Protocol Title:	A First-in-human, Randomized, Parallel Group, Double-blind, 3-arm Study to Investigate the Comparative PK, Safety, and Tolerability Between Subcutaneous AVT05, US-licensed Simponi®, and EU-approved Simponi® in Healthy Adult Participants
NCT Number	NCT05632211
Protocol version and date	Version 4.0, 01 November 2023

TITLE PAGE

Protocol Title:

A first-in-human, randomized, double-blind, single-dose, parallel-group design, 3-arm study to investigate the pharmacokinetic similarity, safety, tolerability, immunogenicity, and pharmacodynamics of subcutaneous AVT05, US-licensed Simponi®, and EU-approved Simponi® in healthy adult participants

Protocol Number: AVT05-GL-P01

Version: 4.0

Compound: AVT05 (golimumab)

Brief Title:

A first-in-human, randomized, double-blind, pharmacokinetic (PK) similarity study of subcutaneous AVT05, US-licensed Simponi, and EU-approved Simponi in healthy adult participants

Sponsor Name: Alvotech Swiss AG

Legal Registered Address: [redacted]

Date of Protocol: 01 November 2023

Sponsor Signatories:

I have read this protocol in its entirety and agree to conduct the study accordingly.

[redacted]

02-Nov-2023 | 11:50 GMT

Date

Head of Clinical and Medical Affairs
Alvotech Swiss AG

[redacted]

02-Nov-2023 | 11:58 GMT

Date

Head of Clinical Development and Patient Safety
Alvotech Swiss AG

[redacted]

02-Nov-2023 | 11:57 GMT

Date

Biostatistics Lead
Alvotech Swiss AG

The Medical Monitor's name and contact information can be found in Section 10.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History			
Document	**Date**	**Substantial**	**Region**
Protocol Version 4.0	01 November 2023	No	Global
Protocol Version 3.0	10 November 2022	Yes	Global
Protocol Version 2.0	13 October 2022	Yes	Global
Original Protocol (Version 1.0)	23 August 2022		

Version 4.0 dated 01 November 2023

Overall Rationale for the Amendment:

The protocol was amended primarily to remove the exploratory endpoint of the study and to clarify how the collected samples will be handled. Additionally, as differences were identified in the drug protein concentration between AVT05, US-licensed Simponi, and EU-approved Simponi, text was revised to confirm that the sensitivity PK similarity analysis will be performed using PK parameters adjusted by protein content. Lastly, changes based on previous protocol clarification letters were incorporated. A summary of the changes with rationale for each change is provided below.

Description of Changes in Amendment

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1, Synopsis; Section 1.3, Table 1 Schedule of Activities, Footnote m; Section 1.3, Table 2, Blood Sampling Time Points for Pharmacokinetic, Immunogenicity, and Pharmacodynamic Assessments; Section 3.0, Objectives and Endpoints; Section 4.1, Overall Design; Section 8.9, Inflammatory Cytokine Pharmacodynamic Assessments; Section 9.4.9, Pharmacodynamic Analyses (Section removed)	• Removed the exploratory objective and endpoints related to the ex-vivo substudy and PD assessments. • Clarified that the analysis of the samples collected from the 45 participants for the PD assessment will not be performed and these samples will be destroyed. • The mention of “pharmacodynamics” was removed from all corresponding sections.	Recent experience with regulatory agencies has confirmed that the assessment of PD markers for biosimilar studies has limited scientifical interest and adds no further actionable information for regulatory decision making, as the PK study remains the most sensitive clinical assay for detecting subtle differences between the products.

Section # and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis; Section 9.4.5, Pharmacokinetic Analyses; Section 9.4.6, Statistical Analysis for PK Similarity	• The protein content for AVT05 and the reference products was specified. • Specified that PK parameters will be adjusted by protein content and the sensitivity PK similarity analysis based on protein-content adjusted exposure PK parameters will be performed.	As differences were identified in the drug protein concentration between AVT05, US-licensed Simponi, and EU-approved Simponi, text was revised to confirm that the sensitivity PK similarity analysis will be performed using PK parameters adjusted by protein content.
Section 5.1, Inclusion Criteria	Inclusion #12: Clarified that participants who do not have documented history of hepatitis B vaccination could confirm this verbally, and the information should be documented under medical history.	Added for clarity.
Section 9.2, Sample Size Determination	Text added to specify that the sample size calculations were performed using SAS Version 9.4.	Added for clarity.
Section 10.2, Clinical Laboratory Tests, Table 8	Replaced blood urea nitrogen with urea under the clinical chemistry parameters	Clarification that the parameter blood urea nitrogen will not be used, and urea will be used instead.

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetic(s).

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Anti-HBc	hepatitis B core antibody
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the serum concentration-time curve from time t extrapolated to infinity, where t is the last time point with a concentration above the LLOQ
$AUC_{0\text{-}t}$	area under the concentration-time curve from zero to the last quantifiable concentration
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
CD	Crohn's disease
CI	confidence interval
CL/F	apparent total systemic clearance
COVID-19	coronavirus disease 2019
C_{max}	maximum serum concentration
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CS	clinically significant (abnormality)
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EoS	end-of-study
EPAR	European public assessment report
ET	early termination
FDA	Food and Drug Administration

Abbreviation	Definition
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GMP	good manufacturing practice
HbA1c	glycated hemoglobin
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HDEC	health and disability ethics committee
HREC	human research ethics committee
HRT	hormone replacement therapy
IB	Investigator's brochure
ICF	informed consent form
ICH	international council for harmonisation
IFN	interferon
Ig	immunoglobulin
IgM	immunoglobulin M
IL	interleukin
IP	investigational product
IV	intravenous
K_{el}	elimination rate constant
LLOQ	lower limit of quantitation
LS	least square
MedDRA	medical dictionary for regulatory activities
MTX	methotrexate
NAbs	neutralizing antibodies
NCS	not clinically significant (abnormality)
OTC	over-the-counter
PFS	prefilled syringe
PCR	polymerase chain reaction
PI	principal Investigator
PK	pharmacokinetic(s)

Abbreviation	Definition
PP	plaque psoriasis
PsA	psoriatic arthritis
PT	preferred term
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
Th	T helper cell
TNF-α	tumor necrosis factor-α
T_{max}	time to reach maximum serum concentration
UC	ulcerative colitis
ULN	upper limit of normal
USPI	United States product information
Vz/F	apparent volume of distribution
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A first-in-human, randomized, double-blind, single-dose, parallel-group design, 3-arm study to investigate the pharmacokinetic similarity, safety, tolerability, immunogenicity, and pharmacodynamics of subcutaneous AVT05, US-licensed Simponi®, and EU-approved Simponi® in healthy adult participants

Brief Title:

A first-in-human, randomized, double-blind, pharmacokinetic (PK) similarity study of subcutaneous AVT05, US-licensed Simponi, and EU-approved Simponi in healthy adult participants

Rationale:

Alvotech (hereafter, the Sponsor) is developing AVT05 globally as a proposed biosimilar to the reference product Simponi (active ingredient golimumab) for subcutaneous (SC) use. The study aims to demonstrate PK similarity of the proposed biosimilar test product AVT05 and the reference products US-licensed Simponi and EU-approved Simponi, in addition to evaluating the safety, tolerability, and immunogenicity of AVT05, when administered as a single 50 mg/0.5 mL SC dose.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To demonstrate the PK similarity of AVT05 with US-licensed and EU-approved Simponi and the PK of EU-approved Simponi with US-licensed Simponi.	• The primary PK parameters to be compared are: C_{max} and $AUC_{0\text{-}inf}$.
Secondary	
• To further characterize the PK of AVT05 with US-licensed Simponi and EU-approved Simponi following a single 50 mg/0.5 mL SC injection in healthy participants.	• Golimumab serum concentration-time profile following single-dose administration. • The secondary parameters to be assessed are, but not limited to: $AUC_{0\text{-}t}$, T_{max}, K_{el}, $t_{1/2}$, Vz/F, and CL/F.

Objectives	Endpoints
• To compare the safety and tolerability of AVT05 with US-licensed Simponi and EU-approved Simponi following a single 50 mg/0.5 mL SC injection in healthy participants.	• The safety parameters to be assessed include AEs, clinical laboratory assessments (hematology, coagulation, clinical chemistry, urinalysis, and urine microscopy), vital signs, ECG, physical examination findings, and injection site reactions.
• To compare the immunogenicity of AVT05 with US-licensed Simponi and EU-approved Simponi following a single 50 mg/0.5 mL SC injection in healthy participants.	• The immunogenicity parameters to be assessed are the frequency and titers of ADAs, and the frequency of NAbs against AVT05, US-licensed Simponi, and EU-approved Simponi.

Abbreviations: ADA = antidrug antibodies; $AUC_{0\text{-}inf}$ = area under the serum concentration-time curve from time t extrapolated to infinity, where t is the last time point with a concentration above the lower limit of quantitation: $AUC_{0\text{-}t}$+ Ct/K_{el}; $AUC_{0\text{-}t}$ = area under the serum concentration-time curve from time zero to the last quantifiable concentration; CL/F = apparent clearance; C_{max} = maximum serum concentration; ECG = electrocardiogram; IFN = interferon; IL = interleukin; K_{el} = elimination rate constant; NAbs = neutralizing antibodies; PK = pharmacokinetics; SC = subcutaneous; $t_{1/2}$ = elimination half-life; T_{max} = time to maximum serum concentration; Vz/F = apparent volume of distribution during the terminal phase after SC administration.
Note: As of Protocol Version 4.0, the analysis of the samples collected for the ex-vivo substudy will not be performed and the exploratory endpoint has been removed from the protocol.

