EU-Simponi/EU-Simponi (N=113) n (%)
Total Antibody Incidence [1]	m=223	m=112	m=113
Binding (ADA)[A]	147 (65.9)	83 (74.1)	75 (66.4)
Neutralising Antibodies (nAb)[B]	71 (48.3)	40 (48.2)	37 (49.3)
Antibody Incidence Before Week 16 [2]	m=223	m=112	m=113
Binding (ADA)[A]	134 (60.1)	76 (67.9)	68 (60.2)
Neutralising Antibodies (nAb)[B]	64 (47.8)	36 (47.4)	33 (48.5)
Treatment-emergent ADA Incidence [3]	m1=88	m1=35	m1=44
Binding (ADA)[C]	13 (14.8)	7 (20.0)	7 (15.9)
Treatment-emergent nAb Incidence [3]	m2=13	m2=7	m2=7
Neutralising Antibodies (nAb)[D]	1 (7.7)	1 (14.3)	0

[1] Positive result at any visit up to Week 24 dose.
[2] Positive result at any visit before Week 16 dose.
[3] Negative result at all visits before Week 16 dose and positive result post-Week 16 dose but before Week 24 dose.
[A] %: n/m, where m is the total number of patients with ADA assessed in the specified time period.
[B] %: n/ADA+, where ADA+ is the total number of patients with positive ADA status in the specified time period.
[C] %: n/m1, where m1 is the number of patients with ADA assessed post-dose of Week 16 dose. Patients with ADA positive before Week 16 are not included in m1.
[D] %: n/m2, where m2 is the number of patients with treatment-emergent ADA Incidence up to Week 24 dose. Patients with ADA / nAb positive before Week 16 are not included in m2.

The titres of pre-existing ADAs were low and treatment emergent ADA titres increased over time in a similar manner in all treatment arms up to week 24.

Effect of ADA and nAb on clinical PK

Study AVT05-GL-P01

The immunogenicity profile of AVT05 was generally similar to that of EU-Simponi and US-Simponi. Across treatment groups, formation of ADAs progressively increased over the duration of the study, with the highest positivity rates seen at Day 75 (EoS visit).

In the ADA-positive and nAb-positive subgroups, the geometric means of the systemic exposure PK parameters were lower compared with those observed in the ADA-negative and nAb-negative subgroups (Table *40*). The geometric mean $t_{1/2}$ was shorter in the ADA-positive subgroup. No apparent differences were observed in the geometric mean CL/F and Vz/F values between the ADA-positive and ADA-negative subgroups.

In the ADA-positive and nAb-positive subgroups, the point estimates of the GMRs for the unadjusted and protein content-adjusted C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$ were within the 80.0% to 125.0% margins, indicating consistency of results for these subgroups with the overall results. Across treatment groups, the geometric mean $t_{1/2}$ was shorter in the nAb-positive subgroup. No apparent differences were observed in the geometric mean CL/F and Vz/F values between the nAb-positive and nAb-negative subgroups.

Table 40: Summary of serum golimumab PK parameters by treatment (Study AVT05-GL-P01, PK population)

	AVT05		**EU-Simponi**		**US-Simponi**	
Parameters	**n**	**GeoMean (GeoCV%)**	**n**	**GeoMean (GeoCV%)**	**n**	**GeoMean (GeoCV%)**
ADA Positive						
		N=87		**N=92**		**N=89**
C_{max} (ng/mL)	87	3227.3 (52)	92	3338.5 (49)	89	3370.6 (52)
$AUC_{0\text{-}inf}$ (h*ng/mL)	86	1345388 (38)	91	1305537 (39)	89	1345049 (36)
$AUC_{0\text{-}t}$ (h*ng/mL)	87	1315166 (41)	92	1289101 (40)	89	1330926 (36)
T_{max} (h)	87	104.54 (52.4)	92	92.41 (52.9)	89	104.81 (56)
$t_{1/2}$ (h)	86	202.23 (32)	91	213.6 (26.8)	89	211.17 (33.3)
Vz/F (L)	86	10.84 (48.2)	91	11.8 (44.1)	89	11.33 (49.1)
CL/F (L/Day)	86	0.89 (38.1)	91	0.92 (39.5)	89	0.89 (35.9)
ADA Negative						
		N=27		**N=19**		**N=21**
C_{max} (ng/mL)	27	4297.4 (47)	19	4174 (51)	21	4535.1 (38)
$AUC_{0\text{-}inf}$ (h*ng/mL)	27	1704525 (30)	19	1670060 (38)	21	1752513 (34)
$AUC_{0\text{-}t}$ (h*ng/mL)	27	1657983 (30)	19	1646036 (37)	21	1731708 (34)
T_{max} (h)	27	86.24 (68.9)	19	81.41 (54.8)	21	75.73 (49.2)
$t_{1/2}$ (h)	27	286.78 (29.6)	19	279.83 (33.6)	21	277.33 (21.7)
Vz/F (L)	27	12.14 (39.8)	19	12.09 (38.3)	21	11.42 (32.9)
CL/F (L/Day)	27	0.7 (30)	19	0.72 (37.5)	21	0.69 (33.9)
nAb Positive						
		N=66		**N=68**		**N=61**
C_{max} (ng/mL)	66	3143.1 (50)	68	3265.2 (50)	61	3407.9 (52)
$AUC_{0\text{-}inf}$ (h*ng/mL)	65	1314257 (38)	67	1284631 (40)	61	1346450 (36)
$AUC_{0\text{-}t}$ (h*ng/mL)	66	1280974 (41)	68	1267873 (41)	61	1339226 (36)
T_{max} (h)	66	104.33 (51.1)	68	94.32 (51.9)	61	105.07 (57.1)
$t_{1/2}$ (h)	65	189.54 (30.6)	67	201.19 (24.3)	61	195.61 (29.5)
Vz/F (L)	65	10.4 (48.5)	67	11.3 (43.1)	61	10.48 (49.8)
CL/F (L/Day)	65	0.91 (37.6)	67	0.93 (40.4)	61	0.89 (36.2)
nAb Negative						
		N=21		**N=24**		**N=28**
C_{max} (ng/mL)	21	3507 (57)	24	3555.2 (48)	28	3290.7 (52)
$AUC_{0\text{-}inf}$ (h*ng/mL)	21	1446499 (40)	24	1365717 (37)	28	1342003 (36)
$AUC_{0\text{-}t}$ (h*ng/mL)	21	1428682 (40)	24	1351197 (37)	28	1313021 (36)
T_{max} (h)	21	105.21 (57.6)	24	87.22 (56.6)	28	104.25 (54.7)
$t_{1/2}$ (h)	21	247.13 (27.4)	24	252.47 (26.3)	28	249.47 (35)
Vz/F (L)	21	12.32 (45.4)	24	13.34 (45.1)	28	13.41 (43)
CL/F (L/Day)	21	0.83 (39.6)	24	0.88 (37)	28	0.89 (35.8)

