Clinical Study Protocol

Drug Substance AZD9291

Study Code D5160C00010

Edition Number 1

A Phase I, Fixed Sequence, Open-label, Study to Assess the Pharmacokinetics of AZD9291 in Healthy Male Volunteers when a Single Oral Dose of AZD9291 80 mg is Administered Alone and in Combination with Omeprazole

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

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, Fixed Sequence, Open-label, Study to Assess the Pharmacokinetics of AZD9291 in Healthy Male Volunteers when a Single Oral Dose of AZD9291 80 mg is Administered Alone and in Combination with Omeprazole

Principal Investigator

Study center(s) and number of subjects planned

The study will be performed at up to 2 sites in the USA.
and . Approximately 50 healthy volunteers may be enrolled to ensure 40 volunteers complete the study.

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2014	I
Estimated date of last subject completed	Q1 2015	

Objectives

Primary objective

To assess the effect of omeprazole (a proton pump inhibitor) on AZD9291 exposure (maximum plasma concentration [C_{max}] and the area under the plasma concentration-time curve from zero to infinity [AUC]) in healthy male volunteers.

Secondary objectives

To assess the effect of omeprazole on the pharmacokinetics of AZD9291 and metabolites (AZ5104 and AZ7550) in healthy male volunteers.

Safety objective

To examine the safety and tolerability of AZD9291 in combination with omeprazole.

Exploratory objectives

To collect and store an optional pharmacogenetic blood sample from consenting healthy volunteers for future exploratory research into genes/genetic variation that may influence

response (ie, distribution, safety, tolerability and efficacy) to AZD9291. These results will be reported separately from the clinical study report.

Study design

This is a Phase I, open-label, 2-period fixed sequence design study to evaluate the interaction of AZD9291 with omeprazole in approximately 50 healthy, adult male volunteers. The study will be performed at up to 2 sites in the USA.

Volunteers will receive Treatment A in Period 1 and Treatment B in Period 2. The dose of AZD9291 in Period 1 and the dose of AZD9291 in Period 2 will be separated by a washout of at least 21 days (the washout will not be more than 5 weeks).

Treatment A: On Days 1 through 4, omeprazole will be administered in the morning after a 10-hour fast with 240 mL of water 1 hour before eating breakfast. On Day 5, omeprazole will be administered together with AZD9291 with 240 mL of water following an overnight fast of 10 hours and the volunteers will remain fasting from food until 4 hours postdose.

Treatment B: Volunteers will receive AZD9291 in the morning on Day 1 with 240 mL of water following an overnight fast of 10 hours. Volunteers will remain fasting from food after dosing until 4 hours postdose.

The study will consist of up to 15 visits depending on whether the final pharmacokinetic (PK) sample of Period 1 is collected as the predose PK blood sample for Period 2 or whether a separate visit is required for the predose PK blood sample. The screening visit (Visit 1) will be conducted within 28 days of Visit 2. Following full written informed consent, healthy male volunteers will be enrolled into the study and screened for eligibility.

In Period 1 the volunteers will report to the clinic on Day -1 (the day prior to first dose of omeprazole) and remain resident until the 48-hour postdose (relative to AZD9291 administration on Day 5) monitoring and evaluations have been performed on Day 7. The volunteers will return to the clinic for outpatient visits on Days 8, 10, 12, 14 and 19. The Day 26 postdose assessments may be used as the Day -1 predose assessments for Period 2 if an exact 21-day washout is used between AZD9291 doses in Period 1 and Period 2. AZD9291 concentrations obtained over the first 72 hours in Period 1 will be evaluated to determine if exposure limit criteria for a given volunteer and/or a group of dosed volunteers are met or exceeded prior to AZD9291 administration in Period 2. Volunteer(s) exceeding PK exposure limits will be withdrawn.

In Period 2 the volunteers will report to the clinic on Day -1 and remain resident until 48-hour postdose (relative to AZD9291 administration) monitoring and evaluations have been performed on Day 3. The volunteers will return to the clinic for outpatient visits on Days 4, 6, 8, 10, 15 and 22. A final follow-up visit (Visit 15) will be performed 7 to 14 days after the last PK blood sample in Period 2.

Target subject population

Healthy male volunteers aged 18 to 55 years old with body mass index 19 to 30 kg/m^2, and body weight between 50 kg and 100 kg, inclusive.

Investigational product, dosage and mode of administration

AZD9291 80 mg oral tablet.

Non-Investigational product, dosage and mode of administration

Omeprazole 40 mg oral capsule.

Comparator, dosage and mode of administration

None.

Duration of treatment

Period 1: On Days 1 through 4 volunteers will receive a single oral dose of 40 mg omeprazole. On Day 5, the volunteers will receive a single oral dose of 40 mg omeprazole together with a single oral dose of 80 mg AZD9291.

Period 2: On Day 1 volunteers will receive a single oral dose of 80 mg AZD9291.

Outcome variable(s):

- Pharmacokinetics (primary endpoints)

  Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from zero to infinity (AUC) for AZD9291.

- Pharmacokinetics (secondary endpoints)

  Area under the plasma concentration time curve from zero to the last quantifiable time point (AUC_{0-t}), area under the plasma concentration-time curve from zero to 72 hours (AUC_{0-72}), time to reach maximum plasma concentration (t_{max}), lag time (t_{lag}), terminal half-life ($t_{½}$), terminal rate constant (λ_z), apparent plasma clearance (CL/F) and apparent volume of distribution (Vz/F) for AZD9291.

  C_{max}, AUC_{0-72}, AUC_{0-t}, AUC, t_{max}, t_{lag}, $t_{½}$, λ_z, and parent to metabolite ratios for AZ5104 and AZ7550.

- Safety

  Safety parameters include adverse events, vital signs, physical examinations, opthalmologic examinations, electrocardiograms, and clinical laboratory assessments.

Statistical methods

Safety, tolerability, pharmacokinetics, and other outcome variables will be analyzed by descriptive statistics, including listings, summary statistics, and graphs, as appropriate.

Influence of omeprazole on pharmacokinetics of AZD9291 will be assessed statistically using mixed effects models on the log-transformed primary PK parameters [AZD9291 AUC and C_{max}] with treatment as a fixed effect, and subject as a random effect. Estimates of the mean difference between treatments and corresponding 90% confidence intervals will be calculated. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs for AUC and C_{max} will be estimated and presented for each treatment. Absence of an effect of omeprazole on AZD9291 exposure will be concluded if the 90% confidence bounds of the ratios of the geometric least square means for both AUC and C_{max} are entirely contained within 80.00 to 125.00%.

Similar analyses will be performed for the secondary PK parameters AUC and C_{max} of AZ5104 and AZ7550 and $AUC_{(0-72)}$ and $AUC_{(0-t)}$ (all analytes).

