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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)

Sponsor: AstraZeneca AB, S-151 85 Södertälje, Sweden

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

CLINICAL STUDY PROTOCOL SYNOPSIS

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)

International Co-ordinating Investigator

PPD

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Study site(s) and number of subjects planned

This Phase 2a Proof of Principle study will be conducted in a maximum of 10 sites in 2-3 countries. Approximately 80-100 patients will be enrolled to achieve 40 randomised.

Study design

This is a Phase 2a, double-blind, double dummy, parallel arm study in patients with active rheumatoid arthritis (RA). It comprises 5 clinic visits and one telephone visit during approximately 5 weeks.

At Visit 1 (screening visit) patients will be consented and screened for eligibility.

At Visit 2, which can occur 1-6 days after Visit 1, pre-dose/baseline assessments will be made. Thereafter, patients will be randomised in the ratio 1:1 to take either 40 mg AZD9567 or 20 mg prednisolone for 14 days once daily. Since this study is double-blind and AZD9567 and prednisolone are different formulations (oral suspension and capsules respectively), all patients will have to take both formulations every day (active AZD9567 + placebo to prednisolone or placebo to AZD9567 + active prednisolone).

A telephone call on study Day 5 to check on patient well-being will be termed Visit 3.

Clinic Visit 4 will occur 7 days into the treatment and Visit 5 will be the end of treatment visit occurring approximately 14 days after Visit 2.

A follow-up visit, Visit 6, will be performed approximately 14 days after last IMP administration on Visit 5, in order to ensure the safety and well-being of patients.

Objectives

Primary Objective:	**Outcome Measure:**
To assess the efficacy of AZD9567, 40 mg, compared to prednisolone 20 mg in patients with active rheumatoid arthritis in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs	Change from baseline in 28 joint Disease Activity Score using CRP (DAS 28 - CRP)

Secondary Objective:	**Outcome Measure:**
To further assess the efficacy of AZD9567, 40 mg, compared to prednisolone 20 mg in patients with active rheumatoid arthritis in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs	Proportion of subjects reaching ACR (American College of Rheumatology) 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 and ACR response criteria (number of swollen and tender joints, patients assessments of global disease activity, pain, physician´s global assessment of disease activity, and CRP)
To evaluate the pharmacokinetic profile of AZD9567 in patients with active rheumatoid arthritis in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs	E g but not limited to plasma $AUC_{(0-24)}$, $AUC_{(0-last)}$, C_{max} and t_{max}.

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability of AZD9567 in patients with active rheumatoid arthritis in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs	Adverse events, vital signs, ECG and laboratory parameters (haematology, clinical chemistry and urine)

Exploratory Objective:	**Outcome Measure:**
To evaluate the pharmacokinetic profile of prednisolone in patients with active rheumatoid arthritis in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs	E g but not limited to plasma $AUC_{(0-24)}$, $AUC_{(0-last)}$, C_{max} and t_{max}.

Exploratory Objective:	Outcome Measure:
To assess the responses to AZD9567 of relevant biomarkers. Whole blood and serum/plasma will be collected to enable relevant analyses such as, but not limited to, effects on bone, metabolism and HPA axis. Exploratory 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.	Exploratory blood biomarkers (e g LPS stimulated TNF_{α}, cortisol and other possible exploratory markers including RNA)
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. Data from the PGx research will not be included in the CSR.	DNA from whole blood

Target subject population

The study population will comprise adult patients with active rheumatoid arthritis in spite of stable treatment with conventional Disease-modifying anti-rheumatic drugs.

Duration of treatment

The total duration of the study for each patient is approximately 5 weeks, which includes a 2 week treatment period and up to 2 week follow up period. The screening period can be up to one week or as short as 1-2 days.

Investigational product, dosage and mode of administration

AZD 9567 is a non-steroidal selective glucocorticoid receptor modulator. In the study the aim is to investigate the safety, efficacy and tolerability of AZD9567 compared to prednisolone in patients with active Rheumatoid Arthritis.

The drug substance is presented as a drug powder and formulated as a suspension for oral administration, using standard excipients. A placebo formulation, an oral suspension, using inactive standard excipients is included in the study. A comparator product, prednisolone capsules and placebo for prednisolone capsules, will also be used. The dose of AZD9567 will be 40 mg once daily (OD) and the dose of prednisolone is 20 mg OD.

Statistical methods

The main objective of this study is to demonstrate that the efficacy of AZD9567 is equivalent to the efficacy of prednisolone 20 mg, where the efficacy endpoint used is change from baseline (CFBL) in DAS28. More precisely, we will use the difference in DAS28 units, X_T-X_P, between, X_T, the average CFBL of the chosen dose of AZD9567 and, X_P, the mean CFBL of prednisolone 20 mg to estimate the average difference in DAS28 between the two arms. This difference will be calculated using a mixed model.

The primary analysis population for efficacy will be the intention to treat (ITT) population. This will include all patients who were randomised and received at least one dose of study medication. Patients will thus be analyzed according to the treatment to which they were intended to be randomised to.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse Event
ACR20	American College of Rheumatology 20% improvement criteria
ACR50	American College of Rheumatology 50% improvement criteria
ACR70	American College of Rheumatology 70% improvement criteria
AUC	Area under the concentration curve - a pharmacokinetic variable
C_{max}	Maximal Concentration of a drug in the blood, ie peak of the plasma concentration curve - a pharmacokinetic variable
CFBL	Change from baseline
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DAS28	Disease Activity Score in 28 joints
DAS28(CRP)	Disease Activity Score in 28 joints using C-reactive protein
DHEA-S	Dehydroepiandrosterone Sulfate
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IMP	Investigational Medicinal Product
IxRS (IWRS/IVRS)	Interactive Web/Voice Response System
ITT	Intention to treat
LIMS	Laboratory Information Management System
LPS	Lipopolysaccharide (used as challenging agent in e g blood cell biomarker analyses)
LSLV	Last Subject Last Visit
OAE	Other Significant Adverse Event
OC	Overencapsulated

