characterize and document the reaction as an AE and AESI. Review of the injection site will continue until the AE is resolved.

Each injection site reaction will be categorized using the intensity grading scheme presented in Table 6: the severity of each resulting AE will also be categorized as described in Section 8.7.2.1 (eg, a moderate intensity injection site reaction may be recorded as a mild AE if considered appropriate according to the Investigator's judgment).

Table 6 Injection Site Reaction Grading Scheme

Injection Site Reaction	Absent (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Absent	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Hospital visit (A&E) or hospitalization
Tenderness	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Hospital visit (A&E) or hospitalization
Erythema/ redness	0 to ≤2.4 cm[50a]	2.5 to 5.0 cm[a]	5.1 to 10.0 cm[a]	>10.0 cm[a]	Necrosis or exfoliative dermatitis
Induration/ swelling	0 to ≤2.4 cm[a]	2.5 to 5.0 cm[a] and does not interfere with activity	5.1 to 10.0 cm[a] or interferes with activity	>10.0 cm[a] or prevents daily activity	Necrosis

Abbreviations: A&E = accident and emergency department.
a. Measurements refer to the reaction at the greatest single diameter.

8.7 Adverse Events

The PI and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IP or study procedures, or that caused the participant to discontinue the study (see Section 7.0). Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in the sections below.

8.7.1 Definitions

8.7.1.1 Adverse Events

An AE is any untoward medical occurrence in a participant, temporally associated with the use of an IP, whether or not considered related to the IP. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the IP.

Events meeting the AE definition include:

- Any abnormal laboratory test results (hematology, coagulation, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, vital signs measurements, physical examinations, or injection site assessments), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the PI (ie, not associated with the participant's health status).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after signing the ICF although it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events that do NOT meet the definition of an AE include:

- Medical or surgical procedures (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not represent a clinically significant exacerbation or worsening.

Adverse events which commence or worsen in severity on or after the time of IP administration will be considered as TEAEs.

8.7.1.2 Serious Adverse Events

If an event is not an AE per definitions above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening: The term 'life-threatening' in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization: In general, hospitalization signifies that the participant has been detained (usually involving a stay of at least 24 hours) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

    - Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent disability/incapacity: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect: Intrauterine development of an organ or structure that is abnormal in form, structure, or position.
- Is a medically important event or reaction: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed above. These events should usually be considered serious. Examples of such events include:

    - Laboratory abnormalities that meet the Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 criteria
    - Invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.7.1.3 Recording of Adverse Events Based on Other Safety Assessments

For protocol-specified laboratory parameters, any laboratory abnormality that is new in onset or which has worsened in severity or frequency from the baseline condition and meets one of

the following criteria will be recorded on the AE pages of the eCRF if not captured as part of an overarching diagnosis (eg, hemoglobin of 8 g/dL captured as part of anemia):

- Requires therapeutic intervention or additional diagnostic tests.
- Has accompanying clinical symptoms or signs.
- Is judged by the PI as clinically significant.

Additionally, any abnormalities in protocol-specified laboratory parameters that meet the CTCAE Grade ≥3 criteria are considered to be clinically significant and will be recorded as AEs.

Any clinically significant deterioration in vital signs, ECGs, and physical examinations as compared with baseline should also be recorded as AEs.

8.7.2 Recording of Adverse Events

All AEs/SAEs will be recorded from the time of signing the ICF until the end of the participant's participation in the study.

When an AE/SAE occurs, it is the responsibility of the PI or designee to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The PI or designee will then record all relevant AE/SAE information in the eCRF, including the following details (each event must be recorded separately):

- A description of the event
- Onset and resolution dates and times
- Seriousness
- Severity (as defined in Section 8.7.2.1)
- Relationship to the IP (as defined in Section 8.7.2.2)
- Action taken (none, treatment given, withdrawn from study, nondrug therapy, other)
- Outcome (Fatal, Not recovered/Not resolved, Recovered/Resolved, Recovered/Resolved with sequelae, Recovering/Resolving, or Unknown)

The PI or designee will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

It is not acceptable for the PI or designee to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page. However, there may be instances when copies of medical records for certain cases are requested by the Medical Monitor and/or Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Medical Monitor and/or Sponsor.

8.7.2.1 Assessment of Severity

Based on their clinical judgment, the PI or designee will make an assessment of severity for each AE and SAE reported during the study and assign it to 1 of the following categories:

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

Note: the term "severe" does not necessarily equate to "serious". Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.7.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be recorded. If an AE changes in frequency or intensity over a number of days, a new entry of the event must be made in the eCRF (with distinct onset dates).

8.7.2.2 Assessment of Causality

The PI or designee is obligated to assess the relationship between the IP and the occurrence of each AE/SAE. The PI or designee will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP will be considered and investigated. The PI or designee will also consult the IB and/or Product Information for Simponi, in their assessment.

The causal relationship of the AE to the IP or study procedures should be assessed by the PI (or medically qualified delegate) using the following definitions:

Related - there is reasonable possibility that the adverse event has been caused by the IP, meaning there are facts, evidence, or arguments to support the causal relationship, such as:

- plausible time relationship
- supporting de-challenge and/or re-challenge information is available
- participants underlying condition(s), concomitant therapy, disease progression, or other causes or risk factors cannot explain the adverse event

Not-related - there is no reasonable possibility that the adverse event was caused by the IP, meaning there is no evidence suggesting a causal relationship and the adverse event can readily be explained by alternative causes, such as:

- participants underlying condition(s), concomitant therapy, disease progression, or other causes or risk factors
- time relationship does not support causal relationship
- the available de-challenge and/or re-challenge information does not support causal relationship

8.7.3 Reporting of Serious Adverse Events

As the Sponsor has a legal responsibility to notify the appropriate regulatory authorities about the safety of a new test drug, prompt notification by the PI or designee of any SAEs to the Sponsor is required.

All SAEs, whether related or unrelated, will be recorded on a paper SAE Form and submitted to the Sponsor and/or designee within 24 hours of site awareness. The PI or designee will submit any clinically or medically significant updated SAE data to the Sponsor and/or designee within 24 hours of it being available. The procedures for completing and transmitting SAE reports and contact information for SAE reporting can be found in the SAE Form.

Copies of all correspondence relating to reporting of any SAEs should be maintained in the site's study files and will be checked routinely by the study monitor.

8.7.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the PI or designee is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs and AESIs (as defined in Section 8.7.7) documented at a previous visit/contact that are designated as ongoing will be followed up until resolution, stabilization, the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 7.3). This activity will continue up to Day 75 (11 weeks after IP administration). The PI or designee will ensure that follow-up includes any supplemental investigations as medically indicated or requested by the Medical Monitor and/or Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. For AEs or SAEs that are reported before or on Day 75, follow-up of ongoing events that are considered related to the IP will continue only up to the time of database lock.

The PI or designee is not obligated to actively seek new AEs or SAEs after conclusion of the study participation. However, if the PI or designee learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event

to be reasonably related to the IP or study participation, the PI or designee must promptly notify the Sponsor.