Overall Design:

This study is a first-in-human (FIH) study and designed as a randomized, double-blind, single-dose, parallel-group design, 3-arm study to investigate the PK similarity, safety, tolerability, and immunogenicity of SC AVT05, US-licensed Simponi, and EU-approved Simponi in healthy adult participants.

Participants will undertake screening between Day -28 and Day -1 to determine their eligibility in the study. Participants who meet the eligibility criteria will be admitted to the study site on the day prior to dosing (Day -1), during which their continued eligibility will be assessed up to Day 1 prior to dosing. On Day 1, eligible participants will be randomized at a 1:1:1 ratio and will receive a single dose of one of the following: AVT05, US-licensed Simponi, or EU-approved Simponi.

A staggered sentinel dosing strategy will be implemented as a safety measure, with equal numbers of participants randomized to each treatment: Sentinel Group 1 (n = 3 participants [1 per group]), Sentinel Group 2 (n = 6 participants [2 per group]), and Sentinel Group 3 (n = 9 participants [3 per group]). Following investigational product (IP) administration, there will be at least 72 hours of close observation and safety monitoring. Safety data for all sentinel cohort participants, from dosing to 72 hours, will be considered when assessing sentinel group safety. There will also be at least 72 hours between sentinel groups (ie. 72 hours monitoring

between dosing for the last participant in a sentinel group and the first participant in the next sentinel group). Provided there are no significant safety or tolerability concerns (or events that meet the study stopping criteria) in the previous Sentinel Group following a safety review and discussion between the PI, Medical Monitor, and Sponsor, the next Sentinel Group of participants will be randomized and dosed. Once the IP dose is deemed to be safe and well tolerated in all 3 Sentinel Groups, the remaining participants (n = 318 participants [106 participants per group]) will be randomized and dosed.

Sentinel participants will undergo inpatient observation at the study site, at a minimum, from Day -1 to Day 4 (at least 72 hours postdose); all remaining participants will undergo inpatient observation at the study site, at a minimum, from Day -1 up to Day 2 (at least 24 hours postdose). Following dosing, PK, safety, tolerability, and other assessments will be performed according to the Schedule of Assessments. Postdose, participants will be followed up daily up to Day 12, then once a week from Day 15 to Day 64, and finally on Day 75 for the End-of-Study (EoS) visit.

Number of Participants:

A total of 336 healthy participants (112 per group) are planned to be enrolled at multiple study sites worldwide. Efforts will be made to include at least 10% of participants (33 participants, 11 per group) who are of Japanese origin or ethnicity (defined as born in Japan, holding a Japanese passport, not living outside Japan for more than five years and have all four grandparents Japanese, as confirmed by interview).

A total of 45 participants (15 per group) were included in the exploratory ex-vivo pharmacodynamic sub-study per site-specific recruitment plans. However, as of Protocol Version 4.0, the analysis of the samples collected for the ex-vivo substudy will not be performed.

Intervention Groups and Duration:

Eligible participants will be randomly assigned in a 1:1:1 ratio to receive a single 50 mg/0.5 mL SC dose of golimumab as AVT05 (test product) or US-licensed Simponi or EU-approved Simponi (reference products) on Day 1. Randomization will be stratified by gender, ethnicity, and body weight at Day -1 as follows: male, female, Japanese, non-Japanese ≤80 kg, and non-Japanese >80 kg.

The study duration per participant will be approximately 15 weeks. The study will consist of a 4-week Screening period, a 11-week treatment and assessment period, and an EoS visit on Day 75.

Study Stopping Criteria:

If either of the following scenarios occur, study enrollment and dosing will be halted:

- If ≥1 participant experiences a serious adverse event that is considered at least possibly related to the IP.
- If ≥2 participants experience severe non-serious adverse events that are considered at least, possibly related to the IP, independent of within or not within the same system-organ-class.
- If the Sponsor or Investigator considers there to be an unfavorable benefit-risk ratio based on emerging safety data.

If the Sponsor becomes aware that the trial has met stopping rules at another site, they will immediately inform all participating sites to stop dosing and await further instruction. A clear communication plan will be provided by the Sponsor for the participating sites.

If following consultation between the PI, Medical Monitor, and Sponsor, it is considered appropriate to restart IP administration in the remaining participants, justification will be submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and/or regulatory authorities for restarting the study.

Statistical Methods:

Determination of Sample Size:

Equivalence for each of the 3 pairwise treatment group comparisons (AVT05 to EU-approved Simponi, AVT05 to US-licensed Simponi, and EU-approved Simponi to US-licensed Simponi) will be established if the 90% confidence interval (CI) for each of these endpoints falls within the range 80% to 125%.

The 90% CI for the geometric mean ratio (GMR) between treatment groups will be calculated for all pairwise comparisons for both of primary endpoints $AUC_{0\text{-}inf}$ and C_{max}. The PK similarity will be demonstrated if the 90% CIs of GMR lie entirely within the prespecified margin of (0.80, 1.25) in all pairwise comparisons for both $AUC_{0\text{-}inf}$ and C_{max}.

The total sample size of 336 is based on a coefficient of variation (CV%) of 35.0% for $AUC_{0\text{-}inf}$ and 37.7% for C_{max} based on PK parameter summary data from Ling and Lyn (2010). Using the standard margin of (0.80, 1.25), a 90% two-sided CI for GMR, an assumed true GMR of 0.95, 101 evaluable participants per group will provide a power of 95.5% for each individual comparison of C_{max} and a power of 97.4% for each individual comparison of $AUC_{0\text{-}inf}$. Considering all 6 pairwise comparisons, the overall study power is estimated as 80.5%. Considering a non-evaluable rate of 10%, a total of 336 participants need to be randomized.

Of the 336 participants, at least 10% (33 participants, 11 per group) participants of Japanese origin are planned to be enrolled.

Analysis Populations:

The Randomized Population will include all participants who are randomized into this study. Participants will be analyzed according to their randomized treatment, regardless of which treatment the participant actually received.

The Safety Population will include all randomized participants who receive any amount of the IP. Participants will be analyzed according to the treatment they actually received, if this differs from that to which the participant is randomized.

The PK Population will include all randomized participants who receive any amount of the IP and have at least 1 evaluable PK parameter. Participants will be analyzed according to the treatment they actually received, if this differs from that to which the participant is randomized. Participants with deviations from dosing and PK sampling timepoints that could potentially affect the PK profile will be excluded from the PK Population, at the discretion of the blinded pharmacokineticist prior to analysis.

The Immunogenicity Population will include all randomized participants who receive any amount of the IP and have at least 1 evaluable postdose immunogenicity result (ie, positive or negative for presence of antidrug antibodies [ADAs]). Participants will be analyzed according to the treatment they actually received, if this differs from that to which the participant is randomized.

Pharmacokinetic Analyses:

Serum golimumab concentrations will be listed and summarized using descriptive statistics by treatment group and nominal PK sampling time point. The PK parameters of serum golimumab will be listed and summarized by treatment group using descriptive statistics. The PK parameters will also be adjusted for protein content and will be listed and summarized (details are provided in the Statistical Analysis Plan [SAP]). In addition, PK parameters will also be summarized by treatment and randomization strata. Body weight-adjusted PK parameters using weight normalization (assuming an average person's body weight of 70 kg) will be summarized by treatment group and randomization strata.

The primary PK parameters for the demonstration of PK similarity between AVT05 and the Simponi reference products will be C_{max} and $AUC_{0\text{-}inf}$. The statistical analysis will be performed using an analysis of covariance (ANCOVA) model on the logarithmic scale (ie, using natural log-transformed values of C_{max} and $AUC_{0\text{-}inf}$) including treatment as fixed effect and with gender as factor and body weight at baseline as the continuous covariate.

For the analysis of PK similarity, point estimates (geometric means and ratio of geometric means) will be calculated by back transforming the least square (LS) means of the natural log-transformed values of C_{max} and $AUC_{0\text{-}inf}$ and the difference in the LS means. The PK

similarity of AVT05 versus EU-approved Simponi, AVT05 versus US-licensed Simponi, and EU-approved Simponi versus US-licensed Simponi will be demonstrated if, for all pairwise comparisons, the 90% CIs for the ratios of geometric means of the primary endpoints are entirely contained within the equivalence margin of 80.00% to 125.00% (when the ratio is expressed as a percentage). Other exploratory analyses of PK similarity by subgroups based on the randomization strata, ADA status, and NAb status may be performed if appropriate.

Differences in drug protein concentration have been identified between AVT05 (101.0 mg/mL), US-licensed Simponi (94.7 mg/mL), and EU-approved Simponi (91.4 mg/mL). Therefore, the PK similarity analysis using PK parameters adjusted by protein content will be performed as a sensitivity analysis. Further details will be provided in the SAP.

Safety Analyses:

All safety analyses will be performed on the Safety Population. AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). All AE summaries will be restricted to treatment-emergent AEs (TEAEs) only (ie, AEs which commence or worsen in severity on or after the time of IP administration). An overview summary of the frequency and percentage of participants with TEAEs overall and by TEAE category will be presented by treatment group and for all participants. Treatment-emergent AEs will also be grouped by MedDRA system organ class and preferred term and summarized by treatment group and for all participants.

Separate summaries are provided for TEAEs by maximum severity (Mild, Moderate, or Severe) and related TEAEs. Any TEAEs with a missing or unknown severity will be considered as severe in the summary tables. Related TEAEs are considered as those reported as having a relationship to IP of certain, probable, or possible.

