AstraZeneca

Revised Clinical Study Protocol

Drug Substance	AZD9291
Study Code	D5160C00005
Edition Number	2.0

A Phase I, Open-label, Single-center, Sequential Design Study in Healthy Volunteers to Determine the Relative Bioavailability of Different Oral Formulations of AZD9291 and the Effect of Food

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Phase I, Open-label, Single-center, Sequential Design Study in Healthy Volunteers to Determine the Relative Bioavailability of Different Oral Formulations of AZD9291 and the Effect of Food

Principal Investigator

Study center and number of subjects planned

The study will be performed at a single center in the United States. Approximately 16 healthy male volunteers aged 18 to 55 years (inclusive) will be enrolled to ensure that data from at least 12 volunteers are available for the primary comparison of the 3 formulations (Part A). For Part B approximately 16 healthy male volunteers aged 18 to 55 years (inclusive) will be enrolled to ensure that data from at least 12 volunteers are available for the food effect comparison.

Study period		Phase of development
Estimated date of first subject enrolled	Quarter 3 2013	I
Estimated date of last subject completed	Quarter 1 2014	

Objectives

The primary objective is to determine the relative bioavailability of a 20-mg AZD9291 solution formulation and a 20-mg tablet formulation in relation to the 20-mg AZD9291 Phase I capsule formulation (Part A).

The secondary objectives are:

- To investigate the effect of food (high-fat breakfast) on the pharmacokinetics of AZD9291 (Part B)
- To investigate the safety and tolerability of AZD9291 in healthy volunteers (Part A and Part B)

Study design

This is a Phase 1, open-label, 2-part (Part A and Part B) study. Part A will be conducted as a 3-period, non-randomized sequential design in which healthy male volunteers will receive single 20-mg doses of AZD9291 as a capsule in Period 1, as a solution in Period 2, and as a tablet in Period 3, all in the fasted state. Part B will be conducted as a 2-period, fixed-sequence design in which a separate cohort of healthy male volunteers will receive a single 20-mg dose of AZD9291 under fasted conditions in Period 1, and under fed conditions (following a high-fat breakfast) in Period 2. The results from Part A will determine whether the 20-mg capsule formulation or the 20-mg tablet formulation will be selected for assessment of the food-effect in Part B. There will be a minimum of a 21-day washout between each dose in both study parts.

Target subject population

The target population is healthy male volunteers between the ages of 18 and 55 years, inclusive, with a body mass index between 19.0 and 30.0 kg/m^2 and body weight at least 50 kg and no more than 100 kg.

Investigational product, dosage, and mode of administration

During each treatment period of Part A, a single dose of 20-mg AZD9291 will be administered in the fasted state as either a capsule formulation, as a solution formulation, or as a tablet formulation, with 240 mL of water. In Part B, a single dose of either the 20-mg AZD9291 capsule or tablet formulation will be administered in both the fasted and fed state. The selection of the formulation for Part B will depend on the relative bioavailability results of Part A.

Comparator, dosage, and mode of administration

None

Duration of treatment

Part A

The duration of volunteer participation will be approximately 14 weeks. This includes a 28-day screening period, 3 treatment periods, and a final follow-up visit. There will be a minimum of 21-day washout between doses in each treatment period. A final post-study visit will take place between 21 and 28 days after the last dose of AZD9291 (up to7 days after completion of Period 3). During the study, each volunteer will receive single, 20-mg doses of AZD9291 on 3 separate occasions.

Part B

The duration of volunteer participation will be approximately 11 weeks. This includes a 28-day screening period, 2 treatment periods separated by a 21-day washout between doses, and a final follow-up visit. A final post-study visit will take place between 21 and 28 days

after the last dose of AZD9291 (up to 7 days after completion of Period 2). During the study, each volunteer will receive a single, 20-mg dose of AZD9291 on 2 separate occasions.

Outcome variable(s):

- Pharmacokinetics
  - AZD9291 and AZ5104 and AZ7550 (AZD9291 metabolites) plasma concentrations will be used to assess the following parameters, as applicable: AUC, $AUC_{(0-72)}$, $AUC_{(0-t)}$, C_{max}, $t_{1/2,\lambda z}$, λ_z, t_{max}, t_{lag}, CL/F (AZD9291 only), and V_z/F (AZD9291 only), and parent to metabolite ratio (calculated as AZD9291/AZ5104 and AZD9291/AZ7550 for both C_{max} and AUC) (Part A and Part B).
  - The primary variables for assessments of relative bioavailability are AZD9291 C_{max}, AUC, and/or $AUC_{(0-t)}$ (Part A).
  - The secondary variable for assessment of relative bioavailability is t_{max} (Part A).
  - The primary variables for assessment of food-effect are AZD9291 C_{max}, AUC, and/or $AUC_{(0-t)}$ (Part B).
  - The secondary variable for assessment food-effect is t_{max} (Part B).
- Safety (secondary endpoints)

  Safety parameters include adverse events, vital signs, physical examinations, ophthalmologic examination, electrocardiograms, and clinical laboratory assessments (Part A and Part B).

Statistical methods

Part A

Inferential statistical analyses will be performed on the pharmacokinetic data only. The bioavailability of the 20-mg solution and a 20-mg tablet relative to the 20-mg capsule will be assessed using the primary pharmacokinetic variables, C_{max}, AUC, and/or $AUC_{(0-t)}$, of plasma AZD9291. These endpoints will be natural log-transformed and analyzed using a linear mixed effects model. The difference in treatment (formulation) means will be determined along with its associated 90% confidence interval and back-transformed to give an estimate of the relative bioavailability. The results of this analysis will be presented in terms of geometric means for each treatment, the relative bioavailability (ie, the ratio of the treatment formulation geometric means) and its 90% confidence interval.

The above treatment comparisons will also be performed for t_{max} as the secondary analyses. Nonparametric methods will be used to compute median t_{max} for each treatment, median t_{max} difference, and associated 90% confidence interval for the median difference. The data will

be analyzed by a Wilcoxon Signed-Rank Test. The 90% confidence interval will be calculated using the method of Hahn and Meeker (Hahn and Meeker 1991).

Part B

For the investigation of the effect of food, the primary PK variables AUC and/or $AUC_{(0-t)}$ and C_{max} of plasma AZD9291 will be analyzed. These endpoints will be natural log-transformed and analyzed using a linear mixed effects model with fixed effect for treatment and random effect for subject. The difference in treatment means will be determined along with its associated 90% confidence interval (CI) and back-transformed to give an estimate of the effect of food on the exposure of AZD9291. The results of this analysis will be presented in terms of geometric means for both treatments, the effect of food on the exposure of AZD9291 (ie, the ratio of the treatment geometric means) and its 90% CI. Similar statistical analyses may be performed for AZ5104 and AZ7550, if appropriate.

All other data will be summarized descriptively.

All volunteers receive treatments in the same order and so results may be confounded with undetectable period effects, which will be considered in interpretation.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol (CSP).

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event (see definition in Section 6.3.1)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve from zero to infinity
$AUC_{(0-72)}$	Area under the concentration-time curve from time zero to 72 hours postdose
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero to the last quantifiable concentration
BLQ	Below the limit of quantitation
BMI	Body mass index
CI	Confidence interval
CL/F	Apparent plasma clearance
C_{max}	Maximum observed concentration
CPA	Clinical Pharmacology Alliance
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Geometric coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
IATA	International Airline Transportation Association
ICH	International Conference on Harmonization
IP	Investigational product

Abbreviation or special term	Explanation
IRB	Institutional Review Board
K_2 EDTA	Dipotassium ethylenediaminetetraacetic acid
λ_z	Terminal rate constant
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NOEL	No observed effect level
NSCLC	Non-small cell lung cancer
OAE	Other significant adverse event (see definition in Section 11.1.2)
PK	Pharmacokinetic
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SOP	Standard operating procedure
SRC	Safety Review Committee
$t_{1/2,\lambda z}$	Terminal half-life
TBD	To be decided
TKI	Tyrosine kinase inhibitor
t_{lag}	Lag time before observation of quantifiable analyte concentrations
t_{max}	Time of maximum concentration
ULN	Upper limit of the normal range
V_z/F	Apparent volume of distribution

1. INTRODUCTION

1.1 Background

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total) (GLOBOCAN 2008). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are now the established first line therapy in patients with non-small cell lung cancer (NSCLC) known to have activating mutations in EGFR (EGFRm+) (NCCN 2012). Selective inhibition of EGFR tyrosine kinase has demonstrated clinical benefit in approximately 70% of patients with advanced NSCLC harboring the sensitivity mutations (the most common of which are L858R and deletions in exon 19 [Ex19del]). The tumors initially respond to EGFR TKIs, but subsequently develop resistance to therapy, with a median time to progression of 9 months. In at least 50% of these initially EGFR TKI-responsive patients, disease progression is associated with the emergence of a secondary EGFR mutation, T790M in exon 20 of EGFR that confers resistance to therapy (Pao et al 2005).

AZD9291 is a potent irreversible inhibitor of both the single EGFRm+ (TKI-sensitivity conferring mutation) and dual EGFRm+/T790M+ (TKI-resistance conferring mutation) receptor forms of EGFR. AZD9291 is currently being investigated in a single clinical trial, using a capsule formulation, in patients with advanced NSCLC whose disease has progressed following treatment with an EGFR TKI agent.

Preliminary pharmacokinetic (PK) data from the ongoing clinical study with AZD9291 in patients with advanced NSCLC who have received at least 1 prior regimen of an EGFR TKI agent (Study D5160C00001) are available following 20-mg (N=6), 40-mg (N=6), and 80-mg (N=6), and 160-mg (N=6) single and once-daily multiple dosing. Following a single dose, all AZD9291 PK profiles showed a lag time; time to maximum concentration (t_{max}) ranged from 3 to 24 hours; half-life ranged from 30 to 110 hours (median 50 hours). However, half-life was not well characterized due to the PK sampling scheme utilized in the majority of patients in these cohorts (a modified PK sampling scheme was used in the 160 mg cohort and will be used in later cohorts). Accumulation was observed for AZD9291, AZ5104, and AZ7550 after multiple dosing, as would be expected based on the single-dose data. Approximately dose-proportional PK was observed across the 20- to 160-mg dose range.