8.7.5 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IP. The Sponsor will comply with any country-specific regulatory requirements relating to safety reporting to the regulatory authority, national clinical trial pharmacovigilance database (if applicable), IRB/IEC, and PIs.

If the Sponsor considers that an SAE is a SUSAR, it will be reported to the appropriate regulatory authorities by the Sponsor (or designee) within the predefined expedited timelines and according to country-specific regulatory requirements. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to PI as necessary. A PI or designee who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB.

If required, individual or expedited reports of SAEs or SUSARs will be submitted by the Sponsor or designee to the IRB/IEC, if appropriate according to local requirements.

8.7.6 Pregnancy

There is no information about the effects that AVT05 could have on the development of the fetus in humans. Therefore, it is important that WOCBPs and participants' partners do not become pregnant until at least 6 months after IP administration and agree to use adequate contraception during this period.

Details of all pregnancies in WOCBPs and participants' partners (after obtaining the necessary signed informed consent from the pregnant partner directly) will be collected via a Pregnancy Report Form from the time of IP administration until at least 11 weeks after IP administration. Since this is a single dose study, participants who become pregnant during the study will be encouraged to remain in the study and will be followed for safety up to EoS visit. Only those follow-up procedures that would not expose the participant to additional undue risk will be performed.

The PI or designee will record pregnancy information on a Pregnancy Report Form and submit it to the Sponsor and/or designee within 24 hours of the site's awareness of the pregnancy. The procedures for completing and transmitting pregnancy reports and contact information for pregnancy reporting can be found in the Pregnancy Report Form.

The pregnant participant or partner will also be followed up to determine the outcome of the pregnancy, including spontaneous or voluntary termination. The PI or designee will collect follow-up information on the pregnant participant or partner and the child (including details of

the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications) and the information will be forwarded to the Sponsor. Generally, the follow-up period for a pregnancy will be deemed to have ended when the health status of the child has been determined on its birth. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, hospitalizations for complications during pregnancy, or if the outcome of the pregnancy meets the criteria of an SAE (eg, spontaneous abortions, fetal death, stillbirth, congenital anomalies [including those in an aborted fetus], ectopic pregnancy) or elective termination of a pregnancy will be reported as an SAE (Sections 8.7.3 and 8.7.5).

8.7.7 Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to golimumab, for which ongoing monitoring is required. Such AESIs may require further investigation to characterize and understand them. The AESIs for this study encompass all relevant warnings and precautions from the Simponi Product Information and include:

- Serious infections, including invasive fungal infections. These include:
    - Active tuberculosis, including reactivation of latent tuberculosis.
    - Invasive fungal infections including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis.
    - Bacterial (including sepsis and pneumonia), viral, and other infections due to opportunistic pathogens, including *Legionella* and *Listeria*.
    - Hepatitis B Reactivation.
- Malignancies, especially lymphoma.
- Hypersensitivity reactions, including anaphylaxis (details in Section 8.7.7.1) and angioedema
- Autoimmune disorders: lupus-like syndrome.
- Demyelinating disorders: new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, optic neuritis, peripheral demyelinating disease, including Guillain-Barré syndrome.
- Congestive Heart Failure:
    - worsening congestive heart failure (CHF): New York Heart Association (NYHA) Class 1 which became Class 2/3/4, or NYHA Class 2 which became Class 3 or 4
    - new onset CHF

- Local injection site reactions: pain, tenderness, erythema/redness, and induration/swelling (details in Section 8.6.6). In addition, pruritus/itching, hematoma/ecchymosis/bruising will be considered as injection site reactions.

While these events are noted to be of special interest, they will be reported and assessed in the same manner as standard AEs (unless seriousness criteria are met).

8.7.7.1 Anaphylaxis

Anaphylaxis may be defined when any 1 of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, or flushing, swollen lips-tongue-uvula), with at least 1 of the following:
   a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   b) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
   a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that participant (minutes to several hours): systolic BP <90 mm Hg or >30% decrease from the participants' baseline.

8.8 Immunogenicity Assessments

Venous blood samples (8 mL per sample) will be collected from all participants at the time points specified in Table 2 for the measurement of ADAs to golimumab in serum at a central laboratory. 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). 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 the Laboratory Manual.

For the immunogenicity assessments, serum samples will be screened for antibodies binding to golimumab in AVT05, US-licensed Simponi, and EU-approved Simponi, and the titer of confirmed positive samples will be reported. Antibodies will be further characterized and/or

evaluated for their ability to neutralize the activity of the IP. All samples collected for detection of antibodies to golimumab will also be evaluated for golimumab serum concentration to enable interpretation of the antibody data.

The immunogenicity assessments will be performed using a validated immunoassay method. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.

8.9 Inflammatory Cytokine Pharmacodynamic Assessments

For the ex-vivo pharmacodynamic assessments, venous blood samples (4 mL) were collected in lithium-heparin tubes from 45 participants (15 per group) for the measurement of IL-8 levels using an ex-vivo TNF-α stimulation assay at the time points specified in Table 2.

NOTE: 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.

8.10 Residual Samples for Future Scientific Research

With participant consent, residual serum samples will be stored and may be used for the assessment of pharmacodynamics that could help to evaluate their association with observed clinical responses to AVT05. Additional biomarkers may be identified during or after the study and be considered for assessment in the future.

Participants may withdraw consent for use of biorepository samples at any time, as described in the ICF. Samples will be shipped and stored according to instructions in the Laboratory Manual. The samples may be stored for a maximum of 2 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor.

8.11 Genetics

Genetic parameters are not evaluated in this study.

8.12 Health Economics/Medical Resource Utilization

Health economics/medical resource utilization parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The following statistical hypotheses will be tested to demonstrate the PK similarity of AVT05, US-licensed Simponi and EU-approved Simponi in terms of C_{max} and $AUC_{0\text{-}inf}$.

- The null hypothesis is:

  H0: $GM_T/GM_R \leq 80\%$ or $GM_T/GM_R \geq 125\%$

- The alternative hypothesis is:

  H1: $80\% < GM_T/GM_R < 125\%$

where GM_T and GM_R denote the geometric mean of PK parameter (eg, C_{max} and $AUC_{0\text{-}inf}$) in the Test and Reference groups, respectively. Following pairwise comparisons will be performed for each primary PK parameter:

- AVT05 (T) vs. US-licensed Simponi (R)
- AVT05 (T) vs. EU-approved Simponi (R)
- EU-approved Simponi (T) vs. US-licensed Simponi (R)

9.2 Sample Size Determination

The primary PK endpoints for this PK study are C_{max} and $AUC_{0\text{-}inf}$. Sample size calculations were performed using SAS Version 9.4, and were based on PK parameter summary data from Ling and Lyn (2010).[1] Based on this study, the inter-participant coefficient of variation (CV%) is assumed to be 35.0% for $AUC_{0\text{-}inf}$ and 37.7% for C_{max}.

