AstraZeneca

Statistical Analysis Plan

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A Phase 2a, Randomised, Double-blind, Parallel Study to Assess the Efficacy, Safety and Tolerability of AZD9567 compared to Prednisolone 20 mg in patients with active Rheumatoid Arthritis (RA)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACR	American College of Rheumatology
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomic therapeutic chemical
AUC	Area under the concentration curve
AUC(0-6)	Area under the concentration curve from time 0 to 6 hours
AUC(0-24)	Area under the concentration curve from time 0 to 24 hours
AUC(0-last)	Area under the concentration curve from time 0 to last measurable concentration
AUEC(0-6)	Area under the effect curve from time 0 to 6 hours
BMI	Body mass index
CFB	Change from baseline
CL/F	Apparent total body clearance for drug following extravascular administration
Cmax	Maximum observed drug concentration
Covance	Clinical Pharmacokinetic Alliance
Ctrough	Observed trough plasma concentration
CRP	C-reactive protein
CSR	Clinical study report
DAS28	Disease Activity Score in 28 joints
DAS28 (CRP)	Disease Activity Score in 28 joints using C-reactive protein
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
ENR	All subjects enrolled analysis set
EULAR	European League Against Rheumatism
FAS	Full analysis set
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire - Disability Index

Abbreviation or special term	Explanation
GCV	Geometric coefficient of variation
GH	Global health
GSD	Geometric standard deviation
HPA	Hypothalamic–pituitary–adrenal
IARA	Investigator's Global Assessment of RA
ICH	International Committee on Harmonisation
ITT	Intent-to-treat
i.v.	Intravenous
LLOQ	Lower limit of quantification
LPS	Lipopolysaccharide
MCP	Metacarpophalangeal joints
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NQ	Non-quantifiable
PD	Pharmacodynamic analysis set
PGx	Pharmacogenetics
PIP	Proximal interphalangeal
PK	Pharmacokinetic
PP	Per protocol analysis set
PT	Preferred term
RA	Rheumatoid arthritis
RNA	Ribonucleic acid
RND	All subjects randomised analysis set
SAE	Serious adverse event
SAF	Safety analysis set
SARA	Subject's Assessment of Rheumatoid Arthritis
REML	Residual/restricted maximum likelihood
s.c	Subcutaneous
SJC 66	Swollen joint count 66
SOC	System organ class

Abbreviation or special term	Explanation
t1/2z	Half-life associated with the terminal slope (λz) of the semi-logarithmic concentration time curve
TEAE	Treatment emergent adverse event
TJC 68	Tender joint count 68
tmax	Time point of the maximal plasma concentration of a drug
TNFα	Tumour necrosis factor alpha
VAS	Visual Analogue Scale

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

The primary objective of this study is to assess the efficacy of AZD9567 40 mg, compared to Prednisolone 20 mg in subjects with active rheumatoid arthritis (RA) in spite of stable treatment with conventional and/or subcutaneous (s.c)/ intravenous (i.v.) biological disease-modifying anti-rheumatic drugs (DMARDs) by assessment of:

- Change from baseline (CFB) in 28 joints Disease Activity Score (DAS28) using C-reactive protein (DAS28 - CRP) after 14 days of treatment at Day 15.

1.1.2 Secondary objectives

The secondary objectives of this study after approximately two weeks treatment period are:

- To further assess the efficacy of AZD9567 40 mg, compared to Prednisolone 20 mg in subjects with active RA in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs by assessment of:
    - Proportion of subjects achieving American College of Rheumatology (ACR) 20, 50 and 70 responses.
    - Change from baseline in Swollen Joint Count 66 (SJC 66).
    - Change from baseline in Tender Joint Count 68 (TJC 68).
    - Change from baseline in individual components of:
        - DAS28 (number of swollen and tender joints 28, subject's assessments of global disease activity (GH) and CRP).
        - ACR response criteria (number of swollen joints 66 and tender joints 68, subject's assessments of global disease activity (GH), physician´s global assessment of disease activity, subject's assessments of pain, subject's assessments of physical function and CRP).
- To evaluate the pharmacokinetic (PK) profile of AZD9567 in subjects with active RA in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs by assessment of:
    - PK parameters including area under the plasma concentration-time curve until the last quantifiable concentration AUC(last), area under the concentration-time curve from time zero to 24 hours after dose AUC(0-24), area under the concentration-time curve from time zero to 6 hours after dose AUC(0-6), maximum plasma concentration during a dosing interval (Cmax), time to reach

maximal plasma concentration (tmax) the last plasma concentration measured before the last dose (Ctrough) and apparent plasma clearance (CL/F).

1.1.3 Safety objective

To assess the safety and tolerability of AZD9567 in subjects with active RA in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs by assessment of:

- Adverse events (AEs).
- Vital signs.
- Electrocardiogram (ECG).
- Laboratory parameters (haematology, clinical chemistry and urine).

1.1.4 Exploratory objectives

The exploratory objectives of this study after approximately two weeks treatment period are:

- To assess the responses to AZD9567 of relevant biomarkers. Whole blood and serum/plasma will be collected to enable relevant analyses such as, effects on bone, metabolism and hypothalamic–pituitary–adrenal (HPA) axis by assessment of exploratory blood biomarkers:
    - Lipopolysaccharide (LPS) stimulated tumour necrosis factor alpha (TNFα).
    - Plasma cortisol.
    - Other possible exploratory biomarkers including RNA.

- Exploratory biomarker variables will be reported in a separate biomarker report and will not be included in the clinical study report (CSR) unless something clinically important is observed, with the exception of plasma cortisol which will be analysed and reported in the

CSR. TNF$_\alpha$ planned analyses will be described in this SAP but will be reported separate to the CSR.

- European League Against Rheumatism (EULAR) response criteria.
- DAS28 remission.
- Clinically important change in DAS28 score.
- Low disease activity based on DAS28 score.

The following exploratory objective is outside the scope of this SAP and will be presented in a separate report:

- To evaluate the PK profile of Prednisolone in subjects with active RA in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs.

The following exploratory objective is outside the scope of this SAP and will not be included in the clinical study report (CSR), unless something clinically important is observed:

- To obtain optional blood samples for future pharmacogenetic (PGx) research aiming to identify/explore pharmacodynamic biomarkers or genetic variations that may affect the efficacy, pharmacodynamics, safety and tolerability profile related to AZD9567 treatment by assessment of:
    - Deoxyribonucleic acid (DNA) from whole blood.

1.2 Study design

This is a Phase 2a, randomised, double-blind, double dummy, parallel study to assess the efficacy, safety and tolerability of AZD9567 40mg compared to Prednisolone 20 mg in subjects with active RA in spite of stable treatment with conventional or biological DMARDs.

At Visit 1 (screening visit) eligible subjects will be identified. Subjects will be asked to provide informed consent after which screening assessments will be performed.

At Visit 2, eligible subjects with established RA and moderate to high disease activity as defined by ACR Guidelines (DAS28 > 3.2) will be randomised in a ratio 1:1 to take either AZD9567 40 mg or Prednisolone 20 mg for 14 days once daily. Since this study is double-blind and AZD9567 and Prednisolone are different formulations (oral suspension and capsules respectively), all subjects will have to take both formulations every day (active AZD9567 + placebo to Prednisolone or placebo to AZD9567 + active Prednisolone).