For AZD9291 and its metabolites, analyses of t_{max} will be performed using the Wilcoxon Signed Rank Test. The Hodges-Lehmann median estimator of the difference in treatments and 90% CIs will be presented.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event (see definition in Section 6.3.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from zero to infinity
AUC_{0-72}	Area under the plasma concentration time curve from zero to 72 hours
AUC_{0-t}	Area under the plasma concentration time curve from zero to the time of the last quantifiable concentration
BMI	Body mass index
CI	Confidence interval
CL/F	Apparent plasma clearance
C_{max}	Maximum plasma concentration
eCRF	Electronic Case Report Form
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid
EDC	Electronic data capture
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EGFRm+	Epidermal growth factor receptor mutation positive
GCP	Good Clinical Practice
GCV	Geometric coefficient of variation
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen

Abbreviation or special term	Explanation
HIV	Human immunodeficiency virus
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ILD	Interstitial lung disease
IP	Investigational Product
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
QT	Interval on the electrocardiogram representing the duration of depolarisation and repolarisation of the heart
QTc	QT interval corrected for heart rate
SAE	Serious adverse event (see definition in Section 6.3.2).
SAP	Statistical analysis plan
SD	Standard deviation
SUSARs	Suspected Unexpected Serious Adverse Reactions
$t_{½}$	Terminal half-life
TKI	Tyrosine kinase inhibitor
t_{lag}	Lag time before observation of quantifiable analyte concentrations in plasma
t_{max}	Time to reach maximum plasma concentration
ULN	Upper limit of normal
USA	United States of America
V_z/F	Apparent volume of distribution
λ_z	Terminal rate constant

1. INTRODUCTION

1.1 Background

Investigators should be familiar with the current AZD9291 Investigator's Brochure (IB).

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) (Ferlay et al 2010). Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and Le Chevalier 2005). Patients presenting with unselected advanced NSCLC have a median overall survival of 10 to 12 months (Bonomi 2010).

Treatment of advanced NSCLC can be guided by the presence of certain molecular drivers such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase and KRAS mutations. Epidermal growth factor receptor-tyrosine kinase inhibitors (TKIs) are now the established first line therapy in patients with NSCLC known to have activating mutations in EGFR (EGFR mutation positive [EGFRm+]) (NCCN 2012). Patients with EGFRm+ NSCLC who receive EGFR-TKIs have a median overall survival of more than 2 years (Heuckmann et al 2012). The incidence of EGFRm+ NSCLC is approximately 10% to 15% and 30% to 40% of patients in the West and Asia, respectively. Second line therapy for EGFRm+ NSCLC is usually a platinum based chemotherapy. There is no global standard of care for third line therapy, but this may include chemotherapy or single agent therapy with an EGFR-TKI (Becker et al 2011, Langer et al 2012).

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 with a significant selectivity margin over wild-type EGFR. Therefore AZD9291 has the potential to provide clinical benefit to patients with advanced NSCLC harbouring both the single sensitivity mutations and the resistance mutation following prior therapy with an EGFR-TKI. The clinical development programme with AZD9291 will initially assess the safety and efficacy of AZD9291 in patients with advanced NSCLC whose cancers have progressed following an EGFR-TKI regimen (with or without additional chemotherapy regimens), as they currently represent a major unmet medical need population. Importantly, preliminary data from an ongoing Phase I study (D5160C00001) in this patient population has demonstrated good evidence of efficacy, while treatment with AZD9291 has been well tolerated across a range of doses (refer to the latest edition of the IB for further details) (Ranson et al 2013).

Pharmacokinetic (PK) data show that AZD9291 was slowly absorbed following oral dosing, with patients and healthy volunteers generally showing a lag time of up to 4 hours in the

AZD9291 plasma concentration versus time profile following single dose administration. Following multiple-dose administration, AZD9291 steady state appeared to be achieved by 22 days of dosing. The geometric mean accumulation of AZD9291 in the plasma was approximately 4.5 fold after 22 days of dosing the capsule and 3.1 fold after 22 days of dosing the tablet. Accumulation of AZD9291 appears to be consistent with the dosing frequency and observed apparent mean (min-max) terminal half-life ($t_{1/2}$) of 55.06 (29.6 – 145) and 49.61 (38.9 – 73.1) hours in patients after dosing of capsules and tablets respectively.

1.2 Rationale for conducting this study

The primary objective of this study is to investigate the effect of coadministration of omeprazole, a proton pump inhibitor, on exposure (maximum plasma concentration [C_{max}] and the area under the plasma concentration-time curve from zero to infinity [AUC]) to AZD9291 in healthy male volunteers. AZD9291 exhibits pH-dependent solubility and it is possible that coadministration of AZD9291 with proton pump inhibitors could cause a decrease in the absorption of AZD9291 and, therefore, the plasma concentrations of AZD9291. The data from this study will be used to derive label text to advise patients about taking AZD9291 and antacids concomitantly in normal clinical practice.

1.3 Benefit/risk and ethical assessment

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.

1.3.1 Emerging safety profile with AZD9291

This study is robustly designed to assess the primary objective while minimising the number of healthy volunteers exposed to AZD9291. AstraZeneca considers that AZD9291 continues to demonstrate an overall acceptable benefit-risk balance to support its further clinical development. Pre-clinical and emerging clinical tolerability data from patients indicate that AZD9291 is generally well tolerated by patients with advanced NSCLC. Importantly, preliminary data from an ongoing Phase I study (D5160C00001) in this patient population has demonstrated AZD9291 to be well tolerated, with good evidence of efficacy (Ranson et al 2013). Of the 174 patients that received at least a single dose of AZD9291 (data cut-off in IB of 19 November 2013), 105/174 (60%) reported any adverse event (AE), with the majority (>55%) being Common Terminology Criteria for Adverse Events (CTCAE) Grade 1. The most common AEs were rash (grouped terms), diarrhoea, pruritis and nausea, with no dose-limiting toxicities reported at any dose in escalation cohorts up to 160 mg (refer to the latest edition of the IB for further information including details of discontinuations, dose reductions, deaths and serious adverse events [SAEs]). All trials of AZD9291 exclude patients with clinically significant toxicities related to prior treatments in addition to specifically excluding patients with a history of interstitial lung disease (ILD) or clinically active ILD as this is an uncommon, but well documented EGFR-related toxicity.

As of 4 August 2014, a total of 32 healthy male volunteers had received a single dose of 20 mg AZD9291(D5160C00005). Preliminary, unvalidated safety data is available for all healthy volunteers in this study. In Part A of the study, 16 volunteers received a single dose of 20 mg AZD9291 capsule followed by a 3-week washout period, then a single dose of 20 mg AZD9291 solution followed by a further 3-week washout period, and then finally a single dose of 20 mg AZD9291 tablet. In Part B of the study, a further 16 volunteers received a single dose of AZD9291 tablet under fasted conditions followed by a 3-week washout, then 14 of these volunteers received a single dose of 20 mg AZD9291 tablet under fed conditions.