The assessment of PK similarity will be based on the 90% confidence interval (CI) for the geometric mean ratio (GMR) between 3 treatment groups will be calculated for all 3 pairwise comparisons (AVT05 to US-licensed Simponi, AVT05 to EU-approved Simponi, and EU-approved Simponi to US-licensed Simponi) for both primary endpoints $AUC_{0\text{-}inf}$ and C_{max}. The PK similarity will be demonstrated if the 90% CIs of the GMR for both $AUC_{0\text{-}inf}$ and C_{max} lie entirely within the prespecified margins of 80% and 125% (when the ratio is expressed as a percentage) in all pairwise treatment comparisons.

Assuming a true GMR of 95%, 101 evaluable participants per treatment 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 a non-evaluable rate of 10%, the total sample size of 336 participants (112 per treatment group) will provide an overall study power of 80.5%.

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

9.3 Analysis Populations

Table 7 Analysis Populations

Analysis Population	Description
Entered Population	All participants who sign the ICF.
Randomized Population	All participants who are randomized into this study. Participants will be analyzed according to their randomized treatment, regardless of which treatment the participant receives.
Safety Population	All randomized participants who receive any amount of the IP. Participants will be analyzed according to the treatment they receive, if this differs from that to which the participant is randomized.
Pharmacokinetic Population	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 receive, if this differs from that to which the participant is randomized. Participants with dosing deviations that could potentially affect the PK profile will be excluded from the PK Population, at the discretion of the blinded pharmacokineticist prior to analysis.
Immunogenicity Population	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 ADAs). Participants will be analyzed according to the treatment they receive, if this differs from that to which the participant is randomized.

Abbreviations: ADA = antidrug antibody; ICF = Informed Consent Form; IP = investigational product; PK = pharmacokinetics.

9.4 Statistical Analyses

The following sections describe the statistical analysis as it is foreseen when the study is being planned. A detailed Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the participant analysis populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. The SAP will also provide the format of listings, tables, and figures to be provided for completion of the Clinical Study Report (CSR). Any deviations from the SAP will be presented in the final CSR. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All statistical analyses, summaries, and listings will be performed using SAS software (Version 9.4 or higher) (SAS Institute, Inc., Cary, North Carolina, USA).

In general, data will be presented by treatment group. Data for all study participants combined will also be presented when appropriate. Individual participant data will be presented in listings by randomization strata.

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: sample size (N), number of non-missing counts (n), mean, SD, median, minimum (min), and maximum (max). The CV%, geometric mean, and geometric CV% will be presented for PK parameters, where applicable.
- Categorical variables: frequency counts and percentages.

Baseline will be defined as the last available, valid, non-missing assessment (scheduled or unscheduled) prior to dosing. Only data from protocol-scheduled visits/time points will be included in the summary tables and figures. All data, including those from unscheduled visits/time points will be included in the listings.

9.4.1 Participant Disposition and Protocol Deviations

All participants who provide informed consent (ie, the Entered Population) will be accounted for in this study. Participant enrollment and disposition will be summarized by treatment group and for all participants and will include: the number of participants entered, screen failed, enrolled, randomized (overall and by randomization strata), and dosed with the IP; the total number of participants who complete the study; and the number of participants who discontinue from the study, along with the reason for discontinuation.

The number and percentage (%) of participants included in each analysis population will also be presented.

Participants who had protocol deviations by severity classification and deviation type by treatment group and for all participants based on the Randomized Population will be listed and summarized using frequency counts and percentages. If applicable, the protocol deviation listing will flag participants whose study participation is impacted by the global pandemic COVID-19 and will include details of the impact.

9.4.2 Demographics, Other Baseline Characteristics, and Medical History

All demographic and baseline data recorded prior to dosing will be summarized using descriptive statistics or frequency counts and percentages, as appropriate, by treatment group and for all participants in the Randomized Population and the PK Population. Individual participant demographics and baseline characteristics (results from urine drug abuse screening, alcohol breath test, COVID-19 test (if performed), viral serology, β-D glucan test, QuantiFERON-TB Gold in Tube test, pregnancy, and FSH tests) will also be presented in listings.

Medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and the data will be listed and summarized using frequency counts and percentages by system organ class (SOC) and preferred term (PT) by treatment group and for all participants in the Safety Population.

9.4.3 Prior and Concomitant Medications/Therapies

Prior and concomitant medications will be coded using the latest version of the WHO Drug Global Dictionary. Prior medications are those medications that are stopped prior to IP administration. Concomitant medications are medications that are taken at least once after IP administration. Medications stopping on the same day as IP administration will be considered as concomitant medications.

Prior and concomitant medications will be listed and summarized separately using frequency counts and percentages by Anatomical Therapeutic Chemical system (Level 2) and drug PT by treatment group and for all participants in the Safety Population.

9.4.4 Efficacy Analyses

Not applicable.

9.4.5 Pharmacokinetic Analyses

Serum golimumab concentrations will be listed for all participants in the Safety Population. Summaries of serum golimumab concentrations, PK parameters, and PK similarity assessment will be based on the PK Population.

Serum golimumab concentrations will be listed and summarized using descriptive statistics by treatment group and nominal PK sampling time point. All serum golimumab concentrations that are below the limit of quantification will be labeled as such in the concentration data listings. Individual and arithmetic mean (per treatment) concentration-time profiles will also be presented graphically.

Pharmacokinetic 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 SAP).

In addition, PK parameters will also be summarized by treatment and randomization strata. A subgroup analysis of PK parameters by gender and Japanese, non-Japanese ≤80 kg, and non-Japanese >80 kg will also be performed.

9.4.6 Statistical Analysis for PK Similarity

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 ANCOVA model on the logarithmic scale (ie, using natural log-transformed values of C_{max} and $AUC_{0\text{-}inf}$) including treatment group as fixed effect and with gender as factor and body weight at baseline as continuous covariate.

Point estimates (geometric means and GMRs) will be calculated by back transforming the 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 US-licensed Simponi, AVT05 versus EU-approved Simponi, and EU-approved Simponi versus US-licensed Simponi will be demonstrated if, for each pairwise comparison, the 90% CIs for the GMRs of the primary endpoints are entirely contained within the equivalence margin of 80% to 125% (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.

9.4.7 Safety Analyses

9.4.7.1 Adverse Events

All safety analyses will be performed on the Safety Population. Adverse events will be coded using the latest version of MedDRA.

All AE summaries will be restricted to TEAEs only (as defined in Section 8.7.1.1). 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 SOC and PT and summarized by treatment group and for all participants.

For the summaries of TEAEs, participants who experience the same TEAE (in terms of the MedDRA SOC and PT) more than once will be only counted once for that event in the number of participants, but all occurrences of the same event will be counted in the number of events.

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.

Adverse events 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.

9.4.7.2 Local Injection Site Reactions

Local injection site reactions will be listed and summarized using frequency counts and percentages by treatment group and for all participants: by most severe reaction (pain,

tenderness, erythema/redness, induration/swelling, and other reactions) and by each reaction for each scheduled time point, and intensity grade (including Grade ≥1). The worst postbaseline injection site reaction intensity grade observed at any time (scheduled or unscheduled) during the study will also be presented.

9.4.7.3 Clinical Laboratory Evaluations

Observed values and change from baseline for clinical laboratory data (hematology, coagulation, and clinical chemistry) will be listed and summarized using descriptive statistics at each protocol-specified time point by treatment group. Separate listings will be produced for all participants with at least 1 out-of-range or abnormal clinical laboratory result.