*%AUC_{extrap}: Percentage of AUC_{0-inf} obtained by extrapolation; AUC_{0-t}: Area under the concentration-curve from time zero to the last quantifiable concentration; AUC_{0-inf}: Area under the concentration-curve from time zero extrapolated to infinite time; CL/F: Apparent Clearance; C_{max}: Maximum serum concentration; CV%: Coefficient of variation. GeoMean: Geometric Mean; Geometric CV%: calculated as gCV%: SQRT(Exp[s^2]-1)*100; where s is the standard deviation of the log-transformed values. NC: not calculable PK: pharmacokinetic; $t_{1/2}$: Apparent terminal elimination half-life; T_{max}: Time of maximum serum concentration; Vz/F: Apparent volume of distribution; N: Total number of participants in the relevant population; Nn Number of participants with an assessment available at the relevant time point; Serum concentrations that are BLQ will be designated a value of half LLOQ except for predose that will be assigned zero.*

Study AVT05-GL-C01

- Up to week 16

After repeated administration up to Week 16, mean golimumab serum trough levels of both AVT05 and EU-Simponi treatment groups were higher in those patients who were ADA negative up to Week 16 and lower in those patients who were ADA positive up to Week 16 compared to the overall population. The median trough drug concentrations were approximately 40% lower in ADA positive subjects than in ADA negative subjects at week 16.

- From week 16 up to week EoS

Patients who were nAb positive had lower serum concentrations of study drug compared to the overall population as expected. Up to Week EoS, mean golimumab serum trough levels of all treatment groups (AVT05/AVT05, EU-Simponi/AVT05 and EU-Simponi /EU-Simponi) were higher in those patients who were ADA negative and lower in those patients who were ADA positive compared to the overall population.

Effect of immunogenicity on safety

Phase 1 study (AVT05-GL-P01)

Overview of key safety results in ADA positive and ADA negative subgroups is shown in Table *41* and in nAb positive and nAb negative subgroups in Table *42*.

Table 41: Overview of TEAEs by ADA Status (Study AVT05 GL P01, Safety Population)

Category	Statistic	AVT05 (N=115)	EU-Simponi (N=111)	US-Simponi (N=110)	Overall (N=336)
ADA Positive					
	N	**87**	**92**	**89**	**268**
At least one TEAE	n (%) E	62 (71.3) 132	59 (64.1) 134	63 (70.8) 169	184 (68.7) 435
At least one IP-related TEAE	n (%) E	25 (28.7) 31	31 (33.7) 42	31 (34.8) 40	87 (32.5) 113
At least one TEAE of special interest	n (%) E	7 (8.0) 8	10 (10.9) 15	7 (7.9) 9	24 (9.0) 32
At least one IP-related TEAE of special interest	n (%) E	6 (6.9) 6	10 (10.9) 12	7 (7.9) 8	23 (8.6) 26
At least one TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	7 (8.0) 7	6 (6.5) 7	6 (6.7) 7	19 (7.1) 21
At least one IP-related TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	-	2 (2.2) 3	4 (4.5) 4	6 (2.2) 7
At least one local administration site reaction	n (%) E	7 (8.0) 8	10 (10.9) 15	6 (6.7) 7	23 (8.6) 30
At least one serious TEAE	n (%) E	1 (1.1) 1	1 (1.1) 1	-	2 (0.7) 2
At least one serious IP-related TEAE	n (%) E	-	-	-	-
ADA Negative					
	N	**28**	**19**	**21**	**68**
At least one TEAE	n (%) E	14 (50.0) 31	16 (84.2) 28	12 (57.1) 20	42 (61.8) 79
At least one IP-related TEAE	n (%) E	7 (25.0) 12	9 (47.4) 11	2 (9.5) 5	18 (26.5) 28
At least one TEAE of special interest	n (%) E	-	2 (10.5) 2	-	2 (2.9) 2

At least one IP-related TEAE of special interest	n (%) E	-	2 (10.5) 2	-	2 (2.9) 2
At least one TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	3 (10.7) 5	5 (26.3) 5	3 (14.3) 3	11 (16.2) 13
At least one IP-related TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	2 (7.1) 3	2 (10.5) 2	1 (4.8) 1	5 (7.4) 6
At least one local administration site reaction	n (%) E	-	2 (10.5) 2	-	2 (2.9) 2
At least one serious TEAE	n (%) E	-	-	-	-
At least one serious IP-related TEAE	n (%) E	-	-	-	-

AE: adverse event; CTCAE: Common Terminology Criteria for AE; IP: Investigational product; TEAE: treatment-emergent AE; n: Number of participants with at least one TEAE in each category (participants with multiple events in each category are counted only once in each category); N: Total number of participants in the relevant population; E: Number of TEAEs in each category; %: Percentage of participants in each category calculated relative to the total number of participants in the relevant population.
A TEAE is defined as any AE which commenced or worsened in severity on or after the start of IP administration. A related TEAE is defined as any TEAE reported as related to study drug and included events with a missing relationship. A serious TEAE is defined as any TEAE for which 'Serious event' is indicated as 'Yes'. A TEAE of special interest is defined as any AE considered to be of special interest per protocol. A local administration site reaction is defined as any AE for which the high-level group term is coded to 'Administration site reactions' and considered to be of special interest per protocol. AEs with missing severity were classified as 'severe'.

a For the summary of TEAEs by severity, participants could appear in each category. Participants are only counted once in each severity category

Table 42: Overview of TEAEs by nAb Status (Study AVT05-GL-P01, Safety Population)

Category	Statistic	AVT05 (N=115)	EU-Simponi (N=111)	US-Simponi (N=110)	Overall (N=336)
nAb Positive					
	N	**66**	**68**	**61**	**195**
At least one TEAE	n (%) E	49 (74.2) 107	46 (67.6) 103	46 (75.4) 132	141 (72.3) 342
At least one IP-related TEAE	n (%) E	20 (30.3) 26	26 (38.2) 34	24 (39.3) 32	70 (35.9) 92
At least one TEAE of special interest	n (%) E	5 (7.6) 6	9 (13.2) 12	6 (9.8) 8	20 (10.3) 26
At least one IP-related TEAE of special interest	n (%) E	4 (6.1) 4	9 (13.2) 9	6 (9.8) 7	19 (9.7) 20
At least one TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	5 (7.6) 5	4 (5.9) 5	5 (8.2) 5	14 (7.2) 15
At least one IP-related TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	-	2 (2.9) 3	4 (6.6) 4	6 (3.1) 7
At least one local administration site reaction	n (%) E	5 (7.6) 6	9 (13.2) 12	5 (8.2) 6	19 (9.7) 24
At least one serious TEAE	n (%) E	-	1 (1.5) 1	-	1 (0.5) 1
At least one serious IP-related TEAE	n (%) E	-	-	-	-
nAb Negative					
	N	**21**	**24**	**28**	**73**
At least one TEAE	n (%) E	13 (61.9) 25	13 (54.2) 31	17 (60.7) 37	43 (58.9) 93
At least one IP-related TEAE	n (%) E	5 (23.8) 5	5 (20.8) 8	7 (25.0) 8	17 (23.3) 21
At least one TEAE of special interest	n (%) E	2 (9.5) 2	1 (4.2) 3	1 (3.6) 1	4 (5.5) 6
At least one IP-related TEAE of special interest	n (%) E	2 (9.5) 2	1 (4.2) 3	1 (3.6) 1	4 (5.5) 6
At least one TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	2 (9.5) 2	2 (8.3) 2	1 (3.6) 2	5 (6.8) 6
At least one IP-related TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	-	-	-	-
At least one local administration site reaction	n (%) E	2 (9.5) 2	1 (4.2) 3	1 (3.6) 1	4 (5.5) 6
At least one serious TEAE	n (%) E	1 (4.8) 1	-	-	1 (1.4) 1
At least one serious IP-related TEAE	n (%) E	-	-	-	-