Abbreviation or special term	Explanation
Gx	Genetic research
OGTT	Oral glucose tolerance test
PI	Principal Investigator
PK	Pharmacokinetics
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGRM	Selective glucocorticoid receptor modulator
SJC66/68	Swollen Joint Count, assessing 66 or 68 joint
TJC	Tender Joint Count
T_{max}	Time point of the maximal plasma concentration of a drug
WBDC	Web Based Data Capture
WOCBP	Women of Child Bearing Potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that is associated with significant morbidity and mortality. The disease is characterized by inflammation of the synovial joints that can result in pain, swelling, and joint damage with secondary deformity and progressive disability. Worldwide, the prevalence of RA is estimated to be between 0.6% and 1.1% with variations across geographical regions (Pincus et al, 1987, Harris, 1997, Symmons, 2002). Uncontrolled active RA causes joint damage, disability and decreased quality of life, comorbidities including cardiovascular disease and osteoporosis, and reduced life expectancy (Wong et al, 2001, Pincus et al, 1989, Harris, 1997).

Oral glucocorticoids (GC), such as prednisolone, have been used for the treatment of signs and symptoms of RA since before the 1950's (Hench et al, 1949) and remain an important component of the treatment paradigm for both early and established RA [ACR guidelines 2015]. GC modulate the activities of a variety of inflammatory cells and mediators in the synovium of RA patients contributing its therapeutic efficacy (Gerlag et al, 2004). The challenge of GC treatment for the clinicians has been the safety/tolerability of GC especially after long-term use particularly with respect to effects on osteoporosis (Siu et al, 2015), risk of diabetes (Gulliford et al, 2006) cardiovascular disease (del Rincon et al, 2014) and mortality (del Rincon et al, 2014).

AZD9567 is a non-steroidal selective glucocorticoid receptor modulator (SGRM) that has potential to be used as an oral treatment for RA. Pre-clinical studies have been able to show significant anti-inflammatory effect with a differentiation between desired efficacy and the unwanted effects (eg, glucose metabolism, bone effects and mineralocorticoid effect) in nonclinical models and systems. AZD9567 has also been safe and well tolerated thus far in clinical studies of healthy volunteers. Therefore, there is strong pre-clinical evidence supporting the use of an oral SGRM in the therapy of RA.

This is a first-in-patients, Phase 2a, randomised, double-blinded, parallel arm study designed to assess the efficacy of one dose level of AZD9567 compared to prednisolone 20mg once daily in rheumatoid arthritis patients as evaluated by change from baseline of DAS28-CRP. This study will also evaluate the safety, tolerability and PK of AZD9567.

1.2 Rationale for study design, doses and control groups

This is a Phase 2a, randomised, double-blind, parallel arm study to assess the efficacy, safety and tolerability of 40 mg AZD9567 compared to prednisolone 20 mg in patients with active RA. According to the American College of Rheumatology Guidelines, short-term glucocorticoid treatment is indicated to control disease in RA patients with moderate to high disease activity. The current study randomizes eligible patients with established RA and

moderate to high disease activity as defined by ACR Guidelines (DAS28>3.2) to prednisolone 20 mg or AZD9567 40 mg for 14 days.

Prednisolone 20 mg is chosen as a moderate dose of prednisolone that falls within the ACR recommendations for treatment of active disease as moderate doses have been shown to be as effective as higher doses in active early RA (ter Wee et al, 2015). A two weeks duration of therapy was chosen on the basis that prior study has suggested that this duration can significantly impact disease activity as measured by DAS28 score (Gerlag et al, 2004).

A dose AZD9567 of 40 mg has been selected based on review of available safety, PK, and PD data from the first studies in humans in which AZD9567 was administered to healthy volunteers as single doses 2, 10, 20, 40, 80, 100, 125 and 155 mg (D6470C00001) and, in a multiple dose setting, once daily for 5 days using 10, 20, 40 and 80 mg. (D6470C00002). AZD9567 was well tolerated in all studied dose levels.

The selected AZD9567 dose 40 mg showed effects on inflammatory activity (reduced lipopolysaccharide (LPS) stimulated TNF_{α} response) and on the HPA axis (plasma cortisol reduction) similar to what was observed for 20 mg prednisolone.

Although the selected comparator dose of 20 mg prednisolone is known to be efficacious in RA and considered safe and tolerable for 14 days administration, it also has significant effect on glucose homeostasis. The 40 mg dose of AZD9567 showed a significantly better side effect profile with respect to glucose levels after an oral glucose tolerance test (OGTT) compared to prednisolone 20 mg in the ongoing MAD study (D6470C00002).

1.3 Benefit/risk and ethical assessment

AZD9567 is an oral, non-steroidal, potent and selective glucocorticoid receptor modulator (SGRM) under development for the treatment of rheumatoid arthritis. Experience has been gathered from non-clinical safety pharmacology, toxicology studies, previous clinical experience with GR agonists and preliminary data from the first in man single ascending dose study (D6470C00001) and the ongoing multiple ascending dose study (D6470C0002).

In preclinical testing AZD9567 displays features consistent with a potent GR agonist and expected findings in humans will be monitorable and reversible. In clinical studies of AZD9567, single doses of AZD9567 up to 155 mg, and multiple doses of AZD9567 up to 80 mg have been well tolerated in healthy volunteers. Based upon this experience, it is expected that the dose of 40 mg will be well tolerated in RA patients.

Potential adverse effects are discussed in the Investigator's Brochures (Section 6.1). They include potential effects on glucose and lipid metabolism, bone metabolism, and inflammation. The occurrence of any AE, abnormality in laboratory variables or any other safety variables will be closely monitored and evaluated on an ongoing basis during the

clinical studies. Potential benefit for patients taking part in the current study include improvement of their symptoms and decrease in RA disease activity. Using the described measures to avoid exposing the subjects participating in studies to unacceptable risks, it is thus concluded that the potential benefits compared to risks of evaluating AZD9567 justify its further evaluation in this Phase 2a Study.