Shifts in the PI's evaluation of laboratory parameters (Normal, Abnormal NCS, Abnormal CS) from baseline to each postbaseline protocol-scheduled time point will be summarized by treatment group, using frequency tabulations.

9.4.7.4 Vital Signs, Electrocardiograms, and Physical Examinations

All vital signs and ECG data and the PI's evaluation of abnormal physical examination findings will be presented in data listings.

In addition, observed values and change from baseline for vital signs and ECG data will be summarized at each protocol-specified time point, by treatment group. Shifts in the PI's evaluation of the results (Normal, abnormal NCS, Abnormal CS) from baseline to each postbaseline protocol-scheduled time point will also be summarized by treatment group using frequency tabulations.

9.4.8 Immunogenicity Analyses

For the immunogenicity assessments, serum samples will be screened for binding antibodies followed by confirmation and titer determination of ADA positive samples. The confirmed positive ADA samples will be further evaluated for their neutralizing ability i.e., NAb positive or negative. All samples collected for detection of antibodies to golimumab will also be evaluated for golimumab concentrations to enable interpretation of the antibody data.

9.4.9 Handling of Missing Data

For participants who are withdrawn from the study prior to their completion for any reason, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal. There will be no imputation for missing data, unless otherwise stated.

9.5 Interim Analyses

No interim analyses are planned for this study.

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
    - All other applicable laws and regulations.
- The protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to the IRB/IEC by the PI and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to participants.
- The PI or designee will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of the conduct of the study at the study site and adherence to requirements of ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each PI will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study site at which the PI has not signed the protocol.

Adequate Resources

The PI is responsible for supervising any individual or party to whom the PI delegates study-related duties and functions conducted at the study site.

If the PI/institution retains the services of any individual or party to perform study-related duties and functions, the PI/institution should ensure this individual or party is qualified to

perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Finance and Insurance

Financing of this study is outlined in a separate agreement.

Participants may be compensated for the time that they spend participating in the study using a formula determined by the study site.

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the participants in this study. The terms of the insurance will be kept in the study files. The participant should not take part in any other clinical study while they are enrolled in this study. The participant should report any health injury that could have occurred as a result of the clinical study to the PI without delay.

Informed Consent Process

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to ICH GCP guidelines. The PI is responsible for ensuring that no participant undergoes any study-related examination or activity before the participant has given written informed consent to participate in the study.

The PI or their representative will explain the nature of the study to the participant and answer all questions regarding the study. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH GCP guidelines, the IRB/IEC, and study site.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign and date the ICF. A copy of the ICF(s) must be provided to the participant. Representative written information for the participant (participant information sheet) and a sample ICF, designated as the master version, is provided in the Trial Master File.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, a new ICF (or an ICF addendum, as appropriate) will be approved by the IRB/IEC (and regulatory authorities, if required). Participants must be reconsented to the new version of the ICF/addendum.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The PI or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason

during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Administrative Structure

The Sponsor will enlist the support of a CRO, [redacted] to coordinate the study. The Sponsor will supervise all outsourced activities. The administrative structure for the study will be covered in a separate document.

Medical Monitor

[redacted] MD
Medical Director
[redacted]
[redacted]

Dissemination of Clinical Study Data

After completion of the study, a CSR will be written by the CRO in consultation with the Sponsor and PI following the guidance in ICH E3. The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the regulatory authority and the IRB/IEC a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- All participant data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). Data collection must be completed for each participant who signs an ICF.

- The PI is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF. The PI must also maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The PI must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The CRO is responsible for the data management of this study, including quality checking of the data. Quality tolerance limits will be predefined in the sites to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the quality tolerance limits and remedial actions taken will be summarized in the CSR.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the PI for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The PI/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the PI's study site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The PI may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Definition of what constitutes source data can be found in the eCRF completion guidelines.

Management of Protocol Amendments and Protocol Deviations

Protocol Amendments:

No changes (amendments) to the protocol may be implemented without prior approval from the Sponsor and the appropriate IRB/IEC, except where necessary to eliminate an immediate hazard to participants, or when the change involves only logistical or administrative aspects of the study. If a protocol amendment requires changes to the ICF, the revised ICF must be approved by the IRB/IEC.

Protocol Deviations:

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes that were approved by the Sponsor and the IRB/IEC and agreed to by the PI. Protocol deviations will be classified by severity ratings of critical, major, or minor, as determined by clinical staff:

- A minor protocol deviation is a deviation from accepted procedures that will not adversely affect participants or data integrity, but should be dealt with appropriately.
- A major protocol deviation is a deviation from Protocol-related procedures that could affect integrity of the data or adversely affect participants. Such deviations require timely action.
- A critical protocol deviation is deviation from Protocol-related procedures that could affect integrity of the data or adversely affect participants. Such deviations require timely action.

Major or critical deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to a regulatory agency's regulations or ICH GCP guidelines, and may lead to the participant being withdrawn from the study or being excluded from statistical analyses.

The PI or designee will document and explain in the participant's source documentation any deviation from the approved protocol. Protocol deviations will also be documented by the study monitor throughout the course of monitoring visits, and the PI will be notified of any deviations in writing by the monitor. The IRB/IEC will be notified of all protocol deviations, if appropriate, in a timely manner.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The PI may only implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments will be submitted to the IRB/IEC (and regulatory authorities if applicable) for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

Protocol deviations will be reviewed and confirmed prior to database lock to decide which participants and/or participant data will be excluded from certain analyses. Decisions regarding the exclusion of participants and/or participant data from analyses will be documented and approved prior to database lock and/or relevant data transfer.

Study Termination and Study Site Closure

The Sponsor designee reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed on study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site close-out visit has been performed.

The PI may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI, and regulatory authorities. If the study is prematurely terminated or suspended, the PI or designee will promptly inform the IRB/IEC and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant study termination or suspension or early closure of a study site by the Sponsor or PI may include, but are not limited to:

- The PI (or delegate) and the Sponsor consider that the number and/or severity of AEs justify discontinuation of the study.
- Failure of the PI to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the PI.
- Discontinuation of further IP development.
- The Sponsor makes a unilateral request to do so.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the PI, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The PI shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the PI and study site will be set forth in the Clinical Trial Agreement.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the PI agrees to submit all manuscripts or abstracts to the Sponsor before

submission. This allows the Sponsor to protect proprietary information and to provide comments.

- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a Coordinating PI will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed locally as per the time points specified in the Schedule of Assessments (Table 1).
- Protocol-specific laboratory-related requirements for inclusion or exclusion of participants are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the PI or required by local regulations or the local laboratory SOPs.
- The PIs (or medically qualified delegate) must document their review of each laboratory safety report.
- Laboratory/analyte results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

Table 8 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Red blood cell count	White blood cell count with differential
	Hemoglobin	
	Platelet Count	
Coagulation	Prothrombin time	International normal ratio
	Activated partial thromboplastin time	
Clinical Chemistry[a]	Albumin	Creatinine
	Albumin/Globulin Ratio	CRP
	ALT	GGT
	Alkaline Phosphatase	Globulin
	AST	Glucose
	Bilirubin direct	Lactate dehydrogenase
	Bilirubin indirect	Phosphorus-inorganic
	Bilirubin-total	Potassium
	Urea	Protein-total
	Urea/creatinine ratio	RF
	Calcium	Sodium
	Cholesterol	Triglycerides
	Chloride	Uric acid
	Creatine kinase	HbA1c (at Screening only)
Urinalysis (dipstick)	Protein	pH of freshly voided specimen
	Glucose	Ketones
	Nitrites	
	Microscopy (if clinically indicated)	

Laboratory Assessments	Parameters	
Viral serology (Screening only)	HIV 1 and 2 antibodies	Anti-HBc
	HBsAg	HCV antibody
	Anti-HBs	
Fungal test (Screening only)	β-D glucan	
COVID-19 test	As per local site, health authority, and Investigator requirements.	
Tuberculosis testing	QuantiFERON®-TB Gold in Tube	
Drugs of abuse (Screening only)	Amphetamines	Benzodiazepines
	Cannabinoids	Methadone metabolites
	Cocaine metabolites	Barbiturates
	Ecstasy (3,4-Methylenedioxymethamphetamine)	Phencyclidine
	Opioids and opiates	
Alcohol testing	Alcohol breath test using a commercial breathalyzer (Screening only)	
Pregnancy and FSH tests	Serum and urine human chorionic gonadotropin (hCG) pregnancy tests will be done for participants of childbearing potential only. Follicle-stimulating hormone test at Screening (to determine postmenopausal state in participants of non-childbearing potential only)	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; anti-HBc = hepatitis B core antibody; hCG = human chorionic gonadotropin; COVID-19 = coronavirus disease 2019; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HbA1c = glycated hemoglobin; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; RF = rheumatoid factor; SAE = serious adverse event; TB = tuberculosis; ULN = upper limit of normal.

NOTE:

a. All events of ALT≥3 × ULN and bilirubin≥2 × ULN (>35% direct bilirubin) or ALT≥3 × ULN and INR>1.5, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.

10.3 Contraceptive and Barrier Guidance and Collection of Pregnancy Information

10.3.1 Definitions

Woman of Childbearing Potential (WOCBP)

Participants with a uterus who are NOT either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are NOT postmenopausal.

Participants in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal participant with 1 of the following:
    a) Documented hysterectomy.
    b) Documented bilateral salpingectomy.
    c) Documented bilateral oophorectomy.

NOTE: Documentation can come from the study site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal participant:
    a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high 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). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    b) 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.

10.3.2 Contraception Guidance

- Participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9 from Screening (signing the ICF) until at least 6 months after IP administration.
- 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 last dose of IP administration. Participants with a partner or partners who is (are) not of childbearing potential are exempt of these requirements.

Table 9 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods that are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Contraceptive Methods that are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). • Bilateral tubal occlusion. • Subdermal progestogen implant.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the* participant.
NOTES: a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b. Hormonal contraception may be susceptible to interaction with the IP, which may reduce the efficacy of the contraceptive method. In this case, 1 highly effective method of contraception and a barrier method (condom) should be utilized starting at Screening and throughout the study period up to 6 months after IP administration. NOTE: Condoms alone are not highly effective methods of contraception. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

Pregnancy Testing

- WOCBPs should only be included in the study after a confirmed menstrual period and a negative highly sensitive serum pregnancy test. For WOCBPs using hormonal contraceptives which may result in menstrual suppression, a negative serum pregnancy test is sufficient for enrollment.
- All subsequent pregnancy testing will be performed using a highly sensitive urine pregnancy test that will be performed at time points specified in the Schedule of Assessments (Table 1) and as required locally. Any positive urine pregnancy test result will be confirmed with a serum β-human chorionic gonadotropin (β-hCG) test.

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

10.4 Risk Mitigation Table

Target System	Effect	Risk Mitigation
Infections and infestations	**Very common**: Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis) **Common**: Bacterial infections (such as cellulitis), lower respiratory tract infection (such as pneumonia), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections, abscess **Uncommon**: Sepsis including septic shock, pyelonephritis **Rare**: Tuberculosis, opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), hepatitis B reactivation, bacterial arthritis, infective bursitis	1) Standard monitoring as with all early phase trials 2) Participants must test negative for β-D Glucan, Hep B, Hep C and HIV 3) Participants will be excluded if they have an active infection or a history of recurrent or chronic infections 4) Participants will be excluded if they have a history of tuberculosis or evidence of active or latent TB infection 5) Restrictions to vaccination with a live vaccine before and after IP administration 6) Inclusion of CRP monitoring as part of the regular safety laboratory assessments (see Section 1.3 [SOA])
Neoplasms	**Uncommon**: Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus) **Rare**: Lymphoma, leukemia, melanoma, Merkel cell carcinoma **Not known**: Hepatosplenic T-cell lymphoma*, Kaposi's sarcoma	1) Participants will be excluded if they have a history of clinically relevant malignancies
Hematological system	**Common**: Leukopenia (including neutropenia), anemia **Uncommon**: Thrombocytopenia, pancytopenia **Rare**: Aplastic anemia, agranulocytosis	1) Standard monitoring as with all early phase trials 2) Participants will be excluded from this trial if they have a hemoglobin or platelet level outside of the reference range at screening. 3) Participants must not have donated blood within 8 weeks prior to IP administration 4) Participants must not donate blood for at least 3 months after IP administration
Immune System	**Common**: Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive **Rare**: Serious systemic hypersensitivity reactions (including anaphylactic reaction), vasculitis (systemic), sarcoidosis	1) Standard monitoring as with all early phase trials 2) Participants will be excluded from this trial if they have a history of relevant drug/food allergies or known/suspected hypersensitivity to golimumab, AVT05 or any of its constituents 3) Inpatient stay to monitor for acute immune reactions

Target System	Effect	Risk Mitigation
		4) Staggered sentinel cohort dosing strategy 5) Anaphylactic reactions will be managed in accordance with local guidelines detailed in site-specific study operation manuals
Renal and Urological System	**Rare**: Bladder disorders, renal disorders	1) Standard monitoring as with all early phase trials 2) Additional assessments may be completed if indicated
Hepatic System	**Common**: Alanine aminotransferase increased, aspartate aminotransferase increased **Uncommon**: Cholelithiasis, hepatic disorders	1) Standard monitoring as with all early phase trials 2) Monitoring of liver function tests as part of the regular safety laboratory assessments (see Section 1.3 [SOA]) 3) Participants will be excluded if they have previous exposure to hepatitis B, C or HIV 4) Additional assessments could be added depending on clinical requirements, including a fibro scan of the liver
Cardiovascular system	**Common**: Hypertension **Uncommon**: Arrhythmia, ischemic coronary artery disorders, Thrombosis (such as deep venous and aortic), flushing **Rare**: Congestive heart failure (new onset or worsening), Raynaud's phenomenon	1) Standard monitoring as with all early phase trials 2) Participants must be normotensive to be included in the study 3) Participants must have ECG recordings without signs of clinically relevant pathology prior to IP administration 4) Local sites can perform additional safety assessments (ie, Holter monitoring and telemetry as per adaptive features)
Respiratory System	**Common**: Asthma and related symptoms (such as wheezing and bronchial hyperactivity) **Uncommon**: Interstitial lung disease	1) Standard monitoring as with all early phase trials
Nervous system (including psychiatry)	**Common**: Dizziness, headache, paresthesia, Depression, insomnia **Uncommon**: Balance disorders **Rare**: Demyelinating disorders (central and peripheral), dysgeusia	1) Standard monitoring as with all early phase trials 2) Participants with a history of demyelinating conditions will be excluded (see Section 5.2)