Following a single 20-mg capsule fasted dose in Study D5160C00001, the AZD9291 mean (minimum to maximum) $AUC_{(0-72)}$ and C_{max} were 2177 (953 to 6890) nM·h and 48 (25 to 133) nM, respectively (N=6). For AZ5104, the $AUC_{(0-72)}$ and C_{max} were 84 (55 to 167) nM·h and 1.6 (0.88 to 3.6) nM, respectively. For AZ7550, the $AUC_{(0-72)}$ and C_{max} were 51 (32 to 3) nM·h and 0.93 (0.54 to 1.5) nM, respectively.

One patient in the 20-mg cohort showed a higher plasma exposure [maximum observed concentration, C_{max}, and area under the concentration-time curve from zero to 72 hours postdose, $AUC_{(0-72)}$], with a longer lag time and later t_{max} than expected based on data from

other patients in the 20-, 40-, and 80-mg cohorts. The reason for this is currently unclear and there may be confounding factors. This patient received a gastric pH modifying concomitant medication, which is likely to have reduced the dissolution rate, based on the results of in vitro dissolution studies; this is in agreement with the longer lag time and later t_{max} observed.

1.2 Rationale for conducting this study

The primary objective of this study is to investigate the relative oral bioavailability of an oral solution and a tablet formulation of AZD9291 compared to the current capsule formulation. This will provide AstraZeneca with information about the influence of formulation on the clinical plasma PK of AZD9291. It is anticipated that future/ongoing patient studies will use a tablet formulation and data from this study will be used to help guide appropriate development of a suitable formulation.

Currently, patients in ongoing clinical studies with AZD9291 are required to receive AZD9291 dose administration in the fasted state since the effect of food has not been investigated. It is therefore of interest to assess if there is any potential food-effect on the PK of AZD9291, to help guide food administration requirements for ongoing and future clinical studies. A high-fat meal has been selected with the aim of assessing the maximum potential effect. The PK data from the relative bioavailability part of the study (Part A) will be used to select the formulation to be used in the food-effect part of the study (Part B). To minimize the total number and duration of exposures to AZD9291, the food-effect comparison will be conducted in a new set of healthy male volunteers in a 2-period, fixed-sequence design.

1.3 Benefit/risk and ethical assessment

1.3.1 Potential benefits

Healthy male volunteers participating in this study will not gain any therapeutic benefit from administration of AZD9291.

1.3.2 Potential risks identified from nonclinical toxicology studies

The key findings in the safety pharmacology, secondary pharmacology, and toxicology studies were as follows:

- AZD9291 was negative in the in vitro genetic toxicology tests (Ames test and mouse lymphoma assay) and in vivo in the rat micronucleus test and is therefore considered not to represent a risk of genetic toxicity in humans. AZD9291 absorbs light in the ultraviolet visible range, but was not phototoxic when tested in an in vitro 3T3 assay.

- During the 1-month rat study, repeated administration of AZD9291 was associated with dose-related atrophic, inflammatory, and/or degenerative changes affecting the skin, eye, tongue, and female reproductive system. There were also histopathological findings in the male reproductive system. Histopathological changes were present in the eye at all doses, but the low dose (4 mg/kg/day) was the no observed effect level (NOEL) for all of the other findings. All findings showed

evidence of reversibility. During the 1-month dog study, repeated administration of AZD9291 was associated with dose-related atrophic changes affecting the skin, eye, tongue, and intestine. There were also histopathological findings in the male reproductive system. The low dose (2 mg/kg/day) was the NOEL for all histopathological changes with the exception of the findings in the male reproductive system. All findings showed evidence of reversibility.

- The findings in the male reproductive system comprised seminiferous tubular atrophy (rat and dog) and spermatid retention (rat) in the testes with secondary changes in the epididymides. These findings were generally of a low severity (minimal to mild with the exception of 1/10 high-dose rats with moderate tubular atrophy), are considered unlikely to be seen on single dosing (no testicular pathology seen in limited dimension, non Good Laboratory Practice dose range finding studies of up to 14 days duration), and would be expected to recover. The mechanism underlying these testicular findings is unknown at present.

- There was some evidence for an increase in QT interval and decrease in heart rate following administration of AZD9291 to guinea pigs and dogs. However, the changes seen in the dog telemetry study were marginal, transient, and not dose-related and were considered to be of limited biological significance. Increases in blood pressure were observed in the rat and guinea pig. Increases in blood pressure were not seen in the dog telemetry or 1-month dog studies.

Further details are provided in the Investigator's Brochure.

1.3.3 Emerging safety profile with AZD9291

There is 1 ongoing clinical study with AZD9291 in patients with advanced NSCLC who have received at least 1 prior regimen of an EGFR TKI agent (Study D5160C00001). All data from this study are preliminary, unvalidated, and subject to change. As of 7 November 2013, 21 patients have received at least a single dose of 20-mg AZD9291 (16 patients currently ongoing with up to 6.5 months continuous daily dosing), 50 patients have received at least a single dose of 40-mg AZD9291 (44 patients ongoing with up to 5 months continuous daily dosing), 40 patients have received at least a single dose of 80-mg AZD9291 (35 ongoing with up to 3 months continuous dosing), and 36 patients have received at least a single dose of 160-mg AZD9291 (all 36 ongoing with up to 2 months continuous dosing). A 240 mg cohort has commenced, with 6 patients having received at least a single 240-mg dose of AZD9291. The majority of nondisease-related adverse events (AEs) reported to date have been mild in intensity and do not occur after the single-dose administration or 7-day washout period before once-daily continuous dosing. The most commonly reported AE on continuous dosing is loose stools or diarrhea, which occasionally requires loperamide for management. Some patients have reported a mild rash, urticaria, dry skin or pruritis.

One patient had Common Terminology Criteria for Adverse Events Grade 4 increases in liver transaminases and Grade 2 bilirubin increase. The patient died 29 days from starting study medication (the day of single dosing followed by a 1-week drug-free period followed by

multiple dosing) and 7 days after discontinuation of study drug. The recorded causes of death were aggravated pneumonia, septic shock, and lung cancer. An in-depth review of the case was done by the study D5160C00001 Safety Review Committee (SRC). Based on the review of all available data by the SRC, it was considered that the main event was continued disease progression in a patient with heavy tumor burden and multiple lines of prior anticancer treatment at time of study entry. Pneumonia and septic shock were considered a complication of the rapidly progressive disease. Transaminases changes were considered of multifactorial etiology, the septic process and severe hypoxemia being the key factors. The SRC Investigators decided that as the patient had only 14 days of continuous dosing and the clinical picture was dominated by disease progression, with a fatal outcome from the complications and NSCLC progressive disease, the patient was considered non evaluable.

1.3.4 Potential risks identified clinically with other small molecule EGFR TKI agents

The established safety/tolerability profile of chronic dosing with small molecule reversible EGFR TKI agents, derived from extensive clinical experience, consists mostly of gastrointestinal disturbances (diarrhea, nausea, and vomiting) and skin reactions (rash, acne, dry skin, and pruritus). These events are well-characterized and are considered to be dose related, usually occurring within the first month of treatment, manageable, generally mild to moderate, reversible, and noncumulative and can be managed by simple medication or a short cessation of therapy. Other types of AEs reported commonly or very commonly with these agents in patients with advanced NSCLC include anorexia, stomatitis, mild to moderate elevations in liver transaminases, asthenia, keratitis, conjunctivitis, and alopecia. These events are generally mild, manageable, and reversible. The frequency of interstitial lung disease documented in this patient population is 1.3% with gefitinib and between >1/100 and ≤1/1000 with erlotinib, including fatalities. Both EGFR TKI agents have demonstrated an increase in embryolethality in nonclinical reproductive toxicity studies.

1.3.5 Overall benefit-risk and ethical assessment

The potential for adverse drug reactions (ADRs) associated with AZD9291 is based on the AE profile of the class of drugs that inhibit the EGFR-signalling pathways and from observations from nonclinical and clinical studies of AZD9291. Specific volunteer selection criteria, appropriate safety assessments, and individual stopping criteria have been incorporated into the clinical program for AZD9291 based on the potential AEs and ADR profile. The limited number of exposures to single doses of AZD9291 in this study are considered to pose no clinically significant risk to study participants given the close safety monitoring planned during this study and the chosen dose (20-mg once daily).

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to determine the relative bioavailability of a 20-mg AZD9291 solution formulation and a 20-mg tablet formulation in relation to the 20-mg AZD9291 Phase I capsule formulation (Part A).

2.2 Secondary objectives

The secondary objectives of this study are:

- To investigate the effect of food (high-fat breakfast) on the PK of AZD9291 (Part B)
- To investigate the safety and tolerability of AZD9291 in healthy volunteers (Part A and Part B)

3. STUDY PLAN AND PROCEDURES

This CSP has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This Phase 1 study is an open-label, 2-part (Part A and Part B) design study.

Part A

Part A will be a 3-period, sequential design study to be conducted in approximately 16 healthy male volunteers who will each receive 20-mg of AZD9291 in the fasted state, once as a capsule (Treatment A) in Period 1, once as a solution (Treatment B) in Period 2, and once as a tablet (Treatment C) in Period 3, in a fixed order. There will be a minimum 21-day washout between each dose.

Part A of the study will consist of 5 visits (for details and timing of assessments see Table 1 and Table 2). The screening visit (Visit 1) will be conducted within 28 days of Visit 2. Following fully written informed consent, healthy volunteers will be enrolled into the study and screened for eligibility.