In Part A of the study (3 formulation comparison), 10/16 (62.5%) volunteers reported an AE during the 9-week duration of the study, with no SAEs, deaths or AEs leading to discontinuation. Only influenza was reported by more than 1 volunteer (n=3, 19%). No events were considered related to administration of AZD9291.

In Part B of the study (food effect), 6/16 (37.5%) volunteers reported an AE during the 6-week duration of the study, with no SAEs or deaths, and 1 AE leading to discontinuation after the first dosing period (alanine aminotransferase [ALT] increased). One further volunteer was lost to follow up after the first dosing period. Only upper respiratory tract infection was reported by more than 1 volunteer (n=2, 13%). Only 1 event of ALT increased was assessed as causally related to administration of AZD9291, which was an increase to a maximum value of 101 U/L on Day 15 after single dose of AZD9291 with no changes in aspartate aminotransferase (AST), bilirubin or alkaline phosphatase over this period. Other than the single event of ALT increased, no volunteers had any other clinically significant abnormal vital signs, clinical laboratory parameters or changes in electrocardiogram (ECG) parameters, including the QT interval corrected for heart rate (QTc).

1.3.2 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 ILD 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.

1.3.3 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 risk to healthy volunteers is considered low given the limited exposure to 2 single doses of AZD9291 and the close safety monitoring planned during this study.

Further details are provided in the IB.

2. STUDY OBJECTIVES

2.1 Primary objective

To assess the effect of omeprazole (a proton pump inhibitor) on AZD9291 exposure (C_{max} and AUC) in healthy male volunteers.

2.2 Secondary objective

To assess the effect of omeprazole on the PK of AZD9291 and metabolites (AZ5104 and AZ7550) in healthy male volunteers.

2.3 Safety objective

To examine the safety and tolerability of AZD9291 in combination with omeprazole.

2.4 Exploratory objective

To collect and store an optional pharmacogenetic blood sample from consenting healthy volunteers for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD9291. These results will be reported separately from the clinical study report (CSR).

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a Phase I, open-label, 2-period fixed sequence design study to evaluate the interaction of AZD9291 with omeprazole in approximately 50 healthy, adult male volunteers. The study will be performed at up to 2 sites in the USA.

Volunteers will receive Treatment A in Period 1 and Treatment B in Period 2; the dose of AZD9291 in Period 1 and the dose of AZD9291 in Period 2 will be separated by a washout of at least 21 days (the washout will not be more than 5 weeks).

Treatment A: On Days 1 through 4, omeprazole will be administered in the morning after a 10-hour fast with 240 mL of water 1 hour before eating breakfast. On Day 5, omeprazole will be administered together with AZD9291 with 240 mL of water following an overnight fast of 10 hours and the volunteers will remain fasting from food until 4 hours postdose.

Treatment B: Volunteers will receive AZD9291 in the morning on Day 1 with 240 mL of water following an overnight fast of 10 hours. Volunteers will remain fasting from food after dosing until 4 hours postdose.

The omeprazole and AZD9291 will be administered with 240 mL of water in the morning after a 10-hour fast. On Days 1 through 4 in Period 1, volunteers will remain fasting from food for at least 1 hour after omeprazole administration; on Day 5 of Period 1 and Day 1 of Period 2, 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 on each occasion.

The study will consist of up to 15 visits depending on whether the final PK sample of Period 1 is collected as the predose PK blood sample for Period 2 or whether a separate visit is required for the predose PK blood sample. Details and timing of assessments are included in Table 1 and Table 2. The screening visit (Visit 1) will be conducted within 28 days of Visit 2. Following full written informed consent, healthy volunteers will be enrolled into the study and screened for eligibility.

In Period 1 the volunteers will report to the clinic on Day -1 (the day prior to first dose of omeprazole) and remain resident until the 48-hour postdose (relative to AZD9291 administration on Day 5) monitoring and evaluations have been performed on Day 7. The volunteers will return to the clinic for outpatient visits on Days 8, 10, 12, 14 and 19. The Day 26 postdose assessments may be used as the Day -1 predose assessments for Period 2 if an exact 21 day washout is used between AZD9291 doses in Period 1 and Period 2. AZD9291 concentrations obtained over the first 72 hours in Period 1 will be evaluated to determine if exposure limit criteria for a given volunteer and/or a group of dosed volunteers are met or exceeded prior to AZD9291 administration in Period 2. Volunteer(s) exceeding PK exposure limits will be withdrawn.

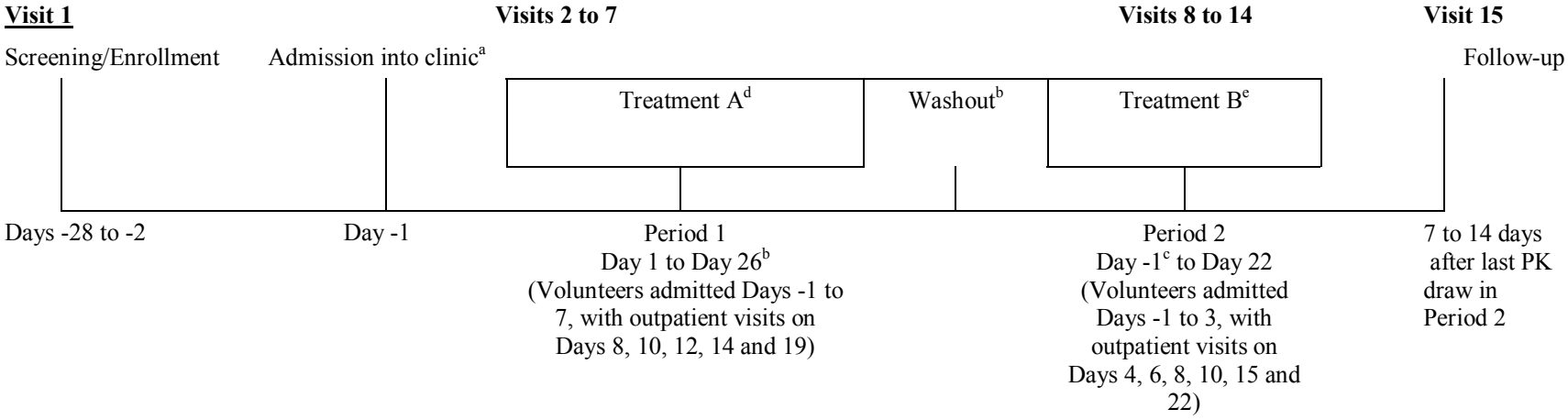
In Period 2 the volunteers will report to the clinic on Day -1 and remain resident until 48-hour postdose (relative to AZD9291 administration) monitoring and evaluations have been performed on Day 3. The volunteers will return to the clinic for outpatient visits on Days 4, 6, 8, 10, 15 and 22. A final follow-up visit (Visit 15) will be performed 7 to 14 days after the last PK blood sample in Period 2.