Target System	Effect	Risk Mitigation
Gastrointestinal system	**Common**: Dyspepsia, gastrointestinal and abdominal pain, nausea, gastrointestinal inflammatory disorders (such as gastritis and colitis), stomatitis **Uncommon**: Constipation, gastro-esophageal reflux disease	1) Standard monitoring as with all early phase trials 2) Any self-reported GI disturbance will be investigated further with appropriate investigation
Skin & Connective Tissue	**Common**: Pruritus, rash, alopecia, dermatitis **Uncommon**: Bullous skin reactions, psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria **Rare**: Lichenoid reactions, skin exfoliation, vasculitis (cutaneous), Lupus-like syndrome **Not known**: Worsening of symptoms of dermatomyositis	1) Standard monitoring and regular AE checks as with all early phase trials
Reproductive system	**Uncommon**: Breast disorders, menstrual disorders	1) Specific contraceptive requirements will be in place for participants 2) Contraceptive guidance will be used in inclusion criteria 3) WOCBP will need evidence of negative pregnancy tests prior to dosing
Endocrine disorders	**Uncommon**: Thyroid disorder (such as hypothyroidism, hyperthyroidism and goiter), Blood glucose increased, lipids increased	1) Standard monitoring as with all early phase trials 2) Participants with known diabetes will be excluded from the study
Ophthalmology	**Uncommon**: Visual disorders (such as blurred vision and decreased visual acuity), conjunctivitis, eye allergy (such as pruritis and irritation)	1) Standard monitoring as with all early phase trials 2) Any self-reported visual disturbance will be investigated further with thorough examination
General disorders and administration site conditions	**Common**: Pyrexia, asthenia, injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paresthesia), chest discomfort **Rare**: Impaired healing	1) Standard monitoring as with all early phase trials 2) Regular injection site checks
Injury, poisoning and procedural complications	**Common**: Bone fractures	1) Standard monitoring as with all early phase trials

*Observed with other TNF-blocking agents.

10.5 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents.

Version 2.0 (13 October 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The protocol was amended primarily to remove some typographical and editorial errors and provide some clarity on some aspects of the study. A summary of the changes with rationale for each change is provided below.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	The following changes were made to the schedule: • Visit added for non-sentinels on Day 3 during the ambulant period to align with Table 2.	Correction of minor error.
	• Additional information added to footnote a "The inpatient observation period may be increased, based on the site's discretion."	• To allow for sites to allow participants for increased inpatient observation, if required.
	• Footnote d changed from "Predose on Day 1 ECG is done 60 mins prior to the dose." to "Predose on Day 1, ECG is done within 60 mins to the dose."	• To allow for a window period for testing.
	• Footnote e – Added 15-minute time windows for the ECG assessments on Day 1 at 4 h and 12 h postdose.	• To allow for a window period for testing.
	• Footnote g – Removed fasting condition for laboratory test sample collection during study days. • Removed superscript (g) from Day 1 (pre-dose)	• To align with the study requirements.
	• "Highly sensitive" was removed from Urine pregnancy test.	• Urine pregnancy tests performed during the study are standard tests.
Section 1.3 Schedule of Activities, Table 2, Section 8.9, Section 8.10, Section	• Text "biomarker" replaced with "pharmacodynamic"	• As per study requirements.

Section # and Name	Description of Change	Brief Rationale
Error! Reference source not found.		
Section 4.1 Overall Design	• Study sites were changed from specific countries (New Zealand, The UK, and South Africa) to worldwide.	• To allow for inclusion of other sites in other countries for sufficient recruitment.
Section 4.5.1 Study Stopping Criteria	• Stopping criteria were revised from >2 to ≥1 participants with an SAE that is at least possibly related to the IP. • A new stopping criterion was added to stop dose escalation if there are ≥2 participants in the same group with severe non-serious AEs which are at least possibly related to the IP.	As recommended by MEDSAFE based on EMA guidelines on study stopping criteria.
Section 5.1 Inclusion Criteria, Criterion no. 6	Text was revised to clarify that vital signs limits for inclusion apply "during screening and Day 1 prior to dosing of IP."	To add clarity.
Section 5.1 Inclusion Criteria, Criteria no. 11	The requirement to discuss with Sponsor, for repeating evaluations for laboratory tests was changed to permit repeats at the discretion of PI or delegate.	For operational reasons, based on feedback from site.
Section 5.1 Inclusion Criteria, Criteria no. 12	Included text "negative for" to clarify that negative test reports are required for viral serology and β-D glucan tests for inclusion in the study.	Editorial – typographical error corrected.
Section 5.1 Inclusion Criteria, Criteria no. 14	New criterion added to specify restriction for donating ova/eggs for female participants.	Added as an additional safety measure.
Section 5.3.2 Caffeine, Alcohol, and Tobacco	Changed restriction on smoking from ≤10 cigarettes or equivalent per day to ≤10 cigarettes or equivalent per week.	Editorial – error corrected.
Section 10.1 Regulatory, Ethical, and Study Oversight Considerations, Informed Consent Process	The word "pharmacogenomic" removed from the text regarding consent for optional exploratory research.	Editorial change. There will be no pharmacogenomic testing as part of optional exploratory research.
Section 10.2 Clinical Laboratory Tests, Table 9	• Removed pathogens from list of urinalysis dipstick tests. • Added coagulation panel.	• Tests not done at site. • Error of omission.
Throughout the protocol	Minor editorial changes were made.	Minor, and therefore have not been summarized

Version 3.0 (10 November 2022)

Overall Rationale for the Amendment:

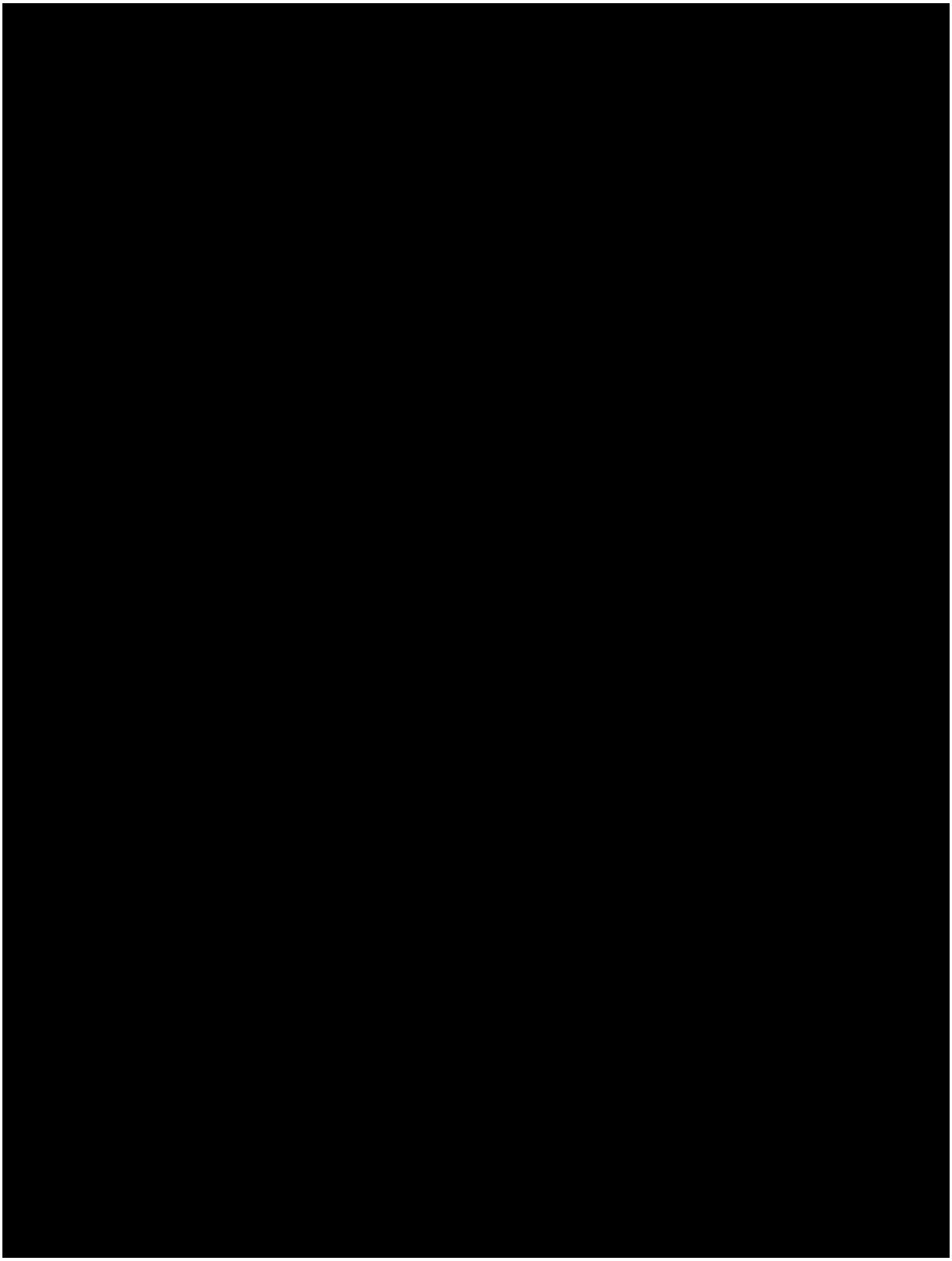
The protocol was amended primarily to remove some typographical and editorial errors and provide some clarity on some aspects of the study. A summary of the changes with rationale for each change is provided below.

Description of Changes in Amendment

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activities informed consent, footnote b, Section 5.4	Added text to specify that informed consent is not required during the screening window if the participant has provided an informed consent (ie, rescreening participants).	To allow for sites to comply with local regulatory guidelines.
Section 1.3 Schedule of activities footnote g, Section 10.2	Removed requirement to fast before clinical laboratory sample collection at Screening.	To allow flexibility with site requirements.
Section 1.3 Schedule of activities 12-lead ECG, footnote e, Section 8.6.3	• Added text to allow for triplicate ECG at the discretion of the Investigator. • Allowed additional non-invasive electrocardiographic safety assessments (Holter monitor at screening and telemetry during inpatient stay) to be done at the discretion of the PI.	For additional participant safety and as required at some sites.
Section 1.3 Schedule of activities, IP administration	Deleted one row of IP administration	Error of duplication. Row is a duplicate.
Section 2.3, Section 10.4	Added risk mitigation plan.	To address the expected risks from administration of the IP
Section 4.5.1 Study Stopping Criteria	Text was added to stopping rules to clarify that the Sponsor will immediately inform all participating sites to stop dosing if the Sponsor becomes aware that the trial has met stopping rules at another site, and the Sponsor will provide a clear communication plan for the participating sites.	To add clarity to stopping rules.
	In one of the criteria, reference to the treatment group was removed.	Groups cannot be ascertained as the study is blinded.
	The word “reactions” from “adverse reactions” was replaced with “events”	These denote adverse events.
Section 5.1 Inclusion Criteria, Criterion no. 4	The inclusion criteria for Japanese participants was revised to include participants born in Japan, holding a Japanese passport, not living outside Japan for more than five years and	This change was made as per site requirements for enrollment of Japanese participants.

Section # and Name	Description of Change	Brief Rationale
	having all four grandparents Japanese, as confirmed by interview.	
Section 5.1 Inclusion Criteria, Criterion no. 11, Table 8	Removed “hematocrit”	To align with study requirements.
Section 5.1 Inclusion Criteria, Criterion no. 12, Section 1.3 Schedule of activities, Table 8	• Changed from “HBsAb” to “Anti-HBS”. • Included note to specify participants with positive anti-HBs alone will be eligible if they have documented history of vaccination	To prevent exclusion of participants who test positive for anti-HBs due to vaccination.
Section 5.1 Inclusion Criteria, Criteria no. 13, 14, 15, and 16, Section 8.7.6, Section 10.3 Contraceptive and barrier guidance	Revised the duration for contraception and other precautions for pregnancy after the end of study, from 11 weeks to at least 6 months	To align with the contraceptive timeframe specified in the Simponi SmPC.
Section 6.3.2 Blinding	Added text “using blinded/unblinded teams”	To add clarity for the site blinding procedures.
Section 8.7.3 Reporting of serious adverse events	Added text for the PI to report clinically or medically significant updated SAEs to the Sponsor/designee within 24 hours of having such information.	As per local regulatory guidelines.
Throughout the protocol	Minor editorial changes were made.	Minor, and therefore have not been summarized

11.0 REFERENCES



Signature of Investigator

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 NO: AVT05-GL-P01

VERSION: 4.0

DATE: 01 November 2023

This protocol is a confidential communication of the Sponsor, Alvotech Swiss AG. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the Sponsor and CRO