For all treatment periods (Visits 2, 3, and 4), volunteers will report to the clinic on Day 1 (the day prior to dosing) and remain resident until the 48-hour postdose monitoring and evaluations have been performed (Day 3). Volunteers will return to the clinic for outpatient visits on Days 4, 6, 8, 10, 15, and 22 (3, 5, 7, 9, 14, and 21 days postdose, respectively). The Day 22 postdose assessments may be used as the Day 1 predose assessments for the subsequent visit if an exact 21-day washout is used (ie, a volunteer may check into the clinic on Day 21 [20 days postdose] for the subsequent treatment period). A final follow-up visit (Visit 5) will be performed 21 to 28 days after the last dose of AZD9291.

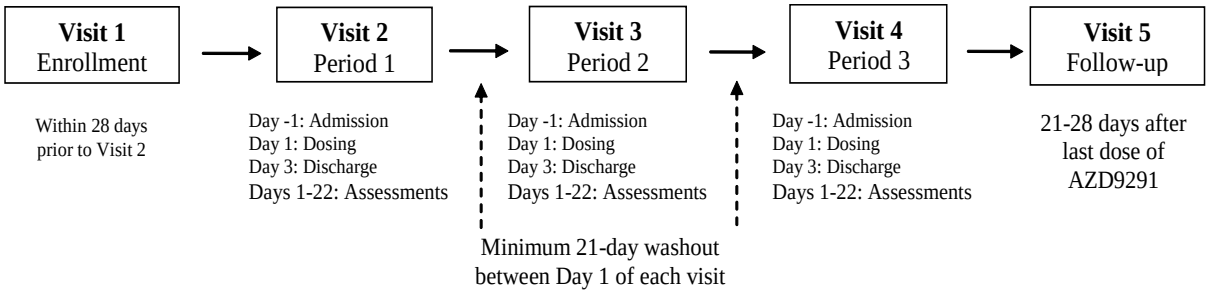
On Day 1 of Periods 1, 2 and 3 volunteers will receive a single, oral dose of 20-mg AZD9291 along with 240 mL water while in an upright position following an overnight fast of 10 hours. The doses will be administered as a capsule in Period 1 (which must be swallowed whole and not chewed, crushed, or divided), as a solution in Period 2, and as a tablet in Period 3 (which must be swallowed whole and not chewed, crushed, or divided). Volunteers will remain fasting from food until 4 hours postdose. Apart from the water given at dosing, volunteers will be fasted from water from 1 hour prior to dosing until 1 hour after dosing.

The dosing of all cohorts in Part A will be staggered, with 3 volunteers being dosed 2 weeks in advance of the remaining cohort of volunteers. This will allow the assessment of safety and the PK profile (up 72 hours) to be reviewed prior to dosing the remaining volunteers.

Blood samples for the determination of AZD9291 and metabolite (AZ5104 and AZ7550) concentrations will be collected prior to dosing and serially postdose through Day 22 in each treatment period. Safety assessments will include monitoring of AEs and concomitant medications; clinical laboratory tests (hematology, clinical chemistry, and urinalysis); measurement of vital signs; electrocardiograms (ECGs); physical examinations; screening for drugs of abuse, alcohol, and cotinine; and ophthalmologic examinations. The PK profile from 0 to 72 hours postdose will be assessed after Periods 1, 2 and 3, and any volunteer with exposures exceeding the PK limits (see Section 5.8) will be withdrawn and may be replaced if required to ensure 12 evaluable volunteers complete the bioavailability assessment.

A study flow chart is shown in Figure 1. The overall study plan and schedule of assessments are presented in Table 1 and Table 3.

Figure 1 Study flow chart (Part A)



Part B

Part B will be a fixed-sequence, 2-period, study design to assess the effect of food on AZD9291. Approximately 16 healthy male volunteers aged 18 to 55 years (inclusive) will be enrolled to ensure 12 completers.

This study will consist of 2 treatment periods during which the following treatments will be administered.

- Period 1: A single 20-mg oral AZD9291 dose under fasted conditions on Day 1.
- Period 2: A single 20-mg oral AZD9291 dose under fed conditions on Day 1.

The 2 treatment periods will be separated by a washout of at least 21 days (from the first AZD9291 administration in Period 1 until the first AZD9291 administration in Period 2)

Based on the bioavailability results from Part A, Part B may be conducted either with the tablet formulation or with the capsule formulation. All volunteers will receive a single, oral dose of 20-mg AZD9291 along with 240 mL water while in an upright position following an overnight fast of 10 hours in Period 1, and a single oral dose of 20-mg AZD9291 along with 240 mL water in the fed state (following a high-fat breakfast) in Period 2.

Part B will consist of 4 visits (for details and timing of assessments see Table 2 and Table 4). The screening visit (Visit 1) will be conducted within 28 days of Visit 2. Following fully written informed consent, healthy volunteers will be enrolled into the study and screened for eligibility.

For both treatment periods (Visits 2 and 3), volunteers will report to the clinic on Day 1 (the day prior to dosing) and remain resident until the 48-hour postdose monitoring and evaluations have been performed (Day 3). Volunteers will return to the clinic for outpatient visits on Days 4, 6, 8, 10, 15, and 22 (3, 5, 7, 9, 14, and 21 days postdose, respectively). The Day 22 postdose assessments may be used as the Day 1 predose assessments for the subsequent visit in Period 2 if an exact 21-day washout is used (ie, a volunteer may check into the clinic on Day 21 [20 days postdose] for the subsequent treatment period). A final follow-up visit (Visit 4) will be performed 21 to 28 days after the last dose of AZD9291 in Period 2.

On Day 1 of Period 2, following an overnight fast of at least 10 hours, volunteers should begin the recommended meal (see Section 5.5.2) 30 minutes prior to administration of the investigational product (IP). The breakfast should be consumed within 30 minutes and volunteers must eat the entire meal. A single dose of 20-mg AZD9291 will be administered 30 minutes after the start of the meal along with 240 mL water. No food should be allowed for at least 4 hours postdose. Water should be withheld from 1 hour before until 1 hour after dosing, apart from the water consumed at IP administration.

Apart from the high-fat breakfast on Day 1 of Period 2, volunteers will receive standardized meals scheduled at the same time during the study.

Blood samples for the determination of AZD9291 and metabolite (AZ5104 and AZ7550) concentrations will be collected prior to dosing and serially postdose. Safety assessments will include monitoring of AEs and concomitant medications; clinical laboratory tests (hematology, clinical chemistry, and urinalysis); measurement of vital signs; ECGs; physical examinations; screening for drugs of abuse, alcohol, and cotinine; and ophthalmologic examinations. The PK profile from 0 to 72 hours postdose will be assessed and any volunteer with exposures exceeding the PK limits (see Section 5.8) will be withdrawn and may be replaced if required to ensure 12 evaluable volunteers complete Part B (food-effect).

A study flow chart is shown in Figure 2. The overall study plan and schedule of assessments are presented in Table 2 and Table 4.

Figure 2 Study flow chart (Part B)

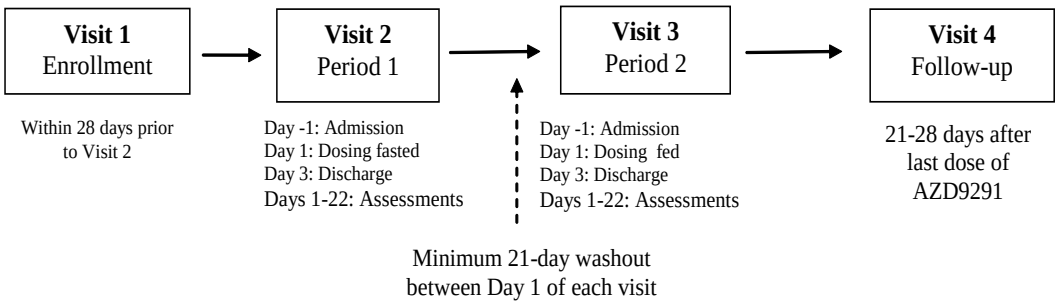


Table 1 Overall study plan (Part A)

Study Visit	**Screening (Visit 1)**	**Treatment Period[a,b] (Visits 2, 3, and 4)**									**Follow-up (Visit 5)**
Study Day	**≤ 28 days of Visit 2**	**Day -1**	**Day 1**	**Days 2-3**	**Day 4**	**Day 6**	**Day 8**	**Day 10**	**Day 15**	**Day 22**	**21-28 days after last dose of AZD9291**
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demographics	X										
Height/weight/BMI	X	X									
Medical/surgical history	X										
Urinary drug, alcohol, and cotinine screen[c]	X	X[c]	←	—	—	—	—	—	—	→	
Serology screen	X										
Physical examination[d]	X	X[d]									X
Ophthalmological assessment[e]		X[e]									
Residential stay[f]		←	—	→							
Nonresidential visits					X	X	X	X	X	X	X
IP administration			X								
Vital signs	X	X[g]	X	X			X		X	X[g]	X[h]
12-lead ECG	X	X[g]	X	X			X		X	X[g]	X[h]
AEs and concomitant medications[i]	X[i]	X[i]	←	—	—	—	—	—	—	—	→
Safety blood and urine[j]	X	X[g]		X[i]			X		X	X[g]	X[h,i]
PK blood sampling			X[g]	X	X	X	X	X	X	X[g]	

BMI body mass index, ECG electrocardiogram, IP investigational product, PK pharmacokinetics

[a] Each dosing day will be a minimum of 21 days apart.

[b] See Table 3 for detailed timing of assessments.

[c] Urinary drug, alcohol, and cotinine screen assessments will be performed on each admission to the clinic. Only the drug and cotinine screen will be performed at the screening visit.

[d] Complete physical examinations will be performed at the screening and follow-up visits; brief physical examinations may be performed on Day 1 of each treatment period.

[e] Ophthalmological examination (corrected visual acuity and slit lamp fundoscopy) will be performed on Day 1 of Period 1 only and as clinically indicated on occurrence of eye symptoms.

[f] Volunteers will be discharged from the clinic after the 48-hour PK sample has been taken on Day 3.