1.4 Study Design

This is a Phase 2a, double-blind, double dummy, parallel study in patients with active rheumatoid arthritis (RA) in spite of stable treatment with conventional disease-modifying anti-rheumatic drugs (DMARDs). A total of 40 patients will be randomised in the study.

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

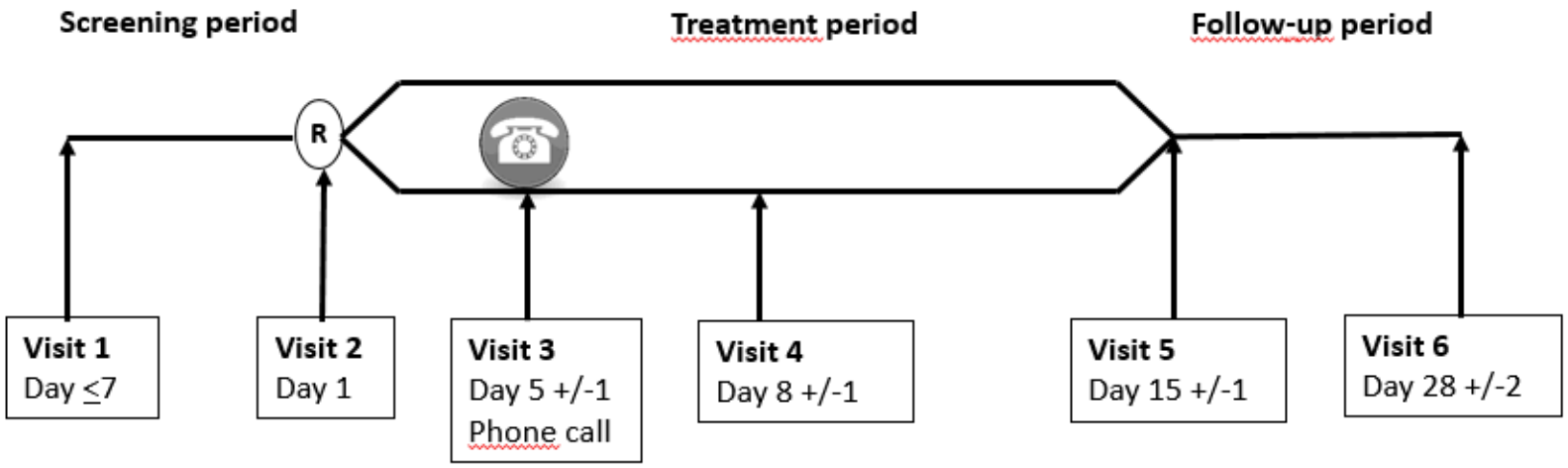
At Visit 2, patients will be randomised in a ratio 1:1 to take either AZD9567 40 mg or prednisolone 20 mg for 14 days once daily. Since this study is double-blind and AZD9567 and prednisolone are different formulations (oral suspension and capsules respectively), all patients will have to take both formulations every day (active AZD9567 + placebo to prednisolone or placebo to AZD9567 + active prednisolone). A telephone call to check patient 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 IMP administration (at Visit 5) in order to ensure the safety and well-being of patients.

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

For details of the study assessments, please see Table 1 in Section 4.

Figure 1 Study flow chart



1.5 Study governance and oversight (Not Applicable)

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To assess the efficacy of AZD9567, 40 mg, compared to prednisolone 20 mg in patients with active rheumatoid arthritis in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs	Change from baseline in 28 joint Disease Activity Score using CRP (DAS 28 - CRP)

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure :**
To further assess the efficacy of AZD9567, 40 mg, compared to prednisolone 20 mg in patients with active rheumatoid arthritis in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs	Proportion of subjects reaching ACR (American College of Rheumatology) 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 and ACR response criteria (number of swollen and tender joints, patients assessments of global disease activity, pain, physician´s global assessment of disease activity, and CRP)
To evaluate the pharmacokinetic profile of AZD9567 in patients with active rheumatoid arthritis in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs	E g but not limited to plasma $AUC_{(0-24)}$, $AUC_{(0-last)}$, C_{max} and t_{max}.

2.3 Safety objectives

Safety Objective:	**Outcome Measure :**
To assess the safety and tolerability of AZD9567 in patients with active rheumatoid arthritis in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs	Adverse events, vital signs, ECG and laboratory parameters (haematology, clinical chemistry and urine)

2.4 Exploratory objectives

Exploratory Objective:	**Outcome Measure :**
To evaluate the pharmacokinetic profile of prednisolone in patients with active rheumatoid arthritis in spite of stable treatment with conventional and/or s.c/i.v. biological DMARDs	E g but not limited to plasma $AUC_{(0-24)}$, $AUC_{(0-last)}$, C_{max} and t_{max}.
To assess the responses to AZD9567 of relevant biomarkers. Whole blood and serum/plasma will be collected to enable relevant analyses such as, but not limited to, effects on bone, metabolism and HPA axis. Exploratory 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.	Exploratory blood biomarkers (e g LPS stimulated TNF_{α}, cortisol and other possible exploratory markers including RNA)
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. Data from the PGx research will not be included in the CSR.	DNA from whole blood

3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1 Provision of informed consent prior to any study specific procedures

2 Male and female patients aged 18 through 80 years at screening

3 Established RA diagnosis according to the 2010 American College of Rheumatology (ACR)/EULAR classification or the 1987 criteria

4 Active RA (DAS28-CRP score ≥ 3.2) with at least 3 swollen joints and 3 tender joints using the DAS28 joint count

5 Patients must have be on stable dosing of conventional and/or s.c./i.v biological DMARDs for the last 8 weeks prior to Visit 1

6 CRP levels >5mg/L at screening if seronegative for RF and anti-CCP Ab, or >2mg/L if seropositive for either marker

7 BMI between 18 and 35 (inclusive)

8 Negative pregnancy test (serum) for female subjects of childbearing potential.

9 Female subjects must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (defined as a barrier method in conjunction with a spermicide) for the duration of the study, for details refer to Section 3.1.1

10 Male subjects must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) for the duration of the study (from the time they sign consent) and for 1 month after the last dose of IMP to prevent pregnancy in a partner.