AE: adverse event; CTCAE: Common Terminology Criteria for AE; IP: Investigational product; TEAE: treatment-emergent AE; n: Number of participants with at least one TEAE in each category (participants with multiple events in each category are counted only once in each category); N: Total number of participants in the relevant

population; E: Number of TEAEs in each category; %: Percentage of participants in each category calculated relative to the total number of participants in the relevant population
A TEAE is defined as any AE which commenced or worsened in severity on or after the start of IP administration. A related TEAE is defined as any TEAE reported as related to study drug and included events with a missing relationship. A serious TEAE is defined as any TEAE for which 'Serious event' is indicated as 'Yes'. A TEAE of special interest is defined as any AE considered to be of special interest per protocol. A local administration site reaction is defined as any AE for which the high-level group term is coded to 'Administration site reactions' and considered to be of special interest per protocol. AEs with missing severity were classified as 'severe'.

a For the summary of TEAEs by severity, participants could appear in each category. Participants are only counted once in each severity category.

Phase 3 study (AVT05-GL-C01)

Overview of safety results up to week 16 in ADA positive and ADA negative subgroups is shown in Table *43* and in nAb positive and nAb negative subgroups in Table *44*.

Table 43: TEAEs by ADA Status – Up to Week 16 (AVT05-GL-C01, Safety Analysis Set)

	AVT05 (N=251)		**EU-Simponi (N=251)**	
	ADA Positive (N=147) n (%)	**ADA Negative (N=104) n (%)**	**ADA Positive (N=159) n (%)**	**ADA Negative (N=92) n (%)**
Any TEAE	54 (36.7)	42 (40.4)	69 (43.4)	30 (32.6)
Maximum Severity of TEAEs				
Grade 1 - Mild	30 (20.4)	22 (21.2)	41 (25.8)	12 (13.0)
Grade 2 - Moderate	23 (15.6)	17 (16.3)	27 (17.0)	16 (17.4)
Grade 3 - Severe	1 (0.7)	3 (2.9)	1 (0.6)	1 (1.1)
Grade 4 - Potentially Life-threatening	0	0	0	0
Grade 5 - Death	0	0	0	1 (1.1)
Treatment-Related TEAEs	12 (8.2)	7 (6.7)	17 (10.7)	11 (12.0)
Serious TEAEs	1 (0.7)	3 (2.9)	0	2 (2.2)
Treatment-Related Serious TEAEs	0	1 (1.0)	0	1 (1.1)
TEAE Leading to Early Termination	1 (0.7)	3 (2.9)	0	1 (1.1)
Treatment-Related TEAE Leading to Early Termination	0	1 (1.0)	0	1 (1.1)
Serious TEAE Leading to Early Termination	1 (0.7)	3 (2.9)	0	1 (1.1)
Treatment-Related Serious TEAE Leading to Early Termination	0	1 (1.0)	0	1 (1.1)
TEAEs of Special Interest	30 (20.4)	17 (16.3)	23 (14.5)	15 (16.3)
Death	0	0	0	1 (1.1)

N: Number of patients treated in the relevant Safety Analysis Set and ADA group and is used as the denominator for percentage calculations; n (%) represents number and % of patients with events starting on or after the first dose of study drug (Day 1) but before the Week 16 dose.
Patients are counted only once at the maximum severity in the following order: Grade 5, 4, 3, 2 and 1 (mild). Events with unknown severity are counted as severe. Patient is presented only once in the respective patient count by highest relationship. Events with unknown relationship to study drug are counted as drug-related. See TEAE definition in SAP. ADA Positive if any positive ADA result observed before Week 16 dose; ADA Negative otherwise.

Table 44: Overview of TEAEs by nAb Status Up to Week 16 (Study AVT05-GL-C01, Safety Analysis Set)

	AVT05 (N=251)		EU-Simponi (N=251)	
	nAb Positive (N=68) n (%)	nAb Negative (N=183) n (%)	nAb Positive (N=76) n (%)	nAb Negative (N=175) n (%)
Any TEAE	24 (35.3)	72 (39.3)	27 (35.5)	72 (41.1)
Maximum Severity of TEAEs				
Grade 1 - Mild	17 (25.0)	35 (19.1)	14 (18.4)	39 (22.3)
Grade 2 - Moderate	7 (10.3)	33 (18.0)	13 (17.1)	30 (17.1)
Grade 3 - Severe	0	4 (2.2)	0	2 (1.1)
Grade 4 - Potentially Life-threatening	0	0	0	0
Grade 5 - Death	0	0	0	1 (0.6)
Treatment-Related TEAEs	6 (8.8)	13 (7.1)	4 (5.3)	24 (13.7)
Serious TEAEs	0	4 (2.2)	0	2 (1.1)
Treatment-Related Serious TEAEs	0	1 (0.5)	0	1 (0.6)
TEAE Leading to Early Termination	0	4 (2.2)	0	1 (0.6)
Treatment-Related TEAE Leading to Early Termination	0	1 (0.5)	0	1 (0.6)
Serious TEAE Leading to Early Termination	0	4 (2.2)	0	1 (0.6)
Treatment-Related Serious TEAE Leading to Early Termination	0	1 (0.5)	0	1 (0.6)
TEAEs of Special Interest	13 (19.1)	34 (18.6)	10 (13.2)	28 (16.0)
Death	0	0	0	1 (0.6)

Overview of safety results from week 16 to EoS in ADA positive and ADA negative subgroups is shown in Table *45* and in nAb positive and nAb negative subgroups in Table *46*.

Table 45: TEAEs by ADA Status – From Week 16 to EoS (AVT05-GL-C01, Safety Analysis Set)

	AVT05/AVT05 (N=223)		EU-Simponi/AVT05 (N=112)		EU-Simponi/EU-Simponi (N=113)	
	ADA Positive (N=146) n (%)	ADA Negative (N=77) n (%)	ADA Positive (N=80) n (%)	ADA Negative (N=32) n (%)	ADA Positive (N=70) n (%)	ADA Negative (N=43) n (%)
Any TEAE	76 (52.1)	38 (49.4)	47 (58.8)	18 (56.3)	41 (58.6)	24 (55.8)
Maximum Severity of TEAEs						
Grade 1 - Mild	29 (19.9)	13 (16.9)	16 (20.0)	8 (25.0)	15 (21.4)	8 (18.6)
Grade 2 - Moderate	43 (29.5)	18 (23.4)	27 (33.8)	8 (25.0)	20 (28.6)	13 (30.2)
Grade 3 - Severe	4 (2.7)	7 (9.1)	4 (5.0)	2 (6.3)	6 (8.6)	2 (4.7)
Grade 4 - Potentially Life-threatening	0	0	0	0	0	1 (2.3)
Grade 5 - Death	0	0	0	0	0	0
Treatment-Related TEAEs	10 (6.8)	5 (6.5)	7 (8.8)	5 (15.6)	10 (14.3)	8 (18.6)
Serious TEAEs	2 (1.4)	4 (5.2)	2 (2.5)	0	4 (5.7)	3 (7.0)
Treatment-Related Serious TEAEs	0	0	0	0	0	1 (2.3)
TEAE Leading to Early Termination	1 (0.7)	2 (2.6)	0	2 (6.3)	3 (4.3)	2 (4.7)
Treatment-Related TEAE Leading to Early Termination	0	0	0	2 (6.3)	1 (1.4)	0
Serious TEAE Leading to Early Termination	0	1 (1.3)	0	0	1 (1.4)	1 (2.3)
Treatment-Related Serious TEAE Leading to Early Termination	0	0	0	0	0	0
TEAEs of Special Interest	42 (28.8)	15 (19.5)	27 (33.8)	9 (28.1)	21 (30.0)	11 (25.6)
Death	0	0	0	0	0	0

N: Number of patients treated in the relevant Safety Analysis Set and ADA group and is used as the denominator for percentage calculations.

n (%) represents number and % of patients with events starting on or after the Week 16 dose through End of Study. Patients are counted only once at the maximum severity in the following order: Grade 5, 4, 3, 2 and 1 (mild). Events with unknown severity are counted as severe. Patient is presented only once in the respective patient count by highest relationship. Events with unknown

relationship to study drug are counted as drug-related. See TEAE definition in SAP. ADA Positive if any positive ADA result obsbserved on or after the Week 16 dose through End of Study; ADA Negative otherwise.

Table 46: TEAEs by nAb Status – From Week 16 to EoS (AVT05-GL-C01, Safety Analysis Set)

	AVT05/AVT05 (N=223)		EU-Simponi/AVT05 (N=112)		EU-Simponi/EU-Simponi (N=113)	
	nAb Positive (N=73) n (%)	nAb Negative (N=150) n (%)	nAb Positive (N=44) n (%)	nAb Negative (N=68) n (%)	nAb Positive (N=44) n (%)	nAb Negative (N=69) n (%)
Any TEAE	36 (49.3)	78 (52.0)	27 (61.4)	38 (55.9)	26 (59.1)	39 (56.5)
Maximum Severity of TEAEs						
Grade 1 - Mild	18 (24.7)	24 (16.0)	10 (22.7)	14 (20.6)	8 (18.2)	15 (21.7)
Grade 2 - Moderate	16 (21.9)	45 (30.0)	15 (34.1)	20 (29.4)	14 (31.8)	19 (27.5)
Grade 3 - Severe	2 (2.7)	9 (6.0)	2 (4.5)	4 (5.9)	4 (9.1)	4 (5.8)
Grade 4 - Potentially Life-threatening	0	0	0	0	0	1 (1.4)
Grade 5 - Death	0	0	0	0	0	0
Treatment-Related TEAEs	3 (4.1)	12 (8.0)	3 (6.8)	9 (13.2)	6 (13.6)	12 (17.4)
Serious TEAEs	1 (1.4)	5 (3.3)	0	2 (2.9)	3 (6.8)	4 (5.8)
Treatment-Related Serious TEAEs	0	0	0	0	0	1 (1.4)
TEAE Leading to Early Termination	1 (1.4)	2 (1.3)	0	2 (2.9)	2 (4.5)	3 (4.3)
Treatment-Related TEAE Leading to Early Termination	0	0	0	2 (2.9)	0	1 (1.4)
Serious TEAE Leading to Early Termination	0	1 (0.7)	0	0	1 (2.3)	1 (1.4)
Treatment-Related Serious TEAE Leading to Early Termination	0	0	0	0	0	0
TEAEs of Special Interest	18 (24.7)	39 (26.0)	14 (31.8)	22 (32.4)	13 (29.5)	19 (27.5)
Death	0	0	0	0	0	0

N: Number of patients treated in the relevant Safety Analysis Set and nAb group and is used as the denominator for percentage calculations.
n (%) represents number and % of patients with events starting on or after the Week 16 dose through End of Study. Patients are counted only once at the maximum severity in the following order: Grade 5, 4, 3, 2 and 1 (mild). Events with unknown severity are counted as severe. Patient is presented only once in the respective patient count by highest relationship. Events with unknown relationship to study drug are counted as drug-related. See TEAE definition in SAP.nAb Positive if any positive nAb result observed on or after the Week 16 dose through End of Study; nAb Negative otherwise.

2.5.8.8. Safety related to drug-drug interactions and other interactions

Not applicable.

2.5.8.9. Discontinuation due to adverse events

Phase 1 study (AVT05-GL-P01)

No TEAEs leading to discontinuation from the study treatment were reported.

Phase 3 study (AVT05-GL-C01)

Up to week 16, TEAEs leading to discontinuation from the study treatment phase were reported in 4 (1.6%) patients in the AVT05 group and in 1 (0.4%) patient in the EU Simponi group (Table *47*). The events of infectious pleural effusion (AVT05 group), and metastatic neoplasm and abdominal pain upper (EU-Simponi group) were considered treatment-related.

Table 47: TEAEs Leading to Discontinuation up to Week 16 (AVT05-GL-C01, Safety Analysis Set)

System Organ Class Preferred Term	AVT05 (N=251) Patients n (%)	Events n	EU-Simponi (N=251) Patients n (%)	Events n
Any Reported	4 (1.6)	4	1 (0.4)	2
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.4)	1	1 (0.4)	1
Benign Neoplasm of Thyroid Gland	1 (0.4)	1	0	0
Metastatic Neoplasm	0	0	1 (0.4)	1
Gastrointestinal Disorders	0	0	1 (0.4)	1
Abdominal Pain Upper	0	0	1 (0.4)	1
Infections And Infestations	1 (0.4)	1	0	0
Infectious Pleural Effusion	1 (0.4)	1	0	0
Nervous System Disorders	1 (0.4)	1	0	0
Meningitis Noninfective	1 (0.4)	1	0	0
Renal And Urinary Disorders	1 (0.4)	1	0	0
Nephrotic Syndrome	1 (0.4)	1	0	0

N: Number of patients treated in the relevant Safety Analysis Set and is used as the denominator for percentage calculations; n (%) represents number and % of patients with events starting on or after the first dose of study drug (Day 1) but before the Week 16 dose; TEAEs: Treatment-Emergent Adverse Events.
Patients are counted once within a system organ class and once for each unique preferred term. See TEAE definition in SAP. Adverse events are coded using MedDRA version 27.1.

From week 16 to EoS, TEAEs leading to discontinuation from the study treatment phase were reported in 2 (0.9%) patients in the AVT05/AVT05 group, in 2 (1.8%) patients in the EU-Simponi/AVT05 group, and in 5 (4.4%) patients in the EU Simponi/EU Simponi group (Table *48*). The TEAEs of latent tuberculosis, eosinophilia, and tuberculosis were considered as treatment-related.

Table 48: TEAEs Leading to Discontinuation from Week 16 to EoS (AVT05-GL-C01, Safety Analysis Set)

	AVT05/ AVT05 (N=223)		EU-Simponi/ AVT05 (N=112)		EU-Simponi/ EU-Simponi (N=113)	
System Organ Class Preferred Term	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Any Reported	2 (0.9)	2	2 (1.8)	2	5 (4.4)	6
INFECTIONS AND INFESTATIONS	0	0	1 (0.9)	1	2 (1.8)	2
Latent tuberculosis	0	0	0	0	1 (0.9)	1
Postoperative wound infection	0	0	0	0	1 (0.9)	1
Tuberculosis	0	0	1 (0.9)	1	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	0	2 (1.8)	2
Back pain	0	0	0	0	1 (0.9)	1
Musculoskeletal disorder	0	0	0	0	1 (0.9)	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.4)	1	0	0	1 (0.9)	1
Breast cancer	1 (0.4)	1	0	0	0	0
Endometrial adenocarcinoma	0	0	0	0	1 (0.9)	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.4)	1	0	0	1 (0.9)	1
Cough	1 (0.4)	1	0	0	0	0
Pleural effusion	0	0	0	0	1 (0.9)	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	1 (0.9)	1	0	0
Eosinophilia	0	0	1 (0.9)	1	0	0

N: Number of patients treated in the relevant Safety Analysis Set and is used as the denominator for percentage calculations.
n (%) represents number and % of patients with events starting on or after the Week 16 dose through End of Study; TEAEs: Treatment-Emergent Adverse Events. Patients are counted once within a system organ class and once for each unique preferred term. See TEAE definition in SAP. Adverse events are coded using MedDRA version 27.1.

2.5.8.10. Post marketing experience

Not applicable.

2.5.9. Discussion on clinical safety

The safety data has been presented separately from the Phase 1 study in healthy adults (AVT05-GL-P01), as well as from the pivotal Phase 3 study in patients with moderate to severe rheumatoid arthritis (AVT05-GL-C01). The safety analyses in both studies were conducted in the safety analysis set, which comprised of all subjects who received at least one dose of the study medication. The total number of subjects who received a dose of AVT05 (phase 1 study – 115 subjects; phase 3 study – 251+112 subjects) and the selection of comparators are considered appropriate.

The safety assessments were adequately chosen, considering the known safety profile of golimumab. AESIs were selected based on warnings and precautions outlined in the Simponi product information, including assessment of injection site reactions (ISRs). Overall, the collection of safety data was considered reliable.

Demographics and baseline characteristics, prior and concomitant medical and surgical history and procedures, prior and concomitant medications were overall balanced between the treatment groups in both studies.

Drug exposure was similar across study groups in both clinical studies, enabling meaningful comparisons. During the evaluation (at Day 121), the applicant submitted the final CSR of the Phase 3 study with data up to week 52. The safety database in these studies is sufficient for evaluating the safety of AVT05 compared to Simponi.

Phase 1 study (AVT05-GL-P01)

The most common TEAEs by SOC (reported in ≥10% of participants overall) were infections and infestations, nervous system disorders, general disorders and administration site conditions, and gastrointestinal disorders. Some minor numerical differences between the treatment groups were observed, e.g. TEAEs in the SOC infections and infestations were somewhat less common in the AVT05 group (21.7%) compared to EU-Simponi group (29.7%) or US-Simponi group (33.6%). In general, however, the incidence of TEAEs by SOC was similar across the treatment groups. The number of participants reporting at least one TEAE was also similar in all study groups. Most TEAEs were mild to moderate in intensity.

TEAEs that were considered related to the study drug were reported for 32 (27.8%) participants in the AVT05 group, 40 (36.0%) participants in the EU-Simponi group and 33 (30.0%) participants in the US-Simponi group. The slight numerical imbalance between AVT05 and EU-Simponi was mainly due to ADRs under SOC general disorders and administration site conditions [8 (7.0%) and 15 (13.5%) participants in the AVT05 and EU-Simponi groups, respectively, and 12 (10.9%) in the US-Simponi group].

In terms of AESIs, local administration site reactions were reported for 7 (6.1%) participants in the AVT05 group, 12 (10.8%) participants in the EU-Simponi group and 6 (5.5%) participants in the US-Simponi group, all were mild in intensity. The remaining two AESIs, rash macular and vulvovaginal candidiasis, were reported for 1 participant each in the US-Simponi group.

Two patients had serious TEAEs, one in the AVT05 group (abortion induced) and one in the EU-Simponi group (abortion spontaneous), both considered unrelated to the study drug.

No TEAEs leading to discontinuation were reported.

No unexpected changes or differences between the treatment groups were observed in the laboratory findings, vital signs or ECG parameters. Eight participants (1 in the AVT05 group, 4 in the EU-Simponi group, and 3 in the US-Simponi group tested positive for M. tuberculosis at their EOS visit. All events were mild (Grade 1) in severity, and were considered not related to the investigational product. No indication of active TB disease was found.

Phase 3 study (AVT05-GL-C01)

Up to week 16 (Stage 1)

The most common TEAEs by SOC (reported in ≥10% of patients in either study group) were infections and infestations, reported for 53 (21.1%) patients in the AVT05 group and 56 (22.3%) patients in the EU-Simponi group, and investigations, reported for 25 (10.0%) patients in the AVT05 group and 24 (9.6%) patients in the EU-Simponi group. The incidence and severity of TEAEs was generally well balanced between the study groups. Most of the TEAEs were mild to moderate.

TEAEs that were considered related to the study drug under SOC infections and infestations were reported for 7 (2.8%) patients in the AVT05 group and 15 (6.0%) patients in the EU-Simponi group. Three (3) TEAEs of bronchitis, pharyngitis, and upper respiratory infection in the EU-Simponi groups were considered related to study treatment compared to none in the AVT05 group, resulting in a slight numerical imbalance. TEAEs of ISR that were considered related to the study drug was reported for 1 (0.4%) patient in the AVT05 group and 6 (2.4%) patients in the EU-Simponi group.

AESIs were reported for 48 (19.1%) patients in the AVT05 group and 38 (15.1%) patients in the EU-Simponi group and the incidence of AESIs was generally well balanced between the study groups. ISR events were less frequently reported in the AVT05 group (1 ISR) compared to the EU-Simponi group (10 ISRs, 1 contusion and 1 injection site hematoma). All ISRs were mild in severity.

Four (1.6%) patients in the AVT05 and 2 (0.8%) patients in the EU-Simponi group experienced serious TEAEs. One serious TEAE in the AVT05 group (infectious pleural effusion) and one in the EU-Simponi group (metastatic neoplasm) were considered to be treatment-related. The metastatic neoplasm resulted in a fatal outcome. It is noted that infections (e.g. lower respiratory tract infection (such as pneumonia)) and neoplasm are already listed as adverse reactions in the product information of golimumab.

Four patients in the AVT05 group (benign neoplasm of the thyroid gland, infectious pleural effusion, meningitis noninfective and nephrotic syndrome) and 1 patient in the EU-Simponi group (2 events: metastatic neoplasm and abdominal pain upper) discontinued the treatment due to TEAEs.

There were no unexpected findings or notable differences between the study groups in the laboratory values, vital signs or ECG parameters. No TEAEs related to TB testing were reported up to week 16.

From week 16 to EoS (Stage 2)

No major imbalances were observed between the groups in terms of incidence or severity of TEAEs. The most common TEAEs by SOC were infections and infestations, reported by 67 (30.0%), 41 (36.6%) and 38 (33.6%) of patients, and investigations, reported by 23 (10.3%), 13 (11.3%) and 13 (11.5%) of patients in the AVT05/AVT05, EU-Simponi/AVT05 and EU-Simponi/EU-Simponi groups, respectively.

TEAEs that were considered related to the study drug were reported for 15 (6.7%) patients in the AVT05/AVT05 group, 12 (10.7%) patients in the EU-Simponi/AVT05 group, and 18 (15.9%) patients in the EU-Simponi/EU-Simponi group. The incidence of AESIs between the study groups was broadly similar from week 16 to EoS. ISRs were reported only for 2 patients in the EU-Simponi/AVT05 group and 1 patient in the EU-Simponi/EU-Simponi group.

Altogether 6 (2.7%), 2 (1.8%) and 7 (6.2%) patients in the AVT05/AVT05, EU-Simponi/AVT05 and EU-Simponi/EU-Simponi groups, respectively, experienced serious TEAES, with no clustering to any specific SOC. No deaths were reported.

There were no unexpected findings or notable differences between the study groups in the laboratory values, vital signs or ECG parameters.

Three Grade 2 TEAEs related to tuberculosis testing were reported; 1 subject in the EU Simponi/AVT05 group had TEAE of tuberculosis, 1 subject in the EU-Simponi/AVT05 group was tested Mycobacterium tuberculosis complex test positive, which was assessed as false positivity, and 1 subject in the EU-Simponi/EU-Simponi group experienced latent tuberculosis. In addition, one patient in the AVT05/AVT05 had Grade 1 TEAE of latent TB.

Overall, the final CSR submitted by the applicant at Day 121 with safety data up to 52 weeks did not reveal any critical findings regarding similarity of safety between AVT05 and Simponi.

Immunogenicity

The immunogenicity profiles of AVT05 vs EU-Simponi and US-Simponi were generally similar. In study AVT05-GL-P01, the frequency of participants with at least 1 positive ADA result was 75.7% in the AVT05 group and comparable with EU-Simponi (82.9%). In study AVT05-GL-C01, the treatment-emergent ADA incidence up to week 16 was 57.8% vs.52.7%, in the EU-Simponi and in the AVT05 groups, respectively.

Effects on immunogenicity on clinical PK

In study AVT05-GL-P01, the geometric means of the systemic exposure PK parameters were lower in the ADA/Nab-positive subgroups, compared with those observed in the ADA/Nab-negative subgroups, as expected. The effect of ADA on PK parameters of golimumab was similar in both treatment arms.

In study AVT05-GL-C01, the ADAs and nAbs developed with a similar onset time in both AVT05 and EU-Simponi treatment groups up to Week 24. At week 16 the median trough drug concentrations were approximately 40% lower in ADA positive subjects than in ADA negative subjects. The effect of ADA on golimumab trough concentrations was similar in both treatment arms.

Effects on immunogenicity on safety

The applicant conducted a separate analysis of safety in immunogenicity subgroups, i.e. in ADA positive and ADA negative, as well as nAb positive and nAb negative subgroups. After single dose administration in the Phase 1 study, the incidence of TEAEs was slightly higher in ADA positive vs. negative and nAb positive vs. negative participants, including local injection site reactions. In ADA negative participants, slightly less TEAEs were reported in the AVT05 group compared to the EU-Simponi group. However, the low number of ADA-negative participants limits the adequacy of this comparison. In the Phase 3 study, no apparent differences in the safety profile by ADA (positive vs. negative) or nAb (positive vs. negative) status, or between AVT05 vs. golimumab in the immunogenicity subgroups were observed up to week 16, or between the AVT05/AVT05, EU-Simponi/AVT05 and EU-Simponi/EU-Simponi study groups from week 16 to EoS. In summary, the safety analysis by immunogenicity status did not reveal any relevant differences between AVT05 and Simponi.

2.5.10. Conclusions on the clinical safety

The submitted data from Phase 1 PK study and Phase 3 study demonstrate that AVT05 and Simponi have similar safety profiles. Apart from some minor numerical differences, the incidence and severity

of TEAEs were generally comparable between AVT05 and Simponi in both clinical studies. The reported IP-related TEAEs were expected and already listed in the SmPC of the reference product. Further, no major imbalances were observed in the safety profile of patients who switched from EU-Simponi to AVT05 at week 16 compared to the safety profile of patients who continued with AVT05 or EU-Simponi

Based on the submitted data from Phase 1 PK study and Phase 3 study up to week 52, AVT05 and Simponi can be considered to be biosimilar from the safety point of view.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 49: Summary of safety concerns (Module SVIII)

Summary of safety concerns	
Important identified risks	Serious infections Demyelinating disorders Malignancy
Important potential risks	Serious depression including suicidality Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero
Missing information	Long-term safety in paediatric patients

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Table 50: Summary table of pharmacovigilance activities and risk minimisation measures (V.3)

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Identified Risk(s)		
Serious infections	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, 4.5, 4.8 PL sections 2 and 4 **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire for serious Infections, opportunistic infections, TB and Progressive

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Patient Reminder Card	Multifocal Leukoencephalopathy (PML)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS) **Additional pharmacovigilance activities:** None
Demyelinating disorders	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Malignancy	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire for malignancies (including lymphoma, second and secondary malignancies) **Additional pharmacovigilance activities:** None
Important Potential Risk(s)		
Serious depression including suicidality	**Routine risk minimisation measures:** SmPC sections 4.8 PL sections 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero*	**Routine risk minimisation measures:** SmPC sections 4.4, 4.6 PL sections 2 **Additional risk minimisation measures:** Patient Reminder Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing Information		
Long-term safety in paediatric patients	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. 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.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Simponi 50 mg and 100 mg solution for injection in pre-filled pen and in pre-filled syringe. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Gobivaz (Golimumab) is included in the additional monitoring list as it is 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

Gobivaz was developed as a biosimilar to the reference medicinal product Simponi (golimumab).

The applicant applied for all approved therapeutic indications of the reference medicinal product Simponi. These indications are summarised:

Adults:

Indicated in combination with methotrexate (MTX) for the treatment of:

- Rheumatoid Arthritis

Indicated alone or in combination with MTX for the treatment of:

- Psoriatic Arthritis

Indicated for the treatment of:

- Axial spondylarthritis
- Ulcerative Colitis

Children:

Indicated in combination with MTX for the treatment of polyarticular Juvenile Idiopathic Arthritis for children ≥2 years of age

The product has been developed for subcutaneous administration. The applicant only applied for the 50 mg and 100 mg solution for injection in pre-filled pen and in pre-filled syringe. The applicant did not apply for the paediatric strength, 45 mg/0.45 ml solution for injection, which is intended for the treatment of active polyarticular juvenile idiopathic arthritis for children with body weight of less than 40 kg.

Summary of Quality data

The overall approach to demonstrate similarity of AVT05 to EU-Simponi is mainly in line with the current guidance of EMA/CHMP/BWP/247713 2012 and EMA/CHMP/138502/2017.

AVT05 has been developed as a proposed biosimilar to Simponi (golimumab). AVT05 FP has the same target concentration (100 mg/mL) and formulation as Simponi, with the exception of containing poloxamer 188 instead of polysorbate 80.

EU-Simponi and US-Simponi batches were included in the head-to-head (H2H) analytical comparability exercise. Comparability between EU- and US-Simponi was demonstrated, however, data for EU-Simponi is considered pivotal for demonstrating analytical similarity. AVT05 batches manufactured from independent AS batches were included in the comparability exercise. The revised analytical similarity data is presented as a standalone package "Comparative analytical similarity assessment 2" in the updated section 3.2.R.3.3, and the final conclusions made by the applicant are based on this dataset.

Altogether, several separate H2H comparative analytical similarity studies were performed including comparison of the primary and higher order structures, N-/C-terminal variants, post-translational modifications (PTMs), charged variants, purity and impurities, protein concentration, Fab and Fc related biological functions, and forced degradation profiles between AVT05 and EU-Simponi.

Summary of non-clinical data

No stand-alone non-clinical data was submitted or evaluated during the biosimilarity assessment.

Summary of clinical data

The clinical development programme was designed to show similarity of the PK profile of AVT05 vs. EU-approved Simponi vs. US-licensed Simponi in healthy participants (a single dose study in healthy subjects including a subgroup of Japanese subjects [study AVT05-GL-P01]), and similarity of efficacy and safety (including immunogenicity) of AVT05 and EU-approved Simponi in participants with rheumatoid arthritis (RA) (a comparative clinical study in patients with moderate to severe RA [study AVT05-GL-C01]).

The clinical development programme is in accordance with the EMA's Guidelines on similar biological medicinal products (CHMP/437/04 Rev 1) and on similar biological medicinal products containing

biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1).

3.2. Results supporting biosimilarity

Quality

Reanalysis of the WCB originated AVT05 batches at an older age addressed differences initially found in various QAs providing additional data to support the similarity claim. The remaining uncertainties were appropriately addressed by extended characterisation and correlation analyses, as well as with relevant scientifically sound discussion. Extended characterisation data indicates that differences in charge variants are associated with variants that have no relevant clinical impact. The differences observed in N-glycosylation profile were thoroughly discussed and conclusions were generally supported with results of the structure-function correlation analyses. The differences in Fc-mediated effector activity were further investigated. The applicant justified that the identified minor differences in the Fc mediated effector activity observed for the batches produced so far would not have an impact on clinical performance.

Similarity has been adequately demonstrated between AVT05 and EU-Simponi for the physicochemical and biological properties (see Quality part for further details).

Non-clinical

None.

Pharmacokinetics

Pivotal PK study (AVT05-GL-P01)

In the primary statistical analysis (=ANCOVA including treatment as fixed effect and sex as factor and body weight at baseline as the continuous covariate) the 90% CIs of the GMRs for the primary PK parameters, C_{max} and $AUC_{0\text{-}inf}$ were within the equivalence margin of 80.00% and 125.00% (including 100%) for each of the 3 pairwise comparisons (i.e., AVT05 vs EU-Simponi, AVT05 vs US-Simponi and EU-Simponi vs US-Simponi).

Also, the means of the secondary PK parameters (i.e., $AUC_{0\text{-}t}$, $t_{1/2}$, K_{el}, Vz/F and CL/F) and median T_{max} were comparable between the study treatments.

In a sensitivity analysis using protein-adjusted primary PK parameters, all 90% CIs of the GMRs of C_{max} and $AUC_{0\text{-}inf}$, were within the prespecified margins of 80.00%-125.00% for each of the 3 pairwise comparisons.

Clinical phase 3 study (AVT05-GL-C01)

The serum trough concentrations were comparable between AVT05 and EU-Simponi, which supports the PK biosimilarity.

Clinical efficacy

A total of 502 screened participants were randomly assigned to receive either AVT05 (251 participants) or EU-Simponi (251 participants).

The mean change in DAS28-CRP from Baseline to Week 16 was similar for the AVT05 and EU-Simponi groups (-2.89 [0.058] and -2.98 [0.058], respectively). The 95% CI for the mean difference (-0.07, 0.25) was completely contained within the equivalence margin of -0.6, 0.6.

The nominal 95% confidence intervals for the assessed subgroups (by age, baseline DAS28-CRP score (≤5.1, >5.1), ADA Nab status and gender) were contained within the equivalence margin except for the subgroup of males for whom the confidence interval only marginally exceeded the equivalence boundaries. No meaningful difference was seen between AVT05 and EU-Simponi up to week 16 in any of the secondary efficacy endpoints, nor between the three treatment arms (including patients who switched from Simponi to AVT05) during Period 2 up to week 52.

Clinical safety

The safety data was presented separately from the Phase 1 study in healthy adults (AVT05-GL-P01), as well as from the pivotal Phase 3 study in patients with moderate to severe rheumatoid arthritis (AVT05-GL-C01). The available data up to week 52 demonstrate that AVT05 and Simponi have similar safety profiles.

3.3. Uncertainties and limitations about biosimilarity

All uncertainties identified during the assessment have been appropriately addressed and no concerns remain.

3.4. Discussion on biosimilarity

Quality

The applicant has evaluated the similarity between AVT05 and the reference product, EU-Simponi in a comprehensive comparability exercise.

In conclusion, primary and higher order structure, physico-chemical properties, as well as Fab and Fc related biological activities were demonstrated to be sufficiently similar between the products supporting the similarity claim. Minor differences observed in glycosylation, size variants and protein content are highly unlikely to have clinically meaningful impact, thus, these differences do not preclude similarity. AVT05 is controlled with sufficiently stringent acceptance limits to ensure similarity will be maintained in the future.

Overall, the analytical biosimilarity at the quality level has been appropriately demonstrated between AVT05 and EU-Simponi. The panel of methods performed is satisfactory covering structural as well as biologicals quality attributes with the necessary level of depth. From the quality perspective, Gobivaz is considered similar to EU-Simponi and is approvable as a biosimilar to Simponi.

Non-clinical

No stand-alone non-clinical data was submitted, and no major objections or other concerns were identified.

Pharmacokinetics

The PK biosimilarity in the pivotal PK study AVT05-GL-P01 using healthy adult subjects has been formally demonstrated between AVT05 and EU-Simponi and US-Simponi as for the primary PK parameters $AUC_{0\text{-}inf}$ and C_{max} (also for the secondary PK parameters $AUC_{0\text{-}t}$), the 90% CIs for the ratio of test-to-reference fell within the acceptance range of 80.00%-125.00% (including 100%).

The serum trough golimumab concentration data obtained from the efficacy/safety study AVT05-GL-C01 supported the PK biosimilarity between AVT05 and EU-Simponi.

Clinical efficacy

The assessment of efficacy was performed according to EMA's Guidelines on similar biological medicinal products (CHMP/437/04 Rev 1) and on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1). Results from the clinical study in patients with RA support biosimilarity of AVT-05 with EU-Simponi. No meaningful difference in efficacy was seen between AVT05 and EU-Simponi up to week 52.

Clinical safety

The safety assessment in the Phase 1 PK and in the Phase 3 studies seem to be adequately performed, taken into consideration the established safety profile of Simponi. The existing data, including safety analysis by immunogenicity status, i.e. ADA positive and ADA negative, as well as nAb positive and nAb negative subgroups, support the overall conclusion of similarity in terms of safety.

3.5. Extrapolation of safety and efficacy

Gobivaz (AVT05) has been developed for indications associated with autoimmune diseases for all the same indications as are licensed for the reference product, Simponi. Approval is sought for 50 mg/0.5mL and 100 mg/mL, Solution for subcutaneous injection pre-filled pen (PFS) and prefilled pen/Autoinjector (AI). The 45 mg/0.45 mL strength of Simponi is out of scope of this biosimilar application. In the present MAA, only the 50 mg/0.5 mL PFS presentation was included in the clinical studies and only adults with RA were studied. With regard to the AI presentation, the applicant has performed a failure modes and effects analysis (uFMEA) and two separate threshold analyses. The analyses concluded that the AVT05 PFS AI and Simponi AI products are comparable. Hence, the following extrapolation is needed:

a) from RA to other indications

b) from adult to paediatric use

In general, factors that should be considered for scientifically justifying extrapolation include mechanism of action (MOA), PK, expected toxicities, and any other factor that may affect safety and efficacy.

The MOA is the same across the approved indications for Simponi (golimumab). Golimumab is a human mAb that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors. The MOA is common for each of the originator indications (Rheumatoid Arthritis, Psoriatic Arthritis, Axial spondylarthritis, Ulcerative Colitis and polyarticular Juvenile Idiopathic Arthritis). Rheumatoid Arthritis is considered a sensitive indication to demonstrate similarity of AVT05 to Simponi and due to similar MOA, hence, similar efficacy was expected in all approved indications. Additional MOAs may include Fc-mediated effector function (ADCC and CDC), especially in the UC-indication.

Comparative analytical *in vitro* biological and functional assay results along with results from supplementary *in vitro* pharmacology studies were performed to show analytical similarity and that AVT05 and Simponi (golimumab) have the same MOA. Provided analytical data supports extrapolation to other indications.

Simponi product information supports the conclusion that, aside from body weight, there is no impact of intrinsic and extrinsic factors on the PK, safety or effectiveness of golimumab in children compared to adults. Measures to account for the impact of body weight (ie, weight-based dosing) are provided in the labelling. Hence, as biosimilarity is established, efficacy is expected to be similar between AVT05 and Simponi in the intended paediatric indication as well. As there is no presentation of AVT05 suitable

for dosing in children below 40kg, the posology instructions (section 4.2 of the SmPC) differ slightly from the originator. It says: There is no dosage form for GOBIVAZ in pre-filled pen that allows for a 45 mg/0.45 mL available for administration to children with polyarticular juvenile idiopathic arthritis weighing less than 40 kg. Thus, it is not possible to administer GOBIVAZ to patients that require a 45 mg dose. If an 45 mg/0.45 mL dose is required, another golimumab product should be used instead.

The clinical evidence presented in this application is supportive of the conclusion that there are no clinically meaningful differences between AVT05 and Simponi. The analytical biosimilarity at the quality level is also considered demonstrated between AVT05 and EU-Simponi. Hence, extrapolation of similarity to other indications and paediatric use is supported.

3.6. Additional considerations

None.

3.7. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Outcome

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

Rheumatoid arthritis (RA)

Gobivaz, in combination with methotrexate (MTX), is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

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

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

GOBIVAZ in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

Psoriatic arthritis (PsA)

GOBIVAZ, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Golimumab 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.

Axial spondyloarthritis

Ankylosing spondylitis (AS)

GOBIVAZ is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)

GOBIVAZ is indicated for the treatment of adults with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative colitis (UC)

GOBIVAZ 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The 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 educational programme consists of a Patient Reminder Card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professional(s) treating the patient about on-going treatment with the product.

The Patient Reminder Card shall contain the following key messages:

- A reminder to patients to show the Patient Reminder Card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using GOBIVAZ.
- A statement that the brand name and batch number should be recorded.
- Provision to record the type, date, and result of TB screenings.
- That treatment with GOBIVAZ may increase the risks of serious infection, opportunistic infections, tuberculosis, hepatitis B reactivation and breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero; and when to seek attention from a HCP.
- Contact details of the prescriber.

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

Not applicable.