Local injection site reactions, other AEs of special interest, TEAEs of clinically significant laboratory abnormalities, TEAEs of Grade ≥3 laboratory abnormalities, TEAEs leading to discontinuation from the study, SAEs, and TEAEs leading to death will be summarized and listed separately.

For clinical laboratory data, vital signs, and electrocardiogram (ECG) data, observed values and change from baseline will be listed and summarized using descriptive statistics at each protocol-specified time point by treatment group. Shifts in the Investigator's evaluation (Normal, Abnormal not clinically significant, Abnormal clinically significant) in these parameters from baseline to each postbaseline protocol-scheduled time point will be summarized by treatment group, using frequency tabulations.

Immunogenicity Analyses:

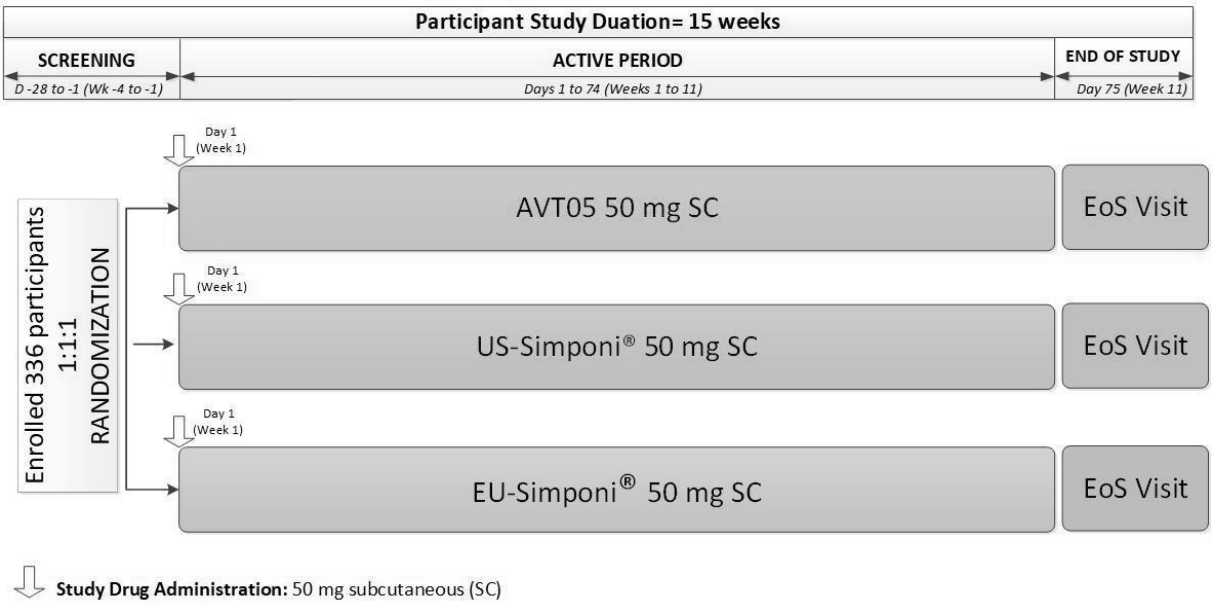
Individual immunogenicity sample collection and ADA results (including neutralizing antibody [NAb] results, if available) will be listed for all participants. Detection of ADAs (ie, positive or negative) will be summarized with frequency counts by treatment group and scheduled time point. The ADA titer/concentration values will also be summarized for all participants within a single treatment group have positive ADA results.

Data Monitoring Committee:

A Data Monitoring Committee will not be used in this study.

1.2 Schema

Figure 1 Study Schema



Abbreviations: EoS = end-of-study; SC = subcutaneous.

1.3 Schedule of Activities

Table 1 Schedule of Assessments

Study Period	**Screening**		**Treatment and Assessment Period**																				**EoS/ ET***
Study Week	**-4 to -1**	**-1**	**1**							**2**					**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Day	**-28 to -2**	**-1**	**1 (DOSING)**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**15**	**22 ±1**	**29 ±2**	**36 ±2**	**43 ±2**	**50 ±2**	**57 ±2**	**64 ±2**	**75 ±2**
			Pre	**Post**																				
Inpatient observation • Sentinels[a]		X	X	X	X	X	X																	
• Non-sentinels[a]		X	X	X	X																			
Ambulant visits: • Sentinels								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
• Non-sentinels						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent[b]	X																							
Eligibility check	X	X	X																					
Demographics	X																							
Medical history	X	X																						
Smoking status	X	X																						
Alcohol and tobacco consumption	X	X	----------Throughout the study period----------																					
Randomization			X																					
IP administration			X																					
Physical examination[c]	X	X	X									X						X						X
Height	X																							
Body weight and BMI	X	X																						

Study Period	**Screening**		**Treatment and Assessment Period**																				**EoS/ ET***
Study Week	**-4 to -1**	**-1**	**1**							**2**					**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Day	**-28 to -2**	**-1**	**1 (DOSING)**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**15**	**22 ±1**	**29 ±2**	**36 ±2**	**43 ±2**	**50 ±2**	**57 ±2**	**64 ±2**	**75 ±2**
			Pre	**Post**																				
Vital signs[d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X	X[f]	X[g]	X			X				X												X
Clinical safety laboratory tests[h,i]	X[i]	X[h,i]	X		X			X				X						X						X
HbA1c test	X																							
Urine drugs of abuse screen and alcohol breath test	X	X																						
QuantiFERON®-TB Gold in Tube test	X																							X
COVID-19 PCR test[j]	X																							
Highly sensitive serum pregnancy test (WOCBP only) [k]	X																							X
Urine pregnancy test (WOCBP only)[k]		X																						
FSH Testing (non-WOCBP only) [k]	X																							
Viral serology (anti-HBs, HBsAg, anti-HBc, HCV, and HIV tests)	X																							
β-D glucan test	X																							
PK blood sampling[l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity blood sampling[l]			X									X				X		X				X	X	X
Blood sampling for pharmacodynamic (only for substudy participants)[m]			X			X			X			X			X			X		X		X		X

Study Period	**Screening**		**Treatment and Assessment Period**																				**EoS/ ET***
Study Week	**-4 to -1**	**-1**	**1**							**2**					**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Day	**-28 to -2**	**-1**	**1 (DOSING)**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**15**	**22 ±1**	**29 ±2**	**36 ±2**	**43 ±2**	**50 ±2**	**57 ±2**	**64 ±2**	**75 ±2**
			Pre	**Post**																				
Injection site reaction assessment[n]			X[n]	X[n]	X	X		X				X						X						X
AE/SAE recording[o]	----------Throughout the study period----------																							
Prior/concomitant medications	----------Throughout the study period----------																							
Prior/concomitant procedures[p]	----------Throughout the study period----------																							

* = Participants who are early withdrawn for other reasons should be followed for 4 weeks following the dose of IP. Participants withdrawing due to an AE should be followed as per Section 8.7.4.

Abbreviations: AE = adverse event; anti-HBc = Hepatitis B core antibody; BMI = body mass index; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; EoS = end-of-study; ET = early termination; HbA1c = glycated hemoglobin; anti-HBs = Hepatitis B surface antibody; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; PCR = polymerase chain reaction; PK = pharmacokinetic; SAE = serious adverse event; TB = tuberculosis; WOCBP = woman of childbearing potential.

General: At visits when multiple postdose procedures are required, the timing of PK blood sample collections will take priority over all other scheduled activities. All other procedures should be performed as close as possible to the scheduled time point but may be obtained before or after PK sampling in accordance with the allowed sampling windows.

a. For Sentinel Group 1 (n = 3 [1 per group]), Group 2 (n = 6 [2 per group]), and Group 3 (n = 9 [3 per group]), as a minimum participants will be on inpatient observation from Day -1 until after collection of the 72-hour postdose samples and study assessments on Day 4, ie, at least 4 nights. As a minimum, all remaining participants will be on inpatient observation at the study site from the evening of Day -1 until after collection of the 24-hour postdose samples and study assessments on Day 2, ie, at least 2 nights. The inpatient observation period may be increased, based on the site's discretion.
b. Informed consent does not have to be performed during the screening window if a participant has previously provided informed consent (ie, rescreening participants). Sites may follow local consenting processes.
c. A full physical examination will be performed at Screening. Details of full physical examination are covered in Section 8.6.4. Brief symptom-directed physical examination will be performed on Day 1 prior to IP administration and at any time throughout the study, as clinically indicated. Height will be measured at Screening, and weight and BMI will be measured at Screening and Day -1.
d. Vital signs on Day 1 will be measured predose (within 60 min prior to dosing), and 1 h (±10 min), 4 h (±30 min), 8 h (±30 min), and 12 h (±30 min) postdose. For details, refer to Section 8.6.2.

e. The ECGs may be performed in triplicate at the discretion of the Investigator, to comply with site-specific standard operating procedures and ensure accurate QTcF calculation. Additional non-invasive electrocardiographic safety assessments (Holter monitor at screening and telemetry during inpatient stay) may be performed at the discretion of the PI to ensure participant safety.
f. On Day 1 pre-dose, ECG will be done within 60 mins prior to dosing.
g. On Day 1 postdose, ECGs will be done at 4 h (±15 min) and 12 h (±15 min) after receiving the dose of IP.
h. If Screening assessments are completed in the week prior to Day -1, the scheduled assessments on Day -1 need not be repeated.
i. Clinical laboratory tests are listed in Section 10.2.
j. COVID-19 testing will be performed at the Investigator's discretion following local health requirements and regulations, or if clinically indicated.
k. WOCBP will have a serum pregnancy test at Screening and at the EoS visit (Day 75). Urine pregnancy test should be done at admission (Day -1). The serum test at screening will include analysis of FSH for non-WOCBP. Additional testing may be performed as per Investigator's discretion or site requirements.
l. Blood samples for PK and immunogenicity assessments will be collected as per the specified time points indicated in Table 2.
m. A blood sample, to be used for pharmacodynamic assessments, was collected from a subset of participants (45 in total, 15 participants per group) after the collection of the PK blood sample (on Day 1 this sample will be taken prior to dosing) as specified in Table 2. Note: As of Protocol Version 4.0, the analysis of the samples collected for the ex-vivo substudy will not be performed. The collected samples will be destroyed.
n. On Day 1, injection site assessments will be performed predose (within 60 min prior to dosing) and at 15 min (±2 min), 30 min (±5 min), 1 h (±5 min), 2 h (±5 min), and 8 h (±15 min) postdose.
o. Adverse events/serious adverse events will be recorded from the time the participant signs the ICF. Any AEs that occur after obtaining informed consent but before IP administration will be recorded as pre-treatment AEs, and those occurring after IP administration will be recorded as treatment-emergent AEs.
p. Procedures within 90 days prior to randomization will be recorded.