[g] The Day 22 postdose assessments in Periods 1 and 2 may coincide with the predose assessments in Periods 2 and 3, respectively, if a 21-day washout is used. In this case, only 1 set of assessments needs to be collected (ie, the predose assessments scheduled for Day 1 of the next period).

[h] The follow-up visit may coincide with the Period 3 Day 22 assessment; in this case, only 1 set of assessments is needed.

[i] Serious AEs will be collected beginning at informed consent; nonserious AEs will be collected beginning at the first intake of IP.

[j] Includes clinical chemistry, hematology, and urinalysis at screening, Day -1, Day 3, Day 8, Day 15, Day 22, and at follow-up; see Table 7 for time points and specific tests to be performed.

Table 2 Overall study plan (Part B)

Study Visit	**Screening (Visit 1)**	**Treatment Period[a,b] (Visits 2 and 3)**									**Follow-up (Visit 4)**
Study Day	**≤ 28 days of Visit 2**	**Day -1**	**Day 1**	**Days 2-3**	**Day 4**	**Day 6**	**Day 8**	**Day 10**	**Day 15**	**Day 22**	**21-28 days after last dose of AZD9291**
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demographics	X										
Height/weight/BMI	X	X									
Medical/surgical history	X										
Urinary drug, alcohol, and cotinine screen[b]	X	X[c]	←	—	—	—	—	—	—	→	
Serology screen	X										
Physical examination[c]	X	X[d]									X
Ophthalmological assessment[d]		X[d]									
Residential stay[e]		←	—	→							
Nonresidential visits					X	X	X	X	X	X	X
IP administration			X								
Vital signs	X	X	X	X			X		X	X	X
12-lead ECG	X	X	X	X			X		X	X	X
AEs and concomitant medications[f]	X[f]	X[f]	←	—	—	—	—	—	—	—	→
Safety blood and urine[g]	X	X		X[i]			X		X	X	X
PK blood sampling			X	X	X	X	X	X	X	X	

BMI body mass index, ECG electrocardiogram, IP investigational product, PK pharmacokinetics

[a] Each dosing day will be a minimum of 21 days apart.
[b] See Table 4 for detailed timing of assessments.
[c] Urinary drug, alcohol, and cotinine screen assessments will be performed on each admission to the clinic. Only the drug and cotinine screen will be performed at the screening visit.
[d] Complete physical examinations will be performed at the screening and follow-up visits; brief physical examinations may be performed on Day 1 of each treatment period.
[e] Ophthalmological examination (corrected visual acuity and slit lamp fundoscopy) will be performed on Day 1 of Period 1 only and as clinically indicated on occurrence of eye symptoms.
[f] Volunteers will be discharged from the clinic after the 48-hour PK sample has been taken on Day 3.
[g] The Day 22 postdose assessments in Period 1 may coincide with the predose assessments in Period 2, if a 21-day washout is used. In this case, only 1 set of assessments needs to be collected (ie, the predose assessments scheduled for Day 1 of the next period).
[h] The follow-up visit may coincide with the Period 2 Day 22 assessment; in this case, only 1 set of assessments is needed.
[i] Serious AEs will be collected beginning at informed consent; nonserious AEs will be collected beginning at the first intake of IP.
[j] Includes clinical chemistry, hematology, and urinalysis at screening, Day -1, Day 3, Day 8, Day 15, Day 22, and at follow-up; see Table 7 for time points and specific tests to be performed.

Table 3 Schedule of assessments for each treatment period (Part A)

Time (hours) relative to dose	Supine pulse and blood pressure	ECG 12-lead	Safety blood and urine	PK blood	Food and fluid	Resident
Predose	X	X		X[a]		
Dosing					D	
0.5				X		
1	X	X		X	F[b]	
1.5				X		
2	X	X		X		
3				X		
4	X	X		X	M[b]	
6				X		
8	X	X		X		
10				X		
12	X	X		X		
24 (Day 2)	X	X		X		
48 (Day 3)	X	X	X	X		
72 (Day 4)				X		
120 (Day 6)				X		
168 (Day 8)	X	X	X	X		
216 (Day 10)				X		
336 (Day 15)	X	X	X	X		
504 (Day 22)[c]	X	X	X	X		

D drink, consisting of 240 mL water; F free access to fluids; M meal.
ECG electrocardiogram, PK pharmacokinetics

[a] Predose sample must be collected within the 30 minutes prior to dosing.

[b] Water can be allowed as desired, except for 1 hour before and after drug administration (apart from the 240 mL water given with the dose). No food should be allowed for at least 4 hours postdose. A standard meal will be given 4 hours postdose after completion of all simultaneously scheduled study procedures.

[c] The Day 22 postdose assessments in Periods 1 and 2 may be the same as the timing of the predose assessments in Periods 2 and 3, respectively, if a 21-day washout is used. In this case, only 1 set of assessments needs to be collected, which are the predose assessments scheduled for Day 1 of the following period.

Table 4 Schedule of assessments for each treatment period (Part B)

Time (hours) relative to dose	Supine pulse and blood pressure	ECG 12-lead	Safety blood and urine	PK blood	Food and fluid	Resident
Predose	X	X		X[a]	Breakfast[b]	
Dosing					D	
0.5				X		
1	X	X		X	F[c]	
1.5				X		
2	X	X		X		
3				X		
4	X	X		X	M[c]	
6				X		
8	X	X		X		
10				X		
12	X	X		X		
24 (Day 2)	X	X		X		
48 (Day 3)	X	X	X	X		
72 (Day 4)				X		
120 (Day 6)				X		
168 (Day 8)	X	X	X	X		
216 (Day 10)				X		
336 (Day 15)	X	X	X	X		
504 (Day 22)[d]	X	X	X	X		

D drink, consisting of 240 mL water; F free access to fluids; M meal.
ECG electrocardiogram, PK pharmacokinetics

[a] Predose sample must be collected within the 30 minutes prior to dosing.

[b] Period 2 only; high-fat meal to be given 30 minutes prior to dosing.

[c] Water can be allowed as desired, except for 1 hour before and after drug administration (apart from the 240 mL water given with the dose). No food should be allowed for at least 4 hours postdose. A standard meal will be given 4 hours postdose after completion of all simultaneously scheduled study procedures

[d] The Day 22 postdose assessments in Periods 1 may be the same as the timing of the predose assessments in Periods 2, if a 21-day washout is used. In this case, only 1 set of assessments needs to be collected, which are the predose assessments scheduled for Day 1 of the following period.

3.2 Rationale for study design, doses, and control groups

This study will investigate the relative bioavailability of a 20-mg AZD9291 solution formulation and tablet formulation in relation to the current 20-mg AZD9291 capsule

formulation in healthy male volunteers. To date, 20-, 40-, 80- and 160-mg doses of AZD9291 have been confirmed as being sufficiently well tolerated for at least a 21-day continuous dosing period to support dose escalation in the ongoing Phase I clinical study; a 240-mg dose is currently being investigated.

A 20-mg dose is considered sufficient to fully evaluate the plasma concentration-time profile for assessment of relative bioavailability and food-effect while minimizing the risk of any significant clinical ADRs. Administration of the same dose for the respective formulation in both Part A and Part B of the study eliminates any influence of possible non-proportionality in PK of the active compound.

Based on the preliminary PK data available to date, the terminal half-life ($t_{1/2,\lambda z}$) of AZD9291 in human plasma is approximately 30 to 110 hours (median 50 hours, based on PK samples collected up to 72 hours following single dose administration in the majority of patients [N=19 out of 24], samples collected to 168 hours in N=5 patients). Based on this, a period of 21 days between doses would be expected to be sufficient to washout AZD9291 plasma concentrations between doses.

In addition, preliminary data on the half-lives of the AZ5104 and AZ7550 metabolites have suggested these to be approximately 70 and 120 hours, respectively (median values based on N=4). Therefore, while it is unlikely that a period of 21 days is sufficient to fully washout plasma concentrations of these metabolites between doses, the primary aim of the study is to assess AZD9291 plasma concentration profiles. The accumulated cumulative data from patients dosed with at least 20-mg AZD9291 for up to 6 months supports the assumption that the risk/benefit profile remains unchanged.

Classically, in a clinical pharmacology study testing 3 different treatment arms, the order of administration would be randomized to compensate for any potential carry-over effect between dosing periods. The expectation is that a 20-mg capsule fasted treatment will be the treatment that will give the lowest PK exposure in this study. The administration of a 20-mg AZD9291 tablet or solution dose in fasted state or either capsule or tablet formulation in the fed state have the potential to result in increased exposures to AZD9291. In order to minimize the risk of volunteers reaching PK exposures which have been associated with toxicity in the preclinical toxicity studies or observed following a 80-mg single dose in the ongoing clinical study, a sequential design will be employed for both study parts with an individual PK limit applied. Any individual volunteer exceeding the PK exposure limit in Period 1 will not progress to Period 2 (both study parts). In Part A all volunteers will receive the capsule under fasting conditions in Period 1(Treatment A). The primary objective of this study is to assess the relative bioavailability of the solution and tablet in relation to the capsule formulation. Due to availability of the tablet formulation, the solution formulation will be administered in Period 2 (Treatment B) and the tablet administration in Period 3 (Treatment C). Administration of the tablet formulation (fasted) is expected to result in exposure that is less than or equal to the exposure following solution administration. Nevertheless, any individual volunteer exceeding the PK exposure limit in Period 2 may not progress to Period 3. In order to minimize the total number of doses and duration of exposure to AZD9291 and

metabolites, the food-effect investigation (Part B) will be performed in a new cohort of volunteers as a 2-period, fixed-sequence design. Since the presence of food may increase the exposure compared to fasted, all volunteers in Part B will receive AZD9291 in the fasted state in Period 1 followed by fed state in Period 2.

The formulation selected for Part B will be determined based on the bioavailability results from Part A.