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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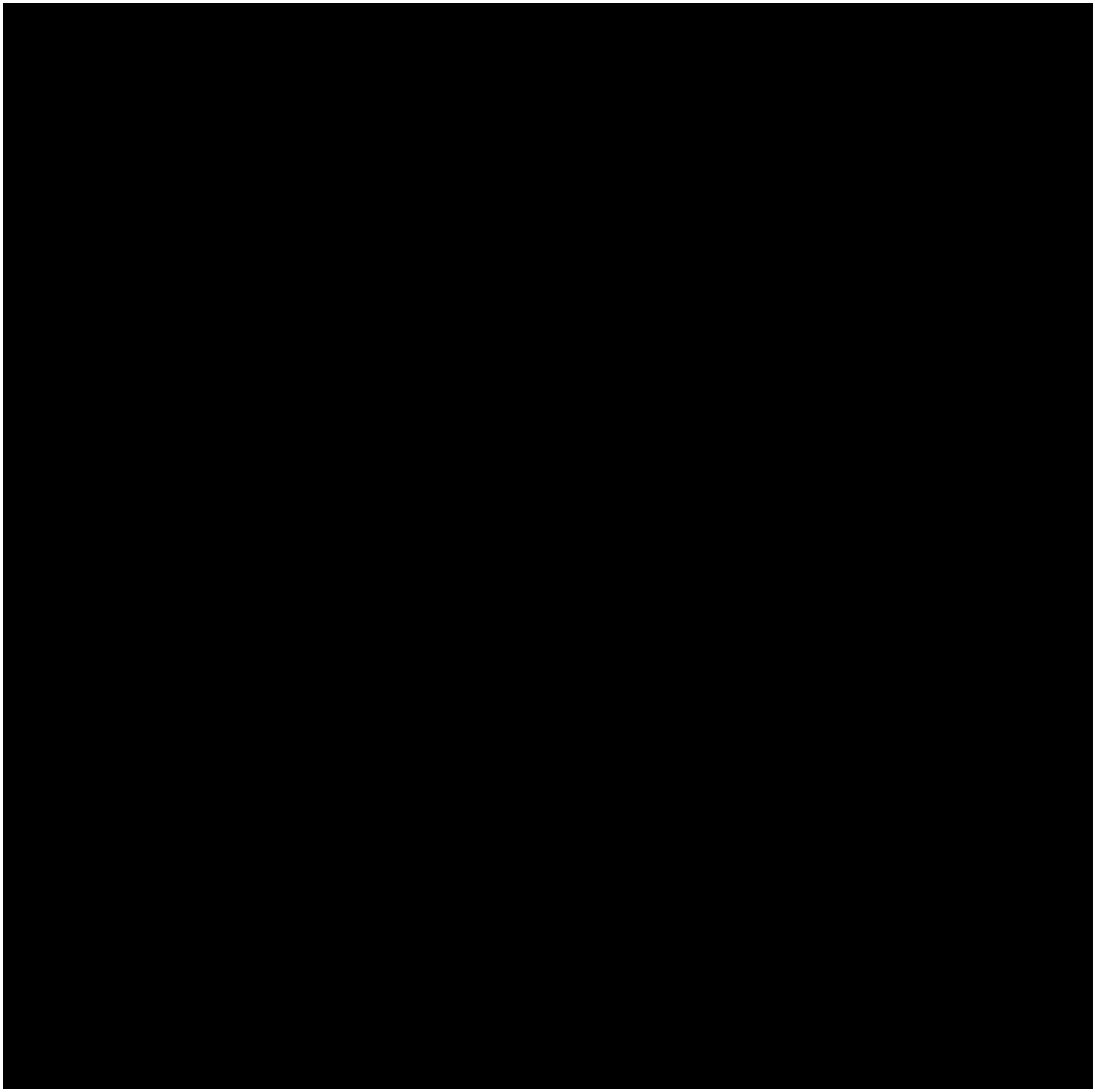

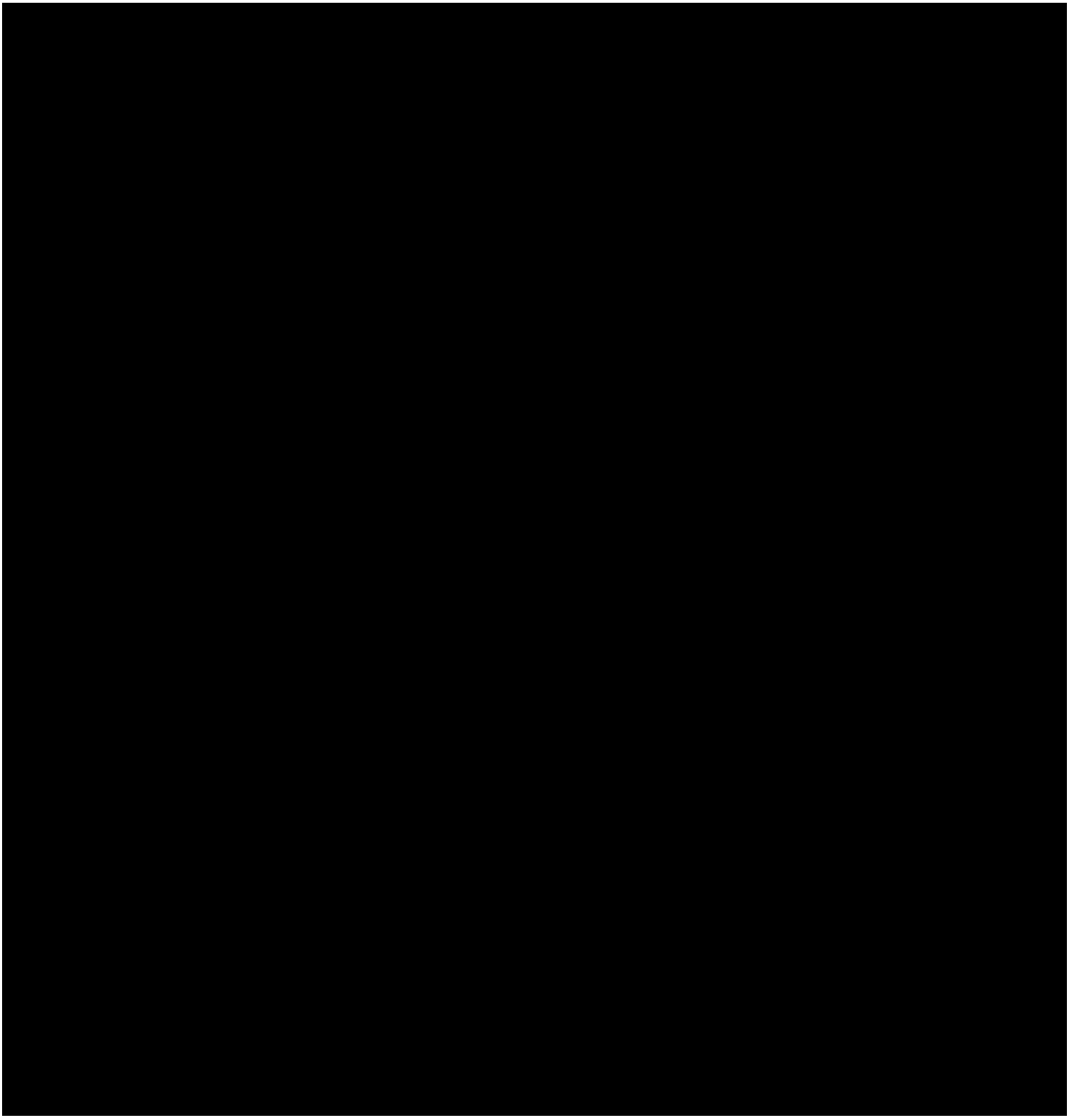

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