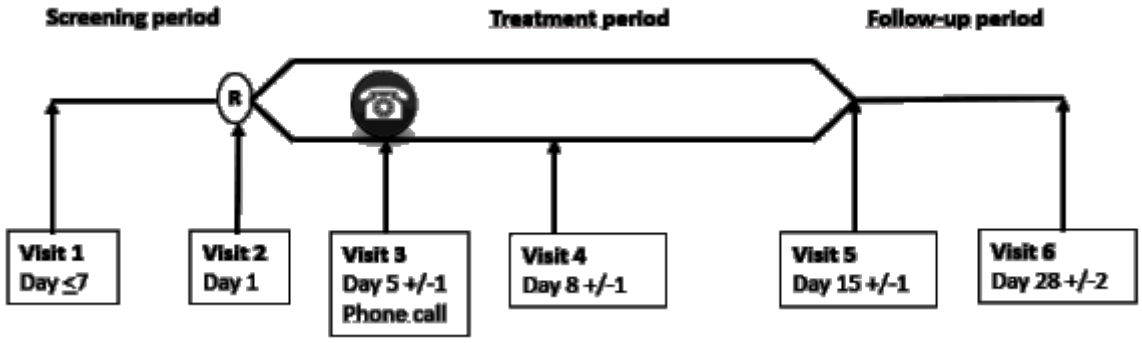
A telephone call to check subject well-being will be termed Visit 3.

Visit 4 will occur approximately 7 days after Visit 2, and Visit 5, which is the end-of-treatment visit, will occur approximately 14 days after Visit 2.

A follow-up visit (Visit 6) will be performed approximately 14 days after last study treatment dose (at Visit 5) to ensure the safety and well-being of subjects.

For more information regarding the visits and time windows refer to the study flowchart, Figure 1.

Figure 1 Study flow Chart



R: Randomised to study treatment

1.3 Number of subjects

It is planned to randomise approximately 40 subjects in total, 20 subjects to each treatment group. It is anticipated that approximately 80-100 subjects will need to be screened in order to achieve randomisation total. Planned recruitment of subjects will take place across 7 sites in 2 countries (Sweden and Netherlands).

The main analysis will be based on the difference in the mean CFB for AZD9567 and the mean CFB of prednisolone.

The details of the sample size calculation are based on internal decision criteria as explained in Frewer et al, 2016. In these calculations we use the reliability threshold of the DAS28 index known to be 0.6 (Siemons et al, 2014).

A sample size of n=10 per group was agreed on however is not sufficiently powered to support hypothesis testing.

2. ANALYSIS SETS

2.1 Definition of analysis sets

The following analysis sets will be used in this study:

2.1.1 All subjects enrolled (ENR) analysis set

The all subjects enrolled (ENR) set will contain all subjects who signed informed consent prior to performing any specific study-related procedures.

2.1.2 All subjects randomised (RND) analysis set

The all subjects randomised (RND) analysis set will contain all subjects in the ENR analysis set and who were randomised to one of the two treatment groups. The all subjects randomised analysis set will be analysed according to their planned treatment arm, regardless of the actual treatment received.

2.1.3 Safety analysis set (SAF)

The safety analysis set (SAF) will include all subjects randomised and received at least one dose of study treatment. The SAF will be analysed according to the actual treatment received, regardless of the randomised treatment assigned.

2.1.4 Full analysis set (FAS)

The primary analysis variable for efficacy will be analysed using the full analysis set (FAS). The FAS, will include all subjects randomised and received at least one dose of study treatment. In accordance with International Committee on Harmonisation (ICH) E9, the FAS will be analysed using the Intent-to-treat (ITT) principle, which is the analysis on planned treatment arm, regardless of actual treatment received. The SAF and FAS will have the same set of subjects but will be analysed differently according to actual vs. planned.

2.1.5 Per protocol (PP) analysis set

The PP analysis set will include subjects from the FAS who:

- Did not have an important protocol deviation that are considered to have an impact on the analysis of the primary endpoints;
- Completed the study.

The PP analysis set will be analysed according to the actual treatment received, regardless of the planned treatment.

Criteria for exclusion from the PP analysis set will be documented in a separate analysis sets and PDs plan.

2.1.6 Pharmacokinetics (PK) analysis set

The PK analysis set will include all subjects with at least one quantifiable AZD9567 concentration with a documented related dosing history. Subjects in the PK analysis set will be analysed according to their planned treatment arm, regardless of actual treatment received.

Subjects may be excluded from the PK analysis set if they have an adverse event (AE) of vomiting that occurs within approximately 2 times the median time of maximum observed drug concentration (tmax) or an important protocol deviation considered to affect PK. All decisions to exclude subjects from the PK analysis set will be made prior to the unblinding of the study.

2.2 Violations and deviations

2.2.1 Protocol deviation monitoring

During study conduct, protocol deviations will be closely monitored by the clinical team via the IMPACT report. A decision will be made prior to unblinding the study to determine which protocol deviations may significantly affect the study outcome and should result in a subject's exclusion from the PP or PK analysis sets.

The following categorisations of the protocol deviations will be used to identify important protocol deviations:

- Did not fulfil eligibility criteria.
- Received incorrect study treatment/dose.
- Received prohibited concomitant medication.
- Protocol-required procedure not adhered to.
- Developed discontinuation criteria but continued.

2.2.2 Protocol deviation reporting

Protocol deviations that may affect the study outcome significantly and the interpretability of the study results are defined as important protocol deviations (IPD).

The criteria for all important protocol deviations will be provided in a separate protocol deviation document from the SAP. Protocol deviations that the study team considers to be important will be tabulated or listed in CSR.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary Variable

The difference in DAS28 units will be used to show that the efficacy of AZD9567 40 mg is equivalent to the efficacy of Prednisolone 20 mg at Day 15:

Diff = X_T - X_P

where X_T is the mean change from baseline in DAS28 of AZD9567 and X_P is the mean change from baseline in DAS28 of Prednisolone.

DAS28 scores will be derived at baseline and each post-baseline assessments using the following formula:

$$DAS28\ (CRP) = 0.56 * \sqrt{TJC28} + 0.28 * \sqrt{SJC28} + 0.014 * GH + 0.36 * \ln(CRP + 1) + 0.96$$

Where:

TJC28 = 28 joint count for tenderness (Section 3.1.1Tender Joint Counts).
SJC28 = 28 joint count for swelling (Section 3.1.2 Swollen Joint Counts).
Global health (GH) = subject's global assessment on Visual Analogue Scale (VAS) of 100 mm (Section 3.1.3 Global Health).
ln (CRP) = natural logarithm of CRP (mg/L) (Section 3.1.4 CRP).

Refer to Section 4.4.1 Missing DAS28 (CRP) for handling of missing DAS28 (CRP) components.

The following supplementary variables will be used to calculate the primary variable DAS28:

3.1.1 Tender Joint Count 28

The following 28 joints (14 left, 14 right) will be evaluated for tenderness as obtained from the Joint Count Right or Left electronic case report form (eCRF):

- 2 each: Interphalangeal joints of the thumbs, wrist joints, elbow joints, shoulder joints, knee joints.
- 8 Proximal interphalangeal (PIP) joints of the fingers.
- 10 Metacarpophalangeal joints (MCP) joints.

The tender joint count represents the number of joints in which pain is reported after either manoeuvre.

TJC28 = Sum of tender joints with present status on the eCRF. Maximum TJC28 = 28.

Refer to Section 4.4.2 Missing tender or swollen joints for missing joint counts.

3.1.2 Swollen Joint Count 28

The same joints mentioned in Section 3.1.1 will be evaluated for swelling.

The swollen joint count represents the number of joints in which there is synovial fluid and or soft tissue swelling, but not if bony overgrowth is found.

SJC28 = Sum of swollen joints with present status on the eCRF. Maximum SJC28 = 28.

Refer to Section 4.4.2 Missing tender or swollen joints for missing joint counts.