11 Subjects who are blood donors should not donate blood during the study and for 3 months following their last dose of IMP.

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described above **and**:

12 Provide informed consent for the genetic sampling and analyses.

3.1.1 Acceptable birth control methods

Female patients are not pregnant and do not plan to become pregnant during the study, are not lactating, or are of non-childbearing potential. Females of childbearing potential must provide a negative serum pregnancy test at screening, have a date of last menstruation consistent with non-pregnancy, negative urine pregnancy tests at the follow-up visit, and must be using at least one highly effective method of contraception.

Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but excludes bilateral tubal occlusion), or who are postmenopausal.

Women will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment prior to the planned date of randomisation without an alternative medical cause and have follicle stimulating hormone (FSH) levels in the postmenopausal range.

Acceptable methods of contraception are tubal occlusion, intrauterine device (provided coils are copper-banded), levonorgestrel intrauterine system (e.g., Mirena™), medroxyprogesterone injections (e.g., Depo-Provera™), etonogestrel implants (e.g., Implanon™, Norplan™), normal and low dose combined oral pills, norelgestromin/ethinylestradiol transdermal system,

intravaginal device (e.g., ethinylestradiol and etonogestrel), desogestrel (e.g., Cerazette™), total sexual abstinence and vasectomized sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia). Women should have been stable on their chosen method of contraception for a minimum of 3 months before entering the trial and should continue with contraception for 1 month after the last dose of IMP. In addition to the acceptable method of contraception (except for the practice of total sexual abstinence), condom should be used by male partner for sexual intercourse from randomisation and for 1 month after the last dose of IMP to prevent pregnancy.

3.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1 History or current inflammatory rheumatic disease other than RA (secondary Sjogren's syndrome excluded)

2 History or current clinically important disease which may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study

3 Any clinical contraindications to treatment with steroids

4 Oral or parenteral steroids (beyond study medication) 8 weeks prior to study start and during the study. Stable use and dose of topical and inhaled steroids for longer than 4 w prior to randomisation is acceptable

5 Use of any prohibited medication during the study or if the required washout time of such medication was not adhered to (for details see Section 7.7.1)

6 History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity to drugs with a similar class to study drugs

7 Any concomitant medications that are known to be associated with Torsades de Pointes, for additional information see Section 7.7.1)

8 Any clinically significant ECG; vital signs or laboratory abnormalities identified at screening or prior to randomisation

9 Known history of drug or alcohol abuse within 1 year of screening

10 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

11 Previous randomisation in the present study

12 Participation in another clinical study with an investigational product during the last 3 months

In addition, any of the following is regarded as criteria for exclusion from the genetic research:

13 Previous bone marrow transplant

14 Whole blood transfusion within 120 days of the date of genetic sample collection

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

3.3 Subject enrolment and randomisation

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

The Investigator(s) will:

1 Obtain signed informed consent from the potential subject before any study specific procedures are performed.

2 Assign potential subject a unique enrolment number, beginning with 'E#'.

3 Determine subject eligibility. See Section 3.1 and 3.2.

4 Assign eligible subject unique randomisation code (obtained via IWRS).

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

Randomisation codes will be assigned strictly sequentially as subjects become eligible for randomisation.

3.4 Procedures for handling incorrectly enrolled or randomised subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

The randomisation scheme for this study will be generated by the biostatistics group at AstraZeneca or designee. This will be done using the AZRand system. Randomisation will be

done through a centralized interactive voice and web response system (IxRS). Patients will be block randomised 1:1 to either AZD9567 or prednisolone.

3.6 Methods for ensuring blinding

The study is double-blind; patients, study site personnel and AZ personnel involved in the evaluation of the data must be kept blinded.

Packaging and labelling of study drug will be performed in a way that ensures blinding. The following personnel will have access to the randomisation list:

- AstraZeneca Supply Chain
- IxRS vendor
- CRO for drug distribution (Fisher)
- Personnel performing the PK sample analysis (Covance BioA)

Randomisation will occur after eligibility has been confirmed based on all study inclusion and exclusion criteria.

If all eligibility criteria are met, blinded personnel will contact the centralized interactive voice and web response system (IxRS) to receive a randomisation number and treatment assignment.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

3.8 Restrictions

The following restrictions are applied during the trial or as indicated below:

- Patients should abstain from donating blood and plasma during the study
- No change or addition of non-steroidal anti-inflammatory drugs (NSAIDs) (including topical administration) less than 24 hours before joint evaluation or paracetamol and other painkillers less than 12 hours before joint evaluation
- Due to the risk for drug-drug interactions certain drugs should be excluded, for details see Section 7.7.1
- Male patients should refrain from fathering a child or donating sperm during the treatment and until 1 month following the last dose
- WOCBP using hormonal contraceptives must abstain from use of any medication with CYP3A4 enzyme inducing properties from three months before Visit 1 until 1 month after last dose of IP, for details see Section 7.7.1

3.9 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event: An AE or SAE that, in the judgment of the Investigator, requires treatment withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to treatment.
- Pregnancy
- Severe non-compliance with the Clinical Study Protocol
- Subject Lost to follow-up: Non-attendance to visits. In these cases, every effort should be made by the Investigator to ascertain the reason and to assure subject´s attendance as soon as possible. Every effort (at least three documented attempts) should be made to contact the subject and documented in the medical records. If subject could not be reached after that, a registered mail letter will be sent to the subject and documented in the medical records.
- Others: At the Investigator´s or Sponsor's request, study cancellation or any other reason not described above

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments - see Section 3.10), without prejudice to further treatment. A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen

and assessed by an Investigator(s). Adverse events will be followed up (See Section 6); and all study drugs should be returned by the subject.