Safety assessments will include monitoring of AEs and concomitant medications; clinical laboratory tests (hematology, clinical chemistry and urinalysis); measurement of vital signs (supine blood pressure and pulse); ECGs; physical examinations; screening for drugs of abuse, alcohol and cotinine; and ophthalmologic examinations.

Blood samples for the determination of AZD9291 and metabolite (AZ5104 and AZ7550) concentrations will be collected prior to dosing of AZD9291 and serially postdose for 21 days in each treatment period. The PK profile from 0 to 72 hours post AZD9291 dose will be assessed after Period 1 and Period 2 and any volunteer with exposures exceeding the PK limits (Section 5.8) will be withdrawn and may be replaced if required to ensure 40 evaluable volunteers complete. For a volunteer to be evaluable the volunteer must have completed the required PK collections for both study periods without important protocol deviations and events.

The overall study flow chart and study is presented in Figure 1.

Figure 1 Study flow chart



a Volunteers will be admitted into the clinic on Day -1 in both periods.

b Each AZD9291 dosing day will be a minimum of 21 days (504 hours) apart (the washout will not be more than 5 weeks).

c Note where the washout is 21days, Day 26of Period 1will coincide with Day-1 of Period 2 (ie, the 504-hour postdose PK assessment from Period 1 will be collected on Day -1 of Period 2); where the washout is slightly longer volunteers may return to the clinic for an additional visit prior to admission to Period 2 to allow for the collection the PK sample.

d Treatment A: On Days 1 through 4, omeprazole will be administered in the morning after a 10-hour fast with 240 mL of water 1 hour before eating breakfast. On Day 5, omeprazole will be administered together with AZD9291 with 240 mL of water following an overnight fast of 10 hours and the volunteers will remain fasting from food until 4 hours postdose.

e Treatment B: Volunteers will receive AZD9291 in the morning on Day 1 with 240 mL of water following an overnight fast of 10 hours. Volunteers will remain fasting from food after dosing until 4 hours postdose.

Table 1 Study plan

Visit	**1**	**2 to 7**			**8 to 13**		**14**
Assessment	**Screening**	**Period 1**		**≥21 day washout[b]**	**Period 2**		**Follow up visit**
Day	**-28 to -2**	**-1**	**1 to 26**		**-1**	**1 to 22**	
Residential period (Day)		**X**	**1 to 7**		**X**	**1 to 3**	
Nonresidential visit	**X**		**X[l]**			**X[l]**	**X**
Informed consent	X						
Informed consent, pharmacogenetic[m]	X						
Demography	X						
Inclusion/exclusion criteria	X	X					
Medical history	X	X					
Clinical laboratory tests[a]	X	X	X		X	X	X
Serology	X						
Height and body mass index	X						
Weight	X	X			X		
Urinary drug, alcohol breath test, and cotinine screen[c]	X	X			X		
Ophthalmological assessment	X[d]						
Physical examination[e]	X	X			X		X
Vital signs (supine blood pressure and pulse)[f]	X	X	X		X	X	X
12-lead electrocardiogram[g]	X	X	X		X	X	X
AZD9291 administration[h]			X			X	
Omeprazole administration[i]			X				
AZD9291 PK blood sampling[j]			X		X	X	X
Concomitant medications	X	X	X	X	X	X	X
Adverse event recording[k]		X	X	X	X	X	X

a Clinical laboratory tests: Period 1, Days -1, 5 (pre-dose), 7, 12 and 19; Period 2; Days -1, Days 3, 8, 15 and 22.

b Each AZD9291 dosing day will be a minimum of 21 days (504 hours) apart (the washout will not be more than 5 weeks).
c Alcohol will be assessed by an alcohol breath test. Alcohol test at admission to Period 1 and Period 2. The investigator may perform random drugs of abuse and/or alcohol screens at any time during the study at his discretion.
d Ophthalmic examination (best corrected visual acuity and slit-lamp fundoscopy and intraocular pressure measurement) will be conducted at screening or admission prior to Period 1 (this will be considered the baseline value; no need to repeat) and for cause (on occurrence of AE only).
e Complete physical examinations will be performed at the screening and follow-up visits; brief physical examinations will be performed on Day -1 of each treatment period.
f Supine blood pressure and pulse rate will be evaluated after the volunteer has rested in a supine position for at least 10 minutes. If possible, the same arm and equipment should be used for each evaluation (refer to Table 2 for time points).
g ECG will be evaluated after the volunteer has rested in a supine position for at least 10 minutes. Refer to Table 2 for ECG time points.
h AZD9291 administration in Period 1 on Day 5 will be in the morning at the same time as the omeprazole. In Period 2 AZD9291 administration will be in the morning of Day 1.
i Omeprazole will be administered in Period 1 in the morning on Days 1 to 5.
j AZD9291 and metabolite (AZ5104 and AZ7550) PK blood sampling times refer to Table 2.
k Adverse event recording will begin at the volunteer's check-in to the study center in Period 1.
l Nonresidential visits:
Period 1: Days 8, 10, 12, 14 and 19 (note where the washout is 21 days, Day 26 coincides with Day-1 of Period 2).
Period 2: Days 4, 6, 8, 10, 15 and 22.
m The pharmacogenetic informed consent can be signed at any time point during the study, as long as it is signed before the pharmacogenetic blood sampling. The pharmacogenetic blood sample can be collected at any time after the volunteer's eligibility has been confirmed on Day -1 of Period 1.

Table 2 Schedule of assessments for each treatment period								
Treatment A: Study Day (Period 1)	**Treatment B: Study Day (Period 2)**	**Time (hours) relative to AZD9291 dose**	**Supine blood pressure and pulse[b]**	**ECG 12-lead[b]**	**Clinical laboratory tests**	**PK blood**	**Food[c] and fluid**	**Resident**
-1 (Visit 2)	-1[e] (Visit 8)							
1								
5	1	Predose	X	X	X[f]	X[a]		
		Dosing					D	
		1	X	X		X	F	
		2	X	X		X		
		3				X		
		4	X	X		X	M	
		5				X		
		6				X		
		7				X		
		8	X	X		X		
		10				X		
		12	X	X		X		
6	2	24 (Day 2)	X	X		X		
7	3	48 (Day 3)	X	X	X	X		
8[d] (Visit 3)	4[d] (Visit 9)	72 (Day 4)				X		
10[d] (Visit 4)	6[d] (Visit 10)	120 (Day 6)				X		
12[d] (Visit 5)	8[d] (Visit 11)	168 (Day 8)	X	X	X	X		
14[d] (Visit 6)	10[d] (Visit 12)	216 (Day 10)				X		
19[d] (Visit 7)	15[d] (Visit 13)	336 (Day 15)	X	X	X	X		
	22[d] (Visit 14)	504 (Day 22)[e]	X	X	X	X		

D drink, consisting of 240 mL water; F Resumption of free access to fluids; M meal (after all scheduled procedures).