3.1.3 Global Health

Subject's GH using patient's global assessment (PGA) of disease activity by means of the VAS.

The PGA VAS consists of a 100 mm long scale ranging for 0 (very well) to 100 (very poor). This VAS score is located on the subject's assessment of RA (SARA) eCRF.

3.1.4 C-reactive protein (CRP)

CRP (mg/L) is collected at the local laboratory for Visit 1. Central laboratory will be used for Visit 2, 4, 5 and 6. Visit 3 will be a phone call only, therefore no laboratory testing will take place on that visit.

3.2 Secondary Variables

There are 12 secondary efficacy variables in this study:

- Percentage of subjects achieving ACR20, ACR50 and ACR70 responses.
- Change from baseline in individual components of DAS28 and ACR response criteria:
    - SJC 66.
    - TJC 68.
    - SJC 28.
    - TJC28.
    - Subject's assessment of pain (VAS).
    - Subject's assessment of global disease activity (GH VAS).
    - Physician's assessment of global disease activity (VAS).
    - Subject's assessment of physical function.
    - CRP.

3.2.1 ACR20, ACR50 or ACR70

Subjects will be considered to have an ACR20, ACR50 or ACR70 response if a 20%, 50% or 70% improvement from baseline (respectively) occurred. The ACR20, ACR50 or ACR70 responses will be derived at each of the following post-baseline scheduled assessments:

- Day 8, Visit 4.
- Day 15, Visit 5.
- Day 28, Visit 6.

As Day 28, Visit 6 is a follow-up visit and two week off-treatment, a possible decrease in efficacy is expected.

A subject will have an ACR20 response if all of the following occur:

- A ≥20% improvement in the SJC 66 (Section 3.2.2 Swollen Joint count).
- A ≥20% improvement in the TJC 68 (Section 3.2.3 Tender Joint count).
- A ≥20% improvement in at least 3 of the following 5 assessments:
    - Subject’s assessment of pain:

      Obtained from the VAS score on the Health Assessment Questionnaire (HAQ) eCRF.

- Subject's global assessment of disease activity (GH):

  Obtained from the VAS score on the SARA eCRF.

- Physician's global assessment of disease activity:

  Derived from the VAS score on the Investigator's Global Assessment of RA (IARA).

- Subject's assessment of physical function:

  As derived by the Total score on the HAQ eCRF. See Appendix A Health assessment questionnaire score derivation for more information.

- Acute phase reactant (CRP measure in mg/L).

A subject will have ACR50 or ACR70 response if a 50% or 70% improvement from baseline (respectively) rather than 20% was observed in the criteria specified above for ACR20.

Refer to Section 4.4.3 Missing ACRxx components for missing ACR components.

3.2.2 Swollen Joint count 66

The following 66 joints (33 left, 33 right) will be evaluated for swelling:

- 2 each: Temporomandibular, sternoclavicular, acromioclavicular, interphalangeal joints of the thumbs, wrist joints, elbow joints, shoulder joints, knee joints, ankle mortise and tarsus.
- 8 each: PIP joints of the fingers, distal interphalangeal joints.
- 10 each: Metatarsophalangeal, MCP joints, toe joints.

The swollen joint count represents the number of joints in which there is synovial fluid and or soft tissue swelling, but not if bony overgrowth is found.

SJC = Sum of swollen joints with present status on eCRF. Maximum SJC = 66.

Refer to Section 4.4.2 Missing tender or swollen joints for missing joint counts.

3.2.3 Tender Joint count 68

The following 68 joints (34 left, 34 right) will be evaluated for swelling:

- 2 each: Temporomandibular, sternoclavicular, acromioclavicular, interphalangeal joints of the thumbs, wrist joints, elbow joints, shoulder joints, knee joints, hip joints, ankle mortise and tarsus.

- 8 each: PIP joints of the fingers, distal interphalangeal joints.
- 10 each: Metatarsophalangeal, MCP joints, toe joints.

TJC = Sum of tender joints with present status on eCRF. Maximum TJC = 68.

Refer to Section 4.4.2 Missing tender or swollen joints for missing joint counts.

3.2.4 Change from baseline in individual components of DAS28

The four individual components of DAS28 (as discussed in Primary Variables Section 3.1: TJC 28, SJC 28, subject's global assessment of disease activity [GH], CRP) will be used in order to calculate change from baseline.

3.2.5 Change from baseline in individual components of ACR

The seven individual components of ACR (as discussed in Section 3.2.1: SJC 66, TJC 68, subject's assessment of pain, subject's global assessment of disease activity [GH], physician's global assessment of disease activity, subject's assessment of physical function, CRP) will be used in order to calculate change from baseline.Appendix A Health assessment questionnaire score derivation

3.3 Pharmacokinetics

The derivation of the PK parameters for AZD9567 will be performed at Covance (Clinical Pharmacology Alliance). The PK parameters will be derived using non-compartmental methods with Phoenix WinNonlin (Version 8.1 or higher).

The PK profile of AZD9567 in subjects with active RA in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs will be assessed by calculating the following parameters where possible:

AUC(0-24): Area under the plasma concentration-time curve from time zero to 24 hours after study treatment dose.

AUC(last): Area under the plasma concentration-time curve until the last quantifiable concentration

AUC(0-6): Area under the plasma concentration-time curve from time zero to 6 hours after study treatment dose.

tmax: Time point of the maximal plasma concentration of a drug.

Cmax: Maximum observed drug concentration.

Ctrough: The last plasma concentration measured before the last dose.

CL/F: Apparent plasma clearance following an extravascular dose.

Vz/F: Apparent volume of distribution following an extravascular dose.

Other pharmacokinetic parameters may be calculated if appropriate.

The following diagnostic parameters for plasma PK analysis may be listed but will not summarised:

λz: Terminal elimination rate constant

λzN: Number of data points included in the log-linear regression analysis

Rsq_adj: Regression coefficient adjusted for n obs, Goodness of fit statistic for the calculation of λz

AUCextr(0-24): Percentage of AUC(0-24) obtained by extrapolating the area under the plasma concentration-time curve from the time of the last quantifiable concentration to 24h. Pharmacokinetic analysis will, where possible times recorded in the raw data. If actual times are missing, nominal times may be used.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory

Cmax and tmax will be obtained directly from the plasma concentration-time profiles. For multiple peaks, the highest post-dose concentration will be reported as Cmax. In the case that multiple peaks are of equal magnitude, the earliest tmax will be reported.

Concentrations below the limit of quantification (BLQ) from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration will be set to zero with the following exceptions:

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will set to missing unless there is a scientific rationale not to do so, which will be documented by the pharmacokineticist.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a pre-dose concentration is missing, these values may be set to zero by default.

The terminal elimination half-life, calculated as ($\ln 2/\lambda z$) will be estimated by log-linear least squares regression of the terminal phase of the concentration-time curve. The choice of data points used to estimate λz should follow the general guidelines:

- The start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systemic deviation from the log-linear decline in plasma concentrations.
- A minimum of 3 data points will be used in calculating λz and the duration of time over which λz is recommended to be at least 3 times the subsequently estimated terminal half-life. Where the elimination half-life is estimated over less than 3 times the subsequently estimated terminal half-life it will be flagged in the data listings and discussed in the study report.
- Should include the last measurable concentration
- Include only observations after Cmax
- The λz may not be assigned if the R^2 adjusted value of the regression line is less than 0.8. In cases where the λz is not assigned all regression-based parameters (including R^2 adjusted) will not be calculated

AUCs will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal rule when concentrations are decreasing (linear up log down). The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the LLOQ.