If a subject is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are subjects who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These subjects should have the reason for study withdrawal recorded as 'Screen failure'(the potential subject who does not meet one or more criteria required for participation in a trial, this reason for study withdrawal is only valid for not randomised subjects). 'Failure to meet randomisation criteria' should be selected for an indication that the subject has been unable to fulfil/satisfy the criteria required for assignment into a randomised group (it is only applicable for randomised studies and should be used for subject withdrawal post-screening).

3.10.2 Rescreening

Possible re screening may be allowed, but will be decided on an ad hoc basis depending on the reason. If re screening will take place, the patient will keep the same E-number.

3.10.3 Withdrawal of the informed consent

Subjects are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan detailing the procedures

Study procedures	**Screening Visit 1**	**Day 1 Visit 2 (within 1 week of V1)**	**Day 5 Phone call Visit 3**	**Day 8 +/- 1 Visit 4**	**Day 15 +/- 1 EOT[a] Visit 5**	**Day 28 +/- 2 Follow-up Visit 6**
Inclusion/exclusion criteria	X					
Demographic data	X					
Medical history (incl. RA history and oral health)	X					
Concomitant medication	X	X	X	X	X	X
Informed consent	X					
Informed consent for genetic sample	X					
Randomisation		X				
Study drug dispensation		X[b]		X		
Study drug administration:		X[b]	→	→ NB: **at site**	X NB: **at site**	
Study drug return					X	
Adverse events		X	→	→	→	X
Serious adverse events	X	→	→	→	→	X
Vital signs (BP/P and body temperature)	X	X[d]		X	X	X
12-lead ECG	X	X[d, f]			X	X
Clinical laboratory evaluations (Haematology, serum biochemistry, endocrinology[e], and urine[e] analysis)	X[c]	X[d]		X[d]	X[d]	X
Pregnancy test (serum)	X					X
Erythrocyte sedimentation rate, ESR (at site)	X	X[d]		X[d]	X[d]	X
Physical examination,	X	X		X	X	X
Body weight & height[e]	X				X	X
DAS28-CRP	X	X[d]		X	X	X
ACR20, 50, and 70	X	X[d]		X	X	X
SJC and TJC 66/68	X	X[d]		X	X	X
Blood sampling for exploratory biomarkers (cortisol, serum)		X[d,g] Profile: 0, 1, 2, 3, 4 and 6 h			Pre dose[g] &1, 2, 3, 4 and 6 h post dose	
Blood sampling for exploratory biomarkers (LPS stimulated TNFα, whole blood)		X[d] Profile: 0, 1, 2, 3, 4 and 6 h			Pre dose &1, 2, 3, 4 and 6 h post dose	
Blood sample (whole blood) for mRNA[i]		X[d]			X[h]	

Table 1 Study Plan detailing the procedures

Study procedures	Screening Visit 1	Day 1 Visit 2 (within 1 week of V1)	Day 5 Phone call Visit 3	Day 8 +/- 1 Visit 4	Day 15 +/- 1 EOT[a] Visit 5	Day 28 +/- 2 Follow-up Visit 6
Blood sample for other potential biomarkers (serum)		X[d]			X[d]	X
Blood sample for DNA (future exploratory research)		X[b]				
Blood sampling for PK of AZD9567/ prednisolone					Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4 and 6 h	

[a] End of treatment
[b] After randomisation
[c] Local lab
[d] Pre-dose
[e] Only at Visit 1
[f] Only performed if Visit 1 was >3 days ago
[g] Preferably starting as close to 08.00 as possible
[h] At 1h post dose (C_{max})
[i] A peripheral blood mononuclear cell method may be used at selective site/s

4.1 Screening/Enrolment period

Procedures will be performed according to the Study Plan, Table 1.

At screening, Visit 1, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled in the study.

Because recruited subjects will have active disease, and require treatment, the screening will be short allowing patients to be randomised 1-6 days after Visit 1, as along as all screening assessments to verify eligibility are available.

4.2 Treatment period

At Visit 2, the pre-dose/baseline assessments will be performed. Thereafter the patients will be randomised 1:1 to receive either 40 mg AZD9567 or 20 mg prednisolone. The treatment period is 2 weeks. Patients will receive IMP to bring home sufficient for one week treatment. They will also receive handling instructions in local language detailing how to take the IMP. Double dummy technique is applied as the IMP has different formulations, see Section 0. The site staff will call the patients 5 days after start of treatment and ask for possible adverse events. This phone call will be called Visit 3 in the eCRF. This precaution is taken to ensure the safety of the patients as 5 days is the longest treatment regimen so far in a clinical study with AZD9567. Patients will then come back to the clinic after one week, Visit 4, to receive medication for the last week and to perform study assessments. After two weeks of treatment the end of treatment visit, Visit 5, will be performed. For details, see Table 1.

4.3 Follow-up period

Approximately 2 weeks after Visit 5, a follow up visit will be scheduled, Visit 6. For details of the study procedures, see Table 1.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the Clinical Study Protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

5.1.1 DAS 28

The DAS28 is a composite, validated index for measuring disease activity in RA and is calculated at timepoints indicated in Table 1. The DAS28 (CRP) has been validated against radiographic progression and physical function (HAQ-DI), and the validation profile is similar to the DAS28 (ESR; Wells et al, 2009).

The DAS28 (CRP/ESR) considers 28 of the 68 TJC and 28 of the 66 SJC and subject's global health (GH) using PGA of disease activity using the VAS of 0 (= best), 100 (= worst) plus levels of CRP (mg/L) or ESR (mm/Hour).