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

b Supine pulse rate and blood pressure measurements and ECG recordings will be measured after 10 minutes bed rest.

c After a minimum of 4 hours fast postdose, meals will be given at same time in each period to volunteers as per clinic standard.

d Nonresidential visit

e If there is a 21 day washout, the 504-hour postdose PK sample from Period 1 may be collected on Day -1 of Period 2. However in case of a slightly longer washout an additional sample will be required and the volunteers may return to the clinic prior to admission to Period 2 to allow for the collection the 504-hour postdose PK sample. If this is necessary a predose sample may be collected prior to dosing in Period 2

f Period 1, Day 5 predose only (ie, sample not required for Period 2, Day 1 predose).

3.2 Rationale for study design, doses and control groups

An 80 mg AZD9291 dose has been selected, since it is the expected therapeutic dose in a patient population and most scientifically relevant to evaluate the effect of changes in gastric pH on AZD9291 pharmacokinetics. Based on preliminary data from Study D5160C00005 in which a 20 mg AZD9291 dose was administered as capsule, solution, and tablet formulations, AZD9291 exposure following an 80 mg dose is not expected to exceed the exposure limits set for healthy volunteers. In case of a potential drug interaction with omeprazole, only a decrease in exposure would be expected based on the physiochemical characteristics of AZD9291. Hence, AZD9291 exposure during coadministration of omeprazole is not expected to exceed the exposure limits.

Pharmacokinetic (PK) data show that AZD9291 was slowly absorbed following oral dosing, with patients (D5160C00001) and healthy volunteers (D5160C00005) generally showing a lag time of up to 4 hours in the AZD9291 plasma concentration versus time profile following single dose administration. In healthy volunteers, after a single oral dose of AZD9291 administered as the capsule, the observed apparent mean (minimum-maximum) terminal half-life ($t_{½}$) was 52.72 (32.5 to 72.0) hours.

After single administration of AZD9291 to healthy volunteers as the capsule, AZ5104 and AZ7550 were slowly produced with the time to reach maximum plasma concentration (t_{max}) ranging from 6 to 72 hours, with a plateau in concentration observed for 3 to 4 days after dosing. The concentration of AZ5104 and AZ7550 then declined monoexponentially: AZ5104 with a similar t½ to AZD9291, and AZ7550 displaying a slightly longer t½. The observed apparent mean (minimum-maximum) t½ was 48.92 (31.1 to 65.2) and 73.21 (52.4 to 105) hours for AZ5104 and AZ7550, respectively. For this reason, a washout of at least 21 days between the AZD9291 doses in Period 1 and Period 2 has been selected for this study (the washout will not be more than 5 weeks).

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.

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.

A sequential design has been selected to optimally manage volunteer visits considering the long treatment period and frequency of outpatient visits for PK collections and to enhance the safety of this study relative to the implemented stopping criteria. Since the study starts with the combination treatment which could result in lower AZD9291 exposure (if an effect is

observed), volunteers showing high exposure may be withdrawn prior to administration of AZD9291 alone which could result in a larger number of volunteers exposed to the investigational product (IP). This study is designed using the principles embodied in the United States Food and Drug Administration guidance on drug interaction studies (Guidance for Industry February 2012).

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the volunteer screening log, of volunteers who enter pre-study 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 the study volunteers must fulfil the following criteria.

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

2. Healthy male volunteers aged 18 to 55 years. (Healthy as determined by medical history, physical examination, laboratory parameters, ECG, and eye examination performed before the first administration of IP.)

3. Body mass index between 19 and 30 kg/m^2, and body weight between 50 kg and 100 kg, inclusive.

4. Veins suitable for cannulation or repeated venepuncture.

5. Volunteers must be willing to use reliable methods of contraception (condom and spermicide), even if 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 and avoid sperm donation for 6 months after the last administration of AZD9291.

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

Optional pharmacogenetic testing inclusion criteria

Provision of signed, written and dated informed consent for optional genetic/biomarker research is required. If a volunteer declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the volunteer. The volunteer will not be excluded from other aspects of the study described in this protocol.

4.2 Exclusion criteria

Volunteers must not enter 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 (HBsAg), 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 in Period 1 or Period 2.

14. History of alcohol abuse or excessive intake of alcohol, defined as regular weekly intake of greater than 21 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. History of hypersensitivity to omeprazole, its excipients, or drugs with a similar chemical structure or class.

17. Use of any prescribed or nonprescribed medication, including drugs with hepatic enzyme-altering properties, such as St John's Wort, antacids, analgesics, herbal remedies, vitamins, and minerals during the 4 weeks (or longer depending on the medication's half-life) prior to the first administration of AZD9291 is not permitted. Occasional use of paracetamol (acetaminophen) and nonsteroidal nasal decongestant is permitted at the discretion of the Investigator.

18. 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.

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

20. Use of another new chemical entity (defined as a compound which has not been approved for marketing) or participation in any other clinical study (including methodology studies where no drugs were given) within 3 months of the first administration of IP in this study.

21. 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.

22. Current smokers or those who have smoked or used nicotine products within the previous 3 months.

23. Planned inpatient surgery, dental procedure, or hospitalisation during the study.

All subjects participating in optional pharmacogenetics

- Previous bone marrow transplant
- Non-leukocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection

Procedures for withdrawal of incorrectly enrolled volunteers are shown in Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Volunteers will be required to comply with the following restrictions:

- On AZD9291 dosing days, volunteers will be fasted for at least 10 hours prior to each dose and no food should be allowed for at least 4 hours postdose. A standard

meal will be given 4 hours postdose after completion of all scheduled study procedures. 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). The volunteers will receive standardized meals scheduled at the same time in each treatment period. When omeprazole is given alone (Treatment A: Days 1 through 4) volunteers will be fasted for at least 10 hours prior to each dose, which will be taken in the morning at least 1 hour before breakfast. 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).

- Volunteers must be willing to use reliable methods of contraception, even if 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 for 6 months after the last administration of AZD9291.

  Acceptable methods for volunteers' partners include

  – implants, injectables, combined oral contraceptives (which must all be combined with barrier methods of contraception), some intrauterine devices, and sexual abstinence.

  Acceptable methods for volunteers include:

  – volunteers will be required to use reliable methods of contraception (condom and spermicide) for the duration of the study until 6 months after the IP administration. If a man has had a vasectomy this should be considered an appropriate method of contraception (along with a condom).

  Alternatively, true abstinence is acceptable when it is in line with the volunteer's preferred and usual lifestyle. If a volunteer is usually not sexually active but becomes active, they, with their partner, should use 2 of the contraceptive methods listed above.

- 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, or nonprescribed medication, including drugs with hepatic enzyme-altering properties such as St John's Wort, 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 the poststudy medical examination. Paracetamol (acetaminophen) (1 gram, every 6 hours, to a maximum daily dose of 4 grams) and nonsteroidal nasal decongestant are permitted; however, the Investigator should be informed so this can be recorded.

- 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.