AUC(0-24) values where the percentage extrapolation is <20% will be reported. AUC(0-24) values where the percentage extrapolation is ≥20% will be flagged.

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and the CSR.

PK parameter data associated with quantifiable pre-dose values >5% of Cmax may be excluded from the summary statistics and statistical analysis at the discretion of the Pharmacokineticist.

3.4 Safety outcomes

3.4.1 Adverse events

Adverse events will be collected throughout the treatment period and including the follow-up period (Visit 6).

Serious AEs (SAEs) will be collected from the time of informed consent (Visit 1) whereas AEs will be collected from randomisation (Visit 2), throughout the treatment period and including the follow-up period (Visit 6).

The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used to code the AEs. The investigator's verbatim term for each AE will be mapped to a system organ class (SOC) and preferred term (PT) from MedDRA. All coding will be performed by the Medical Coding Team.

Treatment emergent adverse event (TEAE) is defined as an AE that started on or after treatment start date and within 14 days after treatment stop date.

3.4.2 Vital signs

Vital signs (systolic and diastolic blood pressure, pulse rate and body temperature, all three in a lying or sitting position after 5 minutes of rest) will be taken at the times indicated in the Study Plan and Timing of Procedures (refer to protocol Table 1).

Change from baseline in vital signs to each post-baseline assessment will be calculated. There will be no imputation for missing values.

Observed values and change from baseline for all assessments will be compared to the relevant AstraZeneca defined reference ranges (see Appendix B AstraZeneca defined reference ranges for vital signs) and all values (observed and change) falling outside the reference ranges will be flagged. The minimum and maximum values post-baseline will be derived for SBP, DBP, pulse rate and temperature based on pre-defined criteria provided by AZ in Appendix B (low, normal, high).

3.4.3 ECG

Twelve-lead ECGs will be obtained at the times indicated in the Study Plan and Timing of Procedures (refer to protocol Table 1). An overall evaluation (normal, abnormal not clinically significant, and abnormal clinically significant) with a reason for abnormality will also be recorded.

3.4.4 Laboratory data

Blood and urine samples for determination of clinical chemistry, haematology, endocrinology, and urinalysis will be taken at the times indicated in the Study Plan and Timing of Procedures (refer to protocol Table 1).

The parameters to be determined are presented in Appendix C Laboratory Parameters.

Changes from baseline in continuous laboratory variables to each post-baseline assessments will be calculated.

Observed values will be compared to the central laboratory reference ranges and all observed values falling outside these reference ranges will be flagged.

For laboratory results below or above the limit of quantification:

- Assign as equal to the limit of quantification, for example < 100 mL will be assigned as 100 mL.

The minimum and maximum values post-baseline will be derived based on reference ranges provided in the most recent Covance lab manual available at database lock (low, normal, high). A listing of normal ranges will be provided.

3.5 Exploratory outcomes

3.5.1 Biomarkers

Whole blood and serum/plasma will be collected to enable relevant analyses such as, effects on bone, metabolism and HPA axis by assessment of:

- Individual LPS-stimulated WB TNFα levels (pg/mL).
- Individual plasma cortisol (nmol/L) $AUEC_{(0\text{-}6)}$.
- Change from baseline for morning plasma cortisol (nmol/L) at Day 15 and follow-up visit.

For each subject, the total AUEC at Day 1 and Day 15 will be calculated for plasma cortisol. Plasma cortisol is collected pre-dose only on Day 1 at 0, 1, 2, 3, 4 and 6 hours, and then pre-dose and post-dose at 1, 2, 3, 4 and 6 hours on Day 15. Each AUEC will be calculated using trapezoids as

$$AUEC = \sum_{i=1}^{6} (t_{i+1} - t_i) \frac{y_{t_{i+1}} + y_{t_i}}{2}$$

The summation is over all available time points. The y_t are the concentration measurements. If any two consecutive measurements are missing, or if one or both of the measurements at time 0 for Day 1, pre-dose for Day 15 or 6 hours on either day are missing, then the AUEC for that day is missing. However, if the measurement at any single intermediate number of hours is missing, the AUEC will be calculated using linear interpolation.

For example, if measurements are available at only 0, 1, 2, 3 and 6 hours for Day 1, then

$$AUEC = (1-0)\frac{y_1 + y_0}{2} + (2-1)\frac{y_2 + y_1}{2} + (3-2)\frac{y_3 + y_2}{2} + (6-3)\frac{y_6 + y_3}{2}$$

3.5.2 Other exploratory outcomes

DAS28 will be used for additional comparison between AZD9567 and Prednisolone 20mg, by means of:

- European League Against Rheumatism (EULAR) response criteria.
- DAS28 remission.

- Clinically important change in DAS28 score.
- Low disease activity based on DAS28 score.

Improvement (can be either positive or negative and is defined as post-baseline minus baseline) in DAS28 score will be calculated at each post-baseline scheduled assessment and categorised using the EULAR response criteria in Table 1. Good, moderate or no response will be determined by the DAS28 score at Day 8, 15 and 28 against the level of improvement (mean change from baseline in DAS28 at Day 8, 15 and 28).

Table 1 DAS28 EULAR Response

DAS28 improvement			
Background DAS28(CRP) Score at Time of DAS28 Improvement Assessment	**Level of Improvement from Baseline**		
	> 1.2	≥ 0.6 to ≤ 1.2	< 0.6
< 3.2	Good response	Moderate response	No response
≥ 3.2 to ≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

DAS28: Disease Activity Score in 28 joints. DAS28(CRP): Disease Activity Score in 28 joints using C-reactive protein/erythrocyte sedimentation rate.

DAS28 remission:

- DAS28 score < 2.6

Clinically important change:

- Improvement from baseline in DAS28 score > 1.2

Low disease activity:

- DAS28 score ≤ 3.2

4. ANALYSIS METHODS

Statistical analysis will be performed by IQVIA™ using SAS® Version 9.4 or higher.

The derivation of the PK parameters will be performed at Clinical Pharmacokinetic Alliance (Covance). The PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® (Version 8.1 or higher), in accordance with “Best Practice Reference Guidelines Pharmacokinetic Evaluations in Clinical Studies”.

4.1 General principles

4.1.1 Reference start date

Study day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the date of the first dose of study treatment.

Relative date will be calculated according to the aforementioned reference date as follows:

- If the date of the event is on or after the reference date, then:
    - Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
    - Study Day = (date of event – reference date).

Revere to Appendix D Partial and missing date conventions for partial dates for calculating relative day.

4.1.2 Baseline measurements

Baseline is defined as the last non-missing assessment (scheduled or unscheduled) on or prior to reference start date.

In the case where the last non-missing assessment and the reference start date and time coincide, that assessment is considered as occurring before the start of the study treatment dose and the assessment is considered as baseline. However, AEs and medications commencing on the start date and time of first dose will be considered as post-baseline and flagged as treatment-emergent AEs and concomitant medications.

For by visit tables, the screening visit will be presented along with baseline as applicable.

In the case where the assessment time is missing, but reference start date and assessment date coincide, that assessment is considered as occurring before the start of the study treatment dose and the assessment is considered as baseline.

In the case where two assessments exist on the same date on or prior to the reference start date, the assessment with more complete data should be used as baseline, i.e. if time is missing on the one assessment, the assessment with time included should be used as baseline.

There will be no baseline record where the first non-missing assessment is after the reference start date.

4.1.3 Visit windowing

No visit windowing will be implemented. Scheduled visits will be used for analysis purposes.