DAS28(CRP) values will be calculated as follows (Wells et al, 2009):

DAS28(CRP) = 0.56 × square root (sqrt) (TJC28) + 0.28 × sqrt(SJC28) + 0.014 × GH + 0.36 × ln(CRP+1) + 0.96

DAS28(CRP) values will be calculated at screening for eligibility assessment using an online calculator (ref link http://www.4s-dawn.com/DAS28/)

DAS28(CRP/ESR) IDAS 28 (CRP/ESR) Improvement

Background DAS28(CRP/ESR) 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(CRP/ESR) = Disease Activity Score in 28 joints using C-reactive protein/erythrocyte sedimentation rate.
Note: DAS28(CRP/ESR)-defined remission is DAS28 (CRP/ESR) of < 2.6. Low disease activity is < 3.2 and high disease activity is > 5.1.

5.1.2 Swollen and Tender Joint Count 66/68

The TJC assesses the following 68 joints for tenderness: temporomandibular (n = 2), sternoclavicular (n = 2), acromioclavicular (n = 2), the 8 proximal interphalangeal joints of the fingers, the interphalangeal joints of the thumbs (n = 2), the 8 distal interphalangeal joints, the 10 metatarsophalangeal, the 10 metacarpo-phalangeal joints plus the wrists (n = 2), elbows (n = 2), shoulders (n = 2), hips (n = 2), ankle mortise and tarsus (n = 4), knees (n = 2), and toes (n = 10; Felson et al, 2011).

The SJC assesses 66 joints, which includes all of the joints in the TJC excluding the hip joints (n = 2).

Swollen and tender joint counts will be assessed by a qualified, independent Joints Counts Assessor who is a skilled arthritis assessor who will be responsible for completing the joint counts.

In order to calculate the ACR20, ACR50, ACR70, and DAS28 (CRP) responses, each of the 66 joints will be evaluated for swelling and each of the 68 joints will be evaluated for tenderness. Standardized metrology training will be provided if necessary.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Section 4).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

A central laboratory will be used in this study (Covance Central Laboratory Services) but for the safety lab panel at Visit 1 also local labs will be used. The clinical chemistry, haematology and urinalysis can therefore be analyzed at a local laboratory at or near to the Investigator site both at Visit 1 and if needed on ad hoc basis if deemed necessary by the investigator. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Reference values from all labs used in the study will be included in the eCRF.

The following laboratory variables will be measured:

Table 2 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (neutrophils, lymphocytes,	S/P-Alkaline phosphatise (ALP)
monocytes, eosinophils and basophils)	S/P-Aspartate transaminase (AST)
B-Platelet count	S/P-Alanine transaminase (ALT)
Erythrocyte sedimentation rate, ESR	S/P-Albumin
	S/P-Potassium
Urinalysis (dipstick)	S/P-Calcium, total
U-Hb/Erythrocytes/Blood	S/P-Sodium

U-Protein/Albumin	S/P-Creatine kinase (CK)
U-Glucose	S/P-C-reactive protein (CRP)
	S/P-Low density lipoprotein (LDL)
	S/P-High density lipoprotein (HDL)
	S/P-Free fatty acids (FFA)
Endocrinology	S/P-fasting glucose[b]
FSH[a]	S/P-insulin

[a] Only at Visit 1 for women under the age of 50 considered to be post-menopausal to determine that the hormones are in the post-menopausal range
[b] Fasting glucose on Visit 2, Visit 4 and Visit 5.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin - Hy's Law', for further instructions.

Table 3 Volume of blood to be drawn from each patient

Assessment	**No of samples[b]**	**Sample volume (mL)**	**Total volume (mL)[b]**
Safety - Clinical Chemistry	5	5	25
Safety - Haematology	5	2	10
Endocrinology (FSH)[a]	1	2.5	2.5
Exploratory Biomarkers (whole blood mRNA)	2	5	10
Other Potential Biomarkers (serum)	3	2 x 8.5	2 x 25.5
Exploratory Biomarkers (whole blood for TNFα)	12	2	24
Exploratory Biomarkers (serum for cortisol)	12	8	96
PK samples for AZD9567/prednisolone	9	3	27
Pharmacogenetics	1	10	10
TOTAL	53		255.5

[a] only females
[b] The number of samples may be changed due to additional sampling at unscheduled visits and the blood volume required may be altered to fit the assay requirements.

5.2.2 Physical examination

A complete physical examination will be performed as indicated in Table 1 and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose, mouth - including teeth and gums - and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

The outcome of the examination is to be recorded as normal/abnormal in the eCRF. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline measurement will be reported as an AE (see Section 6.1).

5.2.3 ECG

5.2.3.1 Resting 12-lead ECG

12-lead pECG recordings will be collected as detailed in Table 1. The investigator will make an overall evaluation of the pECG as normal or abnormal. If abnormal, it will be decided whether or not the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF.

5.2.4 Vital signs

Vital signs will include pulse, and systolic and diastolic blood pressure as well as body temperature. Vital signs will be obtained at timepoints indicated in see Table 1 (and ad-hoc as medically indicated).

5.2.4.1 Pulse and blood pressure

Pulse (beats/minute, radial artery, during 30 seconds) will be measured before blood pressure and in a lying or sitting position after 5 minutes of rest. Thereafter, systolic and diastolic blood pressure (mmHg) will be measured using the same cuff, appropriate for arm circumference, and in the same position, throughout the study.

5.2.4.2 Body temperature

Body temperature (Celcius) will be collected at timepoints indicated in Table 1 and according to standard procedures at the clinics.

5.3 Pharmacokinetics

5.3.1 Collection of samples

Blood samples for determination of AZD9567 in plasma will be taken at the times presented in the study plan Table 1.

Blood samples for determination of prednisolone in plasma will also be taken at the times presented in the study plan Table 1.

Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual.

5.3.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by Covance Laboratory Services on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

5.3.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

5.4 Pharmacodynamics

5.4.1 Collection of samples

The pharmacodynamics (PD) of oral AZD9567 will be assessed by effects on CRP levels as part of the primary endpoint DAS28-CRP. CRP is collected as part of the lab screen at time points indicated in Table 1. ESR is also collected as an exploratory biomarker and is also part of the lab screen at time points indicated in Table 1. In addition, there will be samples collected for exploratory biomarkers for future exploratory research, see Section 5.6.

5.5 Genetics

5.5.1 Collection of optional genetic samples

The subject's consent to participate in the genetic research components of the study is optional.

The blood sample for genetic research will be obtained from the subjects after or at Visit 2, ie after randomisation. Although DNA variants are stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.5.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years or as per local regulations from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any possible future analyses will not be reported in the CSR, but separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA

5.6 Biomarker analysis

The subject's consent to the use of donated biological samples is mandatory.

CCI [redacted]

5.6.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. CCI [redacted]

5.6.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual.

5.6.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca Biobank during the entire life cycle.

5.6.4 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from randomisation, Visit 2 throughout the treatment period and including the follow-up period Visit 6.

SAEs will be recorded from the time of informed consent.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at study Visit 6 are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity,
- Intensity rating scale:
- mild (awareness of sign or symptom, but easily tolerated)

- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study *(*yes or no*)*
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication,
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. 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 unless it meets the criteria shown in Section 6.2. 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 it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures and additional study drug. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: *'Have you/the child had any health problems since the previous visit?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE

6.3.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease under Study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of active RA. Events, which are unequivocally due to disease under study should not be reported as an AE

during the study unless they meet SAE criteria or lead to discontinuation of the investigational product.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and the EU Summary of Product Characteristics (SPC) for the active comparator product.

6.5 Overdose

To date there is no experience of overdose and no antidote to AZD9567. In cases of known or suspected overdose, symptomatic treatment and monitoring of vital functions and e.g. blood parameters should be performed according to routine clinical practice based on the judgment of the investigator. In addition, should an overdose occur the following procedures should be followed:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study subject has received any study drug

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and 1 month following the last dose.

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

6.7 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong subject received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to subject (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If an medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AZD9567 is a differentiated selective-Glucocorticoid-Receptor-Modulator. In the study the aim is to investigate the safety, efficacy and tolerability of AZD9567 compared to prednisolone in patients with active Rheumatoid Arthritis.

The drug substance is presented as a drug powder and formulated as a suspension for oral administration, using standard excipients. A placebo formulation, an oral suspension, using inactive standard excipients is included in the study. A comparator product, Prednisolone capsules and placebo for prednisolone capsules, will also be used.

Investigational product	Dosage form and strength	Manufacturer
AZD9567 Oral suspension	0.5 mg/ml - 10 mg/ml	AstraZeneca R&D Gothenburg
AZD9567 Oral suspension	Placebo	AstraZeneca R&D Gothenburg
OC Prednisolone capsules	5 mg	AstraZeneca R&D Gothenburg
OC Prednisolone capsules	Placebo	AstraZeneca R&D Gothenburg

7.2 Dose and treatment regimens

A total of 40 eligible patients will be randomly assigned 1:1 to the study treatment. This will be managed via IWRS. The dose of IP, AZD9567 40 mg and prednisolone 20 mg, will be

taken once daily (in the morning) for 14 days. Detailed instructions are provided in the Handling instructions each patient will be provided with in local language. The first dose of IMP will be taken at the clinic after the baseline assessments have been performed on Visit 2. Also at the end of treatment visit, Visit 5, the IMP should be taken at the site to allow for a pre dose blood sample to be drawn for PK analyses. As the IMP has different formulations, double dummy technique is applied. Each patient will therefore take both oral suspension and 4 capsules of prednisolone/placebo on a daily basis for 14 days. The oral suspensions of AZD9567 and placebo are not taste neutral. This information will be included in the Patient Informed Consent form. Opening aids for the IMP bottles will be supplied by AstraZeneca and will be described in the Handling instructions.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. Details of storage condition will be provided on the label of the IMP. The IMP storage area must be temperature monitored and the site will maintain documentation of the temperature monitoring. Handling instructions for the patients will be provided separately by AstraZeneca.

7.5 Compliance

The administration of all study drugs should be recorded in the appropriate sections of the Case Report Form.

7.6 Accountability

The study drug provided for this study will be used only as directed in the Clinical Study Protocol.

The study site staff will account for all study drugs dispensed to and returned from the subject.

The study drug should be destructed locally. Study site staff, if applicable, or the AZ monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery and destruction should be signed.

7.7 Concomitant and other treatments

7.7.1 Other concomitant treatment

Pre-clinical *in vitro* data indicate that AZD9567 can inhibit drug transporters such as P-glycoprotein and breast cancer receptor protein. Therefore, digoxin should not be given

together with the IMP due to the risk for elevated plasma levels of digoxin. To avoid drug-drug interaction risks for statins, simvastatin, atorvastatin, rosuvastatin and fluvastatin dose administration should be separated in time such as the AZD9567 is taken in the morning and the statin in the evening.

AZD9567 is metabolised via CYP3A4 and hence moderate and strong inhibitors or inducers of CYP3A should not be administered during this study since that will affect the plasma concentration of AZD9567. Patients should not have taken any of these medications within 3 days of IMP intake (ref exclusion criteria 5). Guidance is provided in Appendix E. However, the list in Appendix E is not a complete list, ie it should be treated with caution.

Guidance for avoiding QT-prolonging medications can also be found in a link provided in Appendix E.

Other medication, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

The purpose of this section is to provide a brief outline of the statistical methods to be employed in this Phase IIa, Randomised Multi-Center, Double- Blind, comparator-Controlled Study of AZD9567 xx mg in patients with Rheumatoid Arthritis (RA) and prednisolone 20 mg. A more detailed description of all statistical matters as well as data derivations and data summaries will be included in separate statistical analysis plan (SAP) based on the current protocol and in accordance to the International Conference on Harmonization (ICH) E3 and E9 Guidelines.

All efficacy and safety variables will be summarized by treatment groups using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum for continuous data and absolute and relative frequencies for categorical data). Data will be summarized for baseline, endpoint and by visit (if applicable).

Descriptive statistics will be presented to assess the distribution of the baseline variables across treatment groups. Assessment of efficacy will be made using the decision framework (cf. 8.2) used to determine the necessary sample size. Formal statistical tests for differences between treatment groups will be applied for exploratory purposes only. Moreover

- All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol violators identified.
- Analyses will be performed by AstraZeneca or its representatives.

- Refer to Statistical Analysis Plan (SAP) for details.

8.2 Sample size estimate

This study, is a Phase IIa study, where the aim is to show that the efficacy of AZD9567 is equivalent to the efficacy of prednisolone 20 mg. The design is a two arm design, one arm receiving prednisolone 20 mg and the other receiving AZD9567.

The endpoint proposed is the change from baseline (CFBL) in DAS28 units for each patient. The main analysis will be based on the difference X_T-X_P, between X_T, the average change from base line of the chosen dose of AZD9567 and, X_P, the mean CFBL of prednisolone 20 mg. Therefore, this difference quantifies the treatment effect i.e. how much better AZD9567 is compared to prednisolone 20 mg in terms of average CFBL in DAS28 units.

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).

Using a sample size of 18 per arm, results in good decision criteria. In comparison with traditional hypothesis testing this corresponds to a test with significance level alpha=0.09 and beta=0.10.

The above results have been evaluated using simulations. Further details of the statistical methodology will be outlined in the SAP.

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

The primary analysis population for efficacy will be analyzed using the intention to treat (ITT) population. This is in accordance to the ICH E9 guideline suggesting that the analysis of the primary endpoint should be analyzed according to the treatment to which patients were actually randomised. The ITT population will include all patients who were randomised and received at least one dose of study medication. Patients will be analyzed according to the treatment to which they were intended to be randomised to. ITT is sometimes referred to as Full Analysis Set.

Moreover, the primary analysis population for efficacy will also be analyzed using the Per Protocol (PP) population which includes all patients who were randomised, treated with study medication and did not have a major protocol deviation. Major protocol deviations leading to exclusion from the PP population will be finalized prior to un-blinding during the blind data review meeting. Full criteria for exclusion from the analysis set will be detailed in the Statistical Analysis Plan (SAP).

8.3.2 Safety analysis set

The Safety Population will include all patients who were randomised and received at least one dose of study medication. Patients will be analyzed according to the treatment which they actually received.

8.3.3 PK analysis set

The PK analysis set will include all subjects with at least one quantifiable AZD9567 concentration with a documented related dosing history.

8.3.4 Other analysis sets

Pharmacodynamic (PD) analysis set will include all subjects who received at least one dose of study treatment and have available pharmacodynamic data.

8.4 Outcome measures for analyses

The primary efficacy endpoint is the difference in change from baseline in DAS28, X_T-X_P, between, X_T, the average CFBL of the chosen dose of AZD9567 and, X_P, the mean CFBL of prednisolone 20 mg.

Secondary efficacy variables are the change from baseline in ACR and the percentage of patients with ACR20, 50 and 70.

8.5 Methods for statistical analyses

8.5.1 Analysis of the primary variable(s)

To show that the efficacy of AZD9567 is equivalent to the efficacy of p20 mg in terms of change from baseline in DAS28, we will use the difference in DAS28 units, X_T-X_P, between, X_T, the average CFBL of the chosen dose of AZD9567 and, X_P, the mean CFBL of prednisolone 20 mg. This difference will be calculated using a mixed model. It will be concluded that the data support better efficacy of AZD9567 whenever the observed difference is positive (larger than 0). Similarly, it will be concluded that the AZD9567 is less efficacious than prednisolone 20 mg if the difference is negative (less than -0.4). Formal statistical testsing will be performed for exploratory purposes only.

8.5.2 Analysis of the secondary variable(s)

Secondary efficacy variables;

The change from baseline in core set measures of ACR and DAS28 will be analyzed with an ANCOVA model approach using PROC MIXED in SAS with baseline value as covariate.

8.5.2.1 Pharmacokinetic analyses

The derivation of the PK parameters will performed at Covance (Clinical Pharmacokinetic Alliance).The PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 6.3, or higher (Pharsight Corp., Mountain View, California), in accordance with "Best Practice Reference Guidelines Pharmacokinetic Evaluations in Clinical Studies". All descriptive statistical computations will be performed using SAS Version 9.2, or higher.

Where possible, the following PK parameters will be assessed for AZD9567 and prednisolone.

$AUC_{(0\text{-}24)}$	Area under the plasma concentration-time curve from time zero to 24 hours after administration (using the pre-dose value as the 24 h time point)
$AUC_{(0\text{-}last)}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
$AUC_{(0\text{-}6)}$	Area under the plasma concentration-time curve from time zero to 6 h after administration
t_{max}	Time to reach maximum plasma concentration
C_{min}	Predose concentration

Additional PK parameters may be determined where appropriate.

Further details regarding the calculation and descriptive statistics of the PK parameters will be described in the SAP.

8.5.3 Subgroup analysis (if applicable)

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

8.5.4 Sensitivity analysis (if applicable)

To be confident in the results of the study, we need to check that the assumptions of the performed analyses are compatible the data at hand. Therefore, sensitivity analysis is required. This can concern (but is not restricted to) issues related to choice of the method of analysis, handling of missing data, simplifying assumptions such as ignoring correlations and interaction terms or handling of outliers. A more detailed description of sensitivity analysis will be included in the SAP.

8.5.5 Exploratory analysis (if applicable)

Exploratory and post hoc analyses may be performed to answer additional questions.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD9567.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by IQVIA, according to the Data Management Plan.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the Medical Coding Team at IQVIA.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data Management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or any other organization contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory (ies) internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician, unless required to do so by law**.**

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Ethics Committee should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the Clinical Study Protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject

- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, National Co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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