- Volunteers should abstain from taking caffeine-containing drinks or foods (eg, coffee, tea, cocoa, chocolate, and cola) while in patient during the study. During the nonresidential period, volunteers should avoid excessive intake of caffeine-containing drinks or food, eg, coffee, tea, chocolate, caffeine-containing energy drinks (Red Bull), and cola (more than 5 cups of coffee or equivalent, per day). One caffeine unit is contained in the following items: 1 (6 oz) cup of coffee, 2 (12 oz) cans of cola, 1 (12 oz) cup of tea, ½ (4 oz) cup of energy drink (eg, Red Bull), or 3 oz of chocolate.

- Volunteers should abstain from drinking alcohol beginning 72 hours before admission to the clinic in Period 1 and continuing until 24 hours after the last dose of AZD9291in Period 2 and also beginning 72 hours prior to blood tests taken at any subsequent outpatient visit or the poststudy medical examination.

- Volunteers should abstain from consuming poppy seeds from screening 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 prior to admission to Period 1 and continuing until after the poststudy medical examination.

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

5.2 Subject enrolment

The Principal Investigator or designee will:

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

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

3. Determine volunteer eligibility. See Sections 4.1 and 4.2.

Enrolment codes will be assigned strictly sequentially as volunteers become eligible for enrolment. If a volunteer withdraws from participation in the study, then his enrolment number cannot be reused.

Replacement volunteers will be assigned a unique volunteer number in the format 1101 to 1150 (ie, if Volunteer Number 1001 is withdrawn and is to be replaced, the replacement volunteer will be assigned Volunteer Number 1101).

5.3 Procedures for handling subjects incorrectly enrolled

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

Where a volunteer does not meet the selection criteria and this is identified before dosing the volunteer should be withdrawn from the study. If a volunteer is withdrawn prior to dosing they will be replaced.

If a volunteer, who does not meet the selection criteria, has been dosed before the error is identified, the volunteer should be advised to continue safety assessments to ensure their safety. The Principal Investigator will inform the AstraZeneca physician of the error and a joint decision will be made as to whether the volunteer should be replaced. The AstraZeneca physician will notify the AstraZeneca clinical project team of the incident and the decision.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

This study is open-label.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
AZD9291	Tablet, 80 mg	AstraZeneca

AstraZeneca will provide the AZD9291 tablets.

Formulation numbers and batch numbers will be presented in the CSR.

5.5.2 Identity of non-investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Omeprazole	Capsule, 40 mg	To be identified by

Omeprazole will be sourced locally in the USA by or delegate. Details of the supplier will be included in the CSR.

5.5.3 Doses and treatment regimens

Treatment A: On Days 1 through 4, omeprazole will be administered in the morning after a 10-hour fast with 240 mL of water 1 hour before eating breakfast. On Day 5, omeprazole will be administered together with AZD9291 with 240 mL of water following an overnight fast of 10 hours and the volunteers will remain fasting from food until 4 hours postdose.

Treatment B: Volunteers will receive AZD9291 in the morning on Day 1 with 240 mL of water following an overnight fast of 10 hours. Volunteers will remain fasting from food until 4 hours postdose.

Volunteers will receive Treatment A in Period 1 and Treatment B in Period 2. There will be a minimum washout of 21 days between the administration of AZD9291 in Period 1 and Period 2.

Each dose will be taken in an upright position. The dose will be administered as an oral tablet (AZD9291) or capsule (omeprazole) which must be swallowed whole and not chewed, crushed, or divided.

Following AZD9291 administration (Day 5 of Period 1 and Day 1 of Period 2), volunteers will remain fasting from food after dosing until 4 hours postdose. Volunteers will remain fasted from 10 hours before until 1 hour after each dose of omeprazole. Apart from the water given at dosing, volunteers will be fasted from water from 1 hour prior to dosing until 1 hour after dosing.

5.5.4 Labelling

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

5.5.5 Storage

All study drugs 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 and non-steroidal nasal decongestants are 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 electronic the Case Report Form (eCRF).

5.7 Treatment compliance

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

5.7.1 Accountability

The study drugs provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the volunteer.

*S*tudy site personnel, if applicable, or the AstraZeneca monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. 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 non-compliance to study protocol
- Development of any study-specific safety criteria for discontinuation (see Sections 6.3.5)
- 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, 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 2 commences. (Note: this applies to each block [cohort] of volunteers, where not all 50 volunteers are enrolled at the same time.)

5.8.1 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).

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 2. 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. PK 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.

For occasions when more than one assessment is required at a particular time point, PK blood samples should be prioritized. Additional assessments may be performed if the Principal Investigator considers them necessary for volunteer safety.

6.1 Recording of data

The Investigator will ensure that data are recorded on the eCRF as specified in the clinical study protocol (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 (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 enrolment and follow-up

6.2.1 Enrolment procedures

Each volunteer will undergo screening in the 28 days prior to the first dose administration on Day 1 of Period 1 (omeprazole). 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 body mass index
- A standard medical, medication, and surgical history with review of the inclusion and exclusion criteria with the volunteer
- An ophthalmological examination (corrected visual acuity and slit lamp fundoscopy and intraocular pressure measurement)
- 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 HBsAg, 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)
- Alcohol breath test
- Assessment of any SAEs
- Assessment of any concomitant medication

6.2.2 Follow-up procedures

A medical examination will be performed on Day 55. This will be similar to the one performed at the pre-entry visit and will include a complete physical examination, assessment of any AEs and concomitant medication, vital signs, a resting 12-lead ECG, and safety laboratory tests.

6.3 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is 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 pre-existing 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, electrocardiogram). 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 non-serious 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 fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- 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 a SAE, see Appendix B to the CSP.

6.3.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from the volunteer's check-in to the study center on Day -1 of Period 1, throughout the treatment period and including the follow-up period.

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 or other assessment/visit as appropriate 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 collected 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 serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- 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
- Causality assessment in relation to Additional Study Drug
- 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 a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

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

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

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

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 protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs or other safety variables should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the 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 non-mandated 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 AST or ALT ≥3x upper limit of normal (ULN) or total bilirubin ≥2x 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 investigational product, non investigational product, 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 one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

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

6.3.5 Laboratory safety assessment

Laboratory assessments will be taken at the times indicated in the Study Plans (Table 1 and Table 2). The date and time of collection of all laboratory tests will be recorded in the appropriate eCRF. Safety laboratory assessments will be performed at the site's local accredited laboratory, unless stated otherwise.

The laboratory variables to be measured are presented in Table 3.

Table 3 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
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 HBsAg, 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. A breath test for alcohol will also be performed. 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.

NB. Cases where a volunteer shows an AST or ALT ≥3x ULN or total bilirubin ≥2x ULN may need to be reported as SAEs. Prompt reporting of cases meeting Hy's law criteria (via the SAE expedited reporting system) is required for compliance with regulatory guidelines. The investigator is responsible for, without delay, determining whether a patient meets potential Hy's law criteria. 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 the time points indicated in Table 1. A complete physical examination will be performed at screening and follow-up visit that includes 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. A brief physical examination (including general appearance, skin, abdomen, cardiovascular system, and lungs) to be performed at each admission.