This study will be conducted in healthy male volunteers aged 18 to 55 years in order to avoid interference with the study results from disease processes and other drugs. The selection criteria are defined such that volunteers selected for participation in the study are known to be free from any significant illness. There is no observed gender difference in patient data; therefore, there is no reason to expose women to AZD9291. Safety monitoring and stopping criteria have been developed based upon knowledge of EGFR TKI class effects, preclinical toxicology, and emerging clinical safety data with AZD9291 to ensure the safety of participating volunteers. In addition the dosing during all periods in Part A will be staggered to assess the safety, tolerability, and PK of the first dose administered in 3 volunteers, before the remaining volunteers are dosed 2 weeks later.

Blinding is not considered necessary, as the primary objective is plasma AZD9291 concentration-time profiles and the resulting PK parameters are objective measurements. Thus, the risk of bias is minimal.

4. SUBJECT SELECTION CRITERIA

The Investigator should keep a record, the volunteers screening log, of volunteers who entered prestudy screening.

Each volunteer 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.

4.1 Inclusion criteria

For inclusion in Part A or Part B of the study volunteers should fulfill the following criteria:

1. Provision of signed and dated informed consent prior to any study-specific procedures

2. Male volunteers aged 18 to 55 years

3. Body mass index between 19 and 30 kg/m^2 and weight at least 50 kg and no more than 100 kg

4. Veins suitable for cannulation or repeated venipuncture

5. Volunteers must be willing to use a condom, unless their partners are postmenopausal, surgically sterile, or using an effective hormonal method of contraception or intrauterine coil. In addition, volunteers must agree to continue to take similar contraceptive precautions until **6** months after the last dose of AZD9291.

6. Be willing and able to comply with study procedures, restrictions, and requirements

4.2 Exclusion criteria

Volunteers should not enter either Part A or Part B of the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca and staff)

2. Previous enrollment in the present study

3. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the healthy volunteer at risk because of participation in the study, or influence the results or the healthy volunteer's ability to participate in the study

4. History or presence of gastrointestinal, hepatic, or renal disease or surgical procedure or any other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs

5. Any clinically significant abnormalities in physical examination, vital signs (supine blood pressure >140 mmHg systolic, >90 mmHg diastolic, or pulse rate ≤35 or ≥100 beats per minute), or clinical laboratory assessment as judged by the Investigator

6. Acute illness, surgical procedures, or trauma from within 2 weeks before enrollment until first administration of IP

7. Volunteers who have received live or live-attenuated vaccine in the 2 weeks prior to dosing

8. Volunteers with active malignancy or neoplastic disease in the previous 12 months

9. A suspected/manifested infection according to International Airline Transportation Association (IATA) Categories A and B infectious substances

10. Positive results on screening tests for serum hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV)

11. Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, as judged by the Investigator

12. Known or suspected history of significant drug abuse as judged by the Investigator

13. Positive screen for drugs of abuse or cotinine (nicotine level above 400 ng/mL) at screening or positive screen for alcohol, drugs of abuse, or cotinine on admission to the unit prior to the first administration of IP

14. History of alcohol abuse or excessive intake of alcohol, defined as regular weekly intake of greater than 14 units of alcohol in men (Note: 1 unit=25 mL spirits, 125 mL wine, or 250 mL beer or lager)

15. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to AZD9291, its excipients, or drugs with a similar chemical structure or class

16. Use of any prescribed or nonprescribed medication including antacids, analgesics, herbal remedies, vitamins, and minerals during the 14 days prior to the first administration of AZD9291 or medication with hepatic enzyme-altering properties, such as St John's Wort, during the 4 weeks (or longer depending on the medication's half-life) prior to the first administration of AZD9291. Occasional use of paracetamol (acetaminophen) and nonsteroidal nasal decongestant is permitted at the discretion of the Investigator.

17. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of IP

18. Blood donation within 1 month of screening or any blood donation/blood loss greater than 500 mL during the 3 months prior to screening

19. Volunteers who received another new chemical entity (defined as a compound which has not been approved for marketing) or participated in any other clinical study (including methodology studies where no drugs were given) within 1 month of the first administration of IP in this study are not eligible.

20. Judgment by the Investigator that the healthy volunteer should not participate in the study if the volunteer is considered unlikely to comply with study procedures, restrictions, and requirements

21. Planned inpatient surgery, dental procedure, or hospitalization during the study

For procedures for withdrawal of incorrectly enrolled volunteers, see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during both Part A and Part B of the study

Volunteers will be required to comply with the following restrictions:

- Volunteers should use barrier contraceptives (ie, by use of condoms) during sex with all partners during the study and for a washout period of 6 months after the last dose of AZD9291.

- Volunteers must avoid fathering a child during the study and for 6 months after the last dose of AZD9291.

- Volunteers should abstain from sperm donation for 6 months after the last dose of AZD9291.

- Volunteers should abstain from donating blood during the study and for at least 3 months after the last visit.

- Volunteers should abstain from taking drugs of abuse.

- Volunteers should abstain from taking any prescribed medication, over-the-counter remedies, herbal medications, high-dose or "mega" vitamins, mineral supplements, or medicines purchased via the Internet beginning 4 weeks before the first dose of AZD9291 and continuing until 3 months after the last dose of AZD9291. Paracetamol (acetaminophen) 1 gram, every 6 hours, to a maximum daily dose of 4 grams is permitted; however, the Investigator should be informed so this can be recorded up to the follow-up visit (Visit 5, Part A and Visit 4, Part B).

- Volunteers should not consume grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges from 7 days prior to the first dose of AZD9291 until after the poststudy medical examination.

- Volunteers who wear contact lenses should discontinue wearing their lenses if they have any mild to moderate eye symptoms following exposure to AZD9291 for at least 1 week after symptoms have resolved. If there is a recurrence of eye symptoms or severe ocular events are experienced, the wearing of contact lenses should be discontinued until at least 1 week after the last exposure of AZD9291.

- Volunteers should not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a study doctor, at any time during the study until 1 week after taking the last dose of AZD9291.

- Caffeine-containing drinks or foods (eg, coffee, tea, cocoa, chocolate, and cola) are permitted during the study but the level of intake should not be changed.

- Volunteers should abstain from drinking alcohol beginning 72 hours before admission to the clinic and continuing until 24 hours after the last dose of AZD9291 and also beginning 72 hours prior to blood tests or the poststudy medical examination.

- Volunteers should abstain from consuming poppy seeds from enrollment until after the poststudy medical examination.

- Volunteers should refrain from strenuous physical activity that is not within the volunteer's normal weekly routine, beginning 5 days before each visit to the clinic and continuing until after the poststudy medical examination.

- **Fasted treatments (Part A and Part B)**: Volunteers will be fasted for at least 10 hours prior to each dose.

- **Fed treatment (Part B):** Volunteers will be fasted for at least 10 hours prior to the scheduled breakfast. The breakfast will be started 30 minutes prior to IP administration and must be consumed within 30 minutes or less. Volunteers must eat all of the breakfast. Dosing will take place 30 minutes after the start of the breakfast.

  All treatments (Part A and Part B): Water can be allowed as desired, except for 1 hour before and after drug administration (apart from the 240 mL water given with the dose). No food should be allowed for at least 4 hours postdose. A standard meal will be given 4 hours postdose after completion of all simultaneously scheduled study procedures. The volunteers will receive standardized meals scheduled at the same time in each treatment period.

- Volunteers should refrain from actively trying to lose weight from the prestudy medical examination until after the poststudy medical examination.

5.2 Subject enrollment

The Investigator will:

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

2. Assign potential volunteer a unique enrollment number, beginning with 'E0001001'.

3. Determine volunteer eligibility. See Sections 4.1 and 4.2

If a volunteer withdraws from participation in the study, then his/her enrollment code cannot be reused. Only volunteers who are discontinued from the study before intake of the IP will be replaced.

The sequence of treatments (Part A) is described in Table 5.

Table 5 Treatment order (Part A)

Period 1 (Visit 2)	Period 2 (Visit 3)	Period 3 (Visit 4)
Treatment A[a]	Treatment B[a]	Treatment C[a]

[a] Treatment A: 20-mg AZD9291 capsule (fasted); Treatment B: 20-mg AZD9291 solution (fasted); Treatment C: 20-mg AZD9291 tablet (fasted).

The sequence of treatments (Part B) is described in Table 6.

Table 6 Treatment order (Part B)

Period 1 (Visit 2)	Period 2 (Visit 3)
Treatment A[a]	Treatment B[a]

[a] Treatment A: 20-mg AZD9291 (To be determined [TBD] if tablet or capsule [fasted]); Treatment B: AZD9291 (TBD if tablet or capsule [fed]).

Volunteer numbers will be assigned strictly sequentially as the volunteers become eligible.

5.3 Procedures for handling subjects incorrectly enrolled or initiated on investigational product

Volunteers who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive IP. There can be no exceptions to this rule.

Where volunteers that do not meet the selection criteria are incorrectly started on treatment, or where volunteers subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Clinical Pharmacology Alliance (CPA) Physician and the Investigator regarding whether to continue or discontinue the volunteer from the study.

The AstraZeneca CPA Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the volunteer should be discontinued from the study.

5.4 Blinding and procedures for unblinding the study (not applicable)

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
AZD9291	Powder for solution, 40-mg	AstraZeneca
AZD9291	Capsule, 20-mg	AstraZeneca
AZD9291	Tablet, 20-mg	AstraZeneca

AstraZeneca will provide the capsules and tablets in high-density polyethylene bottles with child-resistant closures. AstraZeneca will provide the powder for solution in glass bottles with child-resistant closures. Handling instructions detailing how the solutions are to be prepared will be provided to the study center by AstraZeneca.

Formulation numbers and batch numbers will be presented in the Clinical Study Report (CSR).

5.5.2 Doses and treatment regimens

Part A

Volunteers will receive a single, oral dose of the following under fasted conditions:

- Treatment A: 20-mg AZD9291 capsule on Day 1 of Period 1
- Treatment B: 20-mg AZD9291 solution on Day 1 of Period 2
- Treatment C: 20-mg AZD9291 tablet on Day 1 of Period 3

The duration of each treatment period is 21 days and there is a washout period of at least 21 days between doses.

Each administration of the IP will be taken after a 10-hour fast orally with 240 mL of water with the volunteer in an upright position. The dose will be administered either as a capsule (which must be swallowed whole and not chewed, crushed, or divided), as a solution or as a tablet (which must be swallowed whole and not chewed, crushed, or divided). On administration of the solution, the 240 mL water includes that used to rinse the dosing container to ensure no residual dose remains. Volunteers will remain fasting from food after dosing until 4 hours postdose. Apart from the water given at dosing, volunteers will be fasted from water from 1 hour prior to dosing until 1 hour after dosing.

Part B

Volunteers will receive a single, oral dose of the following:

- Treatment A: 20-mg AZD9291 (capsule or tablet) on Day 1 of Period 1 under fasted conditions
- Treatment B: 20-mg AZD9291 (capsule or tablet) on Day 1 of Period 1 under fed conditions

The duration of each treatment period is 21 days and there is a washout period of at least 21 days between doses.

In Period 1 (fasted), IP will be taken orally after a 10-hour fast with 240 mL of water with the volunteer in an upright position. Volunteers will remain fasting from food after dosing until

4 hours postdose. Apart from the 240 mL water given at dosing, volunteers will be fasted from water from 1 hour prior to dosing until 1 hour after dosing.

In Period 2 (fed) following an overnight fast of at least 10 hours, volunteers should begin the recommended meal 30 minutes prior to administration of the IP. The breakfast should be consumed within 30 minutes and volunteers must eat the entire meal. A single 20-mg AZD9291 dose will be administered 30 minutes after the start of the meal.

Volunteers will remain fasting from food after dosing until 4 hours postdose. Apart from the 240 mL water given at dosing, volunteers will be fasted from water from 1 hour prior to dosing until 1 hour after dosing.

The high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories [kcal]) breakfast will include the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces (approximately 113 g) of hash brown potatoes, and 8 ounces (approximately 240 mL) of whole milk. This meal derives approximately 150, 250, and 500 to 600 kcal from protein, carbohydrate, and fat, respectively (FDA 2002).

The start and stop date/time of the breakfast as well as the percentage of the meal consumed will be recorded in the eCRF.

5.5.3 Labeling

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

5.5.4 Storage

All IP should be kept in a secure place under appropriate storage conditions. The IP label specifies the appropriate storage.

5.6 Concomitant and post-study treatment(s)

No concomitant prescribed or nonprescribed medication (including over-the-counter remedies, high-dose or ‘mega’ vitamins, herbal medications and mineral supplements, or medicines purchased via the Internet) will be allowed from at least 4 weeks prior to the first dose of AZD9291 and continuing until the poststudy medical examination. Paracetamol (acetaminophen) 1 gram, every 6 hours, up to a maximum daily dose of 4 g is permitted; however the Investigator should be informed so this can be documented.

Other medication, which is considered necessary for the volunteer’s safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the electronic Case Report Form (eCRF).

5.7 Treatment compliance

The date and time of administration of all IP should be recorded in the appropriate sections of the eCRF. In order to ensure treatment compliance, the administration of IP will be performed under the supervision of the study personnel.

Accountability

The IP provided for this study will be used only as directed in this CSP. The study personnel will account for all IP dispensed to and returned from the volunteer.

Study site personnel will account for all IP received at the site, all unused IP, and for appropriate destruction of unused IP. Destruction must not take place unless the responsible person at AstraZeneca has approved it. Certificates of delivery, destruction, and return should be signed.

5.8 Discontinuation of investigational product

Volunteers may be discontinued from IP in the following situations:

- Volunteer decision. The volunteer is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse event
- Severe noncompliance to CSP as judged by the Investigator or AstraZeneca
- Incorrectly enrolled volunteer
- Volunteer is lost to follow-up.
- Development of any study-specific safety criteria for discontinuation (see Sections 6.3.5 and 6.3.9):
  - Corneal ulceration
  - Alanine aminotransferase > 3 times the upper limit of normal (ULN), or 120 U/L, or increase from baseline > 50 U/L
  - Alkaline phosphatase > 2 times the ULN
  - Bilirubin > 2 times the ULN, 50 μmol/L, or increase from baseline > 24 μmol/L
- Exceeding PK limit criteria:
  - Individual measurement of AZD9291 $AUC_{(0-72)}$ greater than 7005 nM·h

- If an individual measurement of AZD9291 $AUC_{(0-72)}$ is 5000 nM·h or more, then the Investigator in consultation with the sponsor will decide whether the volunteer may continue in the study or be withdrawn.

- If the group mean $AUC_{(0-72)}$ exceeds 5230 nM·h in Period 1 (either Part A or Part B), then no volunteers will proceed to Period 2.

- If the group mean $AUC_{(0-72)}$ exceeds 5230 nM·h in Period 2, then volunteers with the highest exposures will be withdrawn from the study until the group mean $AUC_{(0-72)}$ is below 5230 nM·h before Period 3 commences.

If all subjects are not enrolled on the same day, the evaluation of PK results will take place separately for each subgroup.

Procedures for discontinuation of a subject from investigational product

A volunteer that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Sections 6.3.3 and 6.3.4).

If a volunteer is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Volunteers are at any time free to withdraw from study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such volunteers will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (See Sections 6.3.3 and 6.3.4).

Withdrawn volunteers will be replaced if they are withdrawn from the study before intake of IP or if they are removed from the study for reaching the PK limits (see Section 5.8) during Periods 1 or 2 only.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below. The study plan and timing of these assessments are detailed in Table 1 and Table 3. Additional assessments may be performed if the Investigator considers them necessary for volunteer safety.

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence at a particular time point is:

1. 12-lead ECG

2. Vital signs (blood pressure and pulse rate)

3. Pharmacokinetic blood sample (Note: PK sampling must be performed as close as possible to the scheduled time)

4. Clinical laboratory testing

Apart from the predose PK blood sampling, which should occur within 30 minutes prior to dosing, other predose assessments may be performed up to 60 minutes prior to administration of the IP. Additional details on the collection of blood samples will be provided in the Laboratory Manual.

6.1 Recording of data

The Investigator will ensure that data are recorded on the eCRF as specified in the CSP and in accordance with the instructions provided. For this study, volunteer data will be collected by electronic data capture (EDC). Where EDC is not possible, the source data will be captured on paper.

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 (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRF will be archived at the study site.

Electronic Data Capture

Clinical data (including AEs and concomitant medications) will be entered into a 21 Code of Federal Regulations Part 11-compliant data management system provided by
The data system includes password protection and internal quality checks, such as automatic verification range checks, to identify data that appear to be out of the specified ranges. Programmed edit specifications identify discrepancies in the data which may be addressed by the site.

Data are collected electronically for each study volunteer by an EDC data management and workflow system. It is the Investigator's responsibility to ensure the accuracy, completeness, and timelines of the data captured in the data management system. Data are directly captured at the bedside where the data are collected electronically from instrumentation, or data are entered through touch-pad entry screens by the site personnel at the bedside. Data for AEs (including serious AEs [SAEs]) are recorded on paper source forms and entered into the EDC system. Investigators and study personnel will be responsible for the data capture and will respond to queries within the EDC data management system. For volunteers who discontinue or terminate from the study, the site personnel will complete a termination screen that clearly documents the reason for termination on the end-of-study screens.

Electronic data collection is real-time data collection and reflects the latest observations on the volunteers participating in the study. Correction of any data errors and other such changes are made by changing or updating the data in the system which also requires the entry of the user's name and a password for each change to be captured in the electronic audit trail.

When data have been entered, reviewed, edited, and source data verification performed by the AstraZeneca representative, the data will be frozen to prevent further editing.

6.2 Data collection at enrollment and follow-up

6.2.1 Enrollment procedures

Each volunteer will undergo screening in the 28 days prior to dosing. This will consist of:

- Obtaining written informed consent prior to starting any study-specific procedures
- Recording demographic data – date of birth, sex, race, and ethnicity
- Height, weight, and calculation of BMI
- A standard medical, medication, and surgical history with review of the inclusion and exclusion criteria with the volunteer
- A complete physical examination
- Habits of nicotine and alcohol use
- Vital signs
- Recording a resting 12-lead paper ECG
- A blood sample for routine clinical chemistry and hematology as well as a screen for hepatitis B surface antigen, antibodies to hepatitis C virus, and antibodies to HIV
- A urine sample for routine urinalysis and drugs of abuse screen (including cotinine and excluding alcohol)
- Assessment of any SAEs
- Assessment of any concomitant medication.

6.2.2 Follow-up procedures

A medical examination will be performed 21 to 28 days after the last dose of AZD9291 which would be the final follow up visit for each of Part A and Part B. This will be similar to the one performed at the pre-entry visit and will include a complete physical examination, assessment of any AEs or concomitant medication, vital signs, a resting 12-lead ECG, and safety laboratory tests. However, the follow-up visit may coincide with the Period 3 Day 22 assessment (Part A) or with the Period 2 Day 22 assessment (Part B); in this case, only 1 set of assessments is needed.

6.3 Safety

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

6.3.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and nonserious AEs.

6.3.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the volunteer or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix B to this CSP.

6.3.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from the first administration of IP throughout the treatment period and including the follow-up period (Visit 5, Part A; Visit 4, Part B). Serious AEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the volunteer's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without

further recording in the eCRF. AstraZeneca retains the right to request additional information for any volunteer with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity, rated according to the following 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 IP (yes or no)
- Action taken with regard to IP
- Whether AE caused volunteer's withdrawal from study (yes or no)
- Outcome.

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- 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 in relation 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 6.3.2. 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 an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

The Investigator will assess causal relationship between IP and each AE, 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 IP?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. 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 B to this CSP.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the volunteer or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. 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.

Adverse Events based on examinations and tests

The results from CSP-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in CSP-mandated laboratory values, vital signs, or other safety variables should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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 (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AE(s).

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.

NB. Cases where a volunteer shows an aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) ≥3 times the ULN **or** total bilirubin ≥ 2 times the ULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

6.3.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators 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 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 AEs 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 immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the study plan and time schedule (see Table 1 and Table 3). Safety laboratory assessments will be performed the site's local accredited laboratory unless stated otherwise.

The laboratory variables to be measured are presented in Table 7.

Table 7 Laboratory safety variables

Clinical chemistry	Hematology	Urinalysis
Serum (S)-Albumin	Blood (B)-Hemoglobin	Urine (U)-Glucose
S-ALT	B-Hematocrit	U-Protein
S-AST	B-Erythrocyte	U-Blood

Table 7 Laboratory safety variables

Clinical chemistry	Hematology	Urinalysis
S-Alkaline phosphatase	B-Leukocyte	U-Specific gravity
S-Bilirubin, total	B-Leukocyte differential count (absolute)	U-pH
S-Calcium, total	Neutrophils	
S-Creatinine	Lymphocytes	
S-Glucose	Monocytes	
S-Magnesium	Basophils	
S-Potassium	Eosinophils	
S-Sodium	B-Platelet count	
S-Urea	B-Reticulocyte count	

ALT Alanine aminotransferase, AST Aspartate aminotransferase

Blood will be tested for hepatitis B surface antigen, antibodies to hepatitis C virus, and antibodies to HIV at the screening visit.

Urine will be tested at the screening visit and Day -1 of each treatment period (and randomly throughout the study at the discretion of the Investigator) for cotinine and the following drugs of abuse: methadone, cannabis, cocaine, benzodiazepines, amphetamine, methamphetamines (including ecstasy), opiates, barbiturates, phencyclidine, and tricyclic antidepressants. The test will be performed at the study unit. If a volunteer tests positive for drugs of abuse, a retest may be performed, and they may be excluded from entering or continuing in the study, as judged by the Investigator.

If any laboratory values outside the laboratory's reference limits are suspected to be of clinical significance, as judged by the Investigator and/or AstraZeneca, the sampling will be repeated. Volunteers in whom the suspected clinical significance is confirmed at repeated sampling will either not be included or, if already included (started treatment), the deviating values will be monitored until normalization or for as long as the Investigator considers necessary.

Any volunteer developing the following laboratory values will be discontinued from study immediately and follow-up samples taken until resolution:

- ALT >3 times ULN or 120 U/L (whichever is lowest) or increase >50 U/L from baseline
- Alkaline phosphatase >2 times ULN
- Bilirubin >2 times ULN or 50 μmol/L (2.9 mg/dL) (whichever is lowest) or increase >24 μmol/L (1.4 mg/dL) from baseline

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

For blood volume see Section 7.1.

6.3.6 Physical examination

Physical examinations will be performed at screening and follow-up. A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculoskeletal (including spine and extremities), and neurological systems. Brief physical examinations may be performed at check-in to each study period.

6.3.7 Resting 12-lead electrocardiogram

Twelve-lead ECGs will be recorded in accordance with local procedure at the time points indicated in the study plan (Table 1, Table 2, Table 3 and Table 4).

Electrocardiograms will be recorded in the supine position after the volunteer has rested in this position for at least 10 minutes. Any abnormalities (including QTc values) should be reviewed by a cardiologist or an appropriately qualified person. The overall evaluation (normal/abnormal) and relevant variables (PR, RR, QT, and QRS) will be transcribed to the eCRF. If the ECG is abnormal, the abnormality and its clinical significance will also be specified in the eCRF.

The print-out of the ECG is to be signed, dated, and filed in the Investigator's Study File along with a signed and dated copy (if the print-outs are not on archive-quality paper).

6.3.8 Vital signs

Supine blood pressure and pulse rate will be measured using standard equipment after 10 minutes rest on a bed. For timings of assessments refer to the study plan (Table 1, Table 2, Table 3 and Table 4).

6.3.9 Other safety assessments

A baseline ophthalmological examination will be performed at the time indicated in the study plan (Table 1 and Table 2), including assessments of best corrected visual acuity and slit lamp fundoscopy.

An ophthalmological examination should be performed if the volunteer reports eye symptoms such as dry eyes, grittiness, or irritation during the study. In case of clinically relevant ophthalmological abnormalities, an additional full examination will be performed. Any corneal changes must be monitored frequently, with therapeutic intervention as appropriate until resolution. Any abnormalities elicited will be recorded as an AE.

Any volunteer who develops corneal ulceration will be immediately withdrawn from study participation and the abnormality followed up by an ophthalmologist until resolution.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Venous blood samples (approximately 2 mL using dipotassium ethylenediaminetetraacetic acid [K_2 EDTA] as an anticoagulant) for determination of concentrations of AZD9291 and its metabolites (AZ5104 and AZ7550) in plasma will be taken at the times presented in Table 3and Table 4.

Immediately after the sample is drawn, gently invert the tube 180° and back, 8 to 10 times. Separate the plasma from the cells by centrifuging at 1500 g for 15 minutes. The blood should be centrifuged and plasma separated within 1 hour of the blood draw. The plasma should then be frozen within 30 minutes of being separated from the blood cells.

The plasma should be equally split into 2 aliquots. In case there is a very limited amount of plasma generated, at least 1 tube must have 0.25 mL to be able to complete the analysis. Freeze immediately at -70°C after collection.

Sample tubes and aliquots will be labelled with the study number, volunteer number, treatment period/visit number, and time point.

Samples for determination of AZD9291 (and metabolite) concentrations in plasma will be analyzed by on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

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

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

Samples for determination of AZD9291 (and metabolite) concentrations in plasma will be analyzed by on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest (ie, AZD9291 and its metabolites AZ5104 and AZ7550) at the time of receipt by the bioanalytical laboratory will be analyzed.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each volunteer in this study is as follows:

Table 8 Volume of blood to be drawn from each subject (Part A)

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	8.5	16	136
	Hematology	4	16	64
	Serology	8.5	1	8.5
Pharmacokinetic		2	57	114
Discard volume[a]		1	39	39
Total				361.5

[a] If using an indwelling catheter, 1.0 mL of blood will be removed to flush the catheter prior to each serial PK sample collection time point (up to 48 hours of inpatient sampling only).

Table 9 Volume of blood to be drawn from each subject (Part B)

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	8.5	14	119
	Hematology	4	14	56
	Serology	8.5	1	8.5
Pharmacokinetic		2	38	76
Discard volume[a]		1	38	38
Total				297.5

[a] If using an indwelling catheter, 1.0 mL of blood will be removed to flush the catheter prior to each serial PK sample collection time point (up to 48 hours of inpatient sampling only).

7.2 Handling, storage, and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

Biological samples for future research can be retained on behalf of AstraZeneca for a maximum of 15 years following the last volunteer's last visit in the study. The results from future analysis will not be reported in the CSR but separately in a Scientific Report.

Pharmacokinetic samples

Samples will be disposed of after the CSR has been finalized, unless retained for future analyses, see below.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites, and/or to investigate reproducibility of incurred samples, and/or to investigate stability of incurred samples. Any results from exploratory analyses to identify drug metabolites will not be reported in the CSR but will be reported separately elsewhere. Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report. Samples will be retained for a maximum of 2 years following the finalization of the CSR.

7.3 Labeling and shipment of biohazard samples

The Investigator will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the volunteer unless agreed with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

7.4 Chain of custody of biological samples

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

The Investigator keeps full traceability of collected biological samples from the volunteers while in storage at the center 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 system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a volunteer withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, 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 volunteer is withdrawn from further study participation.

The Investigator:

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

AstraZeneca ensures the laboratory(ies) 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.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 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 International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 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.

8.3 Ethics and regulatory review

An Institutional Review Board (IRB) should approve the final CSP, including the final version of the informed consent form and any other written information and/or materials to be provided to the volunteers. The Investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any volunteer into the study.

The IRB should approve all advertising used to recruit volunteers 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 CSP should be reapproved by the IRB annually.

Before enrollment of any volunteer into the study, the final CSP, 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, IRBs, and Investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

The Investigator is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The Investigator will:

- Ensure each volunteer is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each volunteer is notified that they are free to discontinue from the study at any time
- Ensure that each volunteer is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each volunteer 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 volunteer
- Ensure that any incentives for volunteers who participate in the study as well as any provisions for volunteers harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Investigator and AstraZeneca.

If there are any substantial changes to the CSP, then these changes will be documented in a CSP amendment and where required in a new version of the CSP (Revised CSP).

The amendment is to be approved by the relevant IRB and if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for revised CSPs.

AstraZeneca will distribute any subsequent amendments and new versions of the CSP to the Investigator. For distribution to the IRB see Section 8.3.

If a CSP amendment requires a change to a center's informed consent form, AstraZeneca and the center's IRB are to approve the revised informed consent form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IRB.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB may perform audits or inspections at the center, 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, analyzed, and accurately reported according to the CSP, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Prestudy activities

Before the first volunteer is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate volunteers for the study
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to CSP adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca and the Investigator.

9.2 Training of study site personnel

Before the first volunteer is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

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

9.3 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 CSP, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that IP accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the volunteer's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating volunteers. This will require direct access to all original records for each volunteer (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the volunteer's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the volunteer.

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

Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The Investigator at the center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and

the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of volunteers and in all other respects, not relating to study conduct or treatment of volunteers, the terms of the CSA shall prevail.

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

Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

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

The study is expected to start in Quarter 3 2013 and to end by Quarter 1 2014.

The study may be terminated at the center 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 AZD9291.

10. DATA MANAGEMENT BY QUINTILES

Data management will be performed by . A 21 Code of Federal Regulations part 11-compliant EDC system will be used for this study. Electronic CRFs will be produced by for each volunteer.

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 AstraZeneca Drug Dictionary. All coding will be performed by .

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.

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.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

11.1.1 Calculation of change from baseline

Change-from-baseline variables will be calculated for the safety variables listed below, as the posttreatment value minus the value at baseline. The baseline values will be as follows:

- Clinical laboratory tests: Day -1 of Period 1
- Vital signs: Day 1 predose of Period 1
- ECG: Day 1 predose of Period 1

If a volunteer is missing the baseline collection, the previous nonmissing evaluation will become the baseline value. If no baseline or previous-to-baseline evaluations exist, then the baseline value will be treated as missing and no change-from-baseline value will be calculated.

11.1.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuation of IP due to AEs. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory, vital sign, and other safety data will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

11.2 Calculation or derivation of pharmacokinetic variables

The PK analyses of the plasma concentration data for AZD9291 and its metabolites will be performed at . standard operating procedures (SOPs) and Work Instructions will be used as the default methodology if not otherwise specified.

The actual sampling times will be used in the final PK parameter calculations. Nominal sampling times will be used for interim PK parameter calculations.

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Professional Version 6.3, or higher, and/or SAS® Version 9.2, or higher . All descriptive and inferential statistical computations will be performed using SAS Version 9.2, or higher.

Where possible the following PK parameters will be determined for AZD9291 and its metabolites, AZ5104 and AZ7550, as appropriate:

- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal rate constant (λ_z)
- Terminal half life ($t_{1/2,\lambda z}$)
- Lag time before observation of quantifiable analyte concentrations in plasma (t_{lag})
- Area under the plasma concentration-time curve from zero to the time of the last measurable concentration [$AUC_{(0-t)}$]
- Area under the plasma concentration-time curve from zero to 72 hours [$AUC_{(0-72)}$]
- Area under the plasma concentration-time curve from zero to infinity (AUC)
- Apparent plasma clearance (CL/F) for AZD9291 only
- Apparent volume of distribution (V_z/F) for AZD9291 only
- Parent to metabolite ratio (calculated as AZD9291/AZ5104 and AZD9291/AZ7550 for both C_{max} and AUC). These ratios will be adjusted for differences in molecular weight (AZD9291 = 499.62; AZ5104 and AZ7550 = 485.59).

Additional parameters may also be calculated, if appropriate.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 General principles

The analysis of data will be based on different subsets according to the purpose of analysis, ie, for safety and PK, respectively.

12.1.2 Safety analysis set

All volunteers who received at least 1 dose of IP and for whom any postdose data are available will be included in the safety population.

12.1.3 Pharmacokinetic analysis set

The PK analysis set will be a subset of the safety analysis set and will include only volunteers who receive at least 1 dose of IP and have at least 1 postdose PK measurement without important CSP deviations or significant events thought to significantly affect the PK (eg, volunteer vomited at or before 2 times median t_{max}, wrong dose administered, prohibited concomitant medication, etc).

12.2 Methods of statistical analyses

12.2.1 General principles

The PK and safety summaries, individual figures, and data listings, as well as the statistical analysis of PK variables will be the responsibility of the study biostatistician at using SAS® Version 9.2 or higher and, where appropriate, additional validated software.

Quantitative continuous variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum values. Additionally, for PK parameters, (except for t_{max}), geometric means and geometric coefficient of variation (CV) will be reported. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The CV is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale. Mean, SD, geometric mean, and CV will not be calculated for t_{max}.

Categorical variables (eg, gender) will be summarized in frequency tables (frequency and proportion of volunteers in the analysis set).

In general, descriptive statistics will follow the rounding convention in SOPs.

Baseline characteristics will be summarized across all volunteers.

12.2.2 Subject characteristics

Continuous variables will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) and categorical variables will be summarized in frequency tables (frequency and proportion) for all volunteers overall.

12.2.3 Safety

All safety data (scheduled and unscheduled) will be presented in the data listings.

Safety variables (eg, clinical laboratory values and vital signs) will be reported to the same precision as the source data. Derived variables will be reported using similar precision to those from which they were derived (eg, QTcF derived from QT interval).

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics by scheduled time point, but will be included in data listings. All AEs and clinical laboratory outliers that occur following the first dose of study medication will be included in the tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations.

All available data from volunteers in the safety analysis set will be included in the safety analyses. No adjustment or imputation will be utilized for missing values or for volunteers who withdraw prior to completing the study, neither will analyses be restricted to volunteers with complete data.

Adverse events beginning at or after the first dose of IP will be summarized by preferred term and system organ class using MedDRA vocabulary by treatment and across all treatments. Adverse events that begin during the washout periods will be assigned to the last treatment received prior to the onset of the AE. Furthermore, listings of SAEs and AEs that lead to withdrawal will be made and the number of volunteers who have any AEs, SAEs, AEs that lead to withdrawal, and AEs with severe intensity will be summarized.

Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs, and physical and ophthalmologic examination findings will be presented, as appropriate. All continuous safety data will be summarized by treatment and/or across all treatments, as appropriate, for the observed value at each scheduled assessment and for the corresponding change from baseline. For clinical laboratory tests, listings of values for each volunteer will be presented with abnormal or out-of-range values flagged. Clinical laboratory data will be reported in Système International units in the CSR.

12.2.4 Pharmacokinetics

The PK blood sample collection times, as well as derived sampling time deviations, and plasma concentrations of each analyte will be listed for all volunteers. Plasma concentrations will be summarized by treatment using descriptive statistics (eg, n, arithmetic mean, SD, minimum, median, maximum, geometric mean, and CV). Individual concentration versus time profiles will be prepared.

Plasma concentrations that are below the lower limit of quantitation (LLOQ) will be handled as follows:

- At a time point where less than or equal to 50% of the values are below the limit of quantitation (BLQ), all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated.

- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean and CV will be set to Not Determined. The maximum value will be reported from the individual data, and the minimum and median will be set to BLQ.

- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable will be reported for SD and CV, and BLQ will be reported for mean, geometric mean, minimum, median, and maximum.

- The number of BLQ values (n below LLOQ) will be reported for each time point.

Plasma parameters for all analytes will be summarized by treatment using descriptive statistics (eg, n, arithmetic mean, SD, minimum, median, maximum, geometric mean, and CV). For t_{max}, only n, median, minimum, and maximum will be reported. Individual and geometric mean C_{max}, $AUC_{(0-t)}$, and AUC will be presented graphically.

Data from volunteers excluded from the PK analysis set will be included in the data listings, but not in the summaries.

Part A

The bioavailability of the 20-mg solution and that of the 20-mg tablet relative to the 20-mg capsulewill be assessed using the primary PK variables AUC and/or $AUC_{(0-t)}$ and C_{max} of plasma AZD9291. These endpoints will be natural log-transformed and analyzed using a linear mixed effects model with fixed effect for treatment and random effect for subject. The difference in treatment (formulation) means will be determined along with its associated 90% confidence interval (CI) and back-transformed to give an estimate of the relative bioavailability. The results of this analysis will be presented in terms of geometric means for both treatments, the relative bioavailability (ie, the ratio of the treatment formulation geometric means) and its 90% CI.

The above treatment comparisons will also be performed for t_{max} as secondary analyses. Nonparametric methods will be used to compute median t_{max} for each treatment, median t_{max} difference, and associated 90% CI for the median difference. The data will be analyzed by a Wilcoxon Signed-Rank Test. The 90% CI will be calculated using the method of Hahn and Meeker (Hahn and Meeker 1991).

Similar statistical analyses may be performed for AZ5104 and AZ7550 if appropriate.

For the bioavailability analyses, if there are more than 20% healthy volunteers whose AUCs are not calculable for either treatment due to large residual area (>20%), Rsq <0.80 or any other reason, $AUC_{(0-t)}$ will also be analyzed statistically and presented in the same way as AUC. Otherwise, $AUC_{(0-t)}$ will not be statistically analyzed.

All volunteers receive treatments in the same order and so results may be confounded with undetectable period effects, which will be considered in interpretation.

Part B

For the investigation of the effect of food, the primary PK variables AUC and/or $AUC_{(0-t)}$ and C_{max} of plasma AZD9291 will be analyzed. These endpoints will be natural log-transformed and analyzed using a linear mixed effects model with fixed effect for treatment and random

effect for subject. The difference in treatment means will be determined along with its associated 90% CI and back-transformed to give an estimate of the effect of food on the exposure of AZD9291. The results of this analysis will be presented in terms of geometric means for both treatments, the effect of food on the exposure of AZD9291 (ie, the ratio of the treatment geometric means) and its 90% CI. Similar statistical analyses may be performed for AZ5104 and AZ7550, if appropriate.

For the investigation of the effect of food, if there are more than 20% healthy volunteers whose AUCs are not calculable for either treatment due to large residual area (>20%), Rsq <0.80 or any other reason, $AUC_{(0-t)}$ will also be analyzed statistically and presented in the same way as AUC. Otherwise, $AUC_{(0-t)}$ will not be statistically analyzed.

All volunteers receive treatments in the same order and so results may be confounded with undetectable period effects, which will be considered in interpretation.

12.3 Determination of sample size

No formal sample size calculation has been performed as the number of volunteers in each sequence has been chosen to ensure sufficient data are collected while minimizing exposure to a new drug. There are no within-subject data available to enable an estimate of sample size based on within-subject variability. Based on consideration of information provided in Food and Drug Administration guidances (FDA 2002, FDA 2003), the sample size has been selected with the aim of ensuring a minimum of 12 evaluable volunteers complete for both study parts.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.4**

In the case of a medical emergency, the Investigator may contact the Principal Physician. If the Principal Physician is not available, the Investigator should contact the CPA Program Director.

Name	Role in the study	Address & telephone number

Name	Role in the study	Address & telephone number

13.2 Overdose

A dose of AZD9291 in excess of that planned in this CSP will constitute an overdose. There is currently no known antidote to AZD9291 and treatment of an overdose should be supportive for the underlying symptoms. To date, no subject has experienced an overdose with AZD9291.

Cases of overdose will be reported as follows:

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then Investigators 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 an SAE, standard reporting timelines apply, see Section 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

Women are not allowed to be included in this study.

13.3.2 Paternal exposure

Pregnancy of the volunteers' partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal

birth, or congenital abnormality) from the date of dosing until 4 months after dosing should be reported to AstraZeneca and if possible be followed up for its outcome.

14. LIST OF REFERENCES

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