4.1.4 Table outputs

In general, all summaries will be split by treatment and occasionally added total as follows:

Number (%) of subjects		
AZD9567	**Prednisolone**	**Total**

Continuous data will be summarised by descriptive statistics including number of subjects (n), mean, standard deviation (SD), median and range (i.e. minimum value and maximum value). Additionally, the first and third quartiles will be presented for continuous data summaries of exposure data, laboratory parameters and vital signs parameters. For log transformed data, the following descriptive statistics will be presented: number of subjects (n), geometric mean, geometric SD, median and range (i.e. minimum value and maximum value). The mean and median will be presented with one more decimal place than the original data. Standard deviation with two more decimal places than the original data. Minimum and maximum values with the same number of decimal places than the original data.

For categorical data, the variable counts and percentage n (%) per treatment group will be presented. Summaries of continuous variables will be based on non-missing observations. Unless otherwise stated, percentages will be calculated relative to total number of subjects in the analysis set and treatment group. Percentages will be rounded to 1 decimal place.

4.1.5 Statistical modelling

Standard diagnostic approaches will be used to verify that the key statistical assumptions of the mixed model repeated measures (MMRM), ANCOVA and logistic regression models hold.

If the distributional assumptions of the MMRM for the primary analysis do not hold, alternative models will be explored.

4.2 Analysis methods for efficacy variables

4.2.1 Primary efficacy variable analysis method

The difference in change from baseline in DAS28 between AZD9567 and prednisolone (AZD9567 – prednisolone) will be calculated using a mixed model.

4.2.2 Secondary efficacy variable analysis methods

Percentage of subjects achieving ACR20, ACR50 and ACR70 will be analysed with a logistic regression model using PROC GENMOD.

The change from baseline (CFB) in core set measures of ACR and DAS28 will be analysed with a MMRM, using PROC MIXED.

4.3 Statistical models

Prior to unblinding, the difference between countries in DAS28 scores at Day 1 will be tested using a two-sample t-test and if the result is non-significant (p-value > 5%), the country term may be dropped from the primary and secondary models.

4.3.1 Primary efficacy statistical model

Formal statistical testing will be performed for exploratory purposes only.

The default significant level will be two-sided 5%, CIs will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses. Two-sided p-value ≤ 0.05 will be considered statistically significant.

Confidence intervals (CIs) for the true difference in means, $\mu_{AZD9567} - \mu_{Prednisolone}$, will be calculated using the estimated treatment effect and the mean square error.

A MMRM is to be used to examine the primary efficacy variable, using the PROC MIXED procedure in SAS.

The MMRM model will include the baseline DAS28 score as a covariate.

The MMRM model will include categorical fixed effects of treatment, visit, treatment-by-visit interaction and country:

- Change from baseline (at Day 15) = Treatment group baseline DAS28 score Treatment group*visit

- Treatment group = AZD9567 or Prednisolone.
- Visit = Day 8 and Day 15.
- Country = Netherlands or Sweden
- Change from baseline (at Day 15) = Change in DAS28 from baseline at Day 15.

An unstructured matrix for the within-subject error variance covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method.

In case of non-convergence of the preferred model or memory space issues the following models will be explored in the order given:

1. Country may be removed from the model.
2. The second backup model is the same as the preferred model but the Kenward- Roger method will be replaced by Satterthwaite approximation.

The least squares mean (LSM) change from baseline in DAS28 score and corresponding standard error (SE) and 95% confidence interval (CI) by treatment group at Day 8 and Day 15 will be provided in a table. The least squares mean difference (LSMD) between the two

treatment groups at Day 8 and Day 15 and corresponding 95% CI and two-sided p-value will also be presented in the table.

A figure will be provided displaying the LSM change from baseline by treatment group and visit, along with the 95% CI.

The FAS and PP analysis sets will be used for primary efficacy with FAS analysis set as primary interest.

Results for the PP analysis will be tabulated and displayed graphically in the same manner as the primary analysis.

A summary of all continuous efficacy parameters by visit will be provided: DAS28 score, SJC 66, TJC 68, SJC 28, TJC 28, subject's assessment of pain, GH, physician's assessment of global disease activity, subject's assessment of physical function and CRP. DAS28 score will also be summarised separately by visit for the FAS using summary statistics.

4.3.2 Secondary efficacy statistical models

The same MMRM approach for primary variables will be repeated on the following secondary variables:

- Change from baseline in SJC 66.
- Change from baseline in TJC 68.
- Change from baseline in individual components of DAS28 and ACR response:
    - Change from baseline in TJC28.
    - Change from baseline in SJC28.
    - Change from baseline in subject's assessments of global disease activity (GH).
    - Change from baseline in physician´s global assessment of disease activity.
    - Change from baseline in subject's assessments of pain.
    - Change from baseline in subject's assessments of physical function.
    - Change from baseline in CRP

The MMRM model for each variable will include the baseline value for the variable of interest as a covariate. Categorical fixed effects of treatment, visit, treatment-by-visit interaction and country will also be included in the model.

A table summarising the results, similar to the primary analysis, will be provided for each endpoint. Figures will not be produced for the above secondary endpoints.

Comparisons between treatment groups regarding the ACR20, ACR50 and ACR70 at Day 8, and 15 will be performed using a logistic regression model for both the FAS and PP analysis sets. The PROC GENMOD procedure in SAS will be used. The covariates of interest are treatment, country and baseline DAS28.

Should there not be sufficient number of observations per outcome category (< 5 in either treatment group) the aforementioned logistic regression will be replaced by a Fisher's exact test.

The number and percentage of subjects achieving ACRxx in each treatment group at Day 8 and Day 15, and the odds ratio and corresponding 95% CI and p-value for the comparison between treatment groups will be summarised in tables for the FAS and PP analysis sets. The proportion of subjects achieving ACRxx at Day 15 will be presented in a bar chart for the FAS and PP analysis sets separately.

No formal statistical hypothesis testing will be carried out on any variables, which will be summarised using standard summary statistics. The aforementioned statistical models are only applied for exploratory purposes.

The FAS will be used for both the secondary and exploratory efficacy endpoints unless otherwise specified.

4.3.3 Exploratory outcomes statistical models

4.3.3.1 TNFα

Individual LPS-stimulated WB TNFα levels (pg/mL), will be listed and summarised by treatment, study day and time point using descriptive statistics (n, arithmetic mean, SD, geometric mean, geometric SD, geometric CV%, minimum, median, and maximum).

Arithmetic mean (+/- SE bars) TNFα levels versus time will be plotted by study day and treatment. A panel plot will be used with Day 1 and Day 15 displayed side-by-side. In addition, a graphical presentation of individual LPS-stimulated WB TNFα levels (pg/mL) following AZD9567 treatment versus individual AZD9567 levels (nmol/L) from the same sampling time points will be made, which will include a plot of all timepoints on the final page. For this figure, AZD9567 levels with non-quantifiable results will be displayed as the lower limit of quantification.

4.3.3.2 Plasma cortisol (nmol/L) AUEC(0-6) biomarkers

Individual plasma cortisol (nmol/L), will be listed and summarised by treatment, study day and time point using descriptive statistics (n, arithmetic mean, SD, geometric mean, geometric SD, geometric CV%, minimum, median, and maximum).

Arithmetic mean (+/- SE bars) plasma cortisol (nmol/L) versus time will be plotted by study day and treatment. A panel plot will be used with Day 1 and Day 15 displayed side-by-side. AUEC(0-6) plasma cortisol will be analysed on the log scale for change from baseline (defined as the Day 1 measurements) to Day 15. Therefore, the change from baseline in AUEC(0-6) plasma cortisol, when back-transformed from the log scale, will be a relative change from baseline (ratio).

$$\frac{Day\ 15\ AUEC(0-6)}{Day\ 1\ AUEC(0-6)}$$

The relative change from baseline in AUEC(0-6) plasma cortisol (nmol/L) will be analysed as follows:

- The change from baseline to Day 15 in the log-transformed AUEC(0-6) plasma cortisol will be analysed using ANCOVA model with log plasma cortisol AUEC(0-6) at baseline as covariate and treatment group as factor.

Where:

Log transformed AUEC(0-6) = Change from baseline in the log-transformed AUEC(0-6) plasma cortisol, i.e. log (AUEC(0-6) at Day 15) – log (AUEC(0-6) at Day 1)

- The back-transformed LS-Means and 95% confidence interval will be presented by treatment group to present relative change from baseline to Day 15 (ratio). The difference relative to prednisolone 20mg (ratio) will be presented along with 95% confidence interval and p-value for two-sided comparison.

LS-Means for each treatment group, LS-mean difference between treatment groups and corresponding confidence interval limits will be back-transformed from the log scale by exponentiating.

A figure will be provided displaying the LSM relative change from baseline to Day 15 in plasma cortisol AUEC(0-6) by treatment group, along with the 95% CI. Individual values will be overlaid on the same figure as scatter points. The treatment groups will be presented side-by-side on the x-axis.

4.3.3.3 Morning plasma cortisol (nmol/L) biomarkers

Morning plasma cortisol includes 2 measurements per subject, i.e. first pre-dose measurement (08:00am) at baseline and pre-dose at Day 15.

Change from baseline in morning plasma cortisol (nmol/L) will be analysed using an ANCOVA model with covariate baseline morning plasma cortisol (nmol/L) and treatment group as a factor. LS-Means and 95% confidence interval for the change from baseline in morning plasma cortisol (nmol/L) at Day 15 will be presented by treatment group. P-value for the two-sided comparison

to baseline will be provided for each treatment group. For this variable no comparison to prednisolone 20mg will be done.

4.3.3.4 Pharmacokinetics

Pharmacokinetic summaries will be based on the PK analysis set.

Post-dose concentrations where actual time deviates more than 10% from scheduled time will be excluded from summaries by planned time point.

Plasma concentrations of AZD9567 will be summarised by planned time point using n, counts of the number of subjects with results less than the lower limit of quantification (LLOQ), geometric mean, geometric mean +/- geometric standard deviation (GSD), geometric coefficient of variation (GCV), arithmetic mean, SD, CV, median, minimum and maximum.

PK parameters listed in Section 3.3 will be summarised using n, geometric mean, CV (%), arithmetic mean, SD, CV, median, minimum and maximum. For tmax, only median, minimum and maximum will be presented.

Plasma concentrations that are <LLOQ or if there are missing values (e.g. no result [NR]) will be handled as follows:

- Any values reported as no result or no sample will be excluded from descriptive statistics, inferential statistics and summary tables. However, data from subjects excluded from the PK analysis set will be included in the data listings.
- At a time point where less than or equal to 50% of the concentration values are non-quantifiable (NQ), all NQ values will be substituted with the LLOQ value, and all descriptive statistics will be calculated accordingly.
- At a time point where more than half (but not all) of the values are NQ, the geometric mean, geometric mean +/- GSD, GCV (%), SD, and CV (%) will be set to NC. The maximum value was reported from the individual data and the minimum and median were set to NQ.
- If all values are NQ at a time-point, no descriptive statistics will be calculated for that time-point. Not calculated (NC) will be written in the field for SD and CV% and NQ will be written in fields for mean, geometric mean, minimum, median and maximum

Three observations >LLOQ are required as a minimum for a plasma concentration or PK parameter to be summarised. Two values are presented as a minimum and maximum with the other summary statistics as NC.

Concentration data will be presented to the same number of significant figures as the data received from the bioanalytical laboratory; for PK parameters, the listings will be presented according to the following rules:

- Cmax – will be presented to the same number of significant figures as received from the bioanalytical laboratory
- tmax, t lower and t upper time limit – will be presented as received in the data, usually to 2 decimal places
- AUClast, t½z, CL/F, Vz/F, Rsq adj will be presented to 3 significant figures
- λz – will be presented to 4 significant figures
- λz, N – will be presented as an integer (no decimals)
- AUC(0-24)extr– will be presented to 2 decimal places

For PK concentration data all descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures.

For PK parameters data the descriptive statistics will be presented according to the following rules:

- Cmax, AUClast, t½z, CL/F, Vz/F – all descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures
- λz – all descriptive statistics will be presented to 5 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures
- tmax – all descriptive statistics will be presented as received in the data, usually to 2 decimal places

Individual plasma concentrations of AZD9567 will be plotted for each subject based on actual timepoint the sample was collected in linear and semi-logarithmic scale. NQ results will be plotted as the LLOQ for the linear scale and log(LLOQ) for the semi-logarithmic scale.

The geometric mean (+/-GSD) plasma concentrations of AZD9567 will be plotted by planned timepoint in linear and semi-logarithmic scale (no GSD bars). For mean plots, BLQ values will be handled as described for the summary tabulations; for individual plots plasma concentrations which are <LLOQ prior to the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any <LLOQ plasma concentrations will be regarded as missing.

Pharmacokinetic parameters will be listed.

A listing of plasma concentrations of AZD9567 including sample collection times as well as derived sampling time deviations will be provided.

4.3.3.5 Other exploratory outcomes

EULAR responses, DAS28 remission, clinically important change in DAS28 and low disease activity based on DAS28 score will be summarised separately by treatment group and visit to Day 28 using counts and percentages. No formal statistical testing will be done.

4.4 Missing primary and secondary variables

4.4.1 Missing DAS28 (CRP) components

DAS28-CRP will be set to be missing if one or more components as defined above are missing. Higher DAS28-CRP scores indicate more severe symptoms and greater functional impairment

4.4.2 Missing tender or swollen joints

The number of tender/swollen joints will be calculated by summing all joints checked to have tenderness/swelling present. If at least half but not all of the joints are evaluable, then the observed prorated joint count will be calculated instead. The prorated scores for TJC will be adjusted based upon the number of evaluable joints: the counted score will be multiplied by 68 then divided by the number of joints evaluated (excluding non-evaluable joints and any joints with a missing response). For example: if only 60 of the 68 joints are assessed to be evaluable at a visit, and 32 of those 60 are tender, the prorated joint count is $(32/60)\times68=36.27$ (not 32) and it will be used in calculating the percent change from baseline in TJC. The same algorithm will be applied to the calculation of percent change from baseline in SJC with the exception that the counted score will be multiplied by 66 then divided by the number of joints evaluated. If less than half of the joints are evaluable, the number of tender/swollen joints is missing

This same algorithm will be used for the calculation of TJC and SJC based on 28 joints, which is part of the DAS28-CRP score.

4.4.3 Missing ACRxx components

At any visit, if one or more components are missing, such that a determination of ACR20 response cannot be made, then ACR20 will be set to missing. ACR20 will be set to missing for all visits for subjects with 0 SJC or 0 TJC at baseline. However, ACR20 will not be set to missing in cases where a determination of ACR20 response can be made based on the non-missing components.

In particular, in calculating ACR20:

- If SJC66 ≥ 20% improvement and TJC68 ≥ 20% improvement and if at least 3 of the 5 components are present, then:
    - if at least three are ≥ 20% improvement, then ACR20 = 'Responder'
    - if at least 3 are <20% then ACR20 = 'Nonresponder'
    - else ACR20 is set to missing

- If SJC66 < 20% improvement or TJC68 < 20% improvement, then ACR20 = 'Nonresponder'.

- If either SJC66 or TJC68 is missing and the nonmissing value < 20% improvement, then ACR20 is set to "Nonresponder".

- If either SJC or TJC is missing and the nonmissing value ≥ 20% improvement, then ACR20 is set to missing.

- If SJC and TJC are both missing, then ACR20 is set to missing.

The same rules are followed in calculating ACR50 and ACR70, replacing 20% improvement with 50% and 70%, respectively.

Any subject with missing ACRxx, will be defined as “Nonresponder” for that visit.

4.5 Multiple Comparisons/Multiplicity

Not applicable.

4.6 Subgroups

Exploratory analyses may be performed where subgroups of interest have been identified and depending on the numbers of subjects within each subgroup.

4.7 Sensitivity analysis

A sensitivity analysis for the MMRM analysis of the primary endpoint will be performed using an ANCOVA model of change from baseline to Day 15 in DAS28 score with DAS28 score at baseline as covariate and country and treatment group as factors. The PROC GLM procedure in SAS will be used.

The LS-Means and 95% confidence interval will be presented by treatment group. The difference relative to prednisolone 20mg will be presented along with 95% confidence interval and p-value for two-sided comparison

4.8 Demographic, Dosing, and Safety and Tolerability data

There is no formal statistical analysis of safety and tolerability data required for this study. Demographic and other baseline disease characteristics, protocol deviations, concomitant medication, dosing, exposure, safety and tolerability data will be summarised and listed per AZ corporate CSRHLD reporting standard.

4.8.1 Subject disposition, important protocol deviations and analysis set

Subject disposition will be summarised for all subjects using the ENR analysis set. The number and percentages of subjects will be presented for the following categories: enrolled, randomised to study treatment, not randomised to study treatment (and reason), received study treatment, did not receive study treatment, completed study treatment, discontinued from

study treatment (either), discontinued from AZD9567/AZD9567 placebo treatment (and reason), discontinued from Prednisolone/Prednisolone placebo treatment (and reason), completed study and prematurely withdrawn from study (and reason). A subject will be enrolled and randomised into the study once all the inclusion/exclusion criteria are met as discussed in Section 3 in the latest version of the protocol.

Reasons for subjects not randomised will be obtained from the disposition eCRF, where randomisation code received is no.

Subjects who completed treatment are defined as subjects who completed in both AZD9567/AZD9567 placebo and Prednisolone/Prednisolone placebo groups.

Subjects who discontinued treatment are defined as subjects who discontinued treatment in either treatment group AZD9567/AZD9567 placebo or Prednisolone/Prednisolone placebo.

Reasons for discontinuation of study treatment and prematurely withdrawn from study will also be listed including the study day of treatment discontinuation.

Important protocol deviations and analysis sets will be tabulated using the FAS only on important protocol deviations. Important protocol deviations will also be summarised and listed.

The number and percentage of subjects included and excluded from each analysis set will also be presented, including the reason for exclusion from each analysis set. Listings of subjects excluded from each analysis set (SAF, FAS, PP, PK) will be provided.

4.8.2 Demographic and baseline characteristics

Demographic and baseline characteristics will be summarised based on the all subject analysis set FAS.

Demography data such as age (years), age group (years) (<18, 18-40, 41-65, >65), sex, race, and ethnicity will be summarised and listed.

Various baseline characteristics of the subjects will also be summarised and listed. These include weight, height and body mass index (BMI), disease characteristics, and extent of disease at baseline.

Disease characteristics are obtained from the rheumatoid arthritis history eCRF page. The following will be summarised using frequencies and percentages:

- Presence of radiological erosions (Yes, No)
- Rheumatoid factor positive (Yes, No)
- Current functional capacity class (Class I, Class II, Class III, Class IV)
- Previously treated with TNFα antagonist (Yes, No)
- Reason for TNFα discontinuation (No response, Initial response but subsequent loss of response, Adverse effect/Intolerance, Other)

Years since onset of RA symptoms will be summarised using summary statistics and is calculated relative to informed consent date:

$$Years\ since\ onset\ of\ RA\ symptoms = (informed\ consent\ date - Onset\ of\ RA\ symptoms\ date + 1)/365.25$$

Years since RA diagnosis will be summarised using summary statistics and is calculated relative to start date:

$$Years\ since\ RA\ diagnosis = (informed\ consent\ date\ RA\ first\ diagnosed\ date + 1)/365.25$$

Details on partial date handling for onset of RA symptoms date and RA first diagnosed date can be found in Appendix D.

Age will be summarised as collected on the eCRF and will not be rederived.

BMI will be calculated as the ratio of the subject's baseline weight (in kilograms) to the square of the subject's height (in metres): BMI = kg/m^2.

4.8.3 Prior, concomitant, and post-discontinuation medications and therapies

Concomitant medications and therapies tabulations will be summarised based on the SAF.

Disease-related and other medications and therapies will be classified by the AstraZeneca designee according to the latest version of the World Health Organization (WHO) Drug Dictionary and they will be categorised as follows:

- Prior medications, defined as those medications taken prior to the first AZD9567/Prednisolone dose.

- Concomitant medications, defined as those medications taken during the course of the treatment period (i.e., from the day of the first AZD9567/Prednisolone dose up to the day of the last AZD9567/Prednisolone dose). A medication started prior to the first AZD9567/Prednisolone dose that is still used during the treatment period will be identified as both prior and concomitant.

- Post-discontinuation medications, defined as those medications started after the last AZD9567/Prednisolone dose.

If a medication has a missing start date then unless the stop date of the medication indicates otherwise, this medication will be considered as both prior and concomitant. Similarly, if a medication has a partial start date, then unless the partial start date or the stop date indicate otherwise, this medication will be considered as both prior and concomitant. See Appendix D Partial and missing date conventions for additional details.

All concomitant medications will be summarised by WHO Drug anatomic therapeutic chemical (ATC) level 4 classification and generic term. Prior and post-discontinuation medications will be listed only.

4.8.4 Medical history

Medical history and relevant surgical history will be coded by the AstraZeneca designee using the latest version of the MedDRA and will be summarised and listed.

4.8.5 Exposure

Exposure data will be summarised and listed for the SAF.

Total treatment duration and compliance will be summarised and listed. In addition, interruptions and compliance are not taken into account for duration of exposure. Reason for dose discontinuation will also be summarised and listed.

- Duration (days):
  (End date - start date) + 1.
- Total treatment exposure (months):
  [(End date – start date) + 1]/12

- Actual number of study treatment taken:
  Total number of bottle/capsules dispensed - total number of bottle/capsules returned.

Duration for study treatment will summarised cumulatively in the following categories:

- Treatment received more or equal to 1 day: Treatment duration ≥ 1
- Treatment received more or equal to 15 days: Treatment duration ≥ 15

Subjects taking ≥75% and ≤125% of planned study treatment are considered compliant. The percentage treatment compliance will be calculated as the actual number of study treatment taken relative to the expected number of study treatment to be taken.

- Expected number of study treatment taken:
  AZD9567/AZD9567 placebo: 1 bottle x 15 days = 15
  Prednisolone/Prednisolone placebo: 4 capsules x 15 days = 60

- Percentage treatment compliance:
  (Actual number of study treatment taken) / (Expected number of study treatment taken) x 100

4.8.6 Safety

Safety and tolerability summaries will be presented using the SAF, unless other specified.

The following tables, required by the AZ corporate standards, will not be provided for this study because the relevant data were not planned to be collected on the eCRF.

Urinalysis, baseline versus maximum value on treatment, shift table (<<analysis set>>)
Urinalysis, treatment-emergent changes (<<analysis set>>)
QTcF and QTcF intervals, at <<last>> any observation on treatment (<<analysis set>>)
Electrocardiogram results exceeding ICH reference range boundaries (<<analysis set>>)

4.8.6.1 Adverse events

Summary tables will include TEAEs only, unless otherwise specified. That is, pre- and post-treatment AEs will not be included in the summary tables of AEs. Any AE after discontinuation of study treatment and pre-treatment AEs will be flagged in the data listings as post-treatment AEs and pre-treatment AEs, respectively.

Pre-treatment AEs are defined as AEs with start date before the first dose of study treatment.

TEAEs are defined as AEs with start date and time ≥ the first dose of study treatment and ≤ the last dose of study treatment + 14 days.

Post- treatment AEs are defined as AEs with start date > the last dose of study treatment + 14 days.

If an AE has a missing onset date then unless the stop date of the AE indicates otherwise, this will be considered treatment emergent. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered a TEAE. In cases where the AE start time is missing but the AE start date is the same as the first dose of study treatment, then that AE will be considered a TEAE.

An overall summary table will be produced showing the number and percentage of subjects with at least 1 AE for each of the following categories:

- Any AE.
- Any AE with an outcome = death.
- Any AE with an outcome = death, causally related to study treatment.
- Any SAE (including events with outcome = death).
- Any AE leading to discontinuation of study treatment.
- Any AE causally related to study treatment.
- Any AE with intensity = severe.

AEs will be summarised by MedDRA SOC and MedDRA PT. For each SOC/PT, the number and percentage of subjects reporting at least one occurrence will be presented i.e., for a subject, multiple occurrences of an AE will be only counted once.

Summaries will also be done on AEs with most common frequency (≥ 5%), non-serious AEs occurring in ≥5% subjects, causally related to study treatment, outcome of death, serious AEs, SAEs causally related to study treatment, leading to discontinuation of the study treatment, and leading to discontinuation of study treatment, causally related to study treatment. Number and percentage of subjects with AEs by PT and relationship will also be provided.

A summary of the number and percentage of AEs by SOC and PT will be presented along with a separate summary of the number and percentage of SAEs by SOC and PT.

The number and percentage of subjects with AEs by SOC and PT and maximum reported intensity (mild, moderate, severe) will be summarised.

Key subject information for AEs with outcome of death will be summarised for all subjects. Similarly, key subject information for SAEs and AEs leading to discontinuation of investigational product will be summarised.

Separate listings of AEs leading to death and SAEs will be presented.

AEs with missing relatedness will be considered related and AEs with missing intensity will be considered as maximum intensity.

4.8.6.2 Overdose

Details of subjects who overdosed will only be listed with details regarding actual treatment group.

4.8.6.3 Laboratory variables

Observed results and changes from baseline at each scheduled visit will be summarised for each quantitative haematology and clinical chemistry parameter. The following rules will be applied if more than one observation is available for a subject at a single visit:

- If there are two or more observations at the same scheduled visit, the observation closest to the target day will be used in the summary
- If two observations are equidistant from the target day and the ties are on different sides of the target day, the observation with the earlier assessment date will be used in the analysis.
- If two observations are equidistant from the target day and the ties located on the same sides of the target day (i.e. more than one observation for the same day but different time), the observation with the earlier (if the assessment day is equal or larger than the target day) or later (if the assessment day is smaller than the target day) assessment time will be used in the analysis.

A shift table from baseline to minimum value post-baseline will be provided for qualitative haematology and chemistry values (low, normal, high). Similarly, a shift table from baseline to maximum value post-baseline will be provided for qualitative haematology and chemistry values (low, normal, high). Low, normal and high will be defined based on Covance reference ranges.

To identify potential Hy's Law cases, a listing of subjects who have ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN will be presented. This listing will include all visits for this subset of subjects.

A plot will also present maximum post-baseline ALT/AST versus maximum post-baseline total bilirubin, expressed as multiples of ULN.

Line plots of the mean (+/- SE) of the following clinical chemistry and haematology parameters will be presented in a figure: CRP, glucose, potassium, ESR, haemoglobin, platelets and leukocytes.

Key subject information for haematology and chemistry results outside the Covance reference ranges will be provided, along with an overview of number and percentage of subjects with results outside the reference ranges post-baseline.

Pregnancy test results will only be listed for eligible subjects of childbearing potential.

4.8.6.4 Vital signs

Observed values at baseline and observed and change from baseline values for post-baseline visits will be summarised for each vital sign. A figure with line plots of the mean change from baseline (+/- SE) of selected vital signs parameters (SBP, DBP and pulse) will be provided. Additionally, a qualitative summary over time of vital signs results will be provided for SBP, DBP, pulse and temperature with categories low, normal and high assigned per the AstraZeneca-defined reference ranges for vital signs (Appendix B). A shift table from baseline to minimum value post-baseline for each parameter (SBP, DBP, pulse, temperature) will be summarised. Similarly, a shift table from baseline to maximum value post-baseline for each parameter will be summarised.

Observed values will be listed and values outside AstraZeneca defined reference ranges and clinically significant change criteria (see Appendix B AstraZeneca defined reference ranges for vital signs) will be flagged. If both the baseline and post-baseline values of a parameter are beyond the same limit for that parameter, then the post-baseline value only will be flagged if it is more extreme (farther from the limit) than the baseline value. If the baseline value is beyond the low, and the post-baseline value is beyond the high limit (or vice-versa), then the post-baseline value will be flagged. If the baseline value is not beyond either limit, and the post-baseline value is beyond either limit, then the post-baseline value will be flagged.

Sitting and supine results for vital signs will not be summarised separately. All results will be summarised together regardless of position (e.g. "diastolic blood pressure" could include both supine and sitting results).

4.8.6.5 ECG variables

A shift table from baseline to last observation post-baseline for ECG evaluation (normal, abnormal - not clinically significant, abnormal - clinically significant, and not done) will be summarised and all results listed for each ECG performed.

4.8.6.6 Physical examinations

As any clinically relevant abnormal medical findings should be recorded on the medical history or AE form if the finding was reported during the experimental phase of the study, no physical examination data will be listed.

5. INTERIM ANALYSES

No interim analysis specific to this study will be conducted.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Table 2 Summary of changes from protocol

Reference	Protocol	Change	Justification
SAP Section 1.1.4	Section 2.4.	The following exploratory endpoints will be included: • European League Against Rheumatism (EULAR) response criteria. • DAS28 remission. • Clinically important change. • Low disease activity.	Additional endpoints considered important for efficacy interpretation by study team.
SAP Section 1.3	Section 8.2.	Comparison to traditional hypothesis testing has been removed and replaced with a statement that the study is "not sufficiently powered to support hypothesis testing". The sample size of "n=18" per arm has been updated to "n=10" per arm.	Power of the study expected to be lower than that stated in the protocol, given the sample size and expected effect size. Wording updated to remove power calculation. Update to n reflects agreement to close recruitment early. Hence a reduced n per arm was agreed.
SAP Section 4.2.1	Section 8.5.1	Concluded that the difference in mean CFB in DAS28 of AZD9567 - mean CFB in DAS28 of Prednisolone will show a better efficacy if the observed difference negative (less than 0) instead of positive (larger than 0).	Lower DAS28 score is better.

7. REFERENCES

D6470C00003 Clinical Trial Protocol, Version 3.0, dated 19MAR2019.

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Frewer P, Mitchell P, Watkins C, Matcham J. Decision-making in early clinical drug development. Pharmaceutical statistics. 2016;15(3):255-63.

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Siemons L, ten Klooster PM, Vonkeman HE, van de Laar MA, Glas CA. Further optimization of the reliability of the 28-joint disease activity score in patients with early rheumatoid arthritis. PloS one 2014;9(6):e100544