6.3.7 ECG

Twelve-lead ECGs will be recorded at the time points indicated in the study plan (Table 1 and Table 2).

Electrocardiograms will be recorded in the supine position after the volunteer has rested in this position for at least 10 minutes.

Only the overall evaluation (normal/abnormal) will be captured in the eCRF. Any abnormalities (including QTcB values) should be reviewed by an appropriately qualified person.

The original ECG printouts with variables must be signed and dated and stored in the volunteer's source workbook as source data.

6.3.8 Vital signs

Vital signs assessment will be performed at the time indicated in (Table 1 and Table 2).

6.3.8.1 Pulse rate and supine blood pressure

Supine blood pressure and pulse rate will be measured using standard equipment after 10 minutes rest on a bed. Additional blood pressure/pulse rate assessments may be taken for safety at the discretion of the Principal Investigator or delegate.

6.3.8.2 Height and weight

Height (cm) and weight (kg) will be evaluated at screening and BMI (kg/m^2) will be calculated. Height will be measured at screening only; weight will be measured at the times shown in Table 1. The volunteers will be required to remove their shoes and wear light indoor clothing for these measurements. When requested or judged necessary for the program, body weight and/or BMI can be measured at additional time points.

6.3.9 Ophthalmology

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

A full ophthalmologic examination including a slit-lamp fundoscopy, should be performed if a volunteer experiences any visual symptoms (such as dry eyes, grittiness, or irritation including blurring of vision), with additional tests if clinically indicated.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for central review by AstraZeneca and AstraZeneca representatives if necessary.

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 for determination of concentrations of AZD9291 and its metabolites (AZ5104 and AZ7550) will be taken at the time points detailed in the study plan (Table 1) and the PK sampling schedule (Table 2). Every attempt should be made to collect all samples at the times specified in the PK sampling schedule. The actual time and date of collection of each blood sample must be recorded in the eCRF. Samples will be collected, processed, labelled, and shipped for analysis as detailed in the Laboratory Manual.

A 30-minute window will be allowed for samples taken at pre-dose; a 5-minute window will be allowed for samples taken up to and including 1 hour; a 15-minute window for samples taken at 2 to 12 hours and a 2-hour window for samples taken from 24 to 72 hours onwards. The samples collected after 72 hours may have a 1-day window.

Samples will be collected, labelled 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 its metabolites (AZ5104 and AZ7550) will be analysed by on behalf of the Clinical Bioanalysis Alliance, AstraZeneca R&D, using appropriate bioanalytical methods. Full details of the bioanalytical methods 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 analysed.

6.5 Pharmacogenetics

Volunteers will be offered the possibility to participate in optional genetic exploratory research. After signing a separate consent for optional genetic research, a blood sample will be collected in accordance with the inclusion criteria and study plan.

If for any reason the blood sample is not drawn on Day -1 of Period 1, according to the study plan, it may be taken at any time up until the last study visit. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding volunteers who may withdraw due to an AE, such volunteers would be important to include in any genetic analysis. Only 1 sample should be collected per volunteer for genetic research during the study.

A record of the date the volunteer consented to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the EDC system. Samples will be collected, handled, labelled, stored, and shipped as detailed in Laboratory Manual.

For pharmacogenetic blood sampling volume see Section 7.1.

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 4 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5	12	60
	Hematology	2	12	24
	Serology	3.5	1	3.5
Pharmacokinetic		2	38	76
Pharmacogenetic[b]		10	1	10
Total				173.5

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)
b The pharmacogenetic sample is optional

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.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

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

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AZ Biobank; see details in the Laboratory Manual).

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain volunteer confidentiality. Samples will be stored for a maximum of 15 years, from the date of the last volunteer's last visit, after which they will be destroyed. Deoxyribonucleic acid (DNA) is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or up to the maximum storage time has been reached.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory personnel working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the volunteer enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the volunteer has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled 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 labelling, 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 lifecycle.

The Principal 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 analysed, AstraZeneca is not obliged to destroy the results of this research.

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

The Principal Investigator:

- Ensures volunteers' 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 central 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 Harmonisation (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 should approve the final study protocol, 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 Institutional Review Board, and to the study site staff.

The opinion of the Institutional Review Board should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any volunteer into the study.

The Institutional Review Board 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 protocol should be re-approved by the Institutional Review Board annually.

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

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

AstraZeneca will provide Regulatory Authorities, Institutional Review Board and Principal Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

8.4 Informed consent

The Principal Investigator(s) or designee 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 Institutional Review Board

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal 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 study protocol (Revised CSP).

The amendment is to be approved by the relevant Institutional Review Board and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Institutional Review Board see Section 8.3.

If a protocol amendment requires a change to a center's Informed Consent Form, AstraZeneca and the center's Institutional Review Board 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 each Institutional Review Board.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Institutional Review Board 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, analysed, and accurately reported according to the protocol, 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

9.1 Pre-study 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 protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement 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 Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilized.

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

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

9.3 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 protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the 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.

9.3.1 Source data

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

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

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 Q3 2014 and to end by Q1 2015.

The study may be terminated 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

Data management will be performed by

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of 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.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

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 post treatment value minus the value at baseline. The baseline values will be as follows:

- Clinical laboratory tests: last measureable value taken prior to first dose
- Vital signs: last measureable value taken prior to first dose
- Paper 12-lead ECG: last measureable value taken prior to first dose

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 (OAE)

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

11.2 Calculation or derivation of pharmacokinetic variables

The sample bioanalysis will be performed by The merging of PK concentration data with actual PK sampling times will be performed by . The PK analysis will be the responsibility of the pharmacokineticist at . 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® Version 6.3, or higher, (Pharsight Corp, St. Louis, Missouri, USA) and/or SAS® version 9.2, or higher (SAS Institute, Inc, Cary, North Carolina, USA). 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 following dosing on Day 5 in Period 1 and Day 1 in Period 2:

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (t_{max})
- Lag time before observation of quantifiable analyte concentrations in plasma (t_{lag})
- Terminal rate constant (λ_z)
- Terminal half life ($t_{½}$)
- Area under the plasma concentration-time curve from zero to the time of the last quantifiable 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

- Metabolite to parent ratio (calculated as AZ5104/ AZD9291 and AZ7550/ AZD9291for both C_{max} and AUC). These ratios will be adjusted for differences in molecular weight (AZD9291 = 499.61 AZ5104 and AZ7550 = 485.59)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Safety analysis set

All volunteers who received at least 1 dose of omeprazole or AZD9291 and for whom any postdose data are available will be included in the safety population.

12.1.2 Pharmacokinetic analysis set

The PK analysis set will include all healthy volunteers who receive at least 1 dose of the IP and have at least 1 postdose PK measurement without important protocol deviations/violations or events thought to significantly affect the PK of the IP (eg, healthy volunteer vomited at or before 2 times median t_{max}, wrong dose administered, prohibited concomitant medication, etc). The PK scientist will evaluate the strategy for dealing with data affected by protocol deviations before any formal statistical analysis is performed.