Table 2 Blood Sampling Time Points for Pharmacokinetic, Immunogenicity, and Pharmacodynamic Assessments

Study Day	Time point relative to dosing	Allowed window	PK	Immunogenicity	Pharmacodynamics (Substudy) [a]
Day 1	Predose	Within 1 h prior to dosing	X	X	X
	8 h postdose	±15 minutes	X		
	12 h postdose	±30 minutes	X		
Day 2	24 h postdose	±1 h	X		
Day 3	48 h postdose	±2 h	X		X
Day 4	72 h postdose	±2 h	X		
Day 5	96 h postdose	±2 h	X		
Day 6	120 h postdose	±2 h	X		X
Day 7	144 h postdose	±2 h	X		
Day 8	168 h postdose	±2 h	X		
Day 9	192 h postdose	±4 h	X	X	X
Day 10	216 h postdose	±4 h	X		
Day 11	240 h postdose	±4 h	X		
Day 12	264 h postdose	±4 h	X		X
Day 15	336 h postdose	±4 h	X	X	
Day 22	504 h postdose	±24 h	X		
Day 29	672 h postdose	±48 h	X	X	X
Day 36	840 h postdose	±48 h	X		
Day 43	1008 h postdose	±48 h	X		X
Day 50	1176 h postdose	±48 h	X		
Day 57	1344 h postdose	±48 h	X	X	X
Day 64	1512 h postdose	±48 h	X	X	
Day 75/EoS	1776 h postdose	±48 h	X	X	X

Abbreviations: EoS = end of study: h = hours; PK = pharmacokinetics.

a. As of Protocol Version 4.0, the analysis of the samples collected for the ex-vivo pharmacodynamic substudy will not be performed. The collected samples will be destroyed.

2.0 INTRODUCTION

2.1 Background

Tumor necrosis factor-α (TNF-α) is a naturally occurring cytokine that is key to normal inflammatory and immune responses. TNF-α plays a crucial role in the pathogenesis of inflammatory diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), plaque psoriasis (PP), ankylosing spondylitis (AS), Crohn's disease (CD) and ulcerative colitis (UC).[1] Consequently, anti-TNF-α therapy has become a mainstay treatment for autoimmune diseases. Compared to small molecule compounds, biologics have some clear advantages, including improved safety profile or minimal toxicity, well-understood mechanisms, and target specificity.

Golimumab is a recombinant human IgG1κ monoclonal antibody (mAb) with a molecular mass of approximately 150 kilodaltons and exhibits multiple glycoforms. The mAb binds to both the soluble and transmembrane forms of TNF-α, preventing the binding of TNF-α to its receptors.[2,3,4] By blocking TNF-α, golimumab reduces the inflammation and other symptoms of these diseases.

Golimumab was initially approved in April 2009 under the trade name Simponi® in the US (BLA 125289) [5] for the treatment of adults with moderate to severe active RA in combination with methotrexate, for the treatment of active PsA in adults alone or in combination with methotrexate, and for the treatment of active AS in adults. Simponi was approved in the EU in June 2009 for the treatment of RA, PsA, and AS. Simponi is a solution for injection and is administered subcutaneously (SC). Simponi Aria was approved in the US in July 2013 under BLA 125433 and is an intravenous (IV) formulation approved for the treatment of adult patients with moderate to severe active RA in combination with methotrexate (MTX).

The high cost of Simponi may preclude some patients from being able to access the treatment, especially considering prolonged use is required to treat the chronic conditions indicated for this product. A similar product that provides comparable safety and efficacy at reduced cost would fulfill a broader medical need as a more cost-effective treatment in all settings for the approved indications.

2.2 AVT05, a Golimumab Biosimilar

Alvotech (hereafter, the Sponsor) is developing AVT05 (golimumab) globally (including EU, US, and Japan) as a proposed biosimilar to the reference product Simponi for SC and IV use. The primary amino acid sequences of golimumab in AVT05 are identical to those of Simponi. In line with the reference product Simponi, AVT05 will be supplied in a prefilled syringe (PFS) at a concentration of 50 mg/0.5 mL as a sterile, preservative-free solution for SC administration. The AVT05 drug product is formulated at the concentrations approved for Simponi, using the same excipients qualitatively and quantitatively.

The Sponsor plans to seek approval for all indications for which Simponi has been approved by demonstrating similarity of AVT05 with Simponi through an extensive array of quality, nonclinical, and clinical comparability assessments.

2.2.1 Summary of Nonclinical Experience

Detailed information regarding the analytical similarity and nonclinical pharmacology and toxicology of AVT05 can be found in the Investigator's Brochure (IB).[6] As part of the step-wise development approach of biosimilar products, state-of-the-art and orthogonal physicochemical analytical methods and in vitro functional assays were applied to demonstrate that AVT05 has similar structural, physicochemical, and biological characteristics to Simponi.

Given that analytical similarity was observed using in vitro biological and functional assays which are considered more sensitive than using animal models, and the extensive pharmacology and toxicology data available for the reference product Simponi, in vivo nonclinical studies were not conducted with AVT05.

2.2.2 Summary of Clinical Experience

To date, AVT05 has not been tested in humans. Overall, based on analytical similarity analysis conducted to date, no significant differences between AVT05 and Simponi have been identified that may impact safety or efficacy of participants participating in the planned clinical studies. The purpose of the proposed clinical development plan is to demonstrate pharmacokinetic (PK) and clinical similarity and thereby support biosimilarity of AVT05 with Simponi. In general, the clinical pharmacology, efficacy, and safety of AVT05 are expected to be similar to Simponi; and the clinical experience with Simponi is deemed applicable to AVT05. Therefore, publicly available clinical data on Simponi are summarized below.

An overview of the safety profile of golimumab, including undesirable effects, can be found in the Summary of Product Characteristics (SmPC), US Prescribing Information (USPI), and regulatory assessment reports for Simponi. [2,3,4] The most common adverse reactions with SC administration in patients across the indications were upper respiratory tract infections (nasopharyngitis, pharyngitis, laryngitis, and rhinitis) and injection site reactions. For the SC route of administration, the most serious adverse reactions include serious infections (including sepsis, pneumonia, tuberculosis (TB), invasive fungal and opportunistic infections), demyelinating disorders, hepatitis B virus reactivation, congestive heart failure (CHF), autoimmune processes (lupus-like syndrome), hematologic reactions, serious systemic hypersensitivity (including anaphylactic reaction), vasculitis, lymphoma, and leukemia.

Overall, in healthy volunteers and in patients with RA immunogenicity of golimumab is very low in range of 1.4% and 3.8%.[7,8] The incidence of antibodies to golimumab in all patient population after administration of 50 mg or 100 mg was 57 of 1322 participants (4.3%),

ranging from 2.1% to 6.3%.[5] The absence of MTX increased the rate of antibodies with 7.1% for participants administered 50 mg golimumab in the absence of MTX, compared to 1.7% in the presence of MTX. Healthy participants are the most sensitive to detect differences on immunogenicity and the impact on PK due antidrug antibodies (ADA) neutralizing ADA (NAbs) due to absence of concomitant medication and prior treatment with TNF-α inhibitors. Based on the literature from single-dose studies of golimumab in healthy volunteers, no apparent differences in PK parameters between Japanese and non-Japanese patients were observed.[9]

2.3 Benefit/Risk Assessment

Information about the risks following the administration of golimumab are presented from the European Public Assessment Report (EPAR), full prescribing information, and summary of the risk management plan for Simponi. In view of the structural, biological, and toxicological similarity to Simponi, AVT05 is expected to display a similar safety profile. The potential risks of AVT05 include:

- Upper respiratory tract infections
- Other serious infections and reactivation of latent infections
- Injection site reactions
- Hypersensitivity

A risk mitigation plan (Section 10.4) is provided to address the expected risks from administration of the IP. The proposed exclusion criteria, safety screening, and monitoring assessments are deemed to be sufficient to monitor the potential risks of AVT05 administration. Since AVT05 will be administered only once at the approved dosage for golimumab of 50 mg/0.5 mL, the overall risk of the study for healthy participants is considered to be acceptable.

The Sponsor will immediately notify the PI if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), EU CTR, and applicable regulatory requirements.

During an ongoing global pandemic such as coronavirus disease 2019 (COVID-19), there may be inherent risks with travel to and attendance of on-site visits. Participants will be encouraged to follow the guidance of local health authorities and the local site standard operating procedures (SOPs) in these instances. Details of COVID-19 risk mitigation procedures during the study will be addressed separately.

3.0 OBJECTIVES AND ENDPOINTS

Table 3 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate the PK similarity of AVT05 with US-licensed and EU-approved Simponi and the PK of EU-approved Simponi with US-licensed Simponi.	• The primary PK parameters to be compared are: C_{max} and $AUC_{0\text{-}inf}$.
Secondary	
• To further characterize the PK of AVT05 with US-licensed Simponi and EU-approved Simponi following a single 50 mg/0.5 mL SC injection in healthy participants.	• Golimumab serum concentration-time profile following single-dose administration. • The secondary PK parameters to be assessed are, but not limited to: $AUC_{0\text{-}t}$, T_{max}, K_{el}, $t_{1/2}$, Vz/F, and CL/F.
• To compare the safety and tolerability of AVT05 with US-licensed Simponi and EU-approved Simponi following a single 50 mg/0.5 mL SC injection in healthy participants.	• The safety parameters to be assessed include AEs, clinical laboratory assessments (hematology, coagulation, clinical chemistry, urinalysis, and urine microscopy), vital signs, ECG, physical examination findings, and injection site reactions.
• To compare the immunogenicity of AVT05 with US-licensed Simponi and EU-approved Simponi following a single 50 mg/0.5 mL SC injection in healthy participants.	• The immunogenicity parameters to be assessed are the frequency and titers of ADAs, and the frequency of NAbs against AVT05, US-licensed Simponi, and EU-approved Simponi.

Abbreviations: ADA = antidrug antibodies; $AUC_{0\text{-}inf}$ = area under the serum concentration-time curve from time t extrapolated to infinity, where t is the last time point with a concentration above the lower limit of quantitation: $AUC_{0\text{-}t}$+ Ct/K_{el}; $AUC_{0\text{-}t}$ = area under the serum concentration-time curve from time zero to the last quantifiable concentration; CL/F = apparent clearance; C_{max} = maximum serum concentration; ECG = electrocardiogram; IFN = interferon; IL=interleukin; K_{el}= elimination rate constant; NAbs=neutralizing antibodies; PK=pharmacokinetics; SC = subcutaneous; $t_{1/2}$ = elimination half-life; T_{max} = time to maximum serum concentration; Vz/F = apparent volume of distribution during the terminal phase after SC administration.
Note: As of Protocol Version 4.0, the analysis of the samples collected for the ex-vivo substudy will not be performed and the exploratory endpoint has been removed from the protocol.

4.0 STUDY DESIGN

4.1 Overall Design

This study is designed as a first-in-human, randomized, double-blind, single dose, parallel-group design, 3-arm study to investigate the pharmacokinetic similarity, safety, tolerability, and immunogenicity of subcutaneous AVT05 compared with US-licensed and EU-approved Simponi when administered as a single 50 mg/0.5 mL SC injection in healthy adult participants.

Approximately 336 participants (112 per group) are planned to be enrolled at multiple study sites worldwide. Efforts will be made to include at least 10% of participants (33 participants; 11 per group) who are of Japanese origin and ethnicity (as defined in Section 5.1).

The study duration per participant will be approximately 15 weeks. The study will consist of a 4-week Screening period, a 11-week treatment and assessment period, and an End-of-Study (EoS) visit on Day 75. A schematic of the study design is presented in Figure 1.

Participants will undertake screening between Day -28 and Day -1 to determine their eligibility in the study. Participants who meet the eligibility criteria will be admitted to the study site on the day prior to dosing (Day -1), during which their continued eligibility will be assessed up to Day 1 prior to dosing. On Day 1, eligible participants will be randomly assigned in a 1:1:1 ratio to receive a single dose of one of the following: AVT05, US-licensed Simponi, or EU-approved Simponi. Randomization will be stratified by gender, ethnicity, and body weight at Day -1 as follows: male, female, Japanese, non-Japanese ≤80 kg, and non-Japanese >80 kg.

A staggered sentinel dosing strategy will be implemented as a safety measure, with equal numbers of participants randomized to each treatment in a 1:1:1 ratio:

- Sentinel Group 1 (n = 3): 1 participant per group
- Sentinel Group 2 (n = 6): 2 participants per group
- Sentinel Group 3 (n = 9): 3 participants per group
- Remaining participants (n = 318): 106 participants per group

Following investigational product (IP) administration, there will be at least 72 hours of close observation and safety monitoring. Safety data for all sentinel cohort participants, from dosing to 72 hours, will be considered when assessing sentinel group safety. There will also be at least 72 hours between sentinel groups (ie, 72 hours monitoring between dosing for the last participant in a sentinel group and the first participant in the next sentinel group). Provided no significant safety or tolerability concerns (or events that meet the study stopping criteria specified in Section 4.5.1) have been identified in the previous sentinel group following a safety review and discussion between the PI, Medical Monitor, and Sponsor Medical Lead,

the next sentinel group of participants will be randomized and dosed. Once the IP dose is deemed to be safe and well tolerated in all 3 sentinel groups, the remaining participants will be randomized and dosed.

Sentinel participants will undergo inpatient observation at the study site, at a minimum, from Day -1 to Day 4 (at least 72 hours postdose); all remaining participants will undergo inpatient observation at the study site, at a minimum, from Day -1 up to Day 2 (at least 24 hours postdose). Following dosing, PK, safety, tolerability, and other assessments will be performed according to the Schedule of Assessments (Table 1). Postdose, participants will be followed up daily up to Day 12, then once a week from Day 15 to Day 64, and finally on Day 75 for the End-of-Study (EoS) visit.

4.2 Scientific Rationale for Study Design

The study design follows the recommendations of the FDA[10] and EMA[11] guidance for biosimilar products. A parallel-group design has been selected considering the relatively long half-life of golimumab of 11 to 14 days.

Study Population and Stratification

Healthy adult participants have been selected as the study population in accordance with global regulatory guidelines to avoid potential interference associated with concomitant treatments or medical conditions. No sex differences have been reported for the safety profile of golimumab based on long-term follow-up data from pivotal studies and post-marketing pharmacovigilance.[6] Although sex is not a differentiating factor for the PK of golimumab, subgroup analyses of PK data by sex will be performed in this study. Aligned with the recommendations of the reference product Simponi (USPI),[4] women of childbearing potential (WOCBP) will be required to use adequate contraception to prevent pregnancy.

Although age is not an intrinsic factor and does not influence exposure to golimumab, an upper age boundary has been implemented for safety reasons. Participants over 55 years may be more susceptible to infections while taking golimumab.

PK Assessments

Based on published PK data for golimumab in healthy participants, the apparent half-life ($T_{1/2}$) after SC administration was at approximately 11 to 14 days.[2] However, to capture the entire PK profile (>5 half-lives) of golimumab after single SC administration, PK sampling will be performed up to 75 days (ie, 11 weeks) postdose. Intensive sampling will also be done daily from Day 1 to Day 12 to cover T_{max}.

Based on population PK modeling for Simponi, the mean terminal half-life was 12 ±3 days. The CL/F and Vz/F ranged from 6.9 ±2.0 mL/day/kg and 115 ±19 mL/Kg respectively. A higher apparent clearance of golimumab was observed with increasing weight.[4] Therefore, in

the current study, the statistical analysis comparing treatment groups for each of the PK parameters will be adjusted for body weight through an analysis of covariance (ANCOVA) with weight at baseline as the covariate.

As part of the registration plans for AVT05 in Japan, to demonstrate consistency in PK data between Japanese and non-Japanese participants following AVT05 administration, the Sponsor plans to include at least 10% Japanese participants (33 participants) in the study.

Safety and Immunogenicity Assessments

Safety and immunogenicity will be evaluated throughout the study. Safety assessments include incidence, nature, and severity of AEs, including AEs of special interest (AESIs) and injection site reactions. The double-blind data collected until Week 11 are considered adequate to support a comparative descriptive analysis of safety and immunogenicity between AVT05 and US-licensed and EU-approved Simponi.

As part of the immunogenicity evaluations in the current study, immunogenicity assessments are scheduled at baseline (Day 1 predose), Day 9, Day 15, Day 29, Day 57, Day 64, and Day 75 to observe changes in immunogenicity over time.

This study has been designed as a multicenter, randomized, double-blind study of AVT05 in healthy adult participants. The study aims to demonstrate PK similarity of the proposed biosimilar test product AVT05 and the reference products US-licensed Simponi and EU-approved Simponi, in addition to evaluating the safety and tolerability of AVT05, when administered as a single 50 mg/0.5 mL SC dose.

The study design follows the recommendations of the Food and Drug Administration (FDA) guidance for industry, “Scientific Considerations in Demonstrating Biosimilarity with a Reference Product” [10] and European Medicines Agency (EMA) guidance for biosimilar products. [11]The study was also designed following advice from regulatory agencies including the EMA, FDA, and Japanese Pharmaceutical and Medical Devices agency.

4.3 Justification for Dose

In alignment with the EMA and FDA product information sheets for the reference product,[2,3] the SC route of administration will be evaluated in this study, as the SC route represents the main approved route of administration for the Simponi reference product. Furthermore, the SC route is expected to be the most sensitive in detecting differences in immunogenicity, and can provide insight into potential PK differences during the absorption phase, in addition to the distribution and elimination phases (ie, it covers both absorption and elimination phases).

The proposed dose for the study (50 mg/0.5 mL SC) represents the approved dose of golimumab in adults with a body weight of less than 100 kg across all indications. Pharmacokinetic characterization of golimumab was analyzed in 2 studies in RA patients

administered via SC (C0466T02) at doses 0.3, 0.6, 1.0, and 3.0 mg/kg or IV (C0466T01) at doses 0.1, 0.3, 1.0, 3.0, 6.0, and 10 mg/kg. Exposure of golimumab as assessed by AUC_{inf} and C_{max} was found to be dose proportional, except for the 1.0 mg/kg after SC administration. In addition, 50 mg and 100 mg SC doses of golimumab have been administered in both Caucasian and Japanese healthy volunteers. PK parameters, AUC_{inf} and C_{max} were found to be dose proportional while T_{max} and t1/2 were consistent regardless of dose or race.[9] The proposed dose of 50 mg administered SC, is deemed to be a sensitive dose that is not impacted by nonlinear kinetics and is well tolerated in healthy volunteers and in patients.[2-4,8,13]

4.4 End of Study Definition

A participant is considered to have completed the study if they have completed all periods of the study including the last visit (EoS visit) and the last scheduled procedure, as shown in the Schedule of Assessments in Table 1.

The end of the study is defined as the date of the last visit of the last participant in the study globally.

4.5 Study Stopping Criteria

As only a single dose of IP will be administered, participants cannot be withdrawn from treatment but can be withdrawn from the study.

4.5.1 Criteria for Stopping the Study

If either of the following scenarios occur, study enrollment and dosing will be paused:

- If ≥1 participant experiences a serious adverse event that is considered at least possibly related to the IP.
- If ≥2 participants experience severe non-serious adverse events that are considered at least possibly related to the IP, independent of within or not within the same system-organ-class.
- If the Sponsor or Investigator considers there to be an unfavorable benefit-risk ratio based on emerging safety data.

If the Sponsor becomes aware that the trial has met stopping rules at another site, they will immediately inform all participating sites to stop dosing and await further instruction. A clear communication plan will be provided by the Sponsor for the participating sites.

If following consultation between the PI, Medical Monitor, and Sponsor it is considered appropriate to restart IP administration in the remaining participants, a justification will be submitted and approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and/or regulatory authorities for restarting the study.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply at any time starting from Screening up to Day 1 prior to IP administration:

1. Healthy participants capable of giving signed informed consent as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol.
2. Participants must be 18 to 55 years old (inclusive) at the time of signing the ICF.
3. Have a body weight of 50.0 to 90.0 kg (inclusive) and body mass index (BMI) of 18.0 to 30.0 kg/m^2 (inclusive).
4. Participants in Japanese cohorts must be born in Japan, holding a Japanese passport, not living outside Japan for more than five years and have all four grandparents Japanese, as confirmed by interview.
5. Medical history without evidence of a clinically significant disorder, condition, or disease that, in the opinion of the PI would pose a risk to participant safety.
6. Resting supine systolic blood pressure of ≤140 mmHg and diastolic blood pressure of ≤90 mmHg; and other vital signs showing no clinically relevant deviations according to the PI's judgment at Screening and Day 1 prior to dosing of IP.
7. Computerized (12-lead) electrocardiogram (ECG) recording without signs of clinically relevant pathology or showing no clinically relevant deviations according to the PI's judgment at Screening and Day 1 prior to dosing of IP.
8. Negative urine drug screen (parameters listed in Section 10.2) and negative alcohol breath test at Screening and admission.
9. Nonsmoker or occasional smoker, ie, smokes ≤10 cigarettes (or equivalent of tobacco- or nicotine-containing products) per week within the 3 months prior to Screening and is able to abide by the smoking policy of the site.
10. Ability and willingness to abstain from alcohol from 48 hours prior to IP administration, during inpatient observation at the study site until discharge and 24 hours prior to ambulatory visits.
11. Differentiation of platelet count and hemoglobin result within the reference ranges. All other values for hematology and for biochemistry tests of blood and urine within the normal range or showing no clinically relevant deviations as judged by the PI.
    NOTE: Two repeat evaluations of clinical laboratory tests will be permitted, at the discretion of the PI or delegate.

12. Tested negative for β-D glucan, hepatitis B surface antibody (anti-HBs), hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (anti-HBc), anti-hepatitis C virus (HCV) antibodies, and anti-human immunodeficiency virus (HIV) 1/2 antibodies at Screening.
    NOTE: Participants with positive anti-HBs alone are eligible if they have documented history of vaccination. Participants who can only confirm verbally that they received hepatitis B vaccination should have this documented in their medical history.
13. Female participants are eligible to participate if they have a negative pregnancy test at Screening, not breastfeeding, and at least ONE of the following conditions applies:
    a) If a woman of childbearing potential (WOCBP)
        i) agrees to use a highly effective method of contraception consistently and correctly from Screening (signing the ICF) until at least 6 months after the last dose of IP administration, or
        ii) whose career, lifestyle, or sexual orientation precludes sexual intercourse with a male partner or
        iii) having sexual intercourse exclusively with a sterile male partner
    b) If not a WOCBP (non-WOCBP), defined as:
        i) Surgically sterile (documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, as confirmed by review of the participant's medical records, medical examination, or medical history interview), or
        ii) Postmenopausal (defined as no menses for 12 months without an alternative medical cause). A high follicle-stimulating hormone [FSH] level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy [HRT]. Female participants on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods from Screening (signing the ICF) until at least 6 months after the last dose of IP administration if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
14. Female participants must refrain from donating eggs (ova, oocytes) for the purpose of assisted reproduction from Screening (signing the ICF) until at least 6 months after the IP administration.
15. Male participants who can produce viable sperm are eligible to participate if they agree to use an adequate method of contraception as per the contraceptive guidance in Section 10.3 from Screening (signing the ICF) until at least 6 months after IP administration. Participants with a partner(s) who is (are) not of childbearing potential are exempt of these requirements.
16. Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile

penetration. In addition, male participants must refrain from donating sperm from Screening (signing the ICF) until at least 6 months after the IP administration.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply at any time starting from Screening up to Day 1 prior to IP administration:

1. Have a history of relevant drug and/or food allergies.
2. Known or suspected clinically relevant drug hypersensitivity to golimumab, AVT05, or any of its constituents, which in the opinion of the PI, contraindicates the participant's participation.
3. Have any past or concurrent medical conditions that could potentially increase the participant's risks or that would interfere with the study evaluation, procedures, or study completion. Examples of these include medical history with evidence of clinically relevant pathology (eg, malignancies or demyelinating disorders).
4. Presence of chronic obstructive pulmonary disease. Childhood asthma is allowed.
5. Presence of type 1 or 2 diabetes mellitus.
6. Receipt of any investigational agent or drug within 60 days or 5 half-lives of the previous drug, whichever is longer, prior to drug administration.
7. Previous exposure to other TNF-α inhibitors including golimumab.
8. Treatment with non-topical medications (including over-the-counter (OTC) medications and herbal remedies such as St. John's Wort extract) within 7 days prior to IP administration, with the exception of multivitamins, vitamin C, food supplements and a limited amount of acetaminophen (up to 2 g in 24 hours, but <1 g in 4 hours) or ibuprofen (<1.2 g per day), which may be used throughout the study.
9. Any current active infections, including localized infections, or any recent history (within 1 week prior to IP administration) of active infections, cough or fever, or a history of recurrent or chronic infections.
10. Participant has a history of tuberculosis (TB) diagnosis or evidence of active or latent infection with *Mycobacterium tuberculosis* as defined by one of the following assessments:
    a) Positive or indeterminate QuantiFERON-TB® Gold test result at Screening.
    b) Chest radiograph (posterior anterior view) taken within 12 weeks prior to Screening, read by a qualified radiologist or pulmonologist, with evidence of current active TB or old inactive TB.
    c) Signs or symptoms suggesting active TB.
    d) Recent close contact with active TB.
11. Donation of more than 500 mL of blood within 8 weeks prior to IP administration.
12. A recent history of major surgery within 3 months prior to randomization.

13. A history (within the previous 3 years) or evidence of alcohol abuse (an average intake exceeding 10 drinks/week for women and 15 drinks/week for men: 1 drink = 360 mL of beer, 150 mL of wine, or 45 mL of spirits) or drug abuse (including soft drugs like cannabis products).
14. Vaccination with a live vaccine (with the exception of influenza vaccine) within 4 weeks prior to IP dosing or have the intention to receive vaccination 5 weeks after IP administration.
15. Any other condition which in the view of the PI is likely to interfere with the study or put the participant at risk.
16. Any persons who are:
    a) An employee of the study site, PI, contract research organization (CRO) or Sponsor;
    b) A first-degree relative of an employee of the study site, the PI, CRO, or the Sponsor.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

There are no dietary restrictions in this study. Participants will receive a standard diet while resident in the study site; no additional food or beverages must be consumed while in the study site with the exception of water.

5.3.2 Caffeine, Alcohol, and Tobacco

1. Participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 48 hours before admission to the study site on Day -1 and for the duration of the inpatient observation period of the study. Decaffeinated products are allowed.
2. Participants will abstain from alcohol for 48 hours before admission to the study site on Day -1, during inpatient observation at the study site until discharge, and for 24 hours prior to ambulatory visits. At all other times during the study until completion of the study, participants are discouraged to consume alcohol, but may consume no more than 2 drinks per day or 15 drinks/week. One drink is equivalent to 12 g alcohol = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of 80-proof distilled spirits.
3. Participants will be permitted to smoke ≤10 cigarettes (or equivalent of tobacco- or nicotine-containing products) per week until the EoS visit, but use of tobacco- or nicotine-containing products will not be allowed during inpatient observation at the study site.

5.3.3 Activity

1. Participants should refrain from strenuous exercise within 48 hours prior to admission to the study site on Day -1 up to Day 7. Participants may participate in light recreational

activities during this period (eg, watching television, reading). After Day 7, normal physical activity can be resumed with restrictions as above prior to each visit.
2. Participants will be advised not to donate blood or undergo plasma donation for at least 3 months after IP administration.

5.4 Screen Failures

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The PI will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled or randomized to the IP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure), but at some point in the future meet all of the participant eligibility criteria, may be rescreened once. In the event of rescreening, all other screening procedures need not be repeated if they fall within the initial 28-day screening window. If the rescreening occurs outside the 28-day window, all assessments performed at the initial screening should be repeated during rescreening. Informed consent does not have to be performed during the screening window if a participant has previously provided informed consent (ie, rescreening participants). Sites may follow local consenting processes. Each time a participant is screened/rescreened, they will be assigned a new screening number.

6.0 INVESTIGATIONAL PRODUCTS

Investigational product is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a participant according to the study protocol.

6.1 Investigational Products Administered

The IPs (AVT05, US-licensed Simponi, and EU-approved Simponi) will be supplied by the Sponsor through a qualified vendor. Participants will receive a single administration of one dose of either AVT05, US-licensed Simponi, or EU-approved Simponi as an SC injection on Day 1. The treatments will be administered to the participants according to a predetermined randomization schedule.

Table 4 Investigational Product Details

	Test Product	Reference Products	
IP Name:	AVT05 (golimumab)	EU-approved Simponi (golimumab)	US-licensed Simponi (golimumab)
Dosage Formulation:	50 mg/0.5 mL golimumab. Prefilled syringe formulated with: sorbitol, histidine buffer, and poloxamer.	50 mg/0.5 mL golimumab. Formulated with: histidine, histidine hydrochloride monohydrate, polysorbate 80, sorbitol, water for injection.	50 mg/0.5 mL golimumab. Formulated with: histidine, histidine hydrochloride monohydrate, polysorbate 80, sorbitol, and water for injection.
Unit Dose Strength:	The IP will be supplied as a single-use prefilled syringe, which delivers 50 mg of AVT05 in 0.5 mL, or 50 mg of Simponi in 0.5 mL. Dose modifications are not planned or allowed in this study.		
Route of Administration	SC injection		
Dosing Instructions:	The IP will be administered with the participants in bed in a supine or semi supine position. Before SC injection, the solution will be inspected visually for particulate matter or discoloration. Administration of the IP will be performed in the study site by the PI or designee trained to inject this product. The SC injection will be administered in the abdomen (preferred site) or thigh (secondary site). Injections should never be given into areas where the skin is tender, bruised, red, or hard. Refer to the Pharmacy Manual for further details on administration technique.		
Packaging and Labeling	All clinical study material will be packaged and labeled in compliance with good GMP and local regulatory requirements		
Manufacturer	Alvotech Swiss AG	Janssen Biotech, Inc.	

Abbreviations: IP = investigational product; SC = subcutaneous; GMP = good manufacturing practice

6.2 Handling, Storage, and Accountability of Investigational Products

1. On receipt of the IP, the PI or designee must confirm appropriate temperature conditions (refrigerated, 2°C to 8°C, and protected from light) have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.
2. Only participants enrolled in the study may receive the IP and only authorized study site staff may supply or administer the IP. All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the PI and authorized study site staff. The Sponsor reserves the right to inspect the IP storage area before and during the study. A written record will be made of the storage condition of the study materials and retained for the Investigator File.
3. The unblinded pharmacist and study team is responsible for IP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). The amount of IP received from the Sponsor, the amount supplied and/or administered to participants, if applicable, will be documented.
4. The PI, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all IP using drug accountability records. These records must be available for inspection at any time.
5. The study monitor will review the IP accountability logs and check all IP returns (both unused and used) prior to authorizing the destruction of used IP by the study site. Used IP will be destroyed by the site according to their procedures and unused IP will be returned to the Sponsor. Further guidance and information for the final disposition of unused IP are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

A computer-generated randomization schedule will be created by an unblinded statistician prior to study start and uploaded into the electronic data capture (EDC) system (Viedoc™). Randomization to AVT05, US-licensed Simponi, or EU-approved Simponi will be performed in a 1:1:1 ratio on Day 1. The randomization will be stratified by gender, ethnicity and body weight (measured at Day -1) as follows: male, female, Japanese, non-Japanese ≤80 kg, and non-Japanese >80 kg. A copy of the randomization schedule will be provided to the unblinded study site pharmacist.

After signing the ICF, each participant will be assigned a Screening number according to the screening order. Following confirmation of eligibility on Day 1, participants will be allocated a unique randomization number which will be allocated based on the predetermined strata-based randomization schedule, and according to their chronological order of inclusion in the study. Once a randomization number has been assigned it must not be reassigned. Further

details of randomization number allocation are provided in the Pharmacy Manual. Both the Screening and randomization numbers will be used to identify the participant throughout the study period and on all study-related documentation.

6.3.2 Blinding

This is a double-blind study and therefore, apart from prespecified unblinded individuals, the PI, site staff, Sponsor, Sponsor's delegates (if applicable) and participants will all be blinded to treatment. No individual participant information that can potentially unblind the Investigator or participant will be reported until the end of the study. Appropriate IP blinding techniques will be implemented during the study as per the sites' procedures, using blinded/unblinded teams; refer to the Pharmacy Manual for further details.

The PI will remain blinded, unless knowledge of the participants' treatment assignment is necessary for the clinical management or welfare of the participant. The reason for unblinding will be clearly documented.

In case of an emergency, the PI has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the PI decides that unblinding is warranted, the PI should make every effort to contact the Medical Monitor and Sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable. The eCRF completion guidelines will describe the procedure for participant-level unblinding of the study. An unblinding function will be designed in the randomization form within the EDC (Viedoc) system to allow the PI to determine what treatment was administered to participant in the case of an emergency, if the pharmacist is not contactable. A notification of the unblinding event to the IRB/IEC and/or regulatory authorities may be required, as per local requirements.

6.4 Compliance to the Investigational Product

The prescribed dosage, timing, site of administration, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRF.

The IP administration will be performed in the study site under the supervision of appropriately trained staff. The details of IP administration, including predose and postdose weight of the PFS, will be recorded in both the source documents and eCRF. Further details will be provided in the Pharmacy Manual.

6.5 Measures to Ensure Participant Safety at the Study Site

The study site staff is responsible for the ongoing safety and wellbeing of the participants while they are in the study site. There is a paging system to alert the clinical staff to any area in the study site where a participant may need medical attention. In the case of an emergency, cardiac resuscitation trolleys are found in the main ward areas of the study site. These trolleys contain drugs, equipment for airway insertion, circulation lines, defibrillation etc, together with oxygen cylinders with delivery apparatus and portable suction machines. There will be a physician or appropriately trained site staff on site for at least 72 hours postdose for sentinel participants, and for the remaining participants, a physician or appropriately trained site staff will be on site for at least 3 hours postdose or per site SOPs, whichever is longer. In addition, if necessary, the site staff can contact further on-call physicians or public emergencies services in the event of a serious medical event. Equipment and emergency drugs are available to treat common medical emergencies that might occur in a Phase 1 study.

6.6 Warnings and Precautions

As this is the first administration of AVT05 in humans, not all effects may be reliably predicted. However, considering that AVT05 is being developed as a biosimilar to Simponi, the warnings and precautions for Simponi are also expected to be applicable to AVT05 (refer Section 6.6 of the current IB). [6]

6.7 Prior and Concomitant Medications/Therapy

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment (within 90 days before Screening) or receives during the study must be recorded on the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose, dose form, route, and frequency.
- For vaccines (if applicable) include brand name and manufacturer (plus lot number, if available).

If the use of any concomitant treatment becomes necessary (eg, for treatment of an AE), the treatment and administration details must be recorded in the source documents and the eCRF. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.1 Prohibited Medications

Participants must abstain from taking prescription or nonprescription drugs (including OTC medications and herbal remedies such as St. John’s Wort extract) within 7 days or 5 half-lives of the medication (whichever is longer) starting prior to IP administration until completion of

the EoS visit, unless, in the opinion of the PI and Sponsor, the medication will not interfere with the study.

No live vaccines are allowed from 4 weeks before Screening or at least 5 weeks after IP administration. See Section 6.7.2 for allowed vaccines.

Treatment with abatacept or anakinra.

Use of prohibited medications during the study will be captured as protocol deviations and discussed with the Sponsor.

6.7.2 Allowed Medications

The following medications are allowed at any time during the study:

- Paracetamol/acetaminophen, at doses of up to 2 g in 24 hours, but no more than 1 g in 4 hours.
- Ibuprofen at doses <1.2 g in 24 hours.
- Use of multivitamins, vitamin C, or dietary supplements at daily recommended doses.
- Inactivated vaccines (eg, inactivated influenza vaccines or approved COVID-19 vaccines) are allowed after an interval of at least 7 days following IP administration.
- For participants of childbearing potential, hormonal contraceptives or hormone replacement therapy.

Other concomitant medication, including herbal medication, are permitted on a case-by-case basis if the PI and Medical Monitor agree that the use is not contradicted.

6.8 Dose Modification

Not applicable as only single dose is administered.

6.9 Treatment of Overdose

Not applicable as only single dose is administered.

6.10 Continued Access to the Investigational Product after the End of the Study

Not applicable, as this is a study in healthy participants.

7.0 DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Investigational Product

As only a single dose of IP will be administered, participants cannot be discontinued from the IP but can be withdrawn from the study.

If a participant who does not meet the enrollment criteria is inadvertently enrolled, that participant must not be dosed and the Sponsor or Sponsor designee must be contacted.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at their own request, or may be withdrawn at any time at the discretion of the PI for safety, behavioral, compliance, or administrative reasons, including:

- Withdrawal of consent
- Adverse event
- Lost to follow-up (see Section 7.3)
- Protocol violation
    - Non-compliance with study schedule
    - Use of prohibited concomitant medication
    - Other
- Death
- Investigator decision
- Study terminated by Sponsor
- Technical problems
- Other

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the PI must document this in the study site records.

Should a participant request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Participants who are early withdrawn for other reasons should be followed for 4 weeks following the dose of IP. See the Schedule of Assessments (Table 1) for data to be collected at the time of early termination. Participants withdrawing due to an AE should be followed as per Section 8.7.4.

Participants who decided to withdraw from the study and participants discontinued due to protocol deviations prior to IP administration may be replaced following discussion with the PI and Sponsor. Participants who discontinue after IP administration will not be replaced.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the PI or designee must make every effort to regain contact with the participant (where possible, at least 3 contact attempts including, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

8.1 Schedule of Assessments

Study procedures and their timing are summarized in the Schedule of Assessments (Table 1).

Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct. Protocol waivers or exemptions are not allowed. Safety concerns should be discussed with the Sponsor immediately on occurrence or awareness to determine further course of action.

The maximum amount of blood collected from each participant, including any extra assessments that may be required, will not exceed 450 mL in any 30-day period. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

At visits where multiple postdose procedures are required to be conducted at the same nominal time point, the timing of PK blood sample collections will take priority over all other scheduled activities.

8.2 Demographics and Other Baseline Characteristics

At Screening, the following demographic data will be collected and reported in the eCRF: age at enrollment and year of birth (full date of birth will be documented in the source documents), sex assigned at birth, race, and ethnicity, and reproductive status (WOCBP, postmenopausal, or surgically sterile). Furthermore, history of substance use, including tobacco use, alcohol intake, and recreational drug use will be documented in the source documents.

8.3 Medical and Medication History

A complete medical history will include evaluation for any past or present medical conditions, and history of all known allergies.

A review of prior medications will be completed as specified in Section 6.7. Prior medications are those used within 90 days of Screening until Day 1 prior to IP administration.

8.4 Efficacy Assessments

Not applicable.

8.5 Pharmacokinetics

8.5.1 Collection of Samples

Venous blood samples (approximately 4 mL per sample) will be collected in normal serum tubes for measurement of serum concentrations of golimumab at time points specified in Table 2.

Blood samples will be taken either by direct venipuncture (any suitable vein) or an indwelling cannula inserted in a vein (depending on the time point). The actual date and time (24-hour clock time) of each sample, including the reason for any samples not collected, will be recorded in the eCRF. Instructions for the collection and handling of biological samples, including details for sample collection, labeling, storage, and shipping will be provided in a Laboratory Manual.

8.5.2 Determination of Golimumab Concentrations

Samples for the determination of golimumab concentrations in serum will be analyzed using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.

8.5.3 Derivation of Pharmacokinetic Variables

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.1 or higher (Certara, LP Princeton, New Jersey, USA) and/or SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina, USA). Actual elapsed time from dosing will be used for the final serum PK parameter calculations.

The PK parameters in Table 5 will be determined for serum golimumab, when possible. Additional serum PK parameters may be calculated if deemed appropriate. Drug concentration information that may unblind the study will not be reported to study sites or blinded personnel until the study has been unblinded.

Table 5 Serum Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
C_{max}	Maximum serum concentration, obtained directly from the observed concentration vs. time data.
$AUC_{0\text{-}inf}$	Area under the serum concentration-time curve from time t extrapolated to infinity, where t is the last time point with a concentration above the LLOQ: $AUC_{0\text{-}t} + Ct/K_{el}$.
$AUC_{0\text{-}t}$	Area under the serum concentration-time curve from time zero up to time t, where t is the last time point with concentrations above the LLOQ.
T_{max}	Time to C_{max}, obtained directly from the data.
K_{el}	Terminal elimination rate constant; a minimum of 3 non-zero data points after C_{max} will be used for estimation.
$t_{1/2}$	Elimination half-life; a minimum of 3 non-zero data points will be used for estimation.
Vz/F	Apparent volume of distribution during the terminal phase after SC administration.
CL/F	Apparent total serum clearance after SC administration, where F is the fraction of drug absorbed.

Abbreviations: LLOQ = lower limit of quantitation; SC = subcutaneous.

8.6 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments (Table 1).

8.6.1 Body Weight and Height

Body weight (in kg) (wearing light clothes, no shoes) and height (in cm, only at Screening) will be measured to allow the calculation of BMI (rounded to 1 decimal place).

8.6.2 Vital Signs

Vital signs measurements (tympanic [aural] temperature, pulse rate, and blood pressure [BP]) will be measured at time points outlined in the Schedule of Assessments (Table 1).

Blood pressure and pulse measurements should be preceded by at least 3 minutes of rest for the participant in the supine or semi supine position in a quiet setting without distractions (eg, television, cell phones) and will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Wherever possible, vital signs measurements must be taken using the same body position at subsequent visits and consistent methods between participants.

All vital signs measurements will be documented at each visit, and the details will be recorded in both the source documents and the eCRF. The PI (or a qualified delegate at the

investigational site) will also evaluate the overall results using 1 of the following categories: normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS) and record his/her evaluation in the eCRF.

8.6.3 Electrocardiograms

Single 12-lead ECGs will be obtained at time points outlined in the Schedule of Assessments (Table 1) after the participant has rested comfortably in the supine or semi supine position for at least 3 minutes in a quiet setting without distractions (eg, television, cell phones) using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS duration, QT interval. The QTcF interval (Fridericia's correction formula) will be derived. Wherever possible, ECG measurements must be taken using the same body position at subsequent visits and consistent methods between participants. The ECGs may be repeated at the discretion of the PI to confirm errant readings. The ECGs may be performed in triplicate at the discretion of the PI, to comply with site-specific standard operating procedures and ensure accurate QTcF calculation.

All ECG data will be documented at each visit, and the details will be recorded in both the source documents and the eCRF. The PI (or a qualified delegate at the investigational site) will interpret the ECG using 1 of the following categories: normal, abnormal NCS, or abnormal CS and record his/her evaluation in the eCRF.

Additional non-invasive electrocardiographic safety assessments (Holter monitor at screening and telemetry during inpatient stay) may be performed at the discretion of the PI to ensure participant safety. Assessments will be collected on the Prior and Concomitant Procedures CRF and in the eventuality of clinically significant findings, these will be reported as an adverse event.

8.6.4 Physical Examinations

Full physical examinations will be performed by a study-delegated registered physician at time points outlined in the Schedule of Assessments (Table 1). A full physical examination will include, at a minimum, assessments of the general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory, system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. A brief symptom-directed physical examination will be performed on Day 1 prior to IP administration and at any time throughout the study, as clinically indicated.

In addition, to aid in the early detection of TB reactivation or new TB infection during study participation, participants will be evaluated for signs and symptoms of active TB as part of physical examination.

Any findings made during the physical examination must be noted regardless of if they are part of the participant's medical history. The PI (or a qualified delegate at the investigational

site) will evaluate the findings using 1 of the following categories: normal, abnormal NCS, or abnormal CS and record his/her evaluation in the eCRF. New CS abnormalities that occur after IP administration will recorded as treatment-emergent AEs (TEAEs).

8.6.5 Clinical Safety Laboratory Assessments

Safety clinical laboratory samples will be analyzed at the study site's local laboratory. See Section 10.2 for the list of clinical laboratory tests to be performed and the Schedule of Assessments for the timing and frequency (Table 1).

Venous blood samples will be collected for clinical laboratory evaluations including hematology, clinical chemistry (including HbA1c), QuantiFERON-TB® Gold in Tube testing, viral serology, β-D-glucan test, pregnancy and follicle-stimulating hormone (FSH) testing (when applicable). Blood samples will be collected either by direct venipuncture (any suitable vein) or via an indwelling cannula inserted in a vein (depending on the time point).

Urine will be collected for urinalysis (and urine microscopy, if required), urine drugs of abuse screen, and urine pregnancy testing (when applicable). A commercially available breathalyzer test will be used to determine the concentration of alcohol in the participant's breath. COVID-19 testing will be performed as per PI's discretion following local health requirements and regulations and site guidelines.

The processing, shipping, and analysis of samples for protocol-required laboratory tests will be carried out as per the study site's SOPs. Repeated or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The laboratory reports must be filed with the source documents. The PI or delegate must review the laboratory report, document this review, and for protocol-specified laboratory parameters, evaluate all out-of-range (abnormal) laboratory values for clinical significance using 1 of the following categories: normal, abnormal NCS, or abnormal CS; the evaluation will be recorded in the eCRF. Refer to Section 8.7.1.3 for details on reporting of laboratory abnormalities as AEs.

All laboratory tests with values considered to be abnormal and CS during the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the PI. If such values do not return to normal/baseline within a period of time judged reasonable by the PI, the etiology should be identified, and the Sponsor notified.

8.6.6 Local Injection Site Reactions

Injection site evaluations will be made by clinical staff following SC administration of AVT05, US-licensed Simponi, and EU-approved Simponi at specific time points outlined in the Schedule of Assessments (Table 1). The injection sites will be monitored for pain, tenderness, erythema, and swelling. If an injection site reaction is observed, a physician will