12.2 Methods of statistical analysis

12.2.1 General principles

Statistical analyses will be performed per standard operating procedures using SAS® Version 9.2 or higher and, where appropriate, additional validated software.

A healthy volunteer who withdraws prior to the last planned observation in the study period will be included in the analyses up to the time of discontinuation. No adjustment or imputation will be utilized for missing values or for healthy volunteers who withdraw prior to completing the study, or will analyses be restricted to healthy volunteers with complete data.

Data from nonvalid healthy volunteers (healthy volunteers excluded from the analysis set[s]), which are recorded in the database, will only be presented in listings.

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

All derived variables/parameters will be rounded for reporting purposes in the summary tables and healthy volunteer listings, as per standard operating procedures.

12.2.2 Subject characteristics

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, maximum). Categorical variables will be summarized in frequency tables (frequency and proportion).

12.2.3 Safety and tolerability

Safety data include AEs, vital signs, physical examinations, ophthalmologic examination, electrocardiograms, and clinical laboratory assessments.

All safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarized using descriptive statistics (n, mean, SD, minimum, median, maximum) by treatment. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment.

All AEs that occur following the first dose of omeprazole in Period 1 will be included in the analyses of AEs, including episodes that occur during the wash-out period.

All available data from healthy volunteers in the safety analysis set will be included in the safety analyses.

All AEs will be collected for each healthy volunteer from Day -1, Treatment period 1 (Visit 2) until the follow-up visit (Visit 15). All SAEs will be collected for each healthy volunteer from the time when informed consent is obtained until the follow-up visit (Visit 15).

Adverse events will be listed for all healthy volunteers with AEs that occur before administration of the IP indicated on the listing. The number of AEs experienced following administration of the IP will be summarized in tables using the MedDRA (Version 13.0 or higher) system organ class and preferred term. These summary tables will also be produced with severity and causality of AEs added as additional classification factors. The number of AEs overall, SAEs, OAEs, AEs that lead to withdrawal, AEs of severe intensity, and causally-related AEs will be summarized. Any AE occurring postdose will be considered associated with the last dose of the IMP taken. Any AE occurring on Day -1, Treatment period 1 (Visit 2) will not be included in the summaries.

12.2.4 Pharmacokinetic analysis

All data received will be presented in data listings. Pharmacokinetic summaries will be presented for volunteers in the PK analysis set, as defined in Section 12.1. Data from volunteers excluded from the PK analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will also not be included in summary tables, but will be included in data listings.

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including n, arithmetic mean, SD, coefficient of variation (CV), median, minimum, and maximum values. Additionally,

geometric means, geometric SD, geometric mean multiplied and divided by geometric SD and geometric coefficient of variation (GCV) will be reported for PK variables (concentrations and all PK parameters, except for t_{max} and t_{lag}).

The PK data will be presented by treatment (AZD9291 + omeprazole, AZD9291 alone).

Influence of omeprazole on pharmacokinetics of AZD9291 will be assessed statistically using mixed effects models on the log-transformed primary PK parameters (AZD9291 AUC and C_{max}) with, treatment as a fixed effect, and subject as a random effect. Estimates of the mean difference between treatments and corresponding 90% confidence intervals (CIs) will be calculated. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs for AUC and C_{max} will be estimated and presented for each treatment. Absence of an effect of omeprazole on AZD9291 exposure will be concluded if the 90% confidence bounds of the ratios of the geometric least square means for both AUC abd C_{max} are entirely contained within 80.00 to 125.00%.

Similar analyses will be performed for the secondary PK parameters AUC and C_{max} of AZ5104 and AZ7550 and $AUC_{(0-72)}$ and $AUC_{(0-t)}$ (all analytes).

For AZD9291 and its metabolites, analyses of t_{max} will be performed using the Wilcoxon Signed Rank Test. The Hodges-Lehmann median estimator of the difference in treatments and 90% CIs will be presented

12.3 Determination of sample size

The primary objective of this study is to investigate the effect of omeprazole on AZD9291 exposure. In study D5160C00005, a within-subject CV of 20% and 23% was observed for both AUC and C_{max}, respectively, in healthy normal volunteers.

For this estimate, it will be assumed that the within-subject CV for AZD9291 in both AUC and C_{max} is 23%. A 5% change in the exposure for AZD9291 when given with omeprazole is also assumed. With 40 evaluable volunteers, the experiment-wide power for the 2 sided 90% CI of the geometric mean ratios (AZD9291 + omeprazole / AZD9291 alone) being completely contained within 80 to 125% is 90% (95% power for each parameter).

To account for withdrawal of approximately 20% of volunteers, approximately 50 volunteers will be enrolled in order to obtain 40 evaluable volunteers.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal 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 AstraZeneca Program Director. If the AstraZeneca Program Director is not available, contact the AstraZeneca Physician.

Name	Role in the study	Address & telephone number
	Project Manager	
	Principal Investigator	
	Associate Director of Clinical Development	
	AstraZeneca Physician	
Serious adverse event reporting	24-hour emergency cover at central R&D site	

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 volunteer has experienced an overdose with AZD9291.

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

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

13.3 Pregnancy

13.3.1 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.

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Clinical Study Protocol Appendix A

Drug Substance	AZD9291
Study Code	D5160C00010
Edition Number	1

Protocol Dated _____ _____

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase I, Fixed Sequence, Open-label, Study to Assess the Pharmacokinetics of AZD9291 in Healthy Male Volunteers when a Single Oral Dose of AZD9291 80 mg is Administered Alone and in Combination with Omeprazole

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development
site representative

ASTRAZENECA SIGNATURE(S)

A Phase I, Fixed Sequence, Open-label, Study to Assess the Pharmacokinetics of AZD9291 in Healthy Male Volunteers when a Single Oral Dose of AZD9291 80 mg is Administered Alone and in Combination with Omeprazole

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representativ

SIGNATURE OF PRINCIPAL INVESTIGATOR

A Phase I, Fixed Sequence, Open-label, Study to Assess the Pharmacokinetics of AZD9291 in Healthy Volunteers when a Single Oral Dose of AZD9291 80 mg is Administered Alone and in Combination with Omeprazole

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Centre No.:

Signature:

Clinical Study Protocol Appendix B

Drug Substance	AZD9291
Study Code	D5160C00010
Edition Number	1

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	AZD9291
Study Code	D5160C00010
Edition Number	1

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Clinical Study Protocol Appendix D

Drug Substance	AZD9291
Study Code	D5160C00010
Edition Number	1

Appendix D
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3 x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥2 x ULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥3 x ULN **and** TBL ≥2 x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 x ULN
- AST ≥3 x ULN
- TBL ≥2 x ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria were met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to

determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf