AstraZeneca

Revised Clinical Study Protocol

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A Randomised Open-Label Phase II Study to Assess the Efficacy and Safety of AZD4547 Monotherapy versus Paclitaxel in Patients with Advanced Gastric Adenocarcinoma (including Adenocarcinoma of the Lower Third of the Oesophagus or the Gastro-Oesophageal Junction) with FGFR2 Polysomy or Gene Amplification (Shine study)

Sponsor: *AstraZeneca AB,* [redacted]

AstraZeneca Research and Development site representative [redacted]

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

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
2	[redacted]		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1	[redacted]		

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PROTOCOL SYNOPSIS

A Randomised Open-Label Phase II-Study to Assess the Efficacy and Safety of AZD4547 Monotherapy versus Paclitaxel in Patients with Advanced Gastric Adenocarcinoma (including Adenocarcinoma of the Lower Third of the Oesophagus or the Gastro-Oesophageal Junction) with FGFR2 Polysomy or Gene Amplification (Shine study)

International Co-ordinating Investigators

Two International Co-ordinating Investigators have been appointed for this study, aligned geographically as follows.

[redacted]

Study centre(s) and number of patients planned

Approximately 3300 patients will be pre-screened to ascertain the FGFR2 status of their tumour in order to identify approximately 300 patients eligible for formal screening to enter the study. Approximately 240 patients will be randomised in to this study, from Asia, North America and Europe. It is planned that approximately 100 sites will participate in the study and each site will randomise 1-4 patients.

Study period		Phase of development
Estimated date of first patient enrolled	[redacted]	II

Study period	Phase of development
Estimated date of last patient completed	[redacted]

Objectives

The primary objective of the study is:

- To investigate the efficacy of AZD4547 compared with paclitaxel by assessment of progression-free survival (PFS) in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.

The secondary objectives of the study are:

- To investigate the efficacy of AZD4547 compared with paclitaxel by comparison in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification as measured by:
    - Overall Survival (OS)
    - Change in tumour size at 8 weeks
    - Objective Response Rate (ORR)
    - Duration of Response (DoR)
    - Percentage of patients without progressive disease at 8 weeks
- To compare and assess the safety and tolerability of AZD4547 and paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.
- To investigate the PK of AZD4547 in patients receiving AZD4547.
- To investigate the possible pharmacokinetic/pharmacodynamic (PK/PD) relationships between plasma AZD4547 exposure and plasma concentrations of phosphate, bFGF, FGF23 and efficacy and other exploratory pharmacodynamic endpoints.
- To assess disease-related symptom changes and time to symptom progression in patients receiving AZD4547 or paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.
- To assess changes in and time to deterioration of Health Related Quality of Life (HRQoL) in patients receiving AZD4547 or paclitaxel in all randomised patients,

patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.

- To assess changes in, and time to deterioration of, WHO performance status in patients receiving AZD4547 or paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.

Exploratory objectives:

- To collect and store plasma, serum and archival tumour samples and/or serial tumour biopsies and analyse surplus blood or tissue, if available, for potential future exploratory research into factors that may influence development and progression of cancer and/or response to AZD4547 (where response is defined broadly to include efficacy, tolerability or safety).

- To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD4547 treatment and/or susceptibility to cancer.

- To analyse bone biomarkers from fasting blood samples, for exploratory research into the pharmacological activity of AZD4547 on non-tumour tissues.

- To explore the predictive value of biomarkers of the relative efficacy of AZD4547 compared with paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification and separately in patients with tumours that have high FGFR2 amplification (FISH 6).

- To investigate the relationship between absolute FGFR2 gene copy number, FGFR2 ratio and an alternative cut-off (FISH 5/6 vs. FISH 4), and the efficacy of AZD4547 as compared with paclitaxel.

- To investigate heterogeneity in patients receiving AZD4547 or paclitaxel with respect to FGFR2 gene copy number through the collection and analysis of multiple tumour biopsies.

- To explore changes in health utility in patients receiving AZD4547 or paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.

- To investigate the impact of AZD4547 and paclitaxel on gastric cancer management resource use.

Study design

This is a randomised, open label, multi-centre study to assess the efficacy and safety of AZD4547 monotherapy versus paclitaxel in patients with advanced gastric adenocarcinoma

(including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction) that has either FGFR2 polysomy or gene amplification.

All patients will be formally pre-screened for the FGFR2 status of their tumour, as measured by its FISH (fluorescence in situ hybridization) score. Patients with a tumour FISH score of 4, 5 or 6 will then be screened to determine eligibility for randomisation in to the study.

Patients will be assigned to one of three strata in the study (polysomy, low amplification or high amplification) according to the FGFR2 status of their tumour as measured by FISH. Eighty patients that have tumours with FGFR2 polysomy (FISH 4 or 5) will be randomised in a 1:1 (AZD4547: paclitaxel) ratio in a polysomy stratum and 160 patients that have tumours with FGFR2 gene amplification (FISH 6) will be randomised in a 3:2 (AZD4547: paclitaxel) ratio with 80 patients being recruited to a low amplification stratum and 80 patients to a high amplification stratum. Accrual to one stratum may be completed ahead of the others. Patients will receive either AZD4547 (80 mg orally twice daily, on a 2 weeks on, 1 week off schedule) or paclitaxel (80 mg/m^2 weekly on days 1, 8 and 15 of a 28 day cycle) see Section 5.5.2.

It is estimated that approximately 3300 patients will need to be pre-screened in order to randomise approximately 240 patients. This figure is based on prevalence data for FGFR2 polysomy and amplification (AstraZeneca data on file) and also takes into account the stratification of the study, as it is expected that the prevalence of FGFR2 gene amplification will be lower than the prevalence of FGFR2 polysomy. However, the exact number of patients that will need to be pre-screened will depend on the actual prevalence of FGFR2 polysomy, FGFR2 low level gene amplification and FGFR2 high level gene amplification in this patient population. It is expected that FGFR2 polysomy will be more prevalent than low level amplification and that high amplification will be the slowest stratum to accrue patients on account of the lowest expected prevalence.

There will be 2 interim analyses during the study which will be conducted to ensure adequate evidence of anti tumour activity (as measured by changes in tumour size at 8 weeks) and an acceptable safety profile has been demonstrated in a given stratum prior to recruiting the full 80 patients required per stratum to robustly assess progression free and overall survival in that stratum. Due to the differing prevalence of FGFR2 polysomy, low gene amplification and high gene amplification in this patient population, and hence the differences in time to recruit the different strata, two separate interim analyses are planned:

Interim Analysis 1

The data cut-off for the first interim analysis will occur when the first 30 FISH 4/5 patients and the first 25 FISH 6 low amplification patients have been followed up for a minimum of 8 weeks (or progressed, or died prior to 8 weeks). Enrolment into the FISH 4/5 stratum will be put on hold once sufficient patients have entered screening to achieve the 30 randomised patients required for the first interim analysis. Recruitment to both FISH 6 strata will remain open whilst data for the first interim analysis is being collected and analysed subject to a cap of 40 patients randomised in total within the FISH 6 low amplification stratum.

The first interim analysis will be performed to determine whether there is sufficient evidence of anti-tumour activity and an acceptable safety profile which would warrant continuation of either or both of these strata (polysomy and FISH 6 low amplification) recruiting to the full 80 patients. If either (or both) of these strata are discontinued after the first interim analysis then recruitment to these strata will be stopped (or will not be re-opened, in the case of the FISH 4/5 stratum). Conversely if either (or both) of these strata are continued after the first interim, then recruitment will re-open and/or the cap on recruitment for the FISH 6 low amplification will be removed. Recruitment to the FISH 6 high amplification stratum will remain open throughout and after Interim Analysis 1 as continuation of that stratum will be contingent on a positive outcome from Interim Analysis 2.

Interim Analysis 2

The scope of Interim Analysis 2 will depend on decisions taken at Interim Analysis 1 and will only include data for those strata that were continued after Interim Analysis 1.

If only the FISH 6 high amplification stratum remains open after the first interim analysis, the data cut-off for the second interim analysis will occur when 25 patients with FISH 6 high amplification have been randomised and followed-up for a minimum of 8 weeks (or progressed or died prior to 8 weeks). At this point a decision will be taken concerning the continuation of this FISH 6 high amplification stratum, based on the strength of any evidence of anti tumour activity observed.

If both FISH 6 strata remain open after the first interim analysis and irrespective of whether recruitment has continued in the polysomy stratum, the data cut-off for the second interim analysis will be the earliest of approximately 60 overall survival events having occurred across the combined FISH 6 strata, or the first 25 FISH 6 high amplification patients have been followed up for a minimum of 8 weeks (or progressed or died prior to 8 weeks). The analysis will include data from patients who meet the criteria for the data cut-off including those who were recruited to the polysomy stratum.

Any recruitment that is ongoing at the time of the 2nd interim analysis will remain open whilst data is being collected and the analysis performed provided that the overall recruitment target of 80 patients in a stratum has not already been reached.

If a decision is taken not to continue the study past the second interim analysis, then recruitment to all open strata will be stopped and a primary analysis of all data from all randomised patients will be completed and reported.

Primary Analysis

If the study proceeds beyond the second interim analysis a total of approximately 80 patients will be randomised in each of the stratum which remain open.

Depending on which strata remain open after the interim analyses, the primary analysis will occur at the following times:

- If FISH 6 high amplification strata only remains open – the data cut off for the primary analysis will be when approximately 60 deaths have occurred in the FISH 6 high amplification stratum.

- If both FISH 6 strata remain open only – the data cut off for the primary analysis will be when approximately 102 deaths have occurred across the two FISH 6 strata.

- If all 3 strata remain open – the data cut off for the primary analysis will be when approximately 163 deaths have occurred across all three strata provided that at least 102 deaths have occurred across the two FISH 6 strata.

Follow up for PFS and OS

All randomised patients will be followed up to objective progression for assessment of PFS, with continued contact to determine OS status.

Patients may remain on study treatment until objective disease progression unless they are withdrawn early due to any of the discontinuation criteria detailed in Section 5.8. Patients who discontinue treatment for reasons other than progression or death will continue to be followed for PFS and OS.

For all patients who are pre-screened, a survival status will be obtained at the time of the primary efficacy analysis. Further survival analyses may be performed at a later date to further explore the association between FISH score and prognosis.

Target patient population

The target patient population for the randomised part of the study is defined as pre-screened patients who are male or female, aged 25 years or older with locally advanced or metastatic gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction) that has FGFR2 polysomy (as defined by FISH 4 or 5) or FGFR2 gene amplification (as defined by FISH 6) and whose disease has progressed during or after first line therapy. Patients whose disease has progressed within 6 months following adjuvant or neo-adjuvant therapy may be included at the discretion of the investigator.

Investigational product, dosage and mode of administration

AZD4547 80 mg will be administered orally twice daily as a tablet, on a 2 weeks on, 1 week off schedule, in a 3 weekly cycle.

Based on ongoing evaluation of emerging study data, the Safety Review Committee (SRC) will have the option to propose that a lower dose level and/or a different schedule should be evaluated subject to agreement with AstraZeneca (see Section 5.5.3).

Comparator, dosage and mode of administration

Paclitaxel will be administered as a 1-hour intravenous infusion of 80 mg/m^2 weekly on days 1, 8 and 15 of a 28-day cycle see Section 5.5.2.

Duration of treatment

Patients will continue study treatment until objective disease progression unless they are withdrawn early due to any of the discontinuation criteria detailed in Section 5.8. The maximum number of cycles of paclitaxel to be administered will be according to local clinical practice.

Outcome variable(s):

Efficacy

- Primary Outcome Variable:
  - PFS
- Secondary Outcome Variables:
  - OS
  - Change in tumour size at 8 weeks
  - Objective response rate (ORR) and duration of response (DoR)
  - Percentage of patients without progressive disease at 8 weeks
  - Patient reported outcomes (PRO)
  - WHO Performance status

Safety

- Adverse Events
- Deaths
- Laboratory findings (clinical chemistry, haematology, urinalysis)
- Vital signs
- Physical Examination
- Ophthalmic assessments
- Electrocardiogram parameters
- MUGA/Echo parameters

Pharmacokinetics

- Plasma concentrations of AZD4547

- Pharmacokinetic parameters including (but not restricted to): CL_{ss}/F and V_{ss}/F

Pharmacodynamics

- FISH score/ratio and efficacy (tumour size, PFS, survival) in randomised patients
- Pharmacokinetic/pharmacodynamic relationship
- Biomarker levels and changes from baseline in biomarkers
- Bone biomarker levels
- Correlation between FISH score/ratio and survival in pre-screened patients

Health Economics

- Gastric cancer management resource use
- Health utility

Statistical methods

All efficacy data will be analysed on the efficacy analysis set which will include all randomised patients and data will be analysed by randomised treatment and actual stratum allocation for each patient as applies at the time of the analysis.

In the event that the SRC and AstraZeneca agrees that an alternative dose or schedule should be explored with a consequent increase in the number of patients to be enrolled (reference section 5.5.3), these analyses will be performed for the patients randomised after the last change in dose or schedule (for SRC roles and responsibilities reference section 5.5.3.1). These analyses will be considered as primary, and data from patients randomised prior to the change in dose or schedule will be summarised descriptively.

The following methodology are general principles for analysis methods at the primary analysis and will be adapted depending on which strata remain open at the primary analysis.

PFS and OS in all randomised patients will each be analysed using Cox proportional hazards models with covariates for FGFR2 FISH strata and treatment. PFS and OS within FISH score strata will be estimated from cox proportional hazards models fitted in the overall population with covariates for FGFR2 FISH stratum, treatment and the treatment by FISH stratum interaction. The PFS and OS hazard ratios (HR; AZD4547: paclitaxel) for treatment for all patients, for patients who have tumours with FGFR2 low or high amplification (FISH 6) and for patients that have tumours with FGFR2 polysomy (FISH 4/5) will be estimated together with their 80% and 95% confidence intervals and associated 1-sided p-values (a HR less than 1 favours AZD4547). An overall treatment effect within the combined FISH 6 strata may also be obtained, if appropriate. Kaplan-Meier plots of PFS and OS, and estimates of median PFS and OS will be presented by treatment and by FISH stratum by treatment. Forest plots will be produced for PFS and OS to assess the extent to which the treatment effect is consistent across

subgroups. The Forest plots will present the results overall, and for subgroup defined factors including FISH stratum, age, gender, race and location/type of gastric cancer.

No multiplicity adjustments will be made in the statistical analysis.

The effect of AZD4547 on change in tumour size in all randomised patients will be estimated from an analysis of covariance (ANCOVA) model including terms for baseline tumour size (log transformed), time from baseline scan to randomisation, FGFR2 FISH stratum and treatment. The effect of AZD4547 on change in tumour size within each of the FISH strata will be estimated from the same ANCOVA model as described above but also including the treatment by FISH stratum interaction. An estimate of the treatment effect (difference in lsmeans, AZD4547 – paclitaxel) will be calculated for all patients, for patients that have tumours with FGFR2 low or high amplification and for patients that have tumours with FGFR2 polysomy will be estimated together with its 2-sided 80% confidence interval. An additional estimate of the treatment effect within the pooled FISH 6 strata (ie, all FISH 6 patients) may also be produced, if appropriate. Waterfall plots showing the percentage change in tumour size for individual patients will also be presented. Descriptive data will be provided for the duration of response in responding patients.

In PFS, OS and tumour size analyses, interaction testing will be performed at the 10% level to determine whether the treatment by AZD4547 FGFR2 FISH stratum interaction is significant.

In addition, exploratory analyses may be conducted using the continuous FISH ratio, and the log transformed continuous absolute FGFR2 copy number to explore whether there is a cut-off threshold for this variable that provides superior discrimination between the PFS, OS and tumour size treatment effects in a subgroup compared to the complimentary subgroup.

Objective tumour response rates and proportion of patients without progressive disease at 8 weeks will be analysed using a logistic regression model adjusted for the same covariates as in the PFS and OS analyses. The odds ratio will be estimated together with its 80% confidence interval and associated p-value. Summaries of response rate and proportion of patients without progressive disease at 8 weeks will be produced by FISH stratum, but will not be analysed formally due to the expected small number of responses when split by treatment within each FISH stratum. Descriptive data will be provided for duration of response in responding subjects.

The safety population will include all patients who have received at least one dose of randomised study medication (AZD4547 or paclitaxel) and will be assessed according to treatment received.

The EORTC QLQ-C30 and QLQ-STO22 PRO instruments will be used to evaluate HRQoL and disease-related symptom patient reported outcomes in patients. Subscale scores from these PRO instruments will be summarised by visit for both treatment arms. Outcomes to be assessed include changes in scores from baseline (eg, symptom improvement rates), time to deterioration in HRQoL and time to symptom progression. Performance status, using the WHO scale instrument, will be used to assess changes in and time to deterioration of

performance status. The EQ-5D-5L instrument will be used to explore change in health utility and data on palliative procedures to explore impact on health economic resource use.

The first interim analysis will be performed once the first 30 FISH 4/5 patients and the first 25 FISH 6 low amplification patients have been followed up for a minimum of 8 weeks (or progressed or died prior to 8 weeks). Progression free survival, changes in tumour size and objective response rate will be statistically analysed at this interim analysis (providing there are enough responses to justify a formal analysis) using the same methods as described above for the primary analysis. Descriptive summary statistics and graphical presentations will be used for other efficacy endpoints, biomarkers and safety data. Due to the expected low number of patients with high amplification having been enrolled at the time of the first interim analysis, results from the FISH 6 high amplification stratum in isolation will not be reported until the second interim analysis, which will occur at the earliest of either the 25th FISH 6 high amplification patient having been followed up for 8 weeks or 60 deaths having occurred in the combined FISH 6 strata.

The purpose of the 2nd interim analysis will be dependent on the outcome of the first interim analysis. If only the FISH 6 high amplification stratum remains open at the 2nd interim, then this analysis will be focussed on assessing changes in tumour size and response rate within this stratum alone, to assess if there is sufficient evidence of anti tumour activity to warrant recruiting the full 80 patients in that stratum. If both FISH 6 amplification strata remain open after the first interim analysis, the second interim analysis will have a broader focus and, in addition to assessing changes in tumour size and response rate within the FISH 6 high amplification stratum, an initial assessment of progression free survival and overall survival across both FISH 6 strata will be performed.

Although the primary endpoint of the study is progression free survival, the primary efficacy analysis will be triggered based on sufficient OS maturity being reached, which is defined as at least 60 OS events from the patients in the FGFR2 high amplification stratum, at least 102 events out of the FGFR2 amplified (FISH 6) patients and at least 163 events out of all FGFR2 polysomy or amplified (FISH 4-6) patients, depending on which strata remain open at the time of the primary analysis.

If both FGFR2 amplified (FISH 6) strata remain open at the time of the primary analysis, 102 events (within the FGFR2 amplified patients) will provide 85% power to detect an OS HR=0.63 at the 1 sided 10% significance level, given the randomisation ratio of 3:2 between the treatment arms. Assuming median OS in the paclitaxel arm is 5 months for patients with FGFR2 gene amplification (FISH 6), a HR of 0.63 corresponds to median OS of 8 months in the AZD4547 arm. If only the high FGFR2 gene amplification stratum remains open at the primary analysis, 60 OS events within this stratum will provide 80% power to detect an OS HR=0.57 at the 1 sided 10% significance level, given the randomisation ratio of 3:2 within this stratum. Assuming median OS on the paclitaxel arm is 4 months in high FGFR2 amplified patients, a HR of 0.57 corresponds to median OS of 7 months on AZD4547. If all three strata continue to the primary analysis, 163 events overall will provide 90% power to detect an OS HR=0.67 at the 1 sided 10% significance level, given the overall randomisation

ratio of approximately 1.3:1 between the treatment arms (taking in to account the 3:2 ratio within the FGFR2 amplification strata, and the 1:1 ratio within the FGFR2 polysomy stratum). Assuming median OS in the paclitaxel arm is 6 months for patients with FGFR2 polysomy or gene amplification (FISH 4-6), a HR of 0.67 corresponds to median OS of 9 months in the AZD4547 arm.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
$AUC_{(0-t)}$	Area under plasma concentration-time curve from zero to time t
$AUC_{(0-8)}$	Area under plasma concentration-time curve from zero to 8 h post dose
AUC_{ss}	Area under plasma concentration-time curve during any dosing interval at steady state
AZ	AstraZeneca
bd	Twice daily dose
$C_{ss,max}$	Maximum (peak) steady state drug concentration in plasma during dosing interval
$C_{ss,min}$	Minimum (trough) steady state drug concentration in plasma during dosing interval
CL_{ss}/F	Total body clearance of drug from plasma after an oral dose at steady state
CPS	Clinical Pharmacology Science
CR	Complete Response (RECIST)
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Event
CV	Coefficient of variation
CYP1A1	A member of the CYP450 family
CYP2D6	A member of the CYP450 family
CYP3A4	A member of the CYP450 family
CYP3A5	A member of the CYP450 family
CYP450	Cytochrome P450
DLT	Dose-limiting toxicity

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
DoR	Duration of Response
E-code	Enrolment number
ECG	Electrocardiogram
Echo	Echocardiogram
EC	Ethics Committee, synonymous with Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5 Dimension 5 Level
FGF	Fibroblast Growth Factor
FGF23	Fibroblast Growth Factor 23
bFGF	Basic Fibroblast Growth Factor
FGFR	Fibroblast Growth Factor Receptor
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IB	Investigators' Brochure
IC_{50}	Concentration of a drug causing half maximal inhibitory effect
ICH	International Conference on Harmonisation
International Co-ordinating investigator	The Investigator co-ordinating the investigators and/or activities internationally
IMPD	Investigational Medicinal Product Dossier
IP	Investigational Product
IPS	Investigational Product Supply
IRB	Institutional Review Board
ISR	Independent Statistical Report
ITT	Intention To Treat
IVRS	Interactive Voice Response System

Abbreviation or special term	Explanation
IWRS	Interactive Web Response System
LIMS	Laboratory Information Management System
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRT	Mean Residence Time
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NE	Non-evaluable (RECIST)
NTL	Non-Target Lesion
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
OCT	Optical Coherence Tomography
od	Once Daily
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease (RECIST)
PFS	Progression Free Survivial
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PR (RECIST)	Partial Response (RECIST)
PR	ECG interval measured from the onset of the P wave to the end of the R deviation
PRO	Patient Reported Outcomes
QLQ	Quality of Life Questionnaire
QLQ-C30	EORTC quality of life questionnaire core 30 (a 30 item PRO instrument developed by the EORTC to assess the health status and health-related quality of life of cancer patients)
QLQ-STO22	EORTC quality of life questionnaire gastric cancer 22 (a 22 item PRO instrument developed by the EORTC to assess the impact of disease related symptoms in patients with gastric cancer)
QoL	Quality of Life
QRS	ECG interval measured from the onset of the Q wave to the end of the S deviation

Abbreviation or special term	Explanation
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RPED	Retinal Pigmented Epithelium Detachment
RR	ECG interval measured from the maxima of one R deviation to the maxima of the next R deviation
RVO	Retinal Vein Occlusion
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical Analysis Plan
SD	Stable Disease (RECIST)
SNU16	Human gastric cancer cell line
SRC	Safety Review Committee
SUSARs	Suspected Unexpected Serious Adverse Reactions
t	Time of last measurable plasma concentration
TBC	To be confirmed
$t_{ss\ max}$	Time of maximum concentration at steady state
TL	Target Lesion
ULN	Upper Limit of Normal
V_{ss}/F	Volume of distribution (apparent) at steady state after an oral dose
WBDC	Web Based Data Capture
WHO	World Health Organisation

1. INTRODUCTION

1.1 Background

1.1.1 Gastric cancer

Gastric cancer is the fourth most common malignancy in the world, and second most common cause of death from cancer, with 738,000 deaths annually. The incidence of gastric cancer varies widely by region; more than 70% of cases (714,000 cases) occur in developing countries and half the world total occurs in Eastern Asia (mainly in China). (Ferlay et al. 2010).

Common subtypes of gastric cancer include gastric adenocarcinoma localised to the antrum, gastric cardia and gastroesophageal junction. Although there is geographical variation amongst the subtypes, based on aetiology and associated risk factors, treatment and unmet needs are largely undifferentiated. Early detection and surgery with systemic node dissection have improved treatment outcomes of localised gastric cancer. Sixty percent of those initially treated with curative intent will develop loco regional or metastatic disease. Globally, the majority (60% to 70%) of gastric cancer cases present with locally advanced or metastatic disease and are unresectable. For unresectable advanced or recurrent gastric cancer, systemic chemotherapy has become the standard treatment, and the prognosis remains poor (Field et al. 2008, Wagner et al. 2010). In patients with advanced or metastatic tumours, treatment is generally palliative and the median survival time for such patients is 6 to 9 months.

Globally, there is no agreed standard first-line regimen for the treatment of advanced gastric cancer. Currently there are a number of regimens in use, including doublet and triplet chemotherapy, and the choice of treatment is based on a variety of factors, including clinical study results, availability and cost of drugs, therapy-related toxicity, and the patient's physical status. The majority of patients will progress eventually, and a decision whether to use second-line treatment will depend on the performance status of the patient. Approximately 20% of patients with advanced gastric cancer who progress on first-line treatment will go on to receive second-line treatment. No single regimen has shown superior activity in the second-line setting, indeed the lack of data from randomised trials on comparisons with placebo make it unclear whether any regimen is significantly better than best supportive care alone (Wesolowski et al. 2009). The National Comprehensive Cancer Network advise that in the second-line gastric cancer setting the options for treatment of patients with ECOG performance score ≤ 2 are either chemotherapy (including paclitaxel monotherapy regimens), best supportive care or clinical trial (NCCN11).

Recent findings have suggested that gastro-oesophageal cancers could be considered as a group of heterogeneous diseases that differ in the expression of cell-signaling molecules, and hence which could be classified according to the different oncogenic drivers involved (Asaoka et al. 2011). Approximately 20% of patients with gastric cancer will express ErbB2 (Her-2) on the tumour surface (Im et al. 2005, Bang et al. 2009). In a recent publication, out of 142 gastric cancer samples analysed, 7.1% scored IHC 2+ and 8.6% scored IHC 3+, whereas

9.3% were HER2 amplified (Im et al. 2011). The reported HER2 incidence rates in gastric cancer are variable, which may be due to differences in methodology.

In the ToGA study, in which patients whose tumours expressed Her-2 were treated with trastuzumab (Herceptin; Roche-Genentech) in combination with a chemotherapeutic regimen of fluoropyrimidine and cisplatin or the chemotherapeutic regimen alone, median survival was extended by almost three months in patients treated with trastuzumab (Bang et al. 2010). Despite these results, 80% of patients remain trastuzumab-ineligible, and the investigation of additional targeted therapies is warranted in this area of unmet clinical need.

1.1.2 AZD4547

AZD4547 is a potent and selective inhibitor of FGFR-1, 2 and 3 receptor tyrosine kinases (enzyme and cellular phosphorylation endpoints), and has a significantly lower potency for inhibition of IGF1R and KDR.

The FGFR family consists of four members each composed of an extracellular ligand binding domain, a trans-membrane domain and an intracellular cytoplasmic protein tyrosine kinase domain. Receptor activation leads to the recruitment and activation of specific downstream signalling partners that participate in the regulation of diverse processes such as cell growth, cell metabolism and cell survival. Genetic modifications of FGFR-1, 2, 3 or 4, including amplification, translocation and mutations have been described in a range of tumour types including breast cancer, gastric cancer and multiple myeloma. Non-clinical data indicate that deregulation, or increased activity, of the FGFR signaling pathway resulting from these modifications is susceptible to attenuation by tyrosine kinase inhibitors that target the FGFR. In addition, FGF has also been described as a significant angiogenic factor, and may play a role in resistance to vascular endothelial growth factor (VEGF) inhibitor therapy. Therefore, an FGFR inhibitor has the potential to provide clinical benefit over a range of therapeutic indications.

1.1.2.1 Non-clinical pharmacology

Studies i*n vitro* show AZD4547 to be a potent inhibitor of isolated fibroblast growth factor receptors (FGFRs) 1, 2 and 3 (IC_{50} <5 nM) and to inhibit isolated FGFR4 with moderate potency (IC_{50} 165 nM). In cell-lines, over expressing the relevant receptor, AZD4547 potently inhibits the kinase activity of FGFR 1-3 (IC_{50} <50 nM).

Both *in vitro* and *in vivo* studies were carried out to assess the potential for AZD4547 to deliver therapeutic benefit in patients with gastric cancer tumours with gain of FGFR2 gene copy number. Key points are:

- *In vitro* AZD4547 inhibits the proliferation of SNU16 and KATOIII gastric cancer cell-lines, both of which have amplification of the FGFR2 gene (FISH score = 6).
- Oral treatment of mice bearing SNU16 xenografts, once daily, with doses between 1.5 and 12.5 mg/kg/day AZD4547, for 24 days, resulted in dose-dependent tumour growth inhibition.

- Both continuous and intermittent oral dosing of mice bearing SNU16 xenografts can inhibit tumour growth to a similar extent.

- In models with a FISH score of <6, AZD4547 efficacy is variable and the best response is tumour stasis. Oral treatment of mice bearing two distinct xenografts derived from human gastric cancer explants (FISH score 3 and 4), with 25 mg/kg AZD4547, once daily for 14 days, resulted in significant inhibition of tumour growth.

In rats and dogs, exposure of AZD4547 generally increased more than dose proportionally and accumulation was less than 3-fold on multiple daily dosing in the dog. AZD4547 binding to human serum albumin and to human α1-acid glycoprotein was 93.2 and 69.6% respectively. One of the principal metabolites formed by human hepatocytes was found in the rat, but other human metabolites were not formed in significant amounts in any non-clinical species. CYP3A4, CYP3A5 and CYP2D6 are likely to be responsible for the metabolism of AZD4547 *in vivo*, although CYP1A1 turnover may be important in smokers. AZD4547 produced competitive inhibition of CYP3A4/5 using testosterone as the probe substrate, but not with midazolam, and it was also shown to be a time dependent inhibitor of the same isozymes.

1.1.2.2 Non-clinical safety

All pivotal non-clinical safety studies were conducted to Good Laboratory Practice (GLP). The key findings were as follows:

- AZD4547 was not mutagenic in *in vitro* mutation assays (Ames test and mouse lymphoma assay), or genotoxic in an *in vivo* study. An aromatic amide intermediate (AZ12602108) was evaluated in a full 5 strain Ames test and was negative

- Daily oral doses of AZD4547 given to rats for up to 28 days at doses up to 20 mg/kg/day were well tolerated. AZD4547 caused histopathological changes in several organs including the eyes (atrophy of the corneal epithelium), heart (aortic mineralisation), sternum (cartilage dysplasia) and femoro-tibial joint (periosteal inflammatory cells present) at 20 mg/kg/day. These histopathological changes showed recovery within the one-month off-dosing period. Higher plasma phosphate and calcium levels were observed at 20 mg/kg/day.

- Daily oral doses of AZD4547 given to dogs for up to 28 days at doses up to 8 mg/kg/day were well tolerated, but were associated with clinical signs. Histopathological changes in the heart (endocardium mineralisation), extremities, lacrimal and parotid glands, conjunctival epithelium and tongue were seen at 8 mg/kg/day. The findings in the heart and extremities were not seen at the end of the recovery period. Increased phosphate levels were observed in dogs dosed at 3 and 8 mg/kg/day.

- AZD4547 is not a photo toxin.

For full details of the non-clinical information, please refer to the Investigators' Brochure (IB).

1.1.2.3 Clinical experience with AZD4547

At the time of data cut-off, two Phase I studies (D2610C00001 and D2610C00002) and one Phase IIa study (D2610C00003) (safety run-in part only) are ongoing with AZD4547, using the tablet formulation. No clinical studies have yet completed. Data reported here are preliminary and unvalidated based on a data cut off of [redacted] Updated information from subsequent data cut-offs is included in the latest edition of the IB.

Study D2610C00001 is an open-label, multi-centre, dose escalation Phase I clinical study designed to assess the safety, tolerability, pharmacodynamics, PK and to determine the maximum tolerated dose (MTD) and/or recommended dose of AZD4547 in advanced cancer patients who have progressed following standard therapy or for whom no standard therapy exists.

Study D2610C00002 is an open-label, multi-centre, dose escalation Phase I clinical study designed to assess the safety, tolerability, pharmacodynamics, PK and to determine the MTD and/or recommended dose of AZD4547 in Japanese patients with advanced cancer who have progressed following standard therapy or for whom no standard therapy exists.

Study D2610C00003 is a randomised double-blind Phase IIa clinical study (with safety run-in) designed to assess the safety and efficacy of AZD4547 in combination with exemestane vs. exemestane alone in ER+ breast cancer patients with FGFR1 polysomy or gene amplification who have progressed following treatment with one prior endocrine therapy (adjuvant or first-line metastatic).

Clinical Pharmacokinetics

Preliminary unvalidated pharmacokinetic data are available from studies D2610C00001 (single (od) and multiple twice daily (bd) dosing of 20 to 200 mg AZD4547 oral suspension formulation and 120 to 200 mg AZD4547 tablet formulation) and D2610C00002 (od and bd) dosing of 40 and 80 mg AZD4547 oral tablet formulation).

Key clinical PK findings are:

- D2610C00001: Preliminary data suggest the administration of AZD4547 by either suspension or tablet formulation results in similar systemic exposures. AZD4547 has a moderate rate of absorption, with a median time to maximum plasma concentration (t_{max}) of 3 h across all the dose levels following single doses and at steady state. Following a single dose of AZD4547, peak plasma concentrations declined with a mean terminal elimination half-life ($t_{1/2}$) of approximately 30 h, which was consistent across dose levels. Oral clearance and distribution were independent of dose and appropriate for the intended treatment administration regimen. The oral clearance was approximately 50 L/h and the oral volume of distribution was greater than total body water indicating that AZD4547 was well

distributed in the tissues. Multiple-dose data indicated that the accumulation ratio (RAC) was in keeping with the half-life and there was no unexpected time-dependency (the linearity factor was generally close to unity).

- D2610C00002: The t_{max} and $t_{1/2}$ following single doses in Japanese patients was similar to that found in Western patients (D2610C0001). Oral clearance and distribution were independent of dose and, except for the 160 mg cohort, appeared to be generally higher than those in Western patients. The multiple-dose PK data from 3 cohorts dosed bd and 1 cohort dosed od were generally consistent with the single-dose data (linearity factor was generally close to unity in most patients).

- D2610C00003: Preliminary partial datasets are available from up to 5 individuals. The plasma profiles of AZD4547 are consistent with previous experience (D2610C00001). There are insufficient exemestane and 17-hydroxyexemestane exposure data to compare their PK when exemestane was administered alone or in combination with AZD4547.

Clinical safety and efficacy

Study D2610C00001 – Phase I study

By the [redacted] a total of 65 patients had received at least a single dose of AZD4547 in Study D2610C00001.

Part A (escalation dose phase) of the study has been completed and 43 patients have been dosed.

Part B (expansion phase) of the study has been completed and 6 patients have been dosed at 80 mg bd continuous dose. No patient experienced a DLT in Part B.

A dose expansion phase (Part C) in patients with FGFR1 and/or FGFR2 gene amplified tumours has now commenced at 80 mg bd continuous schedule to explore the safety, tolerability, PK and preliminary anti-tumour activity of AZD4547 in this patient population. Sixteen patients have been enrolled in this cohort.

Part A:

- Cohorts were dosed with the suspension formulation as follows: 20 mg bd (n=3), 40 mg bd (n=5), 80 mg bd (n=6), 150 mg bd (n=7), 200 mg bd (n=6). Cohorts were dosed with the tablet formulation as follows: 200 mg bd (n=4), 160 mg bd (n=6), 120 mg bd (n=6).

- Seven dose-limiting toxicities (DLTs) have been reported: increased liver transaminases (80 mg bd), mucositis (120 mg bd) stomatitis (150 mg bd), uncontrolled phosphate (160 mg bd), acute renal failure (200 mg bd) and renal failure (160 mg bd) increased alanine aminotransferase (ALT) in association with Common Toxicity

Criteria (CTC) Grade 2 increases in phosphate and calcium:phosphate product (200 mg bd).

- The 160 mg bd dose was declared non-tolerated as 2/6 patients experienced DLTs. The Safety Review Committee decided that the 120 mg bd dose was not sufficiently tolerated to support chronic dosing, although it did not achieve the protocol definition of a non-tolerated dose.

- To date, the majority of AEs experienced by patients receiving AZD4547 in Part A (43 patients) have been CTC Grade 1 or 2 in intensity. The most commonly reported AEs were constipation (24 patients), alopecia (21 patients), hyperphosphataemia (21 patients), dry mouth (18 patients), dry skin (18 patients), stomatitis (18 patients), nail disorder (15 patients), diarrhoea (14 patients), back pain (13 patients), decreased appetite (13 patients), general fatigue/asthenia (10 patients)

Overall, in study D2610C00001, there have been 21 on-treatment serious adverse events (SAEs) reported by 12 patients. Eight treatment-related SAEs were reported in 7 patients. Increased creatinine, renal failure and pyrexia are the only SAE terms to be reported on more than one occasion.

Preliminary data on anti-tumour activity: The best objective response observed was prolonged stable disease reported in four patients with stable disease>12 weeks based on tumour assessment by response evaluation criteria in solid tumours (RECIST) 1.1: 211 days in a patient with soft tissue sarcoma (20 mg bd), 168 days in a patient with colorectal carcinoma (200 mg bd), 98 days in a patient with oesophageal carcinoma (160 mg bd) and 119 days in a patient with advanced breast cancer with tumour with FGFR 1 amplification (FISH score 6) (80 mg bd) (part C).

Study D2610C00002 – Phase I study (Japan)

By the [redacted] a total of 25 patients had received at least a single dose of AZD4547 in the Japan dose escalation study (D2610C00002).

Part A (escalation dose phase) commenced with tablet formulation and explored twice daily and once daily schedules.

- Cohorts were dosed with the tablet formulation as follows: 40 mg bd (n=3), 80 mg bd (n=6), 120 mg bd (n=6) and 160 mg od (n=10).

- No DLTs have been reported to date, and the maximum tolerated dose (MTD) has not yet been defined.

A dose expansion phase (Part B) in patients with FGFR1 and/or FGFR2 gene amplified tumours has now commenced at 80 mg bd continuous schedule to explore the safety, tolerability, PK and preliminary anti-tumour activity of AZD4547 in this patient population.

- Twenty-one patients had discontinued from the study, of which 10 patients discontinued due to disease progression, 5 patients discontinued due to AEs (retinal pigmented epithelium detachment (RPED) / related conditions) and 6 patients discontinued due to other reasons.

- All patients had reported at least one AE at the data cut-off. To date, the majority of AEs experienced by patients receiving AZD4547 in Study D2610C00002 have been CTC Grade 1 or 2 in intensity. The most commonly reported AEs were dysgeusia/taste abnormality (12 patients), mucositis oral/stomatitis (12 patients), diarrhoea (9 patients), dry mouth (9 patients), dry skin (9 patients), general fatigue/malaise (9 patients) and hyperphospatemia (8 patients). No deaths due to an AE have been reported during the study treatment. Most AEs occurred within 1 to 3 weeks of beginning multiple dosing with AZD4547.

- There have been 3 SAEs reported by 2 patients: 1 patient reported Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 stomatitis and 1 patient reported CTCAE Grade 3 nausea and CTCAE Grade 3 decreased appetite. The SAEs of nausea and decreased appetite were considered to be related to the study treatment by the Investigator.

Preliminary data on anti-tumour activity: The best objective response observed was prolonged stable disease (stable disease>12 weeks), recorded in 2/25 patients: 513 days in a patient with thymic cancer (40 mg bd) and 289 days in a patient with gastric cancer (80 mg bd).

Study D2610C00003 - Phase IIa

By the [redacted] a total of 15 patients with ER+ breast cancer had received at least a single dose of AZD4547 in the first cohorts of the safety run-in to Study D2610C00003. Patients received 25 mg of exemestane daily for one week prior to the co administration of exemestane with AZD4547, until the patient withdrew from the study. Safety run-phase is ongoing.

- Cohorts were dosed with the tablet formulation as follows: 80 mg bd (n=5), 40 mg bd (n=3), 80 mg bd 1 week on/ 1 week off (n=7)

- No DLTs have been reported to date.

- Although the 80 mg bd AZD4547 cohort did not fulfil the protocol definition of a non-tolerated dose (2/6 patients experiencing a DLT within the 21-day combination evaluation period), the Safety Review Committee decided that the 80 mg bd dose was not appropriate for chronic dosing in this patient population due to the emerging tolerability profile.

- At the time of data cut-off, all patients in cohort 1 discontinued the study treatment due to disease progression. In 40 mg bd cohort, two patients discontinued due to disease progression and 1 patient is ongoing. In cohort 3 (80 mg bd 1 week on/ 1

week off), four patients discontinued the study treatment (2 patients due to disease progression and 2 due to AEs of RPED) and 3 patients are ongoing.

- To date, the majority of AEs have been CTC Grade 1 or 2 in intensity. The most commonly reported AEs were dry mouth (10 patients), hair and nail disorders (9 patients), dry skin (5 patients), fatigue/asthenia (8 patients) and epistaxis (5 patients).

- There have been 15 SAEs reported from 7 patients. Anaemia was the only SAE term reported for more than 1 patient. SAEs of mucosal inflammation, asthenia, oesophageal achalasia and troponin increased in 1 patient were considered treatment-related.

Preliminary data on anti-tumour activity: The best objective response observed was prolonged stable disease (stable disease>12 weeks), recorded in 2 patients with breast cancer: 136 days (40 mg bd) and 160 days (40 mg bd).

Study D2610C00004 - Phase II study – current study

- By [redacted] a total of 25 patients with advanced gastric cancer had received study treatment of AZD4547 (80 mg bd 2 weeks on and 1week off schedule) or paclitaxel in Study D2610C00004.

- At the time of data cut-off ([redacted] 6 patients had discontinued the study treatment due to disease progression and 19 patients were ongoing.

- To date, there have been 120 AEs reported in 23 patients. The majority of AEs have been CTCAE Grade 1 or 2 in intensity.

- Two of the 25 patients had on-treatment SAEs (lower respiratory tract infection and dysphagia). One treatment related SAE (lower respiratory tract infection) was reported in 1 patient.

The adverse events considered to be associated with the administration of AZD4547 can be found in Section 5.4 of the current IB.

1.1.3 Paclitaxel

Paclitaxel is a taxane, which has antineoplastic activity via its action on microtubular structures throughout the cell cycle and in particular during the dynamic reorganisation during cell division. In the UK it is licensed for the treatment advanced ovarian cancer both in the first and second line setting (post-platinum based therapy), in breast cancer in the adjuvant (post anthracycline and cyclophosphamide therapy), first or second line advanced setting (in combination with anthracycline or in anthracycline-unsuitable patients), in non-small cell lung cancer (in combination with cisplatin), and in AIDS-related Kaposi's sarcoma (post-antrhacycline). Posology depends upon clinical indication. For details of National licensed indications please refer to Appendix F. The National Comprehensive Cancer Network advise

that in the 2nd line gastric cancer setting the options for treatment of patients with ECOG performance score ≤2 are either chemotherapy (including paclitaxel monotherapy regimens), best supportive care or clinical trial (NCCN11). A review of clinical trials of paclitaxel containing regimens for advanced gastric cancer supported the administration of paclitaxel by weekly infusion at 80 mg/m^2 (Sakamoto et al. 2009).

Paclitaxel must be administered according to local prescribing information, with pre-medication consisting of corticosteroids, antihistamines and H_2-receptor antagonists. The most frequent significant undesirable effects of monotherapy paclitaxel administration are bone marrow suppression, peripheral neuropathy, arthralgia and myalgia. Severe hypersensitivity reactions, with possible fatal outcomes have been reported infrequently in some clinical, and more frequently there are minor hypersensitivity reactions resulting in flushing and rash. Injection site reactions during intravenous administration may lead to localised oedema, pain, erythema and induration. Other commonly reported adverse events include nausea, vomiting, infection, alopecia, diarrhoea, bradycardia, hypotension, mucosal inflammation, transient nail and skin changes, increases in AST and alkaline phosphatase blood results.

The mean half-life of paclitaxel depends upon duration of infusion. Paclitaxel is primarily metabolised by hepatic metabolism and biliary clearance, with CYP2D8 and CYP3A4 being identified as major contributing enzymes.

See Appendix F for further details.

1.2 Research hypothesis

The research hypothesis is that the molecular driver of a subset of patients with gastro-oesophageal cancer originates from the presence of FGFR2 polysomy or gene amplification. Treatment of these patients with an FGFR inhibitor should result in objective clinical benefit.

1.3 Rationale for conducting this study

Genetic modifications of the FGF receptors -1, 2, 3 or 4 including amplification, translocation and mutations have been described in a range of tumour types. Non-clinical data indicate the presence of such modifications confer sensitivity to FGFR inhibitors in FGFR2 amplified gastric cancer cell lines, xenograft and explant models (see Section 1.1.2.1). AZD4547 is a novel tyrosine kinase inhibitor with specific activity against the Fibroblast Growth Factor Receptors (FGFR1, 2 and 3). Therefore the rationale for conducting this study is to provide data on the efficacy of AZD4547 in the FGFR2 amplified gastric cancer patient population. Patients with advanced gastro-oesophageal cancer who have progressed following first-line chemotherapy have no global standard of care for second-line treatment and are appropriate to be considered for participation in clinical trials (NCCN11). In order to quantify the efficacy of AZD4547 in this population, patients will be randomised into receiving either AZD4547 or a comparator arm of weekly paclitaxel. A review of clinical trials of paclitaxel containing regimens in gastric cancer support the use of weekly infusion of paclitaxel as an appropriate comparator arm in the second-line setting (Emi et al. 2008, Kodera et al. 2007). Monotherapy

regimens with taxanes are used in the second-line setting in all territories participating in this study.

1.3.1 Progression Free Survival

The primary efficacy assessment will be performed by comparison of the progression free survival between the randomised treatment arms. PFS is a widely accepted parameter for the assessment of efficacy of cancer treatments. However, to ensure clinically meaningful improvements in OS are detectable in this study, the study is powered for OS with the primary analysis intended to be performed when there is appropriate maturity of overall survival events within the relevant strata that remain open at the primary analysis (see Section 9.5). This will ensure that the suite of endpoints available at that time will provide a robust assessment of the relative benefit of AZD4547 compared with paclitaxel.

1.3.2 Secondary efficacy assessments

In addition to the secondary assessment of OS, ORR and DoR, the proportion of patients without progressive disease at 8 weeks and changes in tumour size at 8 weeks will also be compared between the randomised treatment arms. The percentage of patients without progressive disease at 8 weeks is expected to convey meaningful clinical benefit in this population. The use of change in tumour size has been proposed as an endpoint to compare treatments and make decisions in early drug development (Bruno and Claret 2009) as it has been shown to be a predictor of OS (Wang et al. 2009, Bruno and Claret 2009) and offers greater statistical power than the traditional categorical response of ORR for comparison of treatment groups.

For this study, if AZD4547 results in better mean tumour shrinkage or in less tumour growth than paclitaxel alone (particularly at the interim analysis (see Section 12.2.11) when the power to assess PFS will be lower), then this would provide evidence of anti-tumour activity. This would provide useful information to help assess if AZD4547 warrants further investigation by proceeding with the completion of recruitment and proceeding to the primary analysis of this study. In addition to these assessments, the impact of treatment on disease-related symptoms and global health status/QoL and patient's WHO performance status will be assessed.

1.3.3 Secondary safety assessments

Secondary objectives of this study also include an assessment of the safety and tolerability of the intermittent schedule of AZD4547 monotherapy compared with paclitaxel alone in the gastro-oesophageal cancer population, as this particular patient population has not been extensively treated with this schedule of AZD4547 monotherapy previously.

1.3.4 Pharmacokinetics and Pharmacodynamics

This study will investigate the PK of the intermittent schedule of AZD4547 as monotherapy in gastro-oesophageal cancer patients. Exposure to AZD4547 in patients with advanced gastric cancer may be different from other patient populations, due to their underlying pathology and previous surgical interventions such as stomach resection. The timings of safety and PK assessments in the study have been designed using both non-clinical findings and emerging

data from the first single and multiple ascending dose study in patients with AZD4547 (D2610C000001). A further secondary endpoint will investigate the PK/PD relationship between plasma AZD4547 exposure and plasma concentrations of pharmacodynamic biomarkers (phosphate, bFGF and FGF23) and clinical measures of efficacy and safety.

1.3.5 Exploratory biomarker assessments

As part of the clinical drug development program for AZD4547, AstraZeneca plans to include investigations into variations in pharmacodynamic and exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from deoxyribonucleic acid (DNA), ribonucleic acids (RNA), proteins and/or metabolites. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or non-responders or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how it can be utilised to bring better drugs to the clinic. The ability to acquire appropriate consent to collect biological samples is of utmost importance in order to establish an archive and allow future meta-analysis of data derived from a number of studies with AZD4547.

From preclinical models it has been established that tumour FGFR2 gene amplification results in FGFR2 gene addiction. Outcome data matched to FGFR status of resected tumour tissue from Korean and Caucasian patients with stage I-IV gastric cancer indicates that patients with disease classified as FISH 6 (amplification) have a statistically significantly poorer prognosis than patients whose disease is classified as FISH 4/5 (polysomy) who in turn show a trend towards having a poorer prognosis than patients whose disease was classified as FISH 1-3 (Kilgour E et al. 2012 and AZD4547 IB). This suggests that the aggressiveness of the disease may increase in line with increasing FISH score. In particular, therefore, this exploratory biomarker research will focus on seeking to identify relationships between FGFR status at baseline and clinical outcomes of efficacy and safety in response to FGFR inhibition or standard treatment with paclitaxel.

It is anticipated that approximately 20-40% of gastric cancers will demonstrate either FGFR2 polysomy or amplification (AstraZeneca data on file). In these studies the EGFR FISH scoring system described by Garcia 2006 has been used and gene amplification is defined as equivalent to FISH 6, while FISH 5 refers to tumour samples with FGFR high polysomy and FISH 4 refers to samples with low polysomy. It is not currently known whether FGFR2 amplification is associated with early relapse or poor survival in advanced gastric cancer. It is possible that changes in FGFR2 gene copy number/amplification status occur during the course of disease, either as a consequence of disease progression or in response to therapy and exploratory biomarker analysis in this study may be able to identify examples of such changes in status via analysis of optional on treatment biopsies.

All samples submitted at pre-screen will be tested for FGFR2 gene copy number by FISH, patients who are FISH 4/5 & 6 are eligible for the study. Gastric cancer is characterised by histological and genetic heterogeneity, therefore, multiple evaluable biopsies from different regions of the tumour are recommended to ensure reliable determination of FGFR2 status. The

highest FISH score and FGFR gene amplification ratio will determine patient eligibility into the study and the stratum into which the patient will be randomised, however, analysis of additional material will assist in furthering understanding the extent and nature of FGFR2 signal distribution within tumours.

Tumour sample collection is detailed in Section 6.7.1.

1.3.6 Pharmacogenetics

Genetic research will be performed in the AZD4547 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD4547. Collection of DNA samples from populations with well-described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and possibly to genetically guided treatment strategies.

Pre-clinical data indicates that AZD4547 is metabolised by CYP2D6. Polymorphisms in the gene encoding this protein can result in some individuals being either poor or ultra metabolisers of substrates of this enzyme. Genotyping participants in this study may provide an understanding of any observed variation in pharmacokinetics or clinical response.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD4547 but also susceptibility to cancer. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action. A research proposal will be submitted for ethical review and approval, should additional analysis of these samples be required to respond to emerging data.

1.3.7 Exploratory health economic assessment

The exploratory assessment of health utility will provide an understanding of how patients rank and rate their health status during and after treatment with AZD4547 or paclitaxel. The assessment of gastric cancer palliative interventions will increase the understanding regarding the relationship between treatment impact on tumour and related cancer symptoms on resource use, such as the need for palliative procedures to address obstruction and bleeding.

1.4 Benefit/risk and ethical assessment

1.4.1 Potential benefit

Dysregulation of the FGFR pathway is observed in a variety of cancers, due to gene amplification, translocations or mutations. Non-clinical data suggests that inhibition of FGFR mediated signalling by AZD4547 can result in an anti-prolifereative and/or proapoptotic activity and may also have an anti-angiogenic effect. A subset of advanced gastro-oesophageal cancers may have disease that is driven by amplification of FGFR2. This study is investigating whether AZD4547 has the potential to provide benefit in terms of efficacy in patients with advanced gastric cancer that has FGFR2 polysomy or gene amplification (FISH ≥4) who have progressed following treatment with one prior chemotherapy regimen.

1.4.2 Potential risks identified from early clinical studies and from non-clinical toxicology studies with AZD4547

This section provides details of the currently identified and potential risks that have been determined both pre clinically from the toxicology studies in rat and dogs, and from the ongoing clinical trial programme.

Details of the results of these studies are provided in Section 1.1.2 of this protocol, and further information is in the IB. The monitoring and management of the potential risks is discussed below and in Section 5.10.1 (Management of toxicity associated with AZD4547).

1.4.2.1 Eyes

Eye changes such as conjunctivitis and corneal atrophy have been seen in rats and dogs dosed with AZD4547. In the clinical studies conducted to date the adverse events reported regarding the anterior aspect of the eye (dry eyes, punctuate keratopathy and keratitis) are consistent with the pathological changes that were seen pre-clinically. It is anticipated that patients will report any refraction disturbance or discomfort relating to the eye in advance of any significant pathology such as ulceration occurring. The decision to continue on study treatment if mild changes in the eye examination are observed will be left to the Investigator's discretion, since a patient may indicate a wish to tolerate a minor reduction of visual clarity if there is perceived clinical benefit from the therapy. A patient should be immediately discontinued from study treatment if corneal ulceration occurs, and appropriate expert ophthalmologic consultation should be initiated.

Retinal Pigmented Epithelium Detachment (RPED) has been identified in clinical studies with AZD4547 (13 occurrences as of [redacted]

Following implementation of regular OCT monitoring, a further 9 cases of RPED were diagnosed in asymptomatic patients, on the scheduled OCT scans in the AZD4547 programme. In addition to RPED events, 6 cases of patients with other retinal abnormalities were reported based on OCT scans.

The majority of these events of RPED and other posterior eye changes were diagnosed after 21 days of treatment. Where OCT follow-up scans were available most cases had partial or complete remission within 2 weeks of stopping treatment. In the patients who went on to recommence treatment at a lower dose after the initial AE of RPED/related conditions had resolved, the condition recurred. After recurrence of the events the study treatment was permanently discontinued and the events resolved without sequelae.

No cases of RPED were classified as SAEs. Analysis of the limited data to date has not identified a relationship between the incidence of RPED and AUC, C_{max} or minimum plasma concentration (C_{min}) of AZD4547.

Patients with conditions pre-disposing to the development or re-occurrence of RPED will be excluded from participation in the study. In order to detect this, patients will have a baseline ophthalmologic examination (including OCT (Optical Coherence Tomography) scan) prior to

initiation of study treatment and approximately monthly for the first 3 months as shown in the study plan (Table 1). Thereafter, patients continuing the study treatment should have a full ophthalmological review every 8 weeks (± 1 week) until permanent discontinuation of AZD4547.

At any time, any abnormal visual symptoms or signs will trigger a full ophthalmological review. An algorithm for management is provided in Figure 3 and Figure 4.

1.4.2.2 Mineralisation, particularly in the heart

The cardiac mineralisation identified in both non-clinical species tested is thought to be as a direct consequence of elevated phosphate levels. The increase in phosphate levels are thought to be pharmacological as a consequence of inhibition of FGF23 modulated phosphate homeostasis in the kidney (Razzaque and Lanske 2007). In the dog, the increase in phosphate level occurred prior to mineralisation, and at lower doses where no mineralisation occurred. Mineralisation was of low incidence, and was not present following 4 weeks off dose. The clinical studies to date have confirmed the pre-clinical finding of increases in serum phosphate and following review of the data hyperphosphataemia is considered to be an expected event in patients treated with AZD4547. There have been no reports and no evidence of any soft tissue, including cardiac, mineralisation in the clinical studies to date. However, based upon the presumption that increases in phosphate precede mineralisation, patients will be excluded from the study if they have phosphate or calcium levels above the upper limit of normal at entry. Phosphate and calcium are included in the standard clinical chemistry safety bloods which will be taken at each study visit. Increases in phosphate have been seen in patients treated with AZD4547. Any patient who experiences a doubling of phosphate from baseline or a corrected calcium: phosphate product >4.5 (if using $mmol^2/L^2$) or >56 (if using mg^2/dl^2), should have phosphate chelation therapy initiated with a non-calcium containing agent, and clinical chemistry monitored weekly until resolution of the parameter to below the intervention limit. Investigators must seek appropriate specialist medical consultation (renal or metabolic) to advise on the prescription and titration of phosphate chelation agents, and to raise the patients awareness of low phosphate diets.

It is expected that mineralisation occurring within the heart would result in functional changes prior to any gross structural changes being apparent by specific imaging technology. Therefore patients will have regular troponin I measurements at the same time as the clinical chemistry safety blood measurements; there will be ECGs performed at screening, day 1 (pre-dose, C_{max}) and day 7 (C_{max}) of cycle 1 then start of each cycle and at discontinuation; and MUGA scan/ echocardiograms will be performed at baseline, at the beginning of cycle 2, and 3-monthly thereafter if the patient is still on study treatment, in order to identify functional changes. The protocol also includes standard exclusion criteria for unstable cardiac conditions and risk factors for QTc prolongation. It is assumed that the myocardial necrosis observed in the rat was preceded by sub-clinical mineralisation, therefore the measures described above for monitoring of phosphate and cardiac function should identify any early changes within the heart and indicate the appropriate time for intervention, therefore no additional specific imaging is proposed.

1.4.2.3 Renal toxicity

There have been 4 reports of renal failure in the first time in man study. In each of these cases there are confounding factors and the patients underlying disease and medical history provide alternative explanations for these events. However 2 of the events were considered as a dose limiting toxicity in their respective cohorts and as a result patients should be closely monitored for any signs of impaired renal function. Patients should be excluded from this study if they have serum creatinine >1.5 times the upper limit of normal concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation). Serum creatinine and blood urea nitrogen should be included in the standard clinical chemistry safety bloods and should be assessed on a regular basis as per the individual study plan.

1.4.2.4 Stomatitis/dry mouth

Events of stomatitis/oral mucositis and dry mouth have been reported in the clinical studies to date. In cases of stomatitis particular attention should be given to prophylaxis, maintaining a high standard of oral hygiene with the regular use of antibacterial mouthwashes during the study. Saline nasal sprays may help nasal mucosal dryness and so reduce the incidence of epistaxis.

1.4.2.5 Dermatological toxicity

There have been a number of events reported in patients receiving treatment with AZD4547 involving the skin and associated appendages. These include events of dry skin, alopecia, hair changes, trichomegaly and changes to the nails and nail beds. Following review of the data these toxicities are considered to be expected events in patients treated with AZD4547.

1.4.2.6 Bone turnover

Histopathological changes in bone structure have been identified in the rat but not the dog. Similar bone changes have been reported in the literature following administration of another FGFR inhibitor to rats (Brown et al. 2005) and have been considered due to a pharmacological effect on growing bones. Patients born with mutations in FGFR genes develop a range of skeletal disorders during childhood such as osteoglyphonic dysplasia, Apert syndrome and hypochondroplastic dwarfism (White et al. 2005). All patients participating in this study are anticipated to be over the age of 25, which is the age at which maturation of the skeleton is completed. Bone AEs should be reviewed on a case-by-case basis as it is not possible to provide specific stopping criteria given the background of extensive metastatic disease seen with this patient population, which might result itself in pathological fractures and bone pain. Regular monitoring of the calcium and phosphate levels have been described above with regards to mineralisation.

1.4.2.7 Genotoxicity

AZD4547 was not mutagenic in *in vitro* mutation assays (Ames test and mouse lymphoma assay), or genotoxic in an *in vivo* study. An aromatic amide intermediate (AZ12602108) was evaluated in a full 5 strain Ames test and was negative.

1.4.2.8 Reproductive organs

No reproductive toxicology nor teratogenic studies have been conducted with AZD4547 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation, and women who are breast-feeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

1.4.2.9 CYP450 induction/inhibition

AZD4547 is a substrate of CYP3A4 and CYP2D6 therefore use of inhibitors/inducers of these isoforms will be excluded prior to the first dose of AZD4547 (time period as specified in Appendix E) and for the duration of study treatment. CYP1A1, an isoform highly inducible by cigarette smoking, is also capable of metabolism of AZD4547 and may lead to lower exposures in smokers, therefore smoking status will be recorded as part of the demographic information for all participating patients. AZD4547 shows weak competitive inhibition of CYP3A4 and is also a time-dependent inhibitor of this isoform. This may lead to reduced metabolism (and increased exposure) of any co-administered drugs that are significantly cleared via this pathway. Concomitant use of medicines significantly metabolised by CYP3A4 will be contraindicated during the course of the study. Use of other agents less significantly metabolised will be permitted with caution if considered clinically indicated for the welfare of the patients, and patients should be monitored closely for signs of possible drug interactions (see Appendix E).

1.4.3 Overall benefit-risk and ethical assessment

Although there can be no certainty of clinical benefit to patients, non-clinical data with AZD4547 support the hypothesis that FGFR inhibition may be a valid target for the treatment of gastro-oesophageal cancers associated with over-activity of this pathway as a result of FGFR2 amplification. The non-clinical safety profile and emerging clinical profile from the early clinical studies have not identified risks that would preclude investigation in this setting. The study design aims to minimise potential risks. A dose modification strategy for management of toxicity and monitoring is in place for those risks deemed to be most likely or serious. Thus the benefit/risk assessment for this study supports the administration of AZD4547 in advanced gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction) cancer patients with FGFR2 polysomy and gene amplification (FISH ≥4).

2. STUDY OBJECTIVES

2.1 Primary objective

- To investigate the efficacy of AZD4547 compared with paclitaxel by assessment of progression-free survival (PFS) in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.

2.2 Secondary objectives

- To investigate the efficacy of AZD4547 compared with paclitaxel by comparison in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification as measured by:
    - Overall Survival (OS)
    - Change in tumour size at 8 weeks
    - Objective Response Rate (ORR)
    - Duration of Response (DoR)
    - Percentage of patients without progressive disease at 8 weeks
- To investigate the PK of AZD4547 in patients receiving AZD4547.
- To investigate the possible pharmacokinetic/pharmacodynamic (PK/PD) relationships between plasma AZD4547 exposure and plasma concentrations of phosphate, bFGF, FGF23 and efficacy and other exploratory pharmacodynamic endpoints.
- To assess disease-related symptom changes and time to symptom progression in patients receiving AZD4547 or paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.
- To assess changes in and time to deterioration of Health Related Quality of Life (HRQoL) in patients receiving AZD4547 or paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.
- To assess changes in, and time to deterioration of, WHO performance status in patients receiving AZD4547 or paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.

2.3 Safety objective

The safety objective in this study will be assessed across 3 patient populations described above:

- To compare and assess the safety and tolerability of AZD4547 and paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.

2.4 Exploratory objectives

- To collect and store plasma, serum and archival tumour samples and/or serial tumour biopsies and analyse surplus blood or tissue, if available, for potential future exploratory research into factors that may influence development and progression of cancer and/or response to AZD4547 (where response is defined broadly to include efficacy, tolerability or safety).

- To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD4547 treatment and/or susceptibility to cancer.

- To analyse bone biomarkers from fasting blood samples, for exploratory research into the pharmacological activity of AZD4547 on non-tumour tissues.

- To explore the predictive value of biomarkers of the relative efficacy of AZD4547 compared with paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification and separately in patients with tumours that have high FGFR2 amplification (FISH 6).

- To investigate the relationship between absolute FGFR2 gene copy number, FGFR2 ratio and an alternative cut-off (FISH 5/6 vs. FISH 4), and the efficacy of AZD4547 as compared with paclitaxel.

- To investigate heterogeneity in patients receiving AZD4547 or paclitaxel with respect to FGFR2 gene copy number through the collection and analysis of multiple tumour biopsies.

- To explore changes in health utility in patients receiving AZD4547 or paclitaxel in all randomised patients, patients with tumours that have FGFR2 amplification (FISH 6) and separately in patients with tumours that have high FGFR2 amplification.

- To investigate the impact of AZD4547 and paclitaxel on gastric cancer management resource use.

The exploratory analyses may 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 randomised, open label, multi-centre study to assess the efficacy and safety of AZD4547 monotherapy versus paclitaxel.

Patients will be male or female, aged 25 years or older with advanced gastric cancer (including adenocarcinoma of the lower third of the oesophagus and the gastro-oesophageal junction) that has either FGFR2 polysomy or FGFR2 gene amplification who have relapsed or have not responded, following one prior chemotherapeutic regimen. In total approximately 240 patients will be randomised into this study.

Patients will be assigned to one of three strata in the study (polysomy, low amplification or high amplification) according to the FGFR2 status of their tumour as measured by FISH. 80 patients that have tumours with FGFR2 polysomy (FISH 4 or 5) will be randomised in a 1:1 (AZD4547: paclitaxel) ratio in a polysomy stratum and 160 patients that have tumours with FGFR2 gene amplification (FISH 6) will be randomised in a 3:2 (AZD4547: paclitaxel) ratio with 80 patients being recruited to a low amplification stratum and 80 patients to a high amplification stratum. Accrual to one stratum may be completed ahead of the others. Patients will receive either AZD4547 (80 mg bd on a 2 weeks on, 1 week off schedule of a 21 day cycle) or paclitaxel (80 mg/m^2 weekly on days 1, 8 and 15 of a 28 day cycle) see Section 5.5.2.

Patients who the investigator considers may be eligible for the study will be pre-screened for the FGFR2 status of their tumour, as defined by their FISH (FISH ratio will also be assessed at this time). It is estimated that around 3300 patients will need to be pre-screened in order to randomise up to approximately 240 patients. This figure is based on available internal AstraZeneca prevalence data for FGFR2 polysomy and amplification and also takes in to account the stratification of the study, as it is expected that the incidence of FGFR2 gene amplification will be lower than the incidence of FGFR2 polysomy. However, the exact number of patients that will need to be pre-screened will depend on the actual prevalence of FGFR2 polysomy, FGFR2 low level gene amplification and FGFR2 high level gene amplification in this patient population. It is expected that FGFR2 polysomy will be more prevalent than low level amplification and that high amplification will be the slowest stratum to accrue patients on account of the lowest expected prevalence.

Consent to Pre-screening (Visit 1) will be closed once sufficient patients have been enrolled to reach the required number of randomised patients. At this point, any patient that has already consented to pre-screening but has yet to enter screening for the randomised part of the study (Visit 2) will be given up to 28 days to provide consent to the main part of the study (following central confirmation of FGFR2 gene amplification) see Section 5.2.1.

Patients randomised to the AZD4547 arm of the study, will receive AZD4547 80 mg twice daily on a 2 weeks on, 1 week off schedule, in a 3-week cycle. The SRC will meet at approximately 2-monthly intervals to review all available safety data. On the basis of these reviews and/or the results of the interim analysis, the SRC will have the option to propose that a lower dose level or a different dose schedule should be evaluated (see Section 5.5.3). In the event that the SRC and AstraZeneca agree that the recommendation to explore an alternative dose or schedule be adopted, any patients already recruited to the AZD4547 arm at this point will continue to receive AZD4547 as per their current dose and schedule; provided that they are tolerating the treatment and the investigator believes they are gaining benefit.

Alternatively, the investigator may elect to change the dose/schedule of patients recruited prior to the dose change to match the new dose/schedule. Any patients already recruited to the paclitaxel arm will continue on their originally assigned treatment. After a change to the dose or schedule of AZD4547, any new patients entering the AZD4547 arm of the study will receive AZD4547 as per the new dose and schedule. AstraZeneca and the SRC may also elect to increase the recruitment target for the study to compensate for those patients who were recruited to either treatment prior to the change in dose or schedule. There will be no more than 2 changes made to dose or schedule during the study (see Table 4).

In the event of any changes, to the FGFR amplification ratio that defines the cut-off for entry to the polysomy and amplification strata (See Section 5.2.1), the recruitment target for one or more stratum may be adjusted to ensure recruitment of sufficient patients for statistical validity relative to the final cut-off criteria.

All randomised patients will be followed up to objective progression for assessment of PFS and with survival contacts to death for assessment of OS.

Patients may remain on study treatment until objective disease progression unless they are withdrawn early due to any of the discontinuation criteria detailed in Section 5.8. Patients in the paclitaxel arm may receive up to the maximum number of cycles according to local practice if they do not withdraw from treatment due to disease progression, AE or withdrawal of consent. Patients who discontinue treatment for reasons other than progression or death will continue to be followed for progression and overall survival.

For all patients who are pre-screened, a survival status will be obtained at the time of the primary efficacy analysis. A further survival assessment may be performed at a later date to further explore the association between FISH score and prognosis.

Patients who are still receiving study treatment at the time of the primary analysis should continue to be monitored and assessed for safety, as per the study plan (Table 1 and Table 2). However, in terms of the data that should be recorded, only SAEs need to be entered on the clinical database until the final survival assessment has taken place. SAEs must also continue to be reported to AZ Patient Safety within the usual reporting timelines.

Patients are permitted to continue to receive study treatment beyond the closure of the database (after the final survival assessment) if, in the opinion of the investigator, they are continuing to receive benefit from study treatment. For patients who do continue to receive treatment, investigators will continue to follow them for safety in accordance with Section 6.4.3 (Time period for collection of adverse events) and all SAEs must continue to be reported to AZ Patient Safety within the usual timelines.

There will be 2 interim analyses during the study which will be conducted to ensure adequate evidence of anti tumour activity (as measured by changes in tumour size at 8 weeks) and an acceptable safety profile has been demonstrated in a given stratum prior to recruiting the full 80 patients required per stratum to robustly assess progression free and overall survival in that stratum. Due to the differing prevalence of FGFR2 polysomy, low gene amplification and

high gene amplification in this patient population, and hence the differences in time to recruit the different strata, two separate interim analyses are planned:

Interim analysis 1

The data cut-off for the first interim analysis will occur when the first 30 FISH 4/5 patients and the first 25 FISH 6 low amplification patients have been followed up for a minimum of 8 weeks (or progressed, or died prior to 8 weeks). Enrolment into the FISH 4/5 stratum will be put on hold once sufficient patients have entered screening to achieve the 30 randomised patients required for the first interim analysis. Recruitment to both FISH 6 strata will remain open whilst data for the first interim analysis is being collected and analysed subject to a cap of 40 patients randomised in total within the FISH 6 low amplification stratum.

The first interim analysis will be performed to determine whether there is sufficient evidence of anti-tumour activity and an acceptable safety profile which would warrant continuation of either or both of these strata (polysomy and FISH 6 low amplification) recruiting to the full 80 patients. If either (or both) of these strata are discontinued after the first interim analysis then recruitment to these strata will be stopped (or will not be re-opened, in the case of the FISH 4/5 stratum). Conversely if either (or both) of these strata are continued after the first interim, then recruitment will re-open and/or the cap on recruitment for the FISH 6 low amplification will be removed. Recruitment to the FISH 6 high amplification stratum will remain open through out and after Interim Analysis 1 as continuation of that stratum will be contingent on a positive outcome from Interim Analysis 2.

Interim Analysis 2

The scope of Interim Analysis 2 will depend on decisions taken at Interim Analysis 1 and will only include data for those strata that were continued after Interim Analysis 1.

If only the FISH6 high amplification stratum remains open after the first interim analysis, the data cut-off for the second interim analysis will occur when 25 patients with FISH 6 high amplification have been randomised and followed-up for a minimum of 8 weeks (or progressed or died prior to 8 weeks). At this point a decision will be taken concerning the continuation of this FISH 6 high amplification stratum, based on the strength of any evidence of anti tumour activity observed.

If both FISH 6 strata remain open after the first interim analysis and irrespective of whether recruitment has continued in the polysomy stratum, the data cut-off for the second interim analysis will be the earliest of approximately 60 overall survival events having occurred across the combined FISH 6 strata, or the first 25 FISH 6 high amplification patients have been followed up for a minimum of 8 weeks (or progressed or died prior to 8 weeks). In addition to assessing changes in tumour size and response rate within the FISH 6 high amplification stratum, an initial assessment of progression free survival and overall survival across both FISH 6 strata will be performed.

Any recruitment that is ongoing at the time of the 2nd interim analysis will remain open whilst data is being collected and the analysis performed provided that the overall recruitment target of 80 patients in a stratum has not already been reached.

If a decision is taken not to continue the study past the second interim analysis, then recruitment to all open strata will be stopped and a primary analysis of all data from all randomised patients will be completed and reported.

Primary Analysis

If the study proceeds beyond the second interim analysis a total of approximately 80 patients will be randomised in each of the stratum which remain open.

Depending on which strata remain open after the interim analyses, the primary analysis will occur at the following times:

- If FISH 6 high amplification strata only remains open – the data cut off for the primary analysis will be when approximately 60 deaths have occurred in the FISH 6 high amplification stratum.

- If both FISH 6 strata remain open only – the data cut off for the primary analysis will be when approximately 102 deaths have occurred across the two FISH 6 strata.

- If all 3 strata remain open – the data cut off for the primary analysis will be when approximately 163 deaths have occurred across all three strata provided that at least 102 deaths have occurred across the two FISH 6 strata.

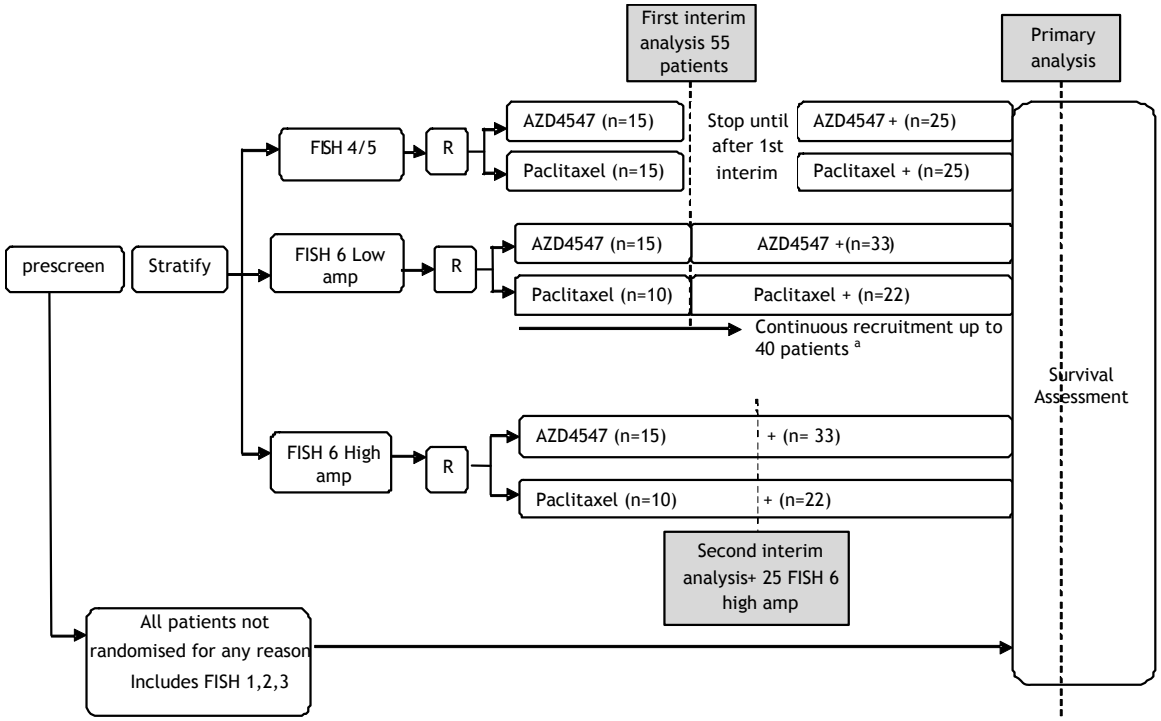
Follow up for PFS and OS

All randomised patients will be followed up to objective progression for assessment of PFS, with continued contact to determine OS status.

Patients may remain on study treatment until objective disease progression unless they are withdrawn early due to any of the discontinuation criteria detailed in Section 5.8. Patients who discontinue treatment for reasons other than progression or death will continue to be followed for PFS and OS.

For all patients who are pre-screened, a survival status will be obtained at the time of the primary efficacy analysis. Further survival analyses may be performed at a later date to further explore the association between FISH score and prognosis.

Figure 1 Study Flow Chart



R = Randomised

[a] – Recruitment to FISH 6 low amplification will continue up to a cap of 40 randomised patients prior to the Second Interim Analysis

3.1.1 Study Plans

Actual assessment days may take place within ±1 day of the scheduled assessment day, eg, assessments scheduled for cycle 1 day 14 may take place on cycle 1 day 15. From cycle 3 onwards assessment days may take place within ±3 days. Some individual assessments (ophthalmic exam 6.4.9.2 and RECIST assessments 6.3.1) may take place ±1 week of scheduled assessment day. MUGA/echocardiogram (6.4.9.1) results may be used on assessments performed within 3 months of commencing AZD4547 and ±1 week of scheduled assessment days thereafter. Assessment days will all be relative to the start of dosing (cycle 1 day 1), irrespective of any dose interruptions. If Day 14 is delayed to Day 15 in cycle 1, the treatment "off period" should also be delayed by a day (ie, the patient must be dosed on day 15 in this case) in order that PK sampling can be taken on a dosing day.

Table 1 Study Plan: AZD4547 patients

	Pre-screen	Screening	Cycle 1				Cycle 2			Cycle 3			Cycle 4 – *xx*	IP w/d	28-day follow-up	Survival assessment	Details in Section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13-xx**				
Activity/ Day	***x* to –1**[e]	**-28 to -1**	**1**	**7**	**14**	**21**[a]	**1**	**14**	**21**[a]	**1**	**14**	**21**[a]	**1**				
Informed consent	X	X															5.2.1, 8.4
Demography& smoking status	X																6.2
Disease status	X	X															6.2
Tumour sample/FISH score	X[b]																6.7.1
Medical/surgical history		X															6.2
Selection criteria	X	X															4.1-4.2
Pregnancy test		X															6.2
WHO Performance status		X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.4.6
Physical examination		X	X				X			X			X	X			6.4.6
Ophthalmic assessments		X					X			X			X				6.4.9.2
Vital signs		X	X		X		X	X		X	X		X	X			6.4.8

Table 1 Study Plan: AZD4547 patients

	Pre-screen	Screening	Cycle 1				Cycle 2			Cycle 3			Cycle 4 – *xx*	IP w/d	28-day follow-up	Survival assessment	Details in Section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13-xx**				
Activity/ Day	***x* to –1**[e]	**-28 to -1**	**1**	**7**	**14**	**21**[a]	**1**	**14**	**21**[a]	**1**	**14**	**21**[a]	**1**				
Safety Lab Assessments		X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.4.5
ECG		X	X	X			X			X			X	X			6.4.7
Echo/MUGA Scan		X					X										6.4.9.1
Concomitant medication/procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X		5.6, 6.9
Anti-cancer treatment	X	X												◄———		———►	5.6, 6.4.10, 6.10, 6.2
Adverse events	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.4.1-6.4.4
Tumour assessments (RECIST v1.1)		X								X[d]	X[d]						6.3.1
Pharmacogenetics (optional)	X		X														6.8
Serial tumour biopsy (optional)		X			X									X			6.7.2

Table 1 Study Plan: AZD4547 patients

	Pre-screen	Screening	Cycle 1				Cycle 2			Cycle 3			Cycle 4 – *xx*	IP w/d	28-day follow-up	Survival assessment	Details in Section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13-xx**				
Activity/ Day	***x* to –1**[e]	**-28 to -1**	**1**	**7**	**14**	**21**[a]	**1**	**14**	**21**[a]	**1**	**14**	**21**[a]	**1**				
Blood borne biomarkers		X			X		X	X		X	X		X	X			6.7.3
Bone biomarker samples			X		X		X	X		X	X						6.7.4
PK				X	X		X	X						X			6.6
Survival status																X	6.10
AZD4547 dispensed			X				X			X			X				5.5
Patient reported outcomes[g]			X		X		X[f]	X[f]		X	X		X	X	X		6.5
ClinPhone IVRS/IWRS	X	X	X				X			X			X	X			6.2.2

[a] – This visit is not required for the initial AZD4547 schedule (3 weekly cycle; 2 weeks on, 1 week off). It will only be required if the schedule is switched to a 4 weekly schedule (2 weeks on, 2 weeks off)

[b] –Patients who had a FISH score of 1-3 when tested at pre-screening for the FGFR2 status of their tumour, can be re-tested on a fresh tumour sample, after they have relapsed or not responded to 1st line treatment

[c] – Procedure related SAEs must be collected for patients who require a fresh tumour biopsy for FGFR2 FISH testing or who agree to a genetic test.

[d] - Tumour assessment required at 8 weeks from randomization date. The 8 week RECIST assessment will be at Cycle 3, day 14 (ie, at 8 weeks) for a 3-week schedule or at Cycle 3, day 1 (ie at 8 weeks) for a 4-week schedule. Subsequent RECIST assessments will be performed every 8 weeks until objective disease progression.

[e]- No specific window will apply during the recruitment period but a window of 28 days will be applied once pre-screening is closed (see Section 5.2.1)

[f] – Assessment only applicable if the dosing schedule is switched to a 4 weekly schedule (2 weeks on, 2 weeks off)

[g] - Patient reported outcomes to be performed every 2 weeks. Where no visit is scheduled the patient can complete the questionnaire at home and return the completed questionnaire during their next scheduled visit.

For clarity, a study plan with a 3 weekly cycle length will be provided to sites at the start of the study. If the cycle duration is subsequently changed to a 4 weekly cycle length, following a decision to amend the schedule, an updated study plan will be sent to the sites.

Table 2 Study Plan: Paclitaxel patients

	Pre-screen	Screening	Cycle 1 (28 day cycle)				Cycle 2 (28 day cycle)			Cycle 3 (28 day cycle)			Cycles 4-*xx* (28 day cycle)			IP w/d	28-day follow-up	Survival assessment	Details in Section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15-*xx***				
Activity/ Day	***x* to –1[e]**	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**				
Informed consent	X	X																	5.2.1, 8.4
Demography& smoking status	X																		6.2
Disease status	X	X																	6.2
Tumour sample/FISH score	X[b]																		6.7.1
Medical/surgical history		X																	6.2
Selection criteria	X	X																	4.1-4.2

Table 2 Study Plan: Paclitaxel patients

	Pre-screen	Screening	Cycle 1 (28 day cycle)				Cycle 2 (28 day cycle)			Cycle 3 (28 day cycle)			Cycles 4-*xx* (28 day cycle)			IP w/d	28-day follow-up	Survival assessment	Details in Section
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-*xx*				
Activity/ Day	*x* to –1[e]	-28 to -1	1	8	15	22	1	8	15	1	8	15	1	8	15				
Pregnancy test		X																	6.2
WHO Performance status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.4.6
Physical examination		X	X				X			X			X			X			6.4.6
Opthalmic assessment		X																	6.4.9.2
Vital signs		X	X		X		X		X	X		X	X			X			6.4.8
Safety Lab Assessments		X	X	X	X	X[a]	X	X[a]	X	X	X[a]	X	X	X[a]	X	X	X		6.4.5
ECG		X	X	X			X			X			X			X			6.4.7
Echo/MUGA Scan		X					X												6.4.9.1
Concomitant medication/procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		5.6, 6.9

Table 2 Study Plan: Paclitaxel patients

	Pre-screen	Screening	Cycle 1 (28 day cycle)				Cycle 2 (28 day cycle)			Cycle 3 (28 day cycle)			Cycles 4-*xx* (28 day cycle)			IP w/d	28-day follow-up	Survival assessment	Details in Section
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-*xx*				
Activity/ Day	*x* to –1[e]	-28 to -1	1	8	15	22	1	8	15	1	8	15	1	8	15				
Anti-cancer treatment	X	X														◄———		———►	5.6, 6.4.10, 6.10, 6.2
Adverse events	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.4.1-6.4.4
Tumour assessments (RECIST v1.1)		X								X[d]									6.3.1
Pharmacogenetics (optional)	X		X																6.8
Serial tumour biopsy (optional)		X			X											X			6.7.2
Blood borne biomarkers		X			X		X		X	X		X	X			X			6.7.3
Survival status																		X	6.10
Paclitaxel infusion			X	X	X		X	X	X	X	X	X	X	X	X				5.5

Table 2 Study Plan: Paclitaxel patients

	Pre-screen	Screening	Cycle 1 (28 day cycle)				Cycle 2 (28 day cycle)			Cycle 3 (28 day cycle)			Cycles 4-*xx* (28 day cycle)			IP w/d	28-day follow-up	Survival assessment	Details in Section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15-*xx***				
Activity/ Day	***x* to –1**[e]	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**				
Patient reported outcomes			X		X		X		X	X		X	X		X	X	X		6.5
ClinPhone IVRS/IWRS	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X			6.2.2

[a] – Safety assessments as per local practice
[b] –Patients who had a FISH score of 1-3 when tested at pre-screening for the FGFR2 status of their tumour, can be re-tested on a fresh tumour sample, after they have relapsed or not responded to 1st line treatment
[c] - Procedure related SAEs must be collected for patients who require a fresh tumour biopsy for FGFR2 FISH testing or who agree to a genetic test.
[d] - Tumour assessment required at 8 weeks from randomisation date. The 8 week RECIST assessment will be at Cycle 3, day 1. Subsequent RECIST assessments will be performed every 8 weeks until objective disease progression.
[e]- No specific window will apply during the recruitment period but a window of 28 days will be applied once pre-screening is closed (see Section 5.2.1)

3.2 Rationale for study design, doses and control groups

3.2.1 Rationale for study design

This is a randomised, open label, multi-centre study to assess the efficacy and safety of AZD4547 monotherapy versus paclitaxel in patients with advanced gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction) who have relapsed or have not responded following treatment with one prior chemotherapy or chemo radiotherapy regimen administered as first line treatment.

The overall purpose of the study is to determine whether the administration of AZD4547 improves clinical outcome compared with paclitaxel in patients with advanced gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction) that have tumours with FGFR2 polysomy or gene amplification (FISH ≥4).

Pre-clinically, gastric adenocarcinoma cell lines that have FGFR2 gene amplification are sensitive to AZD4547, resulting in reduced cell proliferation and cell death. AZD4547 has been shown to induce profound tumour regression in two gastric cancer xenograft models, including a patient derived explant model, in both of which FGFR2 was highly amplified (FISH 6) with high gene copy number/ratio. Based on these data the hypothesis is that tumours with increased FGFR copy number/ratio will be sensitive to treatment with AZD4547. Increased gene copy number can be achieved through two mechanisms, namely gene amplification resulting in elevated ratio of FGFR gene copies to copies of the relevant chromosome and polysomy (FISH 4/5) which also results in elevated FGFR gene copy number due to replication of the relevant chromosome.

Within archival tissues that have been classified as FISH 6, analysis of individual gene copy number and ratio scored indicates that there is a range in the degree of FGFR amplification. The fact that, to date, the preclinical models in which AZD4547 has demonstrated the greatest anti-tumour activity have relatively high levels of gene amplification (ratio ≥3.0) could be consistent with a hypothesis that higher levels of amplification are required to confer sensitivity to FGFR inhibition, however due to a lack of gene amplified models with ratio ≤3.0 the exact cut-off for sensitivity within the gene amplified FISH 6 cohort cannot be inferred from these preclinical studies. It is therefore yet to be determined whether polysomy, low amplification or high amplification of FGFR2 are required to confer sensitivity to treatment with AZD4547.

By stratifying the study according to FGFR2 polysomy (FISH 4/5) FGFR2 low level amplification (FISH 6 with low gene amplification ratio) and FGFR2 high level amplification (FISH 6 with high gene amplification ratio), we will endeavour to investigate whether the level of polysomy or gene amplification of FGFR2 has an impact upon clinical outcome.

As the prevalence of patients with tumours that have FGFR2 gene amplification (FISH 6) tumours is expected to be <10% (AstraZeneca data on file) in the gastric cancer patient population, a 3:2 (AZD4547:paclitaxel) randomisation ratio has been used within the

amplification strata to give patients that have tumours with FGFR2 amplification an increased chance of receiving AZD4547.

The primary efficacy assessment will be performed by comparison of the progression free survival between the randomised treatment arms. PFS is a widely accepted parameter for the assessment of efficacy of cancer treatments, and improvements in PFS in advanced gastric cancer strongly correlate with improvements in OS (Shitara et al. 2011). However, to ensure clinically meaningful improvements in OS are detectable in this study, the study is powered for OS with the primary analysis intended to be performed when there is appropriate maturity of overall survival events within the relevant strata that remain open at the primary analysis (see Section 9.5). This will ensure that the suite of endpoints available at that time will provide a robust assessment of the relative benefit of AZD4547 compared with paclitaxel.

A first interim analysis will be performed once 55 patients (30 to the FISH 4/5 stratum and 25 in the FISH 6 low amplification stratum) have been followed up for a minimum of 8 weeks (or progressed or died prior to 8 weeks). Progression free survival and changes in tumour size will be statistically analysed at this interim analysis and taken together with the safety profile observed will be used by AstraZeneca to support a decision to stop or continue the FISH 4/5 and FISH 6 low amplification strata at that point.

A second interim analysis will be performed once 25 FISH 6 high amplification patients have been followed up for a minimum of 8 weeks (or progressed or died prior to 8 weeks) or 60 OS events have occurred across all FISH 6 patients, if the low FISH 6 stratum continues past the first interim analysis. Progression free survival and changes in tumour size will be statistically analysed at this interim analysis and taken together with the safety profile observed will be used by AstraZeneca to support a decision to stop or continue the FISH 6 high amplification stratum, and any of the other strata remaining open, at that point. If both FISH 6 strata remain open at this analysis, then this interim will also give an early opportunity to assess PFS and OS across all FISH 6 patients.

The randomised part of the study will also assess the prognostic and predictive value of FGFR2 FISH status in gastric cancer. Literature evidence suggests that patients with tumours having aberrant FGFR signalling pathways may have a poorer prognosis (Kunii et al. 2008 and Takeda et al. 2007). Patients with a tumour FISH score ≤3 will not be randomised in to the study, but investigation of this additional patient population may be performed in subsequent clinical studies if emerging data suggest clinical benefit. Data from this study will provide information on the prevalence of the FGFR2 FISH levels in different geographic regions and also the associated survival outcome data.

3.2.2 Rationale for dosing

3.2.2.1 AZD4547

The starting dose for AZD4547 will be 80 mg twice daily, using a 2 weeks on, one week off schedule, in a 3-week cycle, based on the safety and tolerability profile established from continuous dosing in the phase I dose escalation study D2610C00001. The expansion phase of that study is now ongoing at a dose of 80 mg bd, continuous dosing. Non-clinical studies have

identified that intermittent dosing with AZD4547 can still achieve anti-tumour activity in tumour models (see IB Section 4.1.1.2 for further details), providing the cumulative mean weekly dose of the intermittent schedule is equivalent to that of continuous dose. PK/PD modelling of phosphate changes and anecdotal evidence from Study Investigators indicate that both increases in serum phosphate levels and some of the tolerability issues (dry eyes, dry mouth) do resolve substantially within one week of discontinuation of AZD4547. The SRC will meet to review all available safety data at approximately 2 monthly intervals. On the basis of these reviews and/or the results of the interim analysis, the SRC will have the option to propose to AstraZeneca that a lower dose level or a different dose schedule should be evaluated (examples of possible doses and schedules are presented in Table 4).

3.2.2.2 Paclitaxel

The CALGB 9840 study confirmed that weekly administration of paclitaxel was superior to a 3-weekly infusion schedule in metastatic breast cancer, based upon an improved response rate and time to progression (Seidman et al. 2008). Although the evidence was generated in the breast disease area, investigation of monotherapy paclitaxel in both the first and second line gastric cancer setting using a weekly paclitaxel regimen has also confirmed that response rates are similar to those achieved with a 3-weekly regimen, but that there was improved quality of life and compliance with the weekly regimen (Kodera et al. 2007, Emi et al. 2008). Therefore a weekly paclitaxel regimen has been chosen as the comparator regimen for the randomised part of this study. Based upon an AstraZeneca review of clinical practice globally (in Europe, USA and SE Asia), the regimen determined to be acceptable for use in all participating territories was paclitaxel 80 mg/m^2 given weekly on days 1, 8 and 15 of a 28 day cycle (up to the maximum number of cycles per local practice). Treatment in this study is open label as AZD4547 is given in tablet formulation and the comparator, paclitaxel, is given as an infusion. Although placebos to AZD4547 tablets are available it is considered to be unethical to administer a placebo infusion in this clinical setting.

3.2.3 Rationale for PK

The timings of safety and PK assessments in the study have been designed using both non-clinical findings and emerging data from the phase 1 dose escalation study with AZD4547 in patients (D2610C00001). Single dose assessments are not required, as these have already been investigated in Study 1 (D2610C00001). Exposure to AZD4547 in patients with advanced gastric cancer may be different from other patient populations due to their underlying pathology and previous treatment. Therefore the pharmacokinetics of AZD4547 will be investigated using pre-dose samples on Day 7 and Day 14 of Cycle 1 and Day 1 and Day 14 of Cycle 2. **A reduced number of PK samples will be collected in patients randomised after reaching the required number of patients for the interim analysis, this will reduce the time a patient is required to remain at the clinic on Day 14 (cycle 1 and 2) and also reduce operational complexity**. Pharmacokinetic/pharmacodynamic (PK/PD) relationships between plasma AZD4547 exposure and demographics, pathophysiological characteristics, pharmacodynamic markers, safety and clinical outcome measures will be investigated. The overall aim is to refine the therapeutic window, balancing efficacious exposure, biomarkers and safety, using population analysis.

3.2.4 Rationale for exploratory biomarkers

As part of the clinical drug development program for AZD4547, AstraZeneca plans to include investigations into variations in pharmacodynamic and exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from DNA, RNA, proteins and/or metabolites. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or non-responders or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how it can be utilised to bring better drugs to the clinic. The ability to acquire appropriate consent to collect biological samples is of utmost importance in order to establish an archive and allow future meta-analysis of data derived from studies with AZD4547.

3.2.5 Rationale for pharmacogenetics

AstraZeneca intends to perform genetic research in the AZD4547 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD4547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and possibly, to genetically guided treatment strategies. Examples of genes that may be looked at are those encoding metabolising enzymes and transporter proteins such as CYP2D6, UGT1A1, MDR1. Genotyping participants in this study may provide an understanding of any observed variation in pharmacokinetics or clinical response.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD4547 but also susceptibility to cancer. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

3.2.6 Rationale for Patient reported outcomes

Patient reported outcomes (PROs) assess the impact a disease or an intervention on a disease has on the patient from their own perspective. Patients with advanced gastric cancer often experience disease-related symptoms, such as dysphagia, eating restrictions, reflux and abdominal pain; however, the impact of a treatment on these symptoms is unlikely to be systematically captured using traditional clinical endpoints. In addition, treatment related events, such as toxicities, may also adversely affect the quality of life of patients with cancer. Consequently, the addition of validated PRO instruments that assess both health related quality of life and symptoms will provide a measure of health benefit of AZD4547 specifically from a patient perspective, as well as supporting the overall risk-benefit assessment of AZD4547 at the conclusion of the study.

In the study, it is therefore proposed to use the two EORTC validated quality of life questionnaires, the QLQ-C30 instrument, and the gastric cancer specific QLQ-STO22 instrument. In addition, the EQ-5D-5L will be used to assess health utility (see Section 1.3.7).

The clinician reported WHO Performance Status measure will provide an assessment of the functional status of the patient from the treating clinician's perspective.

4. PATIENT SELECTION CRITERIA

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

Each patient 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

4.1.1 Pre-screening part of the study

For inclusion in the pre-screening for FGFR2 status of their tumour, patients should fulfil the following criteria:

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

2. Female or male aged 25 years or older.

3. Histological diagnosis of locally advanced or metastatic gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction).

4. Provision of a least one tumour sample is mandatory in this study, but a minimum of 7 biopsy samples is recommended to ensure reliable determination of FGFR2 status (see also Section 1.3.5). All samples submitted at pre-screen will be tested for FGFR2 gene copy number by FISH and the highest score will determine patient eligibility into the study.

   – In the exceptional circumstance that no tumour tissue is available for central testing (ie, archival tumour samples have been exhausted or are not available, and a fresh biopsy is not possible) but there is clear evidence of FGFR2 gene amplification from local testing, patient entry to the trial will be at the discretion of the Sponsor. In such cases the local test result and local test protocol including information on the test platform must be supplied to the Sponsor to enable a decision to be made.

5. Patients whose disease has progressed during or after first line therapy for advanced or metastatic gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or gastro-oesophageal junction). Patients whose disease has progressed within 6 months following adjuvant or neo-adjuvant therapy may be included at the discretion of the investigator (see Section 5.2.1).

   – During the study AstraZeneca may also elect to allow pre-screening of patients that are on-going on first line treatment for advanced gastric adenocarcinoma (including

adenocarcinoma of the lower third of the oesophagus or gastro-oesophageal junction) whose disease may be likely to progress during the remaining enrolment period of the study.

4.1.2 Randomised part of study

For inclusion in the randomised part of the study patients should fulfil the following criteria:

1. Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses. If a patient declines to participate in any voluntary exploratory research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study (pre-screening consent and main study consent are required).

2. Female or male aged 25 years or older.

3. Suitable for and expected to benefit from paclitaxel monotherapy.

4. Patients must have radiologically confirmed progression following 1st line treatment for advanced or metastatic gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction). Patients who have progressed within 6 months following adjuvant or neo-adjuvant therapy may be included upon investigators discretion.

5. World Health Organisation performance status 0-1, minimum life expectancy of 12 weeks from proposed first dose date, no deterioration within 2 weeks of screening and first dose. Investigator has discretion to exclude rapidly progressive gastric cancer (such as those patients with rapid deterioration of performance status, requiring repeated drainage of ascites, patients with low or rapidly decreasing albumin or patients requiring feeding assistance with devices such as PEG).

6. Histological diagnosis of locally advanced or metastatic gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction).

7. Mandatory provision of archival or fresh tumour biopsy for confirmation of advanced gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction) that has FGFR2 polysomy or gene amplification (FISH ≥4). Must be confirmed by AstraZeneca approved laboratory.

   – Patients who had a FISH score of 1-3 when tested at pre-screening for the FGFR2 status of their tumour, can be re-tested on a fresh tumour sample, after they have relapsed or not responded to 1st line treatment. Where 2 tests are carried out, the results of the 2nd test must be used for assessment of eligibility.

8. At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have

short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

- Local disease confined to the stomach or oesophagus is not considered measurable (patients with locally advanced gastric cancer including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction must have at least one measurable nodal lesion ≥15mm in the short axis).

9. Females should be using adequate contraceptive measures (see restrictions), should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential, or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

   - Post-menopausal defined as:

   Aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.

   Aged under 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.

   - Documentation of irreversible surgical sterilisation by hysterectomy, and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal ligation.

10. Male patients should be willing to use barrier contraception, ie, condoms.

4.1.3 Optional genetics and biomarker analysis

For inclusion in the optional genetic research and biomarker analysis components of the study (blood and archival tumour sampling for DNA extraction and retrospective pharmacogenetic analysis and tumour biomarker analysis), patients must fulfill the following criteria:

1. Provision of written informed consent for blood sampling for genetic research *and/or*

2. Provision of written informed consent for tumour sampling for genetic research and biomarker analysis.

4.2 Exclusion criteria

4.2.1 Pre-screening part of the study

Patients should not enter the pre-screening for 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 staff and/or staff at the study site).

2. Previous enrolment in the present study.

3. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

4.2.2 Randomised part of study

Patients should not enter the randomised part of 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 staff and/or staff at the study site).

2. Previous enrolment in the present study (except for enrolment at the pre-screening stage).

3. Participation in another clinical study with an investigational product within 4 weeks before commencing study treatment.

4. Treatment with any of the following:

   - Treatment with any prior taxane therapy for gastric cancer in the past with the exception of any taxane therapy for adjuvant or neo-adjuvant therapy given >6 months prior to study randomisation.

   - Any chemotherapy, immunotherapy or anticancer agents within 4 weeks before the first dose of study treatment.

   - Prior exposure to AZD4547 or to any agent with FGFR inhibition as its primary pharmacology.

   - Potent inhibitors or inducers of CYP3A4, 2C8 or 2D6 or substrates of CYP3A4 prior to the first dose of study treatment (time period, as specified in Appendix E).

   - Major surgery (excluding placement of vascular access) within 4 weeks before the first dose of study treatment.

   - Radiotherapy with a wide field of radiation within 4 weeks or radiotherapy with a limited field of radiation for palliation within 2 weeks before the first dose of study treatment.

   - Other concomitant anti-cancer therapy except steroids

5. With the exception of alopecia, any unresolved toxicities from prior therapy with a Common Terminology Criteria for Adverse Events (CTCAE) grade >1 at the time of starting study treatment. Any unresolved toxicity >CTC grade 1 from previous radiotherapy except GI or haematological toxicity which must be completely resolved prior to commencing chemotherapy.

6. Spinal cord compression or brain metastases.

7. As judged by the investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.

8. Any of the following cardiac criteria:

   - Mean resting corrected QT interval (QTc) >470 msec obtained from 3 consecutive electrocardiograms (ECGs).
   - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block.
   - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval.

9. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

   - Absolute neutrophil count <1.5 x 10^9/L.
   - Platelet count <100 x 10^9/L.
   - Haemoglobin <90 g/L.
   - Alanine aminotransferase >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases.
   - Aspartate aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases.
   - Total bilirubin >1.5 times ULN.

- Creatinine >1.5 times ULN concurrent with creatinine clearance <50 ml/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.

- Corrected total calcium >ULN (corrected for albumin using a standard formula that will be specified in the protocol).

- Total phosphate >ULN.

10. Any of the following ophthalmological criteria:

    - Current evidence or previous history of retinal pigmented epithelium detachment (RPED)

    - Previous laser treatment or intra-ocular injection for treatment of macular degeneration

    - Current evidence or previous history of dry or wet age-related macular degeneration

    - Current evidence or previous history of retinal vein occlusion (RVO)

    - Current evidence or previous history of retinal degenerative diseases (eg, hereditary)

    - Current evidence or previous history of any other clinically relevant chorioretinal defect

11. Refractory nausea vomiting and chronic malabsorptive states that would preclude adequate intake and absorption of AZD4547.

12. Pregnant or breast-feeding women or women of childbearing potential with a positive pregnancy test prior to receiving study medication.

13. History of hypersensitivity to active or inactive excipients of AZD4547 or paclitaxel or other drugs formulated in Cremaphor EL (polyoxyethylated castor oil – see Appendix F) or other drugs with a similar chemical structure or class to AZD4547 or paclitaxel.

14. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

15. Patients with a history of another primary malignancy within 5 years prior to starting study treatment, except adequately treated basal or squamous cell carcinoma of the skin, carcinoma of the cervix in situ and the disease under study.

4.2.3 Optional genetics analysis

Additional Exclusion Criteria for sampling for future exploratory research into genes/genetic variation:

1. Previous allogeneic bone marrow transplant.

2. Non-leukocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

See Section 5.6 for restrictions relating to concomitant medications.

1. Females of child-bearing potential should use reliable methods of contraception from the time of screening until 4 weeks after discontinuing study treatment. Acceptable methods of contraception include abstinence, tubal ligation, tricycle combined oral or transdermal contraceptives, copper-banded intra-uterine devices and vasectomised partner. It is not known whether AZD4547 or paclitaxel interact and have an effect on the mechanism of action of hormonal contraceptives: if female patients are taking hormonal contraceptives to prevent pregnancy then this should be combined with a barrier method of contraception. Barrier methods of contraception are not suitable when used alone, so should only be used when another method of contraception is also being used.

2. Male patients should use barrier contraception (ie, condoms) and refrain from donating sperm from the start of dosing until 16 weeks after discontinuing study treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

3. Patients who have received bisphosphonates in the last 6 months or who are still receiving bisphosphonates will not provide a blood sample for bone biomarker testing.

4. Patients with uncontrolled glaucoma or intra-ocular pressure ≥21 mmHg at screening should be referred for ophthalmological management and the condition controlled prior to first dose.

5.2 Patient enrolment and randomisation and initiation of investigational product

Prior to enrolment, the Principal Investigator will:

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

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

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

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

5.2.1 Two-step consenting process and screening for FGFR2 status

Patients enrolling in the study will provide consent in a two-stage process.

Stage 1 (pre-screening): Patients whose disease has progressed during or after first line therapy for advanced or metastatic gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or gastro-oesophageal junction), will be pre-screened for the FGFR2 status of their disease, determined by their FISH score (FISH gene amplification ratio will also be assessed at this time). Patients whose disease has progressed within 6 months following adjuvant or neo-adjuvant therapy may be included at the discretion of the investigator. During the enrolment period, AstraZeneca may elect to advise sites they can pre-screen patients that are on-going on first line treatment for advanced gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or gastro-oesophageal junction) whose disease may be likely to progress to requiring 2nd line therapy during the remaining enrolment period of the study. A pre-screening consent will be used for this FGFR2 screening and for consenting to the collection of outcome data. The pre-screening consent can be obtained outside of the 28-day window (all other screening procedures to be performed within 28 days of start of treatment as per study plan in Table 1 and Table 2). Patients must consent to provide either an archival tumour tissue block or a fresh tumour biopsy sample for analysis. If a fresh tumour biopsy is provided for FISH testing, then any study procedure related SAEs must be collected (see Section 6.4.3 and 6.4.4). Provision of at least one archival or fresh tumour biopsy for FGFR2 testing is mandatory in this study, but a minimum of 7 biopsy samples is recommended to ensure reliable determination of FGFR2 status. All samples submitted at pre-screen will be tested for FGFR2 gene copy number by FISH and the highest FISH score and FGFR2 FISH amplification ratio will determine patient eligibility for entry into the three strata in the study as follows:

- High FGFR2 gene amplification (FISH 6)
- Low FGFR2 gene amplification (FISH 6)
- FGFR2 polysomy (FISH 4/5)

Details of the FGFR2 analysis by FISH will be documented within the relevant Standard Operating Procedure held by the central testing laboratory and may be subject to change during the study, for example due to emerging data or refinement of the FISH assay. In the event of a change to the FISH scoring methodology, any patients already pre-screened will be reallocated to the appropriate stratum according to the new scoring criteria. If as a result of a modification to the scoring methodology a patient is reallocated to a stratum that is closed, the patient will be permitted to continue in the study subject to the screening windows described below for the end of recruitment.

For those patients randomised to the FISH 4/5 stratum on the basis of fewer than 7 initial samples, every attempt should be made to obtain the additional pre-treatment samples in order to ensure reliable determination of FGFR2 status. The FISH test will be carried out by a central laboratory.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

Recruitment to both FISH 6 strata will remain open during the data collection and reporting period for the first interim analysis, subject to a cap of 40 patients randomised within the FISH6 low amplification stratum, due to the much lower prevalence of this tumour type in this patient population very few patients are expected to be recruited (see Section 3.1). At the second interim analysis, recruitment to all strata which have remained open following the first interim analysis will continue to accrue provided that target enrolment in any given stratum has not already been reached.

Consent to Pre-screening (Visit 1) will be closed once sufficient patients have been enrolled to reach the required number of randomised patients. At the end of recruitment, any patient that has already consented to pre-screening but has yet to enter screening for the randomised part of the study (Visit 2) will be given up to 28 days to provide consent (following central confirmation of FGFR2 gene amplification).

Stage 2 (Randomised part of study): Patients who are eligible for participation in the study, as per the FGFR2 status of their tumour (FISH 4-6), will subsequently be offered the option of consenting to the randomised part of study and will need to sign the main study consent, in addition to the first consent. They will then undergo all other screening assessments for the randomised part of study.

5.2.2 Procedures for randomisation

Patient eligibility must be established prior to randomisation. The treatment given to individual patients will be determined using a randomisation scheme generated by the AstraZeneca Statistics and Informatics group using a computer-based randomisation system (GRand), internally developed and validated by AstraZeneca. The randomisation scheme will be stratified according to tumour FGFR2 status (see Section 5.2.1 for details on determination of FGFR2 status). Eighty patients that have tumours with FGFR2 polysomy (FISH 4 or 5) will be randomised in a 1:1 (AZD4547: paclitaxel) ratio, 160 patients that have tumours with

FGFR2 gene amplification (FISH 6) will be randomised in a 3:2 (AZD4547: paclitaxel) ratio within each of the FGFR2 gene amplification strata ie, 80 within the FGFR2 low level amplification strata and 80 within the FGFR2 high level amplification strata. Due to anticipated differences in prevalence between FGFR2 polysomy, FGFR2 low level amplification and FGFR2 high level amplification, it is expected that recruitment into individual strata will stop at different times as each stratum becomes full.

The randomisation scheme generated by GRand will be integrated into an Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS). Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation via the IVRS/IWRS. If a patient withdraws from the study their randomisation code cannot be reused.

5.2.3 Procedures for reallocation of patients to strata in response to revision of amplification score and/or change in FISH 6 amplification cut-off

In the event of a change to an individual patient's amplification score (ratio) or stratum classification arising eg, from a change to the FISH scoring methodology, the procedure will be as follows:

- For patients in Stage 1 pre-screening, the patient may enter Stage 2 screening provided that the revised score/classification demonstrates eligibility for a cohort that is still open to recruitment or alternatively additional tumour tissue may be tested.

- For patients in Stage 2 screening, where the revised score/classification meets the criteria for the polysomy or one of the gene amplified strata, the patient may continue to be screened and will be allocated to the stratum most relevant to their revised score/classification. Where the revised score/classification is insufficient for entry into any of the strata, the Investigator will be advised by AstraZeneca on how to proceed.

- For patients who have commenced study treatment and the revised score/classification is consistent with the criteria for entry to one of the strata, the patient will be allocated to the appropriate stratum provided recruitment has not already closed for that stratum. For patients who have commenced study treatment but are below the level required for entry into any stratum or who received a revised score consistent with a stratum that has already been closed, the patient may continue to receive study drug at the discretion of the Investigator and analysed as part of the reassigned stratum unless the analysis of that stratum has already been completed in which case, the patient's data will be reported separately and the patient will not be included in the recruitment total or analysis for any of the three strata.

- Where necessary, a replacement patient may be recruited to the affected stratum/strata to ensure that the statistical robustness of the study and individual strata is maintained.

5.3 Procedures for handling patients incorrectly enrolled or randomised or initiated on investigational product

Patients 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 patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post-initiation, the investigator should inform the AstraZeneca Global Study Delivery Team Physician immediately. The AstraZeneca Global Study Delivery Team Physician is to ensure all such contacts are appropriately documented.

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

N/A

5.5 Treatments

5.5.1 Identity of investigational product(s)

Table 3 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
AZD4547	20 mg – 100 mg tablets	[redacted]
Paclitaxel Injection	100 mg and 30mg multidose vials	[redacted]

Paclitaxel will be given as an infusion, with a dose of 80 mg/m^2. Prophylactic pre-medication may be administered in advance of the paclitaxel infusion according to local prescribing guidelines (see appendix F).

AZD4547 tablets will be packed into white high-density polyethylene bottles with child resistant, tamper evident closures.

AZD4547 and paclitaxel will be supplied by Pharmaceutical Development (Pharm Dev), AstraZeneca, UK as individual patient packs. Additional information about AZD4547 may be found in the IB.

5.5.2 Dose and treatment regimen

AZD4547 will be taken orally twice daily in a tablet formulation (80 mg twice daily on a 2 weeks on, 1 week off schedule, in a 3-week cycle). Based on ongoing evaluation of emerging

study data and/or the results of the interim analysis, the SRC will have the option to propose to AstraZeneca that a lower dose level or a different dose schedule should be evaluated, (see Section 5.5.3). On days when PK samples are being taken, patients should fast 2 hours before and 2 hours after the first dose of AZD4547 (see Section 6.6.1). Water will be allowed in moderate amounts throughout, apart from the 1-hour immediately prior to dosing. For information relating to dose modifications of AZD4547 for the management of toxicities refer to Figure 2 and Section 5.10.

Paclitaxel will be administered as a 1-hour infusion (the infusion time of paclitaxel can vary according to local standard practice) of 80 mg/m^2 weekly on days 1, 8 and 15 of a 28 day cycle (up to the maximum number of cycles per local practice).

5.5.3 AZD4547 dosing: starting dose of AZD4547 and selection of alternative dose and schedule

The initial dosing schedule for AZD4547 will be two weeks of AZD4547 (80 mg administered twice daily) followed by one week with no treatment.

The SRC will meet at approximately 2-monthly intervals to review all available safety data. On the basis of these reviews and/or the results of the interim analysis, the SRC will have the option to propose to AstraZeneca that a lower dose level or a different dose schedule should be evaluated (see Section 5.5.3.1 for details and Table 4 for an example dose and schedule selection scheme). In the event that AstraZeneca adopts the recommendation to explore an alternative dose or schedule, any patients already recruited to the AZD4547 arm at this point will continue to receive AZD4547 as per their current dose and schedule provided that they are tolerating the treatment and the investigator believes they are gaining benefit. Alternatively, the investigator may elect to change the dose/schedule of patients recruited prior to the dose change to the new dose/schedule. Any patients already recruited to the paclitaxel arm will continue on their originally assigned treatment. After a change to the dose or schedule of AZD4547, any new patients entering the AZD4547 arm of the study will receive AZD4547 as per the new dose and schedule. There will be no more than 2 changes made to dose or schedule during the study. For details of managing toxicity for individual patients see Section 5.10.1.

Table 4 Example dose and schedule selection scheme

Initial dose and schedule	80 mg AZD4547 bd two weeks on/one week off
2nd dose and schedule: option 1	40 mg AZD4547 bd two weeks on/one week off
2nd dose and schedule: option 2	80 mg AZD4547 bd two weeks on/two weeks off
3rd dose and schedule	40 mg AZD4547 bd two weeks on/two weeks off

If the dose and/or schedule are changed during the study, the SRC and AstraZeneca may decide to increase the recruitment target (in both the AZD4547 arm and the paclitaxel arm) to compensate for any patients already recruited prior to the change.

5.5.3.1 Safety Review Committee

Approximately every 2 months, the SRC will evaluate the safety, tolerability and PK of AZD4547. There will not be any ongoing review of data from patients receiving paclitaxel. Any dose interruptions and reductions will be taken into account. On the basis of these reviews and/or the results of the interim analysis, the SRC will have the option to propose to AstraZeneca that a lower dose level or a different dose schedule should be evaluated . The SRC and AstraZeneca may also make a decision to increase the recruitment target for the study in order to compensate for any patients already recruited up to the point when the dose or schedule is changed.

The Safety Review Committee Remit document for this study will define the membership of the SRC, roles and responsibilities and who should be present for decisions to be made. The decisions and decision-making of the SRC and AstraZeneca on any changes to the dose and schedule of AZD4547 will be documented and provided to the Investigators prior to dosing any new patients.

5.5.4 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines by IPS. 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 investigational product label on the bottle specifies the appropriate storage.

5.6 Concomitant and post-study treatment(s)

The following treatment restrictions apply, for the safety of patients:

- All patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 or CYP2D6 enzyme activity and drugs that are known to be CYP3A4 substrates from the time they enter the screening period until 2 weeks after the last dose of study treatment. Please refer to Appendix E of this Clinical Study Protocol, for further details.

- Patients who receive paclitaxel should avoid concomitant use of the following: ketoconazole, warfarin and any drugs that significantly inhibit or induce CYP2C8 enzyme activity.

- Patients who have received bisphosphonates in the last 6 months or who are still receiving bisphosphonates will not provide a blood sample for bone biomarker testing.

- Patients who receive AZD4547 should not use any calcium containing phosphate chelation agents.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

See Appendix E for further guidance regarding the use of concomitant medications.

To aid the interpretation of the survival analysis, anti-cancer therapies administered following the discontinuation of study treatment will be recorded on the eCRF.

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

The investigator or pharmacy must retain records of all study drugs administered. The monitor will check these records to confirm the compliance with the protocol administration schedule.

Any dose reductions will be documented, along with reasons for the dose reduction (see Figure 2 and Section 5.10 for the procedures for dose reductions of AZD4547).

Use of study medication in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 13.2 for reporting procedures in case of overdose.

Patients should return all unused medication and empty containers to the Investigator.

5.7.1 Accountability

The study drug 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 patient.

If Investigational Product is destroyed at site then AstraZeneca personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return must be signed.

If Investigational Product is returned to AstraZeneca for destruction then the study site personnel or the AstraZeneca monitor will account for all received study drugs and return all unused study drugs to AstraZeneca. Certificates of delivery and return must be signed.

It is the investigator/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person.
- Such deliveries are recorded.
- Study treatments are handled and stored safely and properly.
- Study treatments are only dispensed to study patients in accordance with the protocol.
- Any unused products are returned for destruction, or destroyed locally, in liaison with their AstraZeneca monitor.

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents "Procedures for drug accountability" and "Procedures for drug storage" which describes the specific requirements. The investigator(s) is responsible for ensuring that the patient has returned all unused study drug.

5.8 Discontinuation of investigational product

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

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event.
- Severe non-compliance to study protocol.
- Patients incorrectly initiated on study medication (Section 5.3).
- Objective disease progression.

5.8.1 Procedures for discontinuation of a patient from investigational product

Once study medication is permanently discontinued it cannot be restarted.

A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). The Investigator will record on the CRF the date of discontinuation of

study treatment and the reasons. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the patient. Any serious adverse events should be communicated to AstraZeneca according to the procedures defined in Section 6.4.4.

See Section 6.4.3 for details of collecting AEs at time of discontinuation.

A patient who discontinues study treatment should not be withdrawn from the study, but should be followed up until progression or death. If a patient is withdrawn from the study, see Section 5.9.

Patients who discontinue study treatment due to objective disease progression will complete the 28-day follow-up visit and then will be followed up objective progression, PRO assessment and survival (see Section 6.10), unless they withdraw consent (see Section 5.9)

Any patients who discontinue study treatment for reasons other than objective disease progression should have tumour assessments scans performed as scheduled in the protocol (see Table 1 and Table 2) until objective disease progression is documented or death occurs, unless consent is withdrawn (see Section 5.9). In particular, if discontinuation for reasons other than objective disease progression occurs prior to week 8, the patient should have a scan at week 8 for the primary analysis (unless consent is withdrawn or a scan was performed within 4 weeks prior to discontinuation). Study procedure related SAEs must be captured until the patient no longer has RECIST assessments (disease progression or permanent withdrawal from the study).

5.9 Withdrawal from study

The term withdrawal from the study refers to discontinuation from both study treatment and study assessments.

Patients are at any time free to withdraw from study, without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4) and all study drugs should be returned by the patient. Withdrawn patients will not be replaced.

Specific reasons for withdrawal from study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.
- Risk to patients as judged by the Investigator and /or AstraZeneca eg, study is terminated by AstraZeneca for safety reasons.
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca.
- Patient lost to follow-up.

- Death.

Patients may withdraw from any aspects of the voluntary exploratory research (see Sections 6.7 and 6.8) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Section 7.5.

Patients who are pre-screened but are not randomised may withdraw their consent for being contacted for survival follow-up at any time, without prejudice to further treatment. For these patients and all patients who are withdrawn from the study or lost to follow-up, the investigator should consult public records to establish survival status for the survival assessments, see Section 6.10.

5.10 Management of toxicity

5.10.1 Management of toxicity associated with AZD4547

If a patient experiences a clinically significant and/or unacceptable toxicity not attributable to the disease or disease-related processes under investigation, where the Investigator considers the AE of concern to be specifically associated with AZD4547, dosing with AZD4547 will be interrupted or the dose modified and supportive therapy administered as required (see Figure 2, Figure 3, Figure 4 and Table 5).

If the toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset and the patient is showing clinical benefit, treatment with AZD4547 may be restarted using the rules below for dose modifications (see Figure 2 and Table 5) and with discussion and agreement with the AstraZeneca Study Team Physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction.

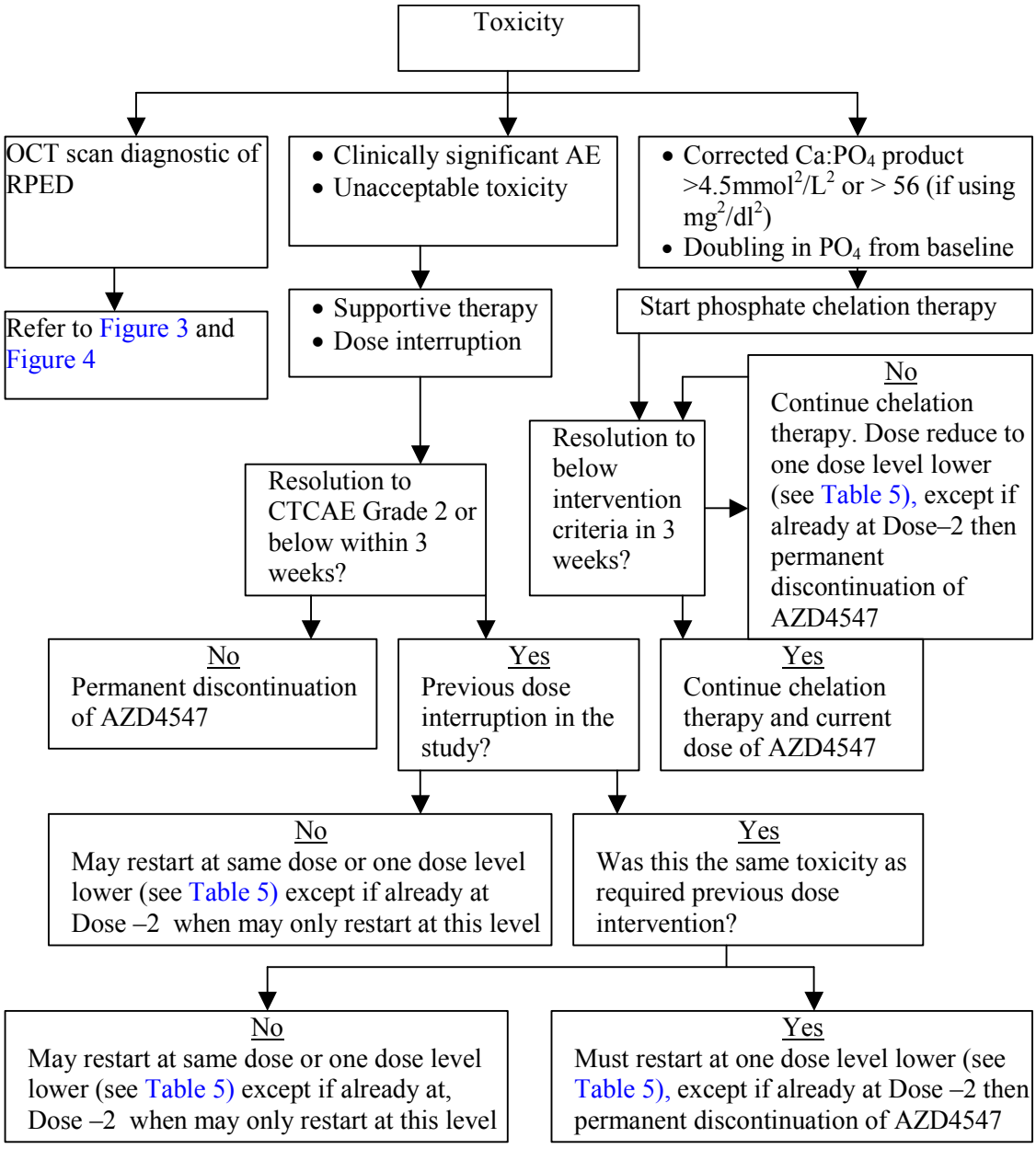
If the toxicity does not resolve to ≤CTCAE grade 2 after 3 weeks, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

Table 5 Dose Interventions

	Dose of AZD4547
Starting Dose	X mg
Reduced Dose –1	X/2* mg
Reduced Dose –2	Reduced Dose -1/2* mg

*If dose is not exact tablet strength, the dose to use will be advised by the AstraZeneca Study Team

Figure 2 AZD4547 Dose modifications for toxicity



5.10.1.1 Increased phosphate

If a patient experiences a doubling of phosphate from baseline or a corrected calcium:phosphate product >4.5 (if using $mmol^2/L^2$) or >56 (if using mg^2/dl^2), then the patient may remain on study treatment but phosphate chelation therapy (non-calcium containing agent) should be initiated, and clinical chemistry monitored weekly until resolution of the parameter to below the intervention limit. Investigators must seek appropriate specialist medical consultation (renal or metabolic) to advise on the prescription and titration of

phosphate chelation agents and to raise the patients awareness of low phosphate diets. An optional PK sample may be taken once titration of the phosphate chelation agent has been completed. Refer to Section 1.4.2.2, 'Mineralisation, particularly in the heart' for the monitoring rationale. Management of patients will be according to the corrected calcium result provided from the Investigational site laboratory. If the Investigational site laboratory does not provide a corrected calcium result the formula below should be used to calculate corrected calcium:

Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 (40 - albumin [g/L]), where 40 represents the average albumin level in g/L

5.10.1.2 Ocular toxicity

If patients experience toxicities regarding the anterior aspect of the eye (dry eyes, punctuate keratopathy and keratitis) such events must be clinically managed to prevent secondary consequences eg, secondary infections following corneal abrasions. Lubricating eye drops/replacement tears should be used; if there is any indication of extra eyelash growth or eyelashes rubbing on the cornea then these eyelashes should be removed. It is anticipated that patients will report any visual disturbances or discomfort relating to the eye in advance of any significant pathology such as ulceration occurring. The decision to continue on study treatment if mild corneal changes in the eye examination are observed will be left to the Investigator's discretion, since a patient may indicate a wish to tolerate minor discomfort if there is perceived clinical benefit from the therapy. A patient should also be immediately withdrawn from AZD4547 if corneal ulceration occurs, and appropriate expert ophthalmologic consultation should be initiated.

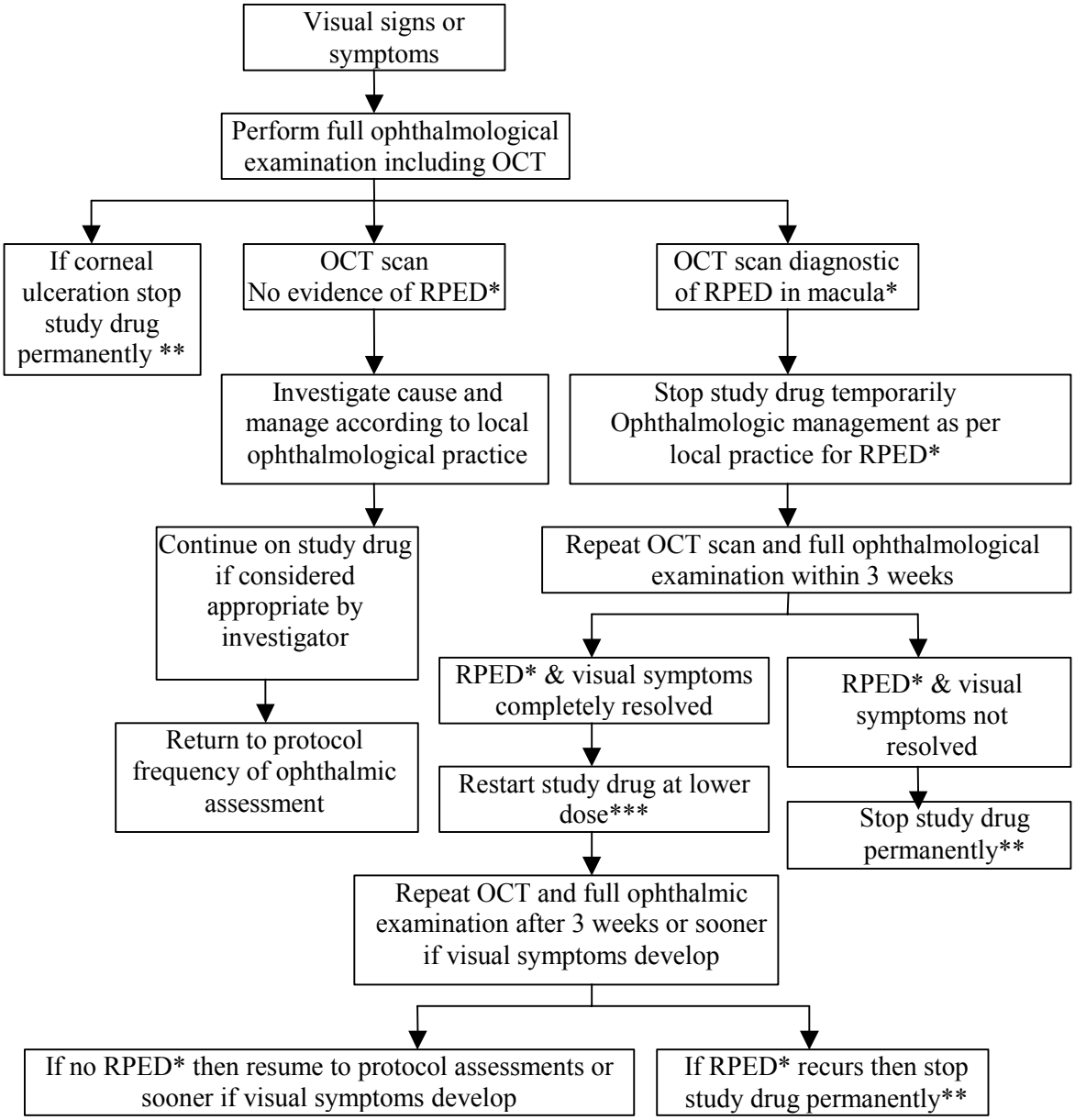
RPED has been identified in clinical studies with AZD4547. The prognosis is generally good if there is no actual haemorrhage from the capillaries and no evidence of any fibrovascular growth in the sub-RPE space.

An ophthalmological assessment is required if there are any of the following at any time:

- Abnormalities in the Amsler grid test
- Changes in near vision acuity
- Blurred vision
- Distortion of central vision

Subsequent management should be according to the algorithm included in Figure 3 and Figure 4. Any patients with an optical coherence tomography (OCT) scan diagnostic of RPED should be managed according to the same algorithm.

Figure 3 Management of eye toxicity (visual symptoms)

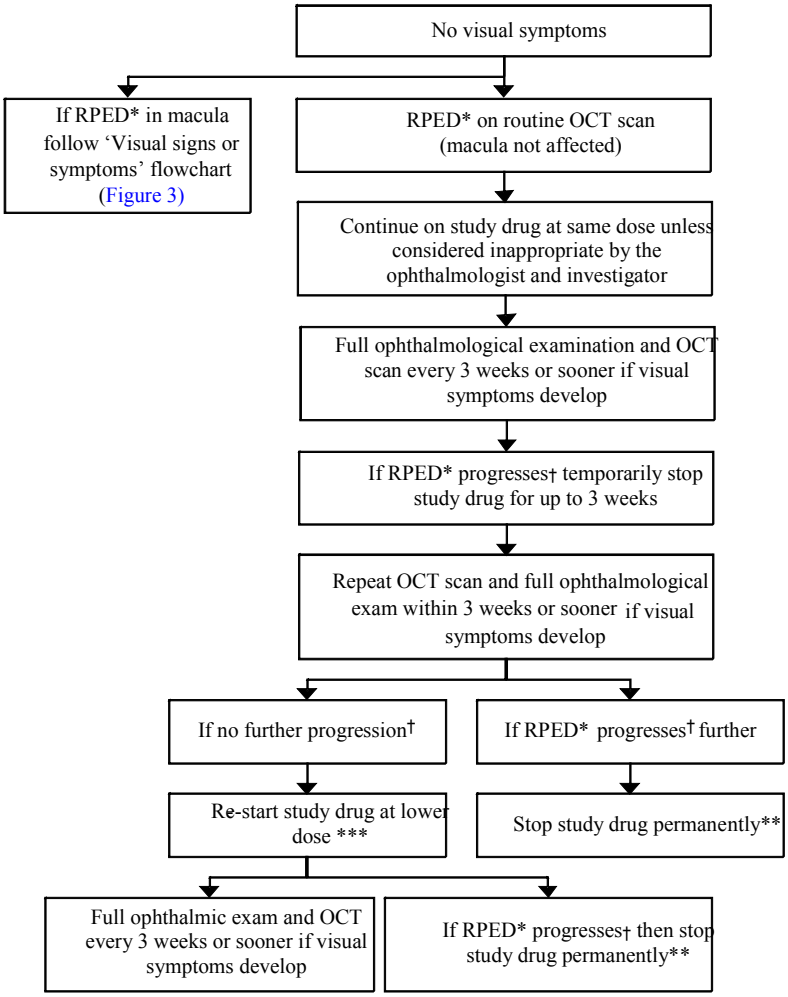


*RPED includes: Retinal Pigmented Epithelial Detachment, central Serous Retinopathy, Central Serous Choriodopathy, Serous Detachment

** After permanent discontinuation of AZD4547 due to ocular toxicity, patient should be managed according to local clinical practice

***Only one dose reduction allowed for management of RPED

Figure 4 Management of eye toxicity (no visual symptoms)



*RPED includes: Retinal Pigmented Epithelial Detachment, Central Serous Retinopathy, Central Serous Choriodopathy, Serous Detachment
**After permanent discontinuation of AZD4547 due to ocular toxicity, patient should be managed according to local clinical practice
***Only one dose reduction allowed for management of RPED
† Progression of RPED is defined as development of symptoms, extension from para-macular to macula, or increase in the number of lesions

5.10.2 Management of toxicity associated with paclitaxel

For management of toxicities to paclitaxel, the investigator should follow local practice and the local prescribing information.

Each patient should receive three paclitaxel doses in a four-week period as toxicity permits however interruption or dose modification of paclitaxel must follow labelled recommendations where appropriate (for example, myelosuppression).

Treatment with paclitaxel may continue at the full dose of 80 mg/m^2 (unless previously dose reduced) on Days 1, 8 and 15 of each cycle as long as the following criteria are met:

- ANC $\geq$1.5 x 10^9/L
- Platelets $\geq$100 x10^9/L

If these criteria are not met, paclitaxel treatment should be delayed until restoration of ANC and platelet count. In the event that a patient has not recovered sufficiently to enable the next chemotherapy cycle to start, then the cycle should be delayed until the toxicity has recovered sufficiently to allow further dosage. The maximum cycle delay permitted is 28 days. See Appendix F for local prescribing information for paclitaxel.

5.10.3 Assessment timings if dosing is delayed

If a patient has AZD4547 treatment delays, please contact the AstraZeneca Study Team for advice regarding appropriate timing of the biomarker and PK assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as per study plan, relative to the baseline assessments.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

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

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

6.2 Data collection and enrolment

Investigators should refer to the study plans (Table 1 and Table 2) for the list of procedures and assessments to be performed at screening and their relative timings prior to randomisation.

Before entering the study, patients will be assessed to ensure that they meet the eligibility criteria (see Section 4.1 and 4.2). Written informed consent must be obtained prior to any

study specific assessments. Procedures that are part of standard care may occur before informed consent is obtained.

Each patient will undergo screening procedures within 28 days prior to randomisation, with the exception of testing for FGFR2 status, which can be done earlier than this, after the separate stage 1 pre-screening consent has been signed (see Section 5.2.1).

The data listed below will be collected:

Pre-screening visit:

- Demography.
- Prior anti-cancer treatment
- Disease status.
- Smoking status.
- Tumour sample details and FGFR2 status.
- Adverse events (procedure related SAEs for patients who have a fresh tumour biopsy for FISH testing or a genetics test).

Screening visit:

- Disease status.
- Tumour sample details and FGFR2 status if re-tested.
- Medical/surgical history.
- Pregnancy testing for female patients.
- WHO performance status.
- Physical examination to assess all conditions that are current and ongoing.
- Vital signs: height, weight, pulse, systolic blood pressure and diastolic blood pressure.
- Ophthalmic assessments.
- ECG.
- Echo/MUGA Scan.
- Clinical chemistry, haematology, urinalysis.

- Concomitant medication/procedures.
- Prior anti-cancer treatment
- Adverse events.
- Tumour assessments (RECIST v1.1).
- Blood borne biomarkers.

6.2.1 Follow-up procedures (procedures post screening)

Refer to the study plan (Table 1 and Table 2) for details on the assessments to be done at follow-up visits.

6.2.2 Clinphone - Interactive Web Response System or Interactive Voice Response System

Contact with Clinphone is required to be made via IVRS/IWRS as per the study plan (Table 1 and Table 2).

6.3 Efficacy

6.3.1 Tumour assessments

RECIST assessments will be performed using CT or MRI scans of chest, abdomen and pelvis. Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

RECIST 1.1 criteria will be used to assess patient response to treatment by determining tumour size, progression free survival (PFS) times and objective response rates (ORR). The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are presented in Appendix D.

The methods of assessment of tumour burden used at baseline CT or MRI scans chest, abdomen, pelvis, must be used at each subsequent follow-up assessment.

Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments at Week 8 (±1 week) and then every 8 weeks (±1 week) relative to the patient's randomisation date until objective disease progression as defined by RECIST 1.1.

This scanning schedule must be followed for all patients, irrespective of which treatment arm they are in.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform assessments at the protocol specified time points relative to the date of randomisation.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST 1.1.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

It is important to follow the assessment schedule as closely as possible. If treatment is delayed for any reason, RECIST assessments should continue as per the study plan and in relation to randomisation. Please refer to the study plans (Table 1 and Table 2).

AstraZeneca will derive best overall response programmatically from target, non-target and new lesion assessments recorded on the eCRF from the site assessment.

6.4 Safety

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

6.4.1 Definition of adverse events

An adverse event 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.

6.4.2 Definitions of serious adverse event

A serious adverse event 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 in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the patient 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 Clinical Study Protocol.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Only procedure-related SAEs will be captured prior to stage 2 informed consent ie, those SAEs occuring during or as a result of collection of a fresh tumour biopsy or genetic blood sample. For patients who provide an archival sample only, capture of AEs will commence from the point that the patient formally provides stage 2 informed consent (for the main part of the study). AEs will be collected throughout the study, from the stage 2 informed consent for the randomised part of the study, until the end of the follow-up period. The follow-up period is defined as 28 days after study treatment (AZD4547 or paclitaxel) is discontinued. SAEs occurring in the follow-up period should be reported to AZ in the usual manner (see Section 6.4.4).

If, after discontinuation of study medication, the patient is followed up for a longer period for tumour assessments, any procedure related SAEs must continue to be collected until tumour assessments are no longer performed.

Following the primary efficacy analysis, the clinical database will remain open until the final survival assessment has taken place. SAEs, deaths and AEs leading to permanent discontinuation of study drug should continue to be recorded on the database for patients on study treatment until this point.

Patients are permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from study treatment. For patients who do continue to receive treatment, investigators will continue to monitor the patient for safety, as per the study plan (Table 1 and Table 2) and will report all SAEs to the AstraZeneca Patient Safety department until 28 days after study treatment is discontinued.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AZ retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to AZD4547, the Investigator should notify AZ.

Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade maximum intensity
- CTCAE grade changes for AE's of interest (see latest edition of the IB for AE's of interest)
- Whether the AE is serious or not
- Investigator causality rating against the study medication (yes or no)
- Action taken with regard to study medication
- 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
- 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 6.4.2. 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.

The grading scales found in the revised National Cancer Institute CTCAE version 4.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Causality collection

The Investigator will assess causal relationship between the investigational product and the comparator treatment 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 study medication?”

For all SAEs causal relationship will also be assessed for other medication and study procedure. 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 of this Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider 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 CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the CSR. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the criteria for a SAE or are the reason for discontinuation of treatment with the study medication unless clearly due to progression of disease under study (see Disease Progression).

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

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

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.

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study medication is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. **Events that are unequivocally due to disease progression should not be reported as AEs during the study.**

New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the CRF module, but should not be reported as a SAE during the study.

- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.

- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AZ representative within the usual timeframes.

6.4.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform 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 within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

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

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

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

The reference document for definition of expectedness is Section 5.4 of the IB for the AZD4547 and the EU Summary of Product Characteristics (SPC) for Paclitaxel.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plans (see Table 1 and Table 2).

Laboratory tests do not need to be repeated on Day 1, cycle 1 if this visit is within 2 days of the screening sample. Samples must be taken pre-dose on day 1 of each cycle during an intermittent dosing schedule. Samples must be processed, and results available prior to administration of the first daily dose of AZD4547, to enable the Investigator to assess the patients suitability to resume dosing.

The date of each collection will be recorded in the appropriate CRF.

Laboratory values that meet the criteria for CTCAE grade 3 or 4, or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

The following laboratory variables will be measured:

Clinical chemistry

Serum (S) or Plasma (P)-Albumin	S/P-Magnesium
S/P-ALT	S/P-Total Phosphate
S/P-AST	S/P-Potassium
S/P-Alkaline phosphatase	S/P-Sodium
S/P-Bilirubin, total	S/P-Troponin I (Troponin T at sites where Troponin I isn't possible)
S/P-Calcium, total	S/P-Urea or BUN depending on local practice
S/P-Creatinine, total	
S/P-Random Glucose	

Urinalysis	**Haematology**
U-Glucose	Blood (B)-Haemoglobin
U-Protein	B-Leukocyte
U-Blood	B-Absolute leukocyte differential count:

U-Microscopy (red blood cells and white blood cells, bacteria, casts and crystals) only perform if urinalysis is abnormal	Neutrophils
	Lymphocytes
	B-Platelet count

For blood volume see Section 7.1

If a patient experiences a doubling of phosphate from baseline or a corrected calcium: phosphate product >4.5mmol^2/L^2 and phosphate chelation therapy (non-calcium containing agent) should be initiated. Management of patients will be according to the corrected calcium result provided from the Investigational site laboratory. If the Investigational site laboratory does not provide a corrected calcium result the formula in Section 11.2 should be used to calculate corrected calcium. Additional clinical chemistry samples will be taken weekly until resolution of the parameter to below the intervention limit. See Section 1.4.2.2 'Mineralisation, particularly in the heart'.

6.4.6 Physical examination

A complete physical examination will be performed at the visits as indicated in the Study Plans (Table 1 and Table 2).

The physical exam can be performed at any time on the scheduled day of assessment during treatment.

WHO Performance status will be assessed at screening and at all visits as indicated in the Study Plans (Table 1 and Table 2) according to WHO criteria as follows:

0 = Normal activity

1 = Symptoms, but nearly full ambulatory

2 = Some time in bed, but needs to be in bed <50% of normal day time

3 = Needs to be in bed >50% of normal daytime

4 = Unable to get out of bed

6.4.7 ECG: Resting 12-lead ECG

A 12-lead ECG will be performed at the visits as shown in the Study Plans (see Table 1 and Table 2).

Twelve-lead ECGs will be recorded at the following times for patients receiving AZD4547:

- Screening
- Day 1 of cycle 1 pre-dose and C_{max} (4 hrs ±15 min)

- Day 7 at C_{max} (2 hrs ±15 min)
- Day 1 of cycle 2 and each subsequent cycle at any time on the scheduled day of assessment
- Discontinuation of study treatment

Twelve-lead ECGs will be recorded at the following times for patients receiving paclitaxel:

- Screening
- Day 1 of cycle 1, pre-dose and at end of infusion
- Day 8 of cycle 1, at end of infusion
- Day 1 of cycle 2 and each subsequent cycle at any time on the scheduled day of assessment
- Discontinuation of study treatment

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at a minimum of 5 minute intervals (all three ECGs must be collected within 30 minutes). A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

The following parameters will be measured: RR, PR, QRS, QT.

After paper ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records.

If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition.

For patients receiving AZD4547 a digital copy of all ECGs will be held centrally for independent review by a central ECG provider and the data from this review will be stored for analysis at the end of the study. The independent review will not replace the local review by the investigator or cardiologist. Clinical interpretation and management of patients for all ECGs will be done locally.

6.4.8 Vital signs: Pulse, blood pressure and weight

Pulse, blood pressure and body weight assessments will be performed at the visits as shown in the Study Plans (see Table 1 and Table 2). Supine blood pressure and pulse will be measured after 10 minutes rest.

Vital signs can be measured at any time on the scheduled day of assessment during treatment. Vital signs assessments on day 1 cycle 1 do not need to be repeated if the screening visit was done within the previous 48hrs.

6.4.9 Other safety assessments

6.4.9.1 MUGA scan / Echocardiogram

A MUGA scan or echocardiogram to assess left ventricular ejection fraction (LVEF) will be conducted at screening (within 3 months of starting dosing), on day 1 of Cycle 2 (± 1 week) and then 3-monthly thereafter until discontinuation of study treatment, as shown in the Study Plans (see Table 1 and Table 2). A scan carried out within 3 months of starting study treatment can be used for eligibility at screening, however, for patients with significant cardiac events or who have had cardiotoxic medication within this interval, the echo/MUGA scan should be repeated within 28 days of starting study treatment. The modality of the cardiac function assessments must be consistent within patient, ie, if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required. The patient should also be examined using the same machine and operator throughout the study wherever possible.

6.4.9.2 Ophthalmic Assessment

An ophthalmic assessment will be performed by an ophthalmic expert at screening and approximately monthly for the first 3 months for AZD4547 patients, as shown in the study plan (Table 1). Thereafter, patients continuing the study treatment should have a full ophthalmological review every 8 weeks (± 1 week) until permanent discontinuation of AZD4547. At any other time, abnormal visual symptoms or signs will trigger a full ophthalmological review.

The ophthalmic assessment should be performed on each occasion by the same ophthalmic expert where possible.

The following assessments will be performed in the order stated:

- Visual acuity (best corrected) including near and far vision for each eye separately
- Amsler grid
- Schirmer's test without anaesthesia – read after 5 minutes (this test should be done before instillation of stains or dilatory agents)
- Slit lamp examination:
  - Apply 1 drop of 2% fluorescein followed by 1 drop of normal saline
  - Apply Lissamine Green*
  - Measure intra-ocular pressure

  - Photograph any abnormalities

  *Note, only applicable if Lissamine Green is used as local standard practice

- Fundoscopy and lens examination following pupil dilatation should be performed using binocular equipment and a 78 dioptre lens (or nearest available equivalent lens)

- OCT scans of the macula area of both eyes should be performed at baseline and monthly for the first 3 months on study treatment. After this time, an OCT scan should be performed on the occurrence of clinical symptoms or signs suggestive of RPED. OCT is the AstraZeneca preferred methodology for diagnosis of RPED. If OCT is not available as part of local clinical practice, an equivalent alternative diagnostic methodology to screen for RPED should be used.

Duplicate copies of the OCT scans should be retained at the site. These should be made available to AstraZeneca upon request.

Clinically significant abnormalities detected during ophthalmic assessments should be reported as AEs and an algorithm for further investigations and management is provided in Figure 3 and Figure 4. The patient should be managed under the care of a competent ophthalmologist with appropriate medication and followed up until the condition has resolved.

6.4.10 Post Study Follow-up

A discontinuation assessment will be performed at the time AZD4547 or paclitaxel is permanently discontinued. See Study Plans (Table 1 and Table 2).

In addition, patients should be followed up for 28 days after the last dose of AZD4547 or paclitaxel for any new reports of adverse events. Patients should also be asked about concomitant medications at this follow-up, including any subsequent cancer therapy they have received during this period.

If a patient discontinues randomised treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed with regular scans until disease progression as defined by RECIST 1.1. Survival follow-up and the recording of subsequent cancer therapy should continue for all patients until death or formal notification of study closure.

For further details regarding discontinuation of treatment and discontinuation of study, please refer to Sections 5.8 and 5.9.

6.5 Patient reported outcomes (PRO)

6.5.1 PRO instruments

PRO instruments will be administered in both treatment groups. Global health status and HRQoL will be assessed using the 30 item EORTC QLQ-C30, symptoms will be assessed

using the 22 item EORTC QLQ-STO22 (gastric cancer specific module) and health utility using the EQ-5D-5L. A copy of these instruments is presented in Appendix G. Each PRO instrument will only be administered to patients for whom an appropriate and validated language version is available.

EORTC QLQ-C30

The QLQ-C30 core questionnaire version 3.0, developed by the EORTC Quality of Life Group, measures patients' global health status and HRQoL (Aaronson et al 1993). This instrument is composed primarily of multi item scales covering the physical, emotional and social dimensions of quality of life (QoL). More specifically, scales are included that assess physical and role functioning, fatigue, nausea and vomiting, emotional functioning, social functioning and overall QoL.

EORTC QLQ-STO22 (gastric cancer module)

The EORTC QLQ-STO22 gastric cancer module consists of 22 items and assesses the following disease-related symptoms: body image, dysphagia, pain, reflux symptoms, eating restrictions, anxiety, dry mouth, taste and hair loss. During its development and validation, patients had one of the following tumour locations: proximal stomach & cardia, body of stomach, distal stomach, overlapping. The EORTC QLQ-STO22 demonstrates psychometric and clinical validity that supports its use to supplement the EORTC QLQ-C30 to assess QoL in patients with gastric cancer undergoing surgery, surgery and chemo radiotherapy, palliative chemotherapy, palliative surgery and best supportive care (Blazeby et al. 2004).

EQ-5D-5L

The EQ-5D-5L instrument assesses overall health utility.

Administration of PRO questionnaires

It is important to understand, from a patient perspective, how their disease and treatment impacts on symptoms and HRQoL. It is expected that in this patient population, disease progression will occur relatively quickly; consequently, it is necessary to capture the impact of this progression on symptoms of HRQoL. During the development of the symptom specific instrument, the EORTC QLQ-STO22 was tested at different follow-up schedules ranging from two weeks to three months, dependent upon the patient population. More specifically, in the palliative treatment intent population, the instrument was administered between two and six weeks after first administration; the instrument was able to detect significant deterioration in symptoms and physical functioning (Blazeby et al. 2004). Therefore, whilst on investigational drug, a two week frequency schedule will be used thereby allowing changes in symptoms and HRQoL to be captured reliably.

The PRO instruments will be first administered pre-dose at Day 1/Cycle 1 (ie, the day when patients receive their first dose of study treatment). The instruments will then be administered every two weeks whilst the patient remains on the investigational drug, as per the study plan (Table 1 and Table 2). In addition to this, they will be administered at the discontinuation visit and 28 days post discontinuation of investigation drug. Where a patient discontinues the

investigational drug prior to progression, the instruments will continue to be administered at each clinic visit when they return for their RECIST assessment.

The administration schedule for the PROs is presented in Table 1and Table 2.

The instructions for administration and completion of the three PRO instruments are:

- The majority of PRO assessment time points coincide with a clinic visit. They must be completed before any study-related procedures, investigations or discussions about the status of the patient's disease with clinic staff.

- It is important that the value and relevance of QoL and symptom data is explained carefully to participating patients so that they are motivated to comply with data collection. The research nurse or appointed individual should also stress that the information is confidential and will not be shared with the treating clinician. Therefore, if the patient has any medical problems these should be discussed directly with the treating clinician.

- All questionnaires must be answered directly by the patient where possible. The patients should be instructed on how to complete the questionnaire and, if necessary, assisted with completion of a training questionnaire that must be destroyed after completion. Help should not be given from relatives or clinic staff unless the patient is blind or illiterate.

- The EORTC QLQ-C30 must be administered before the QLQ-STO22. The EQ-5D-5L should be administered after these.

- For patients receiving AZD4547, there may be some PRO assessment points which do not coincide with a clinic visit. If a clinic visit is not scheduled when a PRO assessment is due, the patient should be provided with a copy of the instruments at the nearest clinic visit prior to this assessment point. The questionnaire should have the required date of completion entered on them. The patients should be asked to complete the instruments on the scheduled day of assessment and bring them with them at their next clinic visit. Where possible, patients should be reminded to complete the questionnaire on the required date and bring the completed instruments with them for their next clinic.

Following completion, the nurse or appointed individual must confirm verbally with the patient that the questionnaires have been completed fully and that only one answer to every question has been provided. The questionnaires should be kept in envelopes and kept strictly apart from any other information about the patients that is not related to the study.

6.6 Pharmacokinetics (AZD4547 patients only)

6.6.1 Collection of samples

Venous blood samples for determination of concentrations of AZD4547 (2 x 2.7 mL) in plasma will be taken on the days presented in the Study Plans (Table 1) at the following times:

Table 6 Pharmacokinetic blood sampling schedule for patients included into the second interim analysis strata

Time relative to dose	Cycle 1		Cycle 2		Study drug Discontinuation
	Day 7	Day 14	Day 1	Day 14	
Pre-dose	X[a]	X[c]	X[a]	X[c]	
30 min – 2 hrs		X		X	
5-6 hrs		X		X	
8-12 hrs		X[b]		X[b]	
0-48 hrs post last dose					X

[a] - Patients will be required to fast 2 hours prior to the first dose on Day 7/Cycle 1 and Day 1/Cycle 2
[b] - The 12h sample should be taken prior to the administration of the second daily dose
[c] - Patients will be required to fast 2 hours prior to and 2 hours after the first dose

Table 7 Pharmacokinetic blood sampling schedule for patients included into the post-second interim analysis strata

Time relative to dose	Cycle 1		Cycle 2		Study drug Discontinuation
	Day 7	Day 14	Day 1	Day 14	
Pre-dose	X[a]	X[b]	X[a]	X[b]	
3 hrs		X		X	
0-48 hrs post last dose					X

[a] - Patients will be required to fast 2 hours prior to the first dose on Day 7/Cycle 1 and Day 1/Cycle 2
[b] - Patients will be required to fast 2 hours prior to and 2 hours after the first dose

Samples should be taken within 10 percent of the nominal time point, for example 6 minutes for the 1-hour sample.

The PK plasma samples will also be analysed for phosphate and the data used with the AZD4547 PK to investigate any PK/PD relationship. These phosphate measurements will not be used in the assessment of safety or to trigger phosphate chelation therapy. The date and time of collection of each sample will be recorded.

The timing of the pharmacokinetic samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration time profiles. The total number of samples and the total volume of blood taken from each patient will not exceed that presented in Table 8 and Table 9.

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

For blood volume see Section 7.1.

6.6.2 Determination of drug concentration

Samples for determination of AZD4547 concentrations in plasma will be analysed by a Contract Research Organisation (CRO) nominated by AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest (ie, AZD4547) at the time of receipt by the bioanalytical laboratory will be analysed. In addition, the pharmacokinetic samples may be subject to further analysis in order to further investigate the presence and/or identity of drug metabolites. Any results from such analyses may be reported separately in a bioanalytical report.

PK samples will also be analysed for phosphate by a CRO nominated by AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

In addition, the pharmacokinetic samples may be subjected to further analyses in order to further investigate the presence and/or identity of drug metabolites. Any results from such analyses will be reported separately from the CSR.

6.7 Pharmacodynamics

For details of biomarker sample collection see the Laboratory Manual.

Biological samples (eg, archived and study-obtained tumour, blood etc) will be collected from consented patients and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug and clinical outcomes.

The results of this exploratory biomarker research may be reported separately from the CSR.

The results of this exploratory biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future studies.

6.7.1 Collection of tumour samples

All patients will be asked to provide consent at pre-screening to submit either archival or fresh tumour tissue. Patients whose FISH score from the pre-screening tumour sample is 1-3 may be retested with a fresh biopsy to determine eligibility. The same archival tumour sample

should not be FISH tested twice. The 2nd result will be used for eligibility in these cases. For patients with gastro-oesophageal junction (GEJ) and oesophageal tumours, sites should ensure that tissue samples submitted for FGFR 2 FISH score primarily consist of invasive adenocarcinoma and preferably do not contain Barrett's (columnar esophageal) tissue with or without dysplasia.

All samples submitted at pre-screen will be tested for FGFR2 gene copy number by FISH and the highest score will determine patient eligibility into the study and determine the stratum into which the patient will be randomised. Provision of a least one tumour sample is mandatory for eligibility into this study. A tumour sample will preferably be in the form of a formalin fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site). If this is not possible, 10-20 slides of freshly prepared unstained 5 micron sections from the archival tumour block may be provided.

Tumour samples may be surgical resection or biopsies:

- One surgical resection tumour sample is required

or

- A minimum of 7 biopsy samples are recommended to ensure reliable determination of FGFR2 status (see Section 1.3.5).

For those patients randomised in the FISH 4/5 stratum on the basis of less than 7 initial biopsy samples, every effort should be made to obtain additional pre-treatment samples in order to ensure reliable determination of FGFR2 status. Any samples that are submitted after a patient has been randomized will be stored for retrospective FISH testing and the impact of any differing results of FISH scores on efficacy outcomes will be explored via sensitivity analyses.

In the exceptional circumstance that no tumour tissue is available for central testing (ie, archival tumour samples have been exhausted or are not available, and a fresh biopsy is not possible) but there is clear evidence of FGFR2 gene amplification from local testing, patient entry to the trial will be at the discretion of the Sponsor. In such cases the local test result and local test protocol including information on the test platform must be supplied to the Sponsor to enable a decision to be made.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

6.7.2 Collection of serial tumour biopsies

Patient participation in this part of the study is optional. For consenting patients in both treatment arms, a fresh tumour biopsy should be collected prior to the start of dosing (unless a fresh biopsy was taken at pre-screening) and then an additional biopsy should be collected at any time point after day 14, (and for AZD4547 patients, after approximately 7 to 14 days of continuous dosing of AZD4547). A final biopsy should be collected at discontinuation of

study treatment, for analysis of biomarkers that may influence development of cancers and/or response to therapy. The date of collection will be recorded on the CRF.

Refer to the Laboratory Manual for details of sample handling, formalin fixation and paraffin embedding, labelling and shipment. AZ or an AZ designated laboratory will carry out the biomarker analysis.

6.7.3 Collection of blood borne biomarkers

Proof of mechanism pharmacodynamic biomarkers, eg, phosphate, bFGF and FGF23 are to be measured in this study and the relationship between plasma AZD4547 exposure and efficacy will be explored.

Proof of principle cancer related pharmacodynamic biomarkers, eg, cell death markers are to be measured in this study and the relationship between plasma AZD4547 exposure and efficacy may be explored.

Blood samples will be taken to provide samples of plasma and serum per time-point, as indicated in the study plans (Table 1 and Table 2). Samples should be taken pre-dose at each visit.

The samples will be analysed for a range of oncology biomarkers (eg, FGF23, bFGF) which may correlate with drug response.

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual.

6.7.4 Collection of bone biomarkers (AZD4547 patients only)

Blood samples (4 mL) will be taken for analysis of biomarkers related to bone turnover (for example 1,25 Vit D, βCTx and P1NP), on the days shown in the Study Plan (Table 1). Patients will be required to be fasted two hours prior to providing blood samples. Water will be allowed in moderate amounts throughout, apart from the 1-hour immediately prior to dosing.

Fasting bone biomarker samples will be taken as per the study plan (Table 1). The sample on day 1, cycle 1 must be taken pre-dose.

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual.

6.8 Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study a blood sample will be collected. The results of this pharmacogenetic research will be reported separately and will not form part of the CSR.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

6.8.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from any consenting patients, at the pre-screen visit. Alternatively the blood sample can be obtained on Cycle 1, Day 1 for patients who consent for the pharmacogenetics at the screening visit. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn on Cycle 1, Day 1 it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

6.9 Health economics

As per the study plan (Table 1and Table 2), procedures undertaken should be captured as part of the "Concomitant procedures data" from Cycle 1 Day 1 onwards. Where a patient discontinues the investigational drug prior to progression, procedures should continue to be collected at each clinic visit when they return for their RECIST assessment.

6.10 Survival assessment

Overall Survival status will be obtained for all patients who were pre-screened (including patients who went on to be randomised). For patients who were pre-screened/screened but not randomised the date of death should be entered into the clinical database as soon as the sites are aware of the patient's death. For patients who were randomised, survival contacts will be made and entered into the database every 3 months (± 1week) post-permanent discontinuation of study treatment and at data cut off. Survival status will continue to be collected until the required maturity for the primary analysis is achieved. The patient does not have to attend the clinic for the survival assessments to be carried out; these can either be done via a telephone call, or through review of the patient's notes, or through the use of public records. If the site become aware that a patient has died prior to the primary analysis, the relevant eCRF on the database should be completed at that time.

To aid the interpretation of the survival analysis, anti-cancer therapies administered following the discontinuation of study treatment will be recorded on the eCRF.

Further survival analyses may be performed after the primary analysis, at a time point to be determined, for all pre-screened patients (including patients who went on to be randomised).

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 8 Approximate volume of blood to be drawn from each of the 55 patients included in the interim analysis stratum (during pre-screening/screening, Cycle 1, subsequent cycles of treatment and discontinuation)

		Pre-screening/Screening and Cycle 1			Cycle 2 (and each subsequent cycle[b])			Discontinuation28 Day Follow-up		
		Sample volume (mL)	**Total number of samples**	**Total volume (mL)**	**Sample volume (mL)**	**Number of samples**	**Total volume (mL)**	**Sample volume (mL)**	**Total number of samples**	**Total volume (mL)**
Safety[a]	Clinical chemistry	6	5[c]	30	6	3[c]	18	6	2	12
	Haematology	9	5[c]	45	9	3[c]	27	9	2	18
Pharmaco-kinetics	AZD4547 patients only	5.4	5	27	5.4	5	27	5.4	1	5.4
Blood borne biomarkers		15	2	30	15	2	30	15	1	15
Bone biomarkers	AZD4547 patients only	4	2	8	4	2	8	-	-	-
Pharmaco-genetics		9	1	9	-	-	-	-	-	-
TOTAL (AZD4547 patients)				149			110			50.4
TOTAL (paclitaxel patients)				114			75			45

[a]-exact volume of blood for clinical chemistry and haematology may vary depending on local practice
[b]-total volume in subsequent cycles may vary, but volume in any one cycle will not exceed the volume required at Cycle 2
[c]-this is the maximum number of samples, for a 4 weekly cycle. For AZD4547 patients, in a 3 weekly cycle, there will only be 4 samples for screening and Cycle 1, and 2 samples for subsequent cycles.

Table 9 Approximate volume of blood to be drawn from each patient included in the post interim analysis stratum (during pre-screening/screening, Cycle 1, subsequent cycles of treatment and discontinuation)

		Pre-screening/Screening and Cycle 1			Cycle 2 (and each subsequent cycle[b])			Discontinuation/28 Day Follow Up		
		Sample volume (mL)	**Total number of samples**	**Total volume (mL)**	**Sample volume (mL)**	**Number of samples**	**Total volume (mL)**	**Sample volume (mL)**	**Total number of samples**	**Total volume (mL)**
Safety[a]	Clinical chemistry	6	5[c]	30	6	3[c]	18	6	2	12
	Haematology	9	5[c]	45	9	3[c]	27	9	2	18
Pharmaco-kinetics	AZD4547 patients only	5.4	3	16.2	5.4	3	16.2	5.4	1	5.4
Blood borne biomarkers		15	2	30	15	2	30	15	1	15
Bone biomarkers	AZD4547 patients only	4	2	8	4	2	8	-	-	-
Pharmaco-genetics		9	1	9	-	-	-	-	-	-
TOTAL (AZD4547 patients)				138.2			99.2			50.4
TOTAL (paclitaxel patients)				114			75			45

[a]-exact volume of blood for clinical chemistry and haematology may vary depending on local practice
[b]-total volume in subsequent cycles may vary, but volume in any one cycle will not exceed the volume required at Cycle 2
[c]-this is the maximum number of samples, for a 4 weekly cycle. For AZD4547 patients, in a 3 weekly cycle, there will only be 4 samples for screening and Cycle 1, and 2 samples for subsequent cycles.

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 below.

Any PK sample remaining after analysis for AZD4547 may be used for biomarker analyses. These analyses are for AZ use only and will not be included in the CSR.

Biological samples for future research can be retained at an AZ approved laboratory on behalf of AZ for a maximum of 25 years (depending on restrictions in country of sample origin) following the last patient's last visit in the study. The results from future analysis will not be reported in the CSR but separately in a CSR Addendum, a Scientific Report or Scientific Publication.

7.2.1 Pharmacokinetic samples

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report. PK samples will either be used up or disposed of after analysis.

7.2.2 Samples for exploratory analysis (biomarker and pharmacogenetics)

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

Each sample for exploratory research will be identified with the study number and patient enrolment number. In this way exploratory biomarker and genetic data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled.

Where genetic analysis will be undertaken the processes adopted for the coding and storage of samples will be more stringent in order to maintain patient confidentiality. As an added precaution, irrespective of the type of 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 will be used to identify the sample and corresponding data at the AZ genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AZ employee or contract laboratory staff) working with the DNA.

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment 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 AZ. 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 patient has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

The Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C of this Clinical Study Protocol 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples taken from the patient unless agreed with AZ and appropriate labelling, shipment and containment provisions are approved.

All archival tumour samples should be shipped at ambient temperature as per the Laboratory Manual to the AZ designated central CRO.

7.4 Chain of custody of biological samples

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

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

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

As collection of the following biological samples is a voluntary part of the study, if patients withdraw consent for use then the patient may continue in the study:

- Pharmacogenetics
- Serial tumour biopsy

As collection of the PK and biomarker blood samples is an integral part of the study, if patients withdraw consent for use then the patient is withdrawn from further participation in the study.

The Investigator:

- Ensures AZ is notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples.
- Ensures that biological samples from that patient, 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 of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the patient and AZ are informed about the sample disposal.

AZ ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the document returned to the study site.

AZ ensures that tumour blocks will be repatriated upon request.

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 ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

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

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

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

8.3 Ethics and regulatory review

An Ethics Committee (EC)/Institutional Review Board (IRB) 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 patients will ensure the distribution of these documents to the applicable Ethics Committee/IRB, and to the study site staff.

The opinion of the Ethics Committee/IRB should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients 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 Ethics Committee/IRB annually.

Before enrolment of any patient 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, Ethics Committees/IRBs and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

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

8.4 Informed consent

A two-step consent will be used (see Section 5.2.1)

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.

- Ensure each patient 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 patient.

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

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigators and AstraZeneca.

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

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

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

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

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

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

applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

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

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

9.3 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 CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.3.1 Source data

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

9.4 Study agreements

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

9.4.1 Archiving of study documents

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

9.5 Study timetable and end of study

The end of the study is defined as the date when the last study assessment of the last patient undergoing the study has taken place.

The study is expected to start in [redacted].

The first formal data cut-off will be for the purposes of conducting the first interim analysis. This will occur when the first 30 FISH 4/5 patients and the first 25 FISH 6 low amplification patients have been followed up for a minimum of 8 weeks (or progressed, or died prior to 8 weeks).

A second interim analysis will be performed once the first 25 FISH 6 high amplification patients have been followed up for a minimum of 8 weeks (or progressed, or died prior to 8 weeks) or 60 OS events across the FISH 6 strata are observed if the FISH 6 low amplification stratum continues after the first interim analysis.

If the study proceeds to the primary analysis, the cut-off for the primary analysis will be dependent on which strata remain open after the interim analyses:

- If FISH 6 high amplification strata only remains open – the data cut off for the primary analysis will be when approximately 60 deaths have occurred in the FISH 6 high amplification stratum.

- If both FISH 6 strata remain open only – the data cut off for the primary analysis will be when approximately 102 deaths have occurred across the two FISH 6 strata.

- If all 3 strata remain open – the data cut off for the primary analysis will be when approximately 163 deaths have occurred across all three strata provided that at least 102 deaths have occurred across the two FISH 6 strata.

In the event that the recruitment target is increased to compensate for those patients who were recruited prior to a change of dose and/or schedule, the data cut-offs for interim and primary analyses will occur when the respective required number of PFS/OS events have occurred in patients recruited after the change in dose/schedule. In the event that a change to dose and/or schedule is made at the interim analysis, a further interim analysis may be performed on the basis of the same number of patients and events as were required for the first interim analysis.

If the study does not proceed past either interim analysis then recruitment will be stopped and an updated analysis will be performed including all patients recruited to the study up to that point. A CSR will be written based on this final data set which will include the results of the interim and updated analyses. If the study proceeds to the primary analysis then the CSR will be written after the primary analysis including all analyses conducted up to that point.

Any patients still receiving AZD4547 at the time of the data cut-off for the final full analysis of the study (either interim or primary analysis, depending on if the study progresses past the interim analysis), will be able to continue to receive AZD4547 while deriving clinical benefit. Such patients will continue to be monitored for safety, as per the study plan (Table 1 and Table 2), and SAEs will continue to be reported as per Section 6.4.4, until the AZD4547 is discontinued. In addition, these patients should be followed up for 28 days after the last study treatment for any new reports of adverse events.

Further assessments of survival may also be performed following the primary analysis (within a maximum of 1 year after the initial survival assessment), if it is expected to provide additional data of value. A CSR Addendum will be prepared to summarise any additional safety data collected after a final survival analysis

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD4547.

10. DATA MANAGEMENT BY COGNIZANT

Data management will be performed by Cognizant Data Management Centre staff.

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

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

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.

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate. Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

Patients will undergo regular tumour assessments until documented objective disease progression as defined by RECIST 1.1 (see Appendix D).

At each visit patients will be programmatically assigned a RECIST visit response of CR, PR, SD or PD depending on the status of their disease compared to baseline and previous assessments.

Progression of TLs will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of

progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) unless there is evidence of progression in which case the response will be assigned as PD.

For TL measurements, if ≤1/3 of the TL sizes are missing then a scaling up rule will be applied as follows:

- If ≤1/3 of lesions recorded at baseline are missing then the results will be scaled up (based on the baseline sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the baseline sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing).

- If >1/3 of lesions recorded at baseline are missing then the TL response will be NE. However, if the sum of non-missing TL diameters would result in PD (ie, if using a value of 0 for missing lesions the sum of diameters has still increased by >20% or more compared to the smallest sum of diameters on study), PD takes precedence over NE.

- A visit response of CR will not be allowed if any of the TL data is missing.

11.1.1 Progression-free Survival (PFS)

PFS is defined as the time from randomisation until objective disease progression as defined by RECIST 1.1 or death (by any cause in the absence of progression).

Patients who have not progressed or died at the time of the statistical analysis will be censored at the time of their last evaluable RECIST assessment. If a patient has no RECIST follow up assessments or has no evaluable baseline assessment and is still alive at the time of the analysis then they will be censored at 0 days for PFS. Symptomatic deterioration will not be regarded as a progression event.

If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression then these patients will continue to be followed until evidence of objective disease progression as defined by RECIST 1.1 and their PFS time will be derived as defined above.

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression.

- When censoring individual patient data for PFS, the censoring will be applied at the latest of the dates contributing to a particular overall visit assessment.

11.1.2 Change in tumour size at 8 weeks

A secondary outcome variable in the study is change in tumour size at 8 weeks. This is based on RECIST measurements taken at baseline and at week 8. Tumour size is the sum of the longest diameters of the target lesions that have been selected at baseline. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment. The change in tumour size will be assessed using the log (ratio) of the week 8 tumour size over the baseline tumour size for each patient. More details on target lesions selection and assessment during the treatment can be found in Appendix D of the protocol.

Patients who progress before week 8 should conduct a tumour assessment at the time of progression prior to treatment discontinuation. The tumour size from the progression assessment will be used instead of the week 8 assessment for these patients.

Patients who discontinue study treatment for reasons other than objective disease progression should have tumour assessments scans performed as scheduled in the protocol and the tumour size from the week 8 assessment will be used in this analysis.

11.1.2.1 Missing Data Imputation Methods

Whenever tumour size data for the week 8 assessment is available then this should be used in the analysis of change in tumour size at 8 weeks. A windowing rule will be applied and will follow the protocol allowed visit window; therefore, any RECIST scan performed within ± 1 week of the protocol scheduled visit will be used for the week 8 visit.

If a patient has an incomplete week 8 assessment then provided ≤1/3 of the lesions sizes are missing, the sum of diameters at week 8 can be estimated by applying the scaling up rule described in Section 11.1. This estimated sum of diameters will be used in the analyses to estimate change in tumour size at 8 weeks.

If after target lesion imputation and applying a window around the week 8 visit there remains more than 10% missing tumour size measurement data, a non-parametric method will be considered for the primary analysis, assigning patients who have died with the worst rank and ranking other imputed data.

If, after applying the above considerations to the missing data, there is still missing tumour size measurement data at week 8, the imputation process outlined below will be followed for each individual patient where data is missing.

(a) If there is no tumour size measurement data at week 8, but there is tumour size measurement data collected at a visit prior to week 8 or the first visit after week 8, all of the available data up to and including the first visit after week 8 will be used to fit a linear regression to the individual subject's baseline and follow-up

assessment(s) to generate an estimated value for tumour size measurement at week 8 and hence impute a change from baseline at week 8.

(b) If there is evidence of progression for the individual, where evidence of progression is defined as progression of non target lesions, the appearance of new lesions or progression as determined by an investigator, impute a change from baseline at week 8 as 20%. If the patient has an imputed value from a), use the maximum of 20% or the imputed value in the TSA.

(c) If there is no evidence of progression for the individual, use the imputed value calculated in a) if data available. If no data available, assume that the data is missing completely at random, the patient will be excluded from the analysis.

(d) If it is known that the patient has died, impute a change from baseline at week 8 as the maximum of 20% or the largest percentage increase calculated from actual or imputed data.

11.1.3 Objective Response Rate (ORR)

ORR is defined as the percentage of patients who have at least one visit response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1).

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

The denominator for ORR will be all randomised patients.

11.1.4 Duration of response

Duration of response will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

11.1.5 Proportion of patients without progressive disease at 8 weeks

The proportion of patients without progressive disease at 8 weeks is defined as the percentage of patients with an 8 week visit response of CR, PR or SD (as defined by RECIST 1.1) with no evidence of previous progression. The denominator will be the number of patients randomised.

11.1.6 Overall survival

For all randomised patients OS is defined as the interval from the date of randomisation to the date of death. Patients who have not died by the date of the data cut-off, or who are lost to follow-up or withdraw consent, will be censored at the date they were last known to be alive. This definition will be used for the main analyses where only randomised patients will be included. For any exploratory analyses exploring the effect of FISH score on OS considering all pre-screened patients, OS will be derived from the date of signing consent rather than randomisation.

11.2 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs, ECG, LVEF and ophthalmic assessments. These will be collected for all patients. Appropriate summaries of these data will be presented as described in Section 12.2.

ECG Changes

QTc will be calculated by Cognizant, on behalf of AstraZeneca, using both Bazett's and Fridericia's formulae.

Creatinine Clearance

Estimated creatinine clearance will be calculated using the Cockcroft and Gault formula below, from creatinine:

For creatinine values in mol/L

Men: [(140 – age) x weight (kg) x 1.23] / creatinine (μmol/L)

Women: [(140 – age) x weight (kg) x 1.04] / creatinine (μmol/L)

Corrected Calcium

Corrected calcium will be calculated using the formula below, from total calcium and albumin:

Corr. Calcium = Total Calcium (mmol/L) + ([40 – Albumin (G/L)] x 0.02)

11.2.1 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 and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory, vital signs and ECG data will be performed for identification of OAEs.

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

11.3 Calculation or derivation of patient reported outcome variables

Subscales for the EORTC PRO instruments will be derived including symptom specific items (for example pain, dysphagia and reflux symptoms) as well as HRQoL domains (for example, physical and emotional functioning) and overall quality of life and global health status. Scores will be derived based on each specific instrument's scoring manual and minimally important differences will be defined.

In addition, best overall response from baseline, time to deterioration and comparison to population norm values (where available) will also be analysed. Scores will be derived based on each specific instrument's scoring manual and minimally important differences (MID) will be defined.

11.4 Calculation or derivation of performance status variables

The performance status will be assessed using the WHO scale instrument.

11.5 Calculation or derivation of pharmacokinetic variables

The investigation of the pharmacokinetic relationship between plasma AZD4547 exposure and demographics and pathophysiological characteristics will be the responsibility of the Clinical Pharmacology and Pharmacometrics Director, AstraZeneca, or a nominated representative.

The analysis will take place on the full PK dataset using actual sampling times and may be combined with the data from other studies within the AZD4547 program. The data are likely to be analysed using NONMEM (a nonlinear mixed effect approach) but may be analysed using other appropriate software that can handle sparse data. The PK model will be parameterised in terms of clearances (CL/F) and volumes (Vss/F) and if appropriate, the following secondary parameters may be derived for each individual from the final population PK model:

Table 10 Calculation of Secondary PK Paramaters

Paramater	
t ½	Effective half-life: ln(2) x (Vss/F) / (CL/F)
C_{max}	The maximum individual predicted concentration in the central compartment (where the derivative approaches zero) in a standard dosing interval at steady-state ie, 12 hrs
t_{max}	The time of C_{max}

Table 10 Calculation of Secondary PK Paramaters

Paramater	
C_{min}	The individual predicted concentration at the end of the dosing interval (actual time immediately prior to the next dose or 12 hours, if longer)
AUC	Integration of the area under the concentration time curve from the time of dosing to the end of the dosing interval (tau) at steady -state ie, 12 hrs or less if the dose is administered prior to the 12 hr time point

11.6 Calculation or derivation of pharmacodynamic variable(s)

Appropriate levels and changes from baseline in soluble biomarkers will be produced for each patient with evaluable samples.

11.6.1 Calculation or derivation, using population analysis, of the relationship between pharmacokinetic and pharmacodynamic variables

The PK/PD relationship between plasma AZD4547 exposure and pharmacodynamic markers, safety and clinical outcome measures may be investigated. This may be approached graphically or follow a similar approach to that described in Section 11.5. The variables that may be assessed are:

- The pharmacodynamic markers are likely to include plasma concentrations of phosphate, bFGF and FGF23.
- Clinical outcome measures are likely to be tumour size assessment, progression free survival, overall survival and objective response rate.
- The three most prevalent adverse events and of clinical interest will be assessed.

The results of any such analyses will not form part of the CSR for this study.

11.7 Calculation or derivation of exploratory research variables

Results from the exploratory biomarker research and from the exploratory tumour volume measurements may be reported separately from the main CSR for this study.

11.8 Calculation or derivation of pharmacogenetic variables

Results from the exploratory pharmacogenetic research and from the exploratory tumour volume measurements may be reported separately from the main CSR for this study.

11.9 Calculation or derivation of health economic variables

A health utility value will be estimated from the EQ-5D-5L. The visual analogue scale component will be scored separately. Resource use will be primarily based on procedures

captured on the concomitant procedure module. Details of the exploratory health economic analysis of resource use and health utility will be provided in the SAP.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Efficacy Analysis Set

All efficacy data (PFS, change in tumour size at 8 weeks, PFS, ORR and percentage of patients without progression at 12 weeks and OS) will be analysed by comparing treatment groups on the basis of randomised treatment, regardless of the treatment actually received, and using the stratum to which they were re-assigned after changes to an individual patient's amplification score (ratio) see Section 5.2.1.

In the event of a change to an individual patient's amplification score (ratio) arising eg, from a change to the FISH scoring methodology (see Section 5.2.1) a patient will be re-allocated to the appropriate stratum where possible and/or an additional patient may be recruited to the affected stratum to compensate. This will ensure that the FISH 6 high amplification stratum achieves 80 randomised patients for the efficacy analysis set at the final dose/schedule.

In the event that the dose/schedule is changed following recommendation by the SRC, and the total number of patients has been increased to compensate for patients recruited prior to the change, the primary analyses will be performed on the subset of the efficacy analysis set randomised to the new dose/schedule. Summary analyses may be performed including all patients randomised to either dose/schedule.

12.1.2 Safety analysis set

All patients who received at least one dose of randomised investigational product, (AZD4547 or paclitaxel) will be included in the safety population. Throughout the safety results sections, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

12.2 Methods of statistical analyses

The characterisation of the efficacy profile of AZD4547 compared with paclitaxel will be based upon assessment of the PFS and OS treatment effects in the overall population, separately in those who have FGFR2 gene amplified tumours at baseline (FISH 6 stratum) and in those who have FISH 6 high amplification tumours, along with supportive information from other key secondary endpoints of changes in tumour size, objective response rate, duration of response and proportion of patients without progressive disease at 8 weeks.

In the event that the SRC and AstraZeneca agrees that an alternative dose or schedule should be explored with a consequent increase in the number of patients to be enrolled, these analyses will be performed for the patients randomised after the last change in dose or schedule (for

SRC roles and responsibilities reference section 5.5.3.1). These analyses will be considered as primary, and data from patients randomised prior to the change in dose or schedule will be summarised descriptively.

A comprehensive statistical analysis plan (SAP) will be prepared which will document details of sensitivity analyses and imputation methods for missing data.

For the primary and secondary analyses, the null hypothesis is that there is no treatment effect ie, there is no difference in progression free survival between patients treated with AZD4547 and patients treated with paclitaxel.

No multiplicity adjustments will be made in the statistical analysis.

FGFR2 FISH score subgroups used in the primary analyses will be determined based on actual FISH test results known at the time of analysis, ie, in the case of a re-scoring of a tumour later in the study, the later test result will allocate the patient to the stratum they will remain in for the analysis, not necessarily the result that was known at the time of randomisation.

The exploratory objectives relating to exploring the association between FISH ratio and efficacy in randomised patients and exploring the prevalence of FISH scores and correlation with survival in pre-screened patients will be reported in the CSR. Details of the analysis will be documented in the SAP.

All summaries and analyses (baseline, efficacy and safety data) will be presented by dose and schedule to allow for any changes to the planned dose/schedule following SRC review.

The methodologies described below are general principles for analysis methods at the primary analysis, and will be adapted depending on which strata remain open at the primary analysis.

12.2.1 Progression Free Survival

The main analysis of PFS will be at the primary analysis of the study, see section 9.5 for description of primary analysis timings which relate to reaching the required level of maturity in the OS endpoint. At this analysis, PFS will be analysed by the methodology described below. PFS will also be presented at the interim analyses, primarily just in the overall FISH 4-6 population given the small number of events at this time, with some supportive summaries in the FISH 4/5 and FISH6 low amplification stratum at the first interim analysis, and each FISH 6 stratum at the second interim analysis.

PFS will be analysed in all randomised patients using a Cox proportional hazards model with the Efron method for handling any ties, with covariates for FGFR2 FISH stratum (4/5 vs. 6 low amplification vs 6 high amplification) and treatment. PFS in patients with FGFR2 low and high amplified (FISH 6) tumours and in patients with FGFR2 polysomy (FISH 4/5) tumours will each be estimated from a cox proportional hazards model fitted in the overall population (FISH 4-6) with covariates for FGFR2 FISH stratum (4/5 vs 6 low amplification vs 6 high amplification), treatment and the treatment by FISH strata interaction.

The PFS hazard ratios (HR; AZD4547:paclitaxel) for all patients, for patients who have tumours with FGFR2 amplification (FISH 6), for patients with FISH 6 low amplification, for patients with FISH 6 high amplification and for patients who have tumours with FGFR2 polysomy (FISH 4/5) will be estimated together with their 80% and 95% confidence intervals and associated 1-sided p-values (a HR less than 1 favours AZD4547). P-values will be based on the likelihood ratio test and confidence intervals will use a profile likelihood approach. Kaplan-Meier plots of PFS and estimates of median PFS and proportion of patients who are progression free at 3 and 6 months will be presented by treatment arm and, in addition, by treatment and FISH stratum (4/5 vs 6 low amplification vs 6 high amplification) for the overall analysis. Additional summaries across all FISH 6 patients may also be produced, if appropriate.

The assumption of proportionality will be assessed using plots of complementary log-log event times versus log time. If evidence of non-proportionality is indicated, a time-dependent covariate will be fitted to assess the extent to which this represents random variation. If a lack of proportionality is evident, the HR may still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves.

Full details of any sensitivity analyses for PFS will be fully documented in the SAP, including assessment of alternative cut-offs.

Along with exploring the PFS treatment effect in each stratum of patients as described above, the consistency of the PFS effect in the overall FISH 4-6 population will also be explored in a small number of key subgroups of interest, full details of which will be documented in the SAP. The key subgroups of interest will include age (<65 versus ≥ 65), gender, race, key biomarkers of interest and location/type of gastric cancer, providing there are a sufficient number of patients with PFS events in each level of the subgroups. Depending on how many strata continue to the primary analysis it may not be possible to explore the treatment effect in the individual FISH 6 strata patients within these additional subgroups, due to small numbers of events when splitting this subgroup further, so these additional subgroup analyses will only be performed within those strata that have sufficient numbers of patients and events.

Forest plots will be produced that illustrate the PFS hazard ratios and confidence intervals for each strata along with any other subgroup treatment effects that are explored.

The existence of any treatment by covariate interactions, primarily for the FISH strata subgroups, but considering any other subgroups secondarily, will be investigated by the difference in the log likelihoods for the full (including interactions) and reduced (excluding interactions) models. If this difference is found significant ($p<10\%$), an attempt to determine the cause and type of interaction will be made. Additional interaction testing may be performed to assess whether any observed differential treatment effect between subgroups is due to confounding by other prognostic factors. It is important to note that the PFS subgroup analyses described in this section have limited power to detect treatment-subgroup interactions. The interaction testing result will provide supportive information rather than whether or not to move to the confirmatory Phase III testing of AZD4547.

12.2.2 Overall Survival

The primary analysis of OS will be analysed when sufficient maturity is reached in those strata which continue beyond the interim analysis. This is defined as at least 60 OS events in the high FGFR2 amplified patients stratum at least 102 OS events overall out of the FISH 6 patients and at least 163 events overall out of the FISH 4-6 patients. The analysis of OS will use the same methodology and models as described for PFS and adjusting for the same set of covariates and performing any sensitivity analyses and subgroup analyses deemed appropriate for PFS. Kaplan-Meier estimates of survival at 3 months, 6 months and 12 months will be tabulated by treatment arm along with all other analyses and summaries described for PFS.

12.2.3 Change in tumour size at week 8

The change in tumour size at week 8 (or discontinuation tumour assessment scan if prior to week 8) will be assessed at the interim and primary analyses in all patients and separately, in FGFR2 gene amplified patients, and FISH 6 high amplification patients alone, as the log of the ratio of the week 8 over the baseline tumour size measurement for each patient (see Section 11.1.2 for detailed description of this variable).

The effect of AZD4547 on change in tumour size in all randomised patients will be estimated from an analysis of covariance (ANCOVA) model including terms for baseline tumour size (log transformed), time from baseline scan to randomisation, FGFR2 FISH strata (4/5, 6 low amplification and 6 high amplification) and treatment. The effect of AZD4547 on change in tumour size in patients with FGFR2 polysomy (FISH 4/5) tumours, FGFR2 amplified (FISH 6) tumours and in patients with FISH 6 low and high amplification tumours will be estimated from the same ANCOVA model as described above but also including the treatment by FISH strata interaction. If the week 8 tumour size is 0, this will be imputed as 0.01 as the log transformed value in the log transformed analysis of these data.

The results will be presented in terms of adjusted means (lsmeans) for each treatment together with their 2-sided 80% confidence intervals. An estimate of the treatment effect in all patents (difference in lsmeans, AZD4547 – paclitaxel), an estimate of the treatment effect in FGFR2 polysomy patients, FGFR2 amplified patients and an estimate of the treatment effect in FISH 6 low and high amplification patients alone will be calculated together with their 2-sided 80% confidence interval. These point and interval estimates will be exponentially back transformed to provide estimates of the percentage change from baseline tumour size at 8 weeks. The number of patients and percentage of patients in each treatment group whose week 8 data is imputed due to missing data (see Section 11.1.1) will be presented on the footnote to the table of output from this analysis.

The distribution of the tumour size measurement data will be assessed prior to the first interim analysis without knowledge of the randomised treatment assignment. If the week 8 changes in tumour size data follow a log-normal distribution, these data will be analysed as described previously. If however it is judged the data do not adequately follow a log-normal distribution then the use of untransformed percentage changes or a non-parametric approach could replace the log transformed analysis as the primary approach. If the log transformed or untransformed analyses are used as the primary analysis, a sensitivity analysis will be performed using a non-

parametric method. The Hodges-Lehmann estimator for the median will be presented for each treatment group. Full details of the methods to be used to determine whether the data follow a log-normal distribution will be included in the SAP.

The week 8 change in tumour size will also be presented graphically by waterfall plots for each treatment group which present each patients week 8 change in tumour size as a separate bar, with the bars ordered from the largest increase to the largest decrease. Reference lines at the +20% and –30% change in tumour size levels will be added to the plots, which correspond with the changes in sum of target lesions that would result in target lesion responses of progression and complete or partial response respectively. In these waterfall plots (and also in the listings) the patients whose week 8 change in tumour size is based on an imputation due to missing target lesion data but known to be progressors will be clearly identified (by different coloured bars for the waterfall plots and a flag in the listings). In addition, these waterfall plots will also be presented for each treatment group and stratum separately.

Change in tumour size at week 8 will be summarized for each treatment group using standard summary statistics for all patients and for patients categorised by FISH 4/5 and FISH 6.

Exploratory data summaries of the efficacy outcomes by FGFR2 FISH ratio will also be produced.

12.2.4 Objective Response Rate

ORR as defined in Section 11.1.3 will be reported overall by treatment and by FGFR2 FISH strata (4/5 vs. 6 low amplification vs 6 high amplification) patients. Additional summaries across the combined FISH 6 strata may also be produced, if appropriate. Summaries will be produced at the interim and primary analyses of best response at 8 weeks and best overall response during the study (CR, PR, SD, PD, NE).

Objective response will also be statistically analysed at the primary analysis in the overall population and in the FISH 4/5 and FISH 6 low amplification and FISH 6 high amplification strata, assuming there are a sufficient number of responding patients, using logistic regression models adjusting for the same set of covariates as described for the PFS and OS analyses. Odds ratios will be estimated together with their 80% confidence intervals and associated p-values.

12.2.5 Duration of Response

At the interim analyses, if there are sufficient numbers of responders, and sufficient numbers of responses that have progressed by the interim analysis DCO's, Kaplan-Meier plots of duration of response in the responding patients will be produced and appropriate summary statistics will be presented (number of response, number of responses that have progressed, median, quartile, minimum and maximum duration of response in the responders using the Kaplan-Meier estimate).

At the primary analysis, along with the presentations described above for the interim analyses, duration of response may also be formally statistically analysed between the arms by deriving

the Expected Duration of Response (EDoR) for each treatment stratum (Ellis S et al.). The EDoR is the product of the proportion of patients responding to treatment and the mean DoR in responding patients and provides an estimate based on all randomised patients. Full details of this analysis will be documented in the SAP.

12.2.6 Percentage of patients without progression at 8 weeks

The percentage of patients without progression at 8 weeks as defined in Section 11.1.5 will be reported both overall and by FGFR2 FISH strata (4/5 vs. 6 low amplification vs 6 high amplification). An additional summary pooling the data across all FISH 6 patients may also be produced.

12.2.7 Patient Reported Outcomes

At the primary analysis, subscale scores from the PRO instruments will be summarised by visit for both treatments, overall and by FGFR2 FISH stratum (4/5 vs. 6 low amplification vs 6 high amplification), as will the change from baseline score over time. An additional summary pooling the data across all FISH 6 patients may also be produced. In addition, best overall response from baseline, time to deterioration and comparison to population norm values (where available) will also be summarised. Time to deterioration endpoints will be analysed using the same methodology and models as described for PFS and adjusting for the same set of covariates

Details of the exploratory analyses of the EQ-5D-5L will be provided in the SAP.

12.2.8 WHO Performance status

At the primary analysis, the proportion of patients classified by performance status score, will be summarised by visit for both treatments, overall and by FGFR2 FISH stratum (4/5 vs. 6 low amplification vs. 6 high amplification). An additional summary pooling the data across all FISH 6 patients may also be produced. Time to deterioration in performance status will be analysed using the same methodology and models as described for PFS and adjusting for the same set of covariates.

12.2.9 Health Economics

Details of the exploratory health economic analysis of resource use and health utility will be provided in the SAP.

12.2.10 Safety

Safety data will not be analysed formally. All patients who receive at least one dose of study treatment will be included in the assessment of the safety profile (safety analysis set). Safety and tolerability data will be presented by treatment received and will be assessed in terms of AEs (including SAEs related to procedures associated with tumour biopsies following 1st consent, or genetics test (for those who consent) but prior to main consent), laboratory data, vital signs, ECG assessments, MUGA scans/echocardiograms and ophthalmic assessments.

Adverse event data, both in terms of Medical Dictionary for Regulatory Activities (MedDRA) preferred term and CTCAE grade, will be listed individually by patients and summarised by treatment group. For patients who have a dose modification (ie, dose reduction, interruption), all AE data will be assigned to the initial dose received for the purpose of data summaries.

Laboratory, vital signs and ECG data will be listed for all patients in the safety analysis set and changes from baseline will be summarized.

Relevant safety outputs will be presented by FISH status (full details will be given in the SAP).

12.2.11 Interim analyses

There will be 2 interim analyses during the study which will be conducted to ensure that adequate evidence of anti tumour activity (as measured by changes in tumour size at 8 weeks) has been demonstrated in a given stratum prior to recruiting the full 80 patients required per stratum to robustly assess progression free and overall survival in that stratum. Due to the differing prevalence of FGFR2 polysomy, low gene amplification and high gene amplification in this patient population, and hence the differences in time to recruit the different strata, two separate interim analyses are planned:

Interim Analysis 1

The data cut-off for the first interim analysis will occur when the first 30 FISH 4/5 patients and the first 25 FISH 6 low amplification patients have been followed up for a minimum of 8 weeks (or progressed, or died prior to 8 weeks). Due to the anticipated higher prevalence of FGFR2 polysomy (FISH 4/5) than FGFR2 amplification (FISH 6), enrolment into the FISH 4/5 stratum will be put on hold once sufficient patients have entered screening to achieve the 30 randomised patients required for the first interim analysis. Recruitment to both FISH 6 strata will remain open whilst data for the first interim analysis is being collected and analysed., subject to a cap of 40 patients randomised within the FISH 6 low amplification stratum.

The first interim analysis will be performed to determine whether there is sufficient evidence of anti-tumour activity and an acceptable safety profile which would warrant continuation of either or both of these strata (polysomy and FISH 6 low amplification) recruiting to the full 80 patients. If either (or both) of these strata are discontinued after the first interim analysis then recruitment to these strata will be stopped (or will not be re-opened, in the case of the FISH 4/5 stratum). Conversely if either (or both) of these strata are continued after the first interim, then recruitment will re-open and/or the cap on recruitment for the FISH 6 low amplification will be removed. Recruitment to the FISH 6 high amplification stratum will remain open throughout and after interim analysis 1 as continuation of that stratum will be contingent on a positive outcome from Interim Analysis 2.

Progression free survival and changes in tumour size will be statistically analysed at the first interim analysis using the same methods as described in the previous sections. Descriptive summary statistics and graphical presentations will be used for other efficacy endpoints (best

response at 8 weeks, best objective response during the study, duration of response and proportion of patients without progressive disease at 8 weeks), biomarkers and safety data . OS data will not be presented at this interim analysis. Due to the expected low number of patients with high amplification having been enrolled at the time of the first interim analysis, results from the FISH 6 high amplification stratum in isolation will not be reported until the second interim analysis.

Interim Analysis 2

The scope of Interim Analysis 2 will depend on decisions taken at Interim Analysis 1 and will only include data for those strata that were continued after Interim Analysis 1.

If only the FISH 6 high amplification stratum remains open after the first interim analysis, the data cut-off for the second interim analysis will occur when 25 patients with FISH 6 high amplification patients have been randomised and followed-up for a minimum of 8 weeks (or progressed or died prior to 8 weeks). At this point a decision will be taken concerning the continuation of this FISH 6 high amplification stratum, based on the strength of any evidence of anti tumour activity observed.

If both FISH 6 strata remain open after the first interim analysis and irrespective of whether recruitment has continued in the polysomy stratum, the data cut-off for the second interim analysis will be the earliest of approximately 60 overall survival events having occurred across the combined FISH 6 strata, or the first 25 FISH 6 high amplification patients have been followed up for a minimum of 8 weeks (or progressed or died prior to 8 weeks). The analysis will include data from patients who meet the criteria for the data cut-off including those who were recruited to the polysomy stratum.

Any recruitment that is ongoing at the time of the 2nd interim analysis will remain open whilst data is being collected and the analysis performed provided that the overall recruitment target of 80 patients in a stratum has not already been reached.

The purpose of the 2nd interim analysis will be dependent on the outcome of the first interim analysis. If only the FISH 6 high amplification stratum remains open at the 2nd interim, then this analysis will be focussed on assessing changes in tumour size and response rate within this stratum alone, to assess if there is sufficient evidence of anti tumour activity to warrant recruiting the full 80 patients in that stratum. If both FISH 6 amplification stratum remain open after the first interim analysis, then the second interim will have a broader focus and as well as assessing changes in tumour size and response rate within the FISH 6 high amplification stratum, an initial assessment of progression free survival and overall survival across all FISH 6 patients will also be performed.

If the study proceeds beyond the second interim analysis a total of approximately 80 patients will be randomised in each of the stratum which remain open.

Depending on which strata remain open after the interim analyses, the primary analysis will occur at the following times:

- If FISH 6 high amplification strata only remains open – the data cut off for the primary analysis will be when approximately 60 deaths have occurred in the FISH 6 high amplification stratum.

- If both FISH 6 strata remain open only – the data cut off for the primary analysis will be when approximately 102 deaths have occurred across the two FISH 6 strata.

- If all 3 strata remain open – the data cut off for the primary analysis will be when approximately 163 deaths have occurred across all three strata provided that at least 102 deaths have occurred across the two FISH 6 strata.

If a decision is taken not to continue the study past the second interim analysis, then recruitment to all open strata will be stopped and a primary analysis of all data from all randomised patients will be completed and reported.

If a dose or schedule change has occurred and the total number of patients has been increased to compensate for patients recruited prior to the change, both interim and primary efficacy analyses will occur when the revised recruitment target has been met and the appropriate follow up time for TSA or number of PFS/OS events have occurred in patients randomised after the change to dose/schedule.

12.2.12 Assessment of prevalence and survival in pre-screened patients

The proportion of all pre-screened (including randomized) patients in each FGFR2 FISH score category (1-6) will be summarized along with the median FISH ratio. For all pre-screened (including randomized) patients survival, calculated as the time from date of consent to date of death will be presented in a Kaplan-Meier plot, grouped by FISH score. Kaplan-meier estimates of survival at 3 months, 6 months and 12 months will also be tabulated by FISH score. A summary of demographic characteristics will be produced for all pre-screened patients.

12.3 Pharmacokinetics (Not applicable)

N/A

12.4 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

Although the primary endpoint of the study is progression free survival, the primary efficacy analysis will be triggered based on sufficient OS maturity being reached, which is defined as at least 60 OS events from the patients in the FGFR2 high amplification stratum, at least 102 events out of the FGFR2 amplified (FISH 6) patients and at least 163 events out of all FGFR2 polysomy or amplified (FISH 4-6) patients, depending on which strata remain open at the time of the primary analysis.

If both FGFR2 amplified (FISH 6) strata remain open at the time of the primary analysis, 102 events (within the FISH 6 patients) will provide 85% power to detect an OS HR=0.63 at the 1 sided 10% significance level, given the randomisation ratio of 3:2 between the treatment arms. Assuming median OS in the paclitaxel arm is 5 months for patients with FGFR2 gene amplification (FISH 6), a HR of 0.63 corresponds to median OS of 8 months in the AZD4547 arm. A HR of 0.77 in the FISH 6 population is the smallest treatment effect that would be statistically significant at the 10% 1 sided significance level.

If only the high FGFR2 gene amplification stratum remains open at the primary analysis, 60 OS events within the high FGFR2 amplified patients stratum will provide 80% power to detect an OS HR=0.57 at the 1 sided 10% significance level, given the randomisation ratio of 3:2 within this stratum. Assuming median OS on the paclitaxel arm is 4 months in high FGFR2 amplified patients, a HR of 0.57 corresponds to median OS of 7 months on AZD4547. A HR of 0.71 in the FISH 6 population is the smallest treatment effect that would be statistically significant at the 10% 1 sided significance level.

If all three strata continue to the primary analysis, 163 events overall will provide 90% power to detect an OS HR=0.67 at the 1 sided 10% significance level, given the overall randomisation ratio of approximately 1.3:1 between the treatment arms (3:2 within the FGFR2 amplified patients, and 1:1 within the FGFR2 polysomy patients). Assuming median OS in the paclitaxel arm is 6 months for patients with FGFR2 polysomy or gene amplification (FISH 4-6), a HR of 0.67 corresponds to median OS of 9 months in the AZD4547 arm. A HR of 0.82 in the overall population is the smallest treatment effect that would be statistically significant at the 10% 1 sided significance level.

In the event that the dose/schedule is changed following recommendation by the SRC, and the SRC decide to increase the recruitment target for the study to compensate for any patients already recruited prior to the change, approximately 240 patients will be randomised into the study.

In the event of a change to an individual patient's amplification score (ratio) arising eg, from a change to the FISH scoring methodology (see Section 5.2.1) a patient will be re-allocated to the appropriate stratum where possible and/or an additional patient may be recruited to the affected stratum to compensate. This will ensure that the FISH 6 stratum achieves 80 randomised patients for the efficacy analysis set at the final dose/schedule.

12.5 Data monitoring committee (not applicable)

N/A

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 6.4.4**

In the case of a medical emergency the Investigator may contact the Study Team Physician. If the Study Team Physician is not available, contact the Study Delivery Team Leader or the Patient Safety Physician at AstraZeneca, Alderley Park.

Name	Role in the study	Address and telephone number
Dr Dana Ghiorghiu	Study Team Physician responsible for the protocol at central R&D site	AstraZeneca, Alderley Park, Macclesfield, UK +44 (0) 1625 233954
Jayne Rankine	Study Delivery Team Leader responsible for the protocol at central R&D site	AstraZeneca, Alderley Park, Macclesfield, UK +44 (0) 1625 516103
Dr Andrew Hastie	Patient Safety Physician responsible for the protocol at central R&D site	AstraZeneca, Alderley Park, Macclesfield, UK +44 (0) 1625 516787

13.2 Overdose

There is no known antidote to AZD4547. Investigators should be advised that any patient who receives a higher dose of AZD4547 than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

- An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the CRF and on the overdose CRF module
- An overdose with no associated symptoms is only reported on the overdose CRF module

If an overdose of AZD4547 occurs in the course of the study, then Investigators or other site personnel inform appropriate AZ representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

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

For overdoses associated with a SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

For treatment of overdose with paclitaxel please refer to the local prescribing information. Overdose of paclitaxel with associated AEs/SAEs should be recorded in the relevant AE/SAE module of the eCRF and reported according to the standard timelines. The overdose does not need to be entered into the overdose eCRF module.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study AZD4547 should be discontinued immediately.

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

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy modules in the CRF are used to report both the pregnancy and the outcome of the pregnancy.

If a female patient becomes pregnant whilst receiving paclitaxel treatment, local prescribing information should be followed.

13.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and 16 weeks following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 30 days after the last dose of AZD4547 should be followed up and documented.

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Clinical Study Protocol Appendix B

Drug Substance	AZD4547
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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	
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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.

AstraZeneca

Clinical Study Protocol Appendix D	
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Appendix D
Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

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1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D2610C00004 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion that has not been previously irradiated.

Measurable lesions

- A lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

- Local disease confined to the stomach or oesophagus is not considered measurable (patients with locally advanced gastric including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction must have at least one measurable nodal lesion ≥15mm in the short axis).

Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline. Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)

- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI

- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment

- Skin lesions assessed by clinical examination

- Brain metastasis

Special cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as the target lesions (TLs).

Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

Non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline.

3. METHODS OF MEASUREMENT

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided below in Table 1 and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 1 Summary of Methods of Assessment

Target Lesions	Non target lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		Bone Scan
		FDG-PET

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identification of new lesions.

In the D2610C00004 study it is recommended that CT examinations of the chest, abdomen and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesions assessment, MRI is the preferred method.

3.2 Clinical examination

In the D2610C00004 study, clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3 X-rays

3.3.1 Chest X-ray

In the D2610C00004 study, chest x-ray assessment will not be used for assessment of TLs as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTLs and to identify the presence of new lesions.

3.3.2 Plain X-ray

In the D2610C00004 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In the D2610C00004 study, ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the D2610C00004 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

3.6 Tumour markers

In the D2610C00004 study, tumour markers will not be used for tumour response assessments per RECIST 1.1.

3.7 Cytology and histology

In the D2610C00004 study, histology will not be used as part of the tumour response assessment per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs or disease progression due to new lesions.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTLs and followed by the same method as per baseline assessment.

In the D2610C00004 study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

In the D2610C00004 study, FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinically indicated, in order to confirm new lesions.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days

before the start of study treatment. Follow-up assessments should be performed at Week 8 (±1 week) and then every 8 weeks (±1 week) after randomisation until discontinuation of study treatment or withdrawal of consent. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

4.2 Target lesions

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions) but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

- When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc, during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

Table 2 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 2 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

4.3 Non-Target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. Table 3 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 3 Overall Visit Response for Non-Target Lesions

Complete Response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more NTLs.
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST clinically significant for the physician to consider changing or stopping therapy
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

4.6 Evaluation of Overall Visit Response and Best Overall Response

The overall visit response will be derived using the algorithm shown in Table 4

Table 4 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no NTLs at baseline)

5. CONFIRMATION OF RESPONSE

N/A

6. CENTRAL REVIEW

N/A

7. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

7.1 CT Scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic coverage

Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

Intravenous contrast administration

Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without intravenous contrast is an option for the thorax, abdomen and pelvis examination.

Slice thickness and reconstruction material

It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

7.2 MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

7.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

7.3.1 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

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Clinical Study Protocol Appendix E	
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Appendix E
Guidance Regarding Potential Interactions With Concomitant Medications

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GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

1. DRUGS AFFECTING CYP3A4 OR CYP2D6 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH AZD4547

Table 1 Potent CYP3A4 or CYP2D6 inhibitors may increase exposure to AZD4547 more than 3-fold

Ketoconazole Ritonavir Saquinavir Indinavir Nefazodone	Minimum of 48 hours washout prior to AZD4547 administration and must avoid for the duration of the study and for 14 days following discontinuation of AZD4547
Itraconazole Clarithromycin (250mg or 500mg bd) Erythromycin Fluconazole 400mg Quinidine Methimazole	Minimum of 7 days washout prior to AZD4547 administration and must avoid for the duration of the study and for 14 days following discontinuation of AZD4547
Diltiazem Paroxetine	Minimum of 14 days washout prior to AZD4547 administration and must avoid for the duration of the study and for 14 days following discontinuation of AZD4547
Fluoxetine	Minimum of 35 days washout prior to AZD4547 administration and must avoid for the duration of the study and for 14 days following discontinuation of AZD4547

Table 2 Potent CYP3A4 or CYP2D6 inhibitors may increase exposure to AZD4547 more than 3-fold

Barbiturates Carbamazepine Phenytoin Rifampicin, Rifabutin all Glitazones (thiazolidinediones)	Minimum of 14 days washout prior to AZD4547 administration and for 14 days following discontinuation of AZD4547
St John's Wort	Minimum of 21 days washout prior to AZD4547 administration and for 14 days following discontinuation of AZD4547

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and AZD4547; a potential interaction is considered on the basis of preclinical data only. This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 or CYP2D6 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

2. DRUGS AFFECTING CYP3A4 METABOLISM THAT ASTRAZENECA CONSIDERS MAY BE ALLOWED WITH CAUTION

Table 3 Moderate Inhibitors of CYP3A4 or CYP2D6 may increase exposure to AZD4547

Warning of possible interaction	
Aprepitant Diltiazem Duloxetine Erythromycin Fluconazole Sertraline Terbinafine Verapamil	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD4547.
Grapefruit juice Seville oranges (and other products containing Seville oranges)	Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study **(**e.g., no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15 g) of Seville orange marmalade daily).

3. MEDICINES THAT ARE SIGNIFICANTLY METABOLISED BY CYP3A4 THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH AZD4547

Table 4 Exposure, pharmacological action and toxicity may be increased by inhibition of CYP3A4 by AZD4547

Alfentanil Cyclosporin Tacrolimus Atorvastatin Lovastatin Simvastatin	Minimum of 7 days washout prior to AZD4547 administration and for 14 days following discontinuation of AZD4547
Carbamazepine	Minimum of 14 days washout prior to AZD4547 administration and for 14 days following discontinuation of AZD4547.

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and AZD4547; a potential interaction is considered on the basis of preclinical data only. This list is not intended to be exhaustive, and a similar restriction will apply to other agents with narrow therapeutic windows that are known to depend on CYP3A4 for metabolism. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

4. MEDICINES THAT ARE SIGNIFICANTLY METABOLISED BY CYP3A4 THAT ASTRAZENECA CONSIDERS MAY BE ALLOWED WITH CAUTION

Table 5 Exposure, pharmacological action and toxicity may be increased by inhibition of CYP3A4 by AZD4547

Warning of possible interaction:	
Alprazolam Erythromycin Felodipine Isradipine Midazolam Nifedipine Tamoxifen Trazodone Triazolam And possibly other calcium antagonists Methylprednisolone Quinidine	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD4547.

5. DRUGS THAT MAY PROLONG QT INTERVAL

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland.

Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm

5.1 Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with AZD4547. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

Contraindicated drug	**Withdrawal period prior to AZD4547 start**
Droperidol	2 days
Erythromycin	
Procainamide	
Cisapride	7 days
Clarithromycin	
Disopyramide	

Contraindicated drug	Withdrawal period prior to AZD4547 start
Dofetilide	
Domperidone*	
Ibutilide	
Sotalol	
Sparfloxacin	
Thioridazine	
Bepridil	14 days
Chlorpromazine	
Halofantrine	
Haloperidol	
Mesoridazine	
Levomethadyl	4 weeks
Methadone	
Pimozide	
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone	1 year
Chloroquine	

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

5.2 Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Warning of possible interaction	
Drug	**Minimum treatment period on medication prior to AZD4547 start**
Alfuzosin	2 days
Chloral hydrate	
Ciprofloxacin	
Dolasetron	
Foscarnet	
Galantamine	

Warning of possible interaction	
Drug	**Minimum treatment period on medication prior to AZD4547 start**
Gemifloxacin	
Isradipine	
Levofloxacin	
Mexiletine	
Nicardipine	
Octreotide	
Ofloxacin	
Ondansetron	
Quetiapine	
Ranolazine	
Telithromycin	
Tizanidine	
Vardenafil	
Venlafaxine	
Ziprasidone	
Amantadine	7 days
Amitriptyline	
Amoxapine	
Clozapine	
Doxepin	
Felbamate	
Flecainide	
Fluconazole	
Fosphenytoin	
Gatifloxacin	
Granisetron	
Imipramine	
Indapamide	
Lithium	
Moexipril/HCTZ	

Warning of possible interaction	
Drug	**Minimum treatment period on medication prior to AZD4547 start**
Moxifloxacin	
Risperidone	
Roxithromycin	
Sertraline	
Trimethoprim-Sulfa	
Trimipramine	
Voriconazole	
Azithromycin	14 days
Citalopram	
Clomipramine	
Itraconazole	
Nortriptyline	
Paroxetine	
Solifenacin	
Tacrolimus	
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

Clinical Study Protocol Appendix F	
Drug Substance	AZD4547
Study Code	D2610C00004
Edition Number	1
Date	[redacted]

Appendix F
Paclitaxel Label

This appendix is used for the local SmPC for paclitaxel and will be populated as per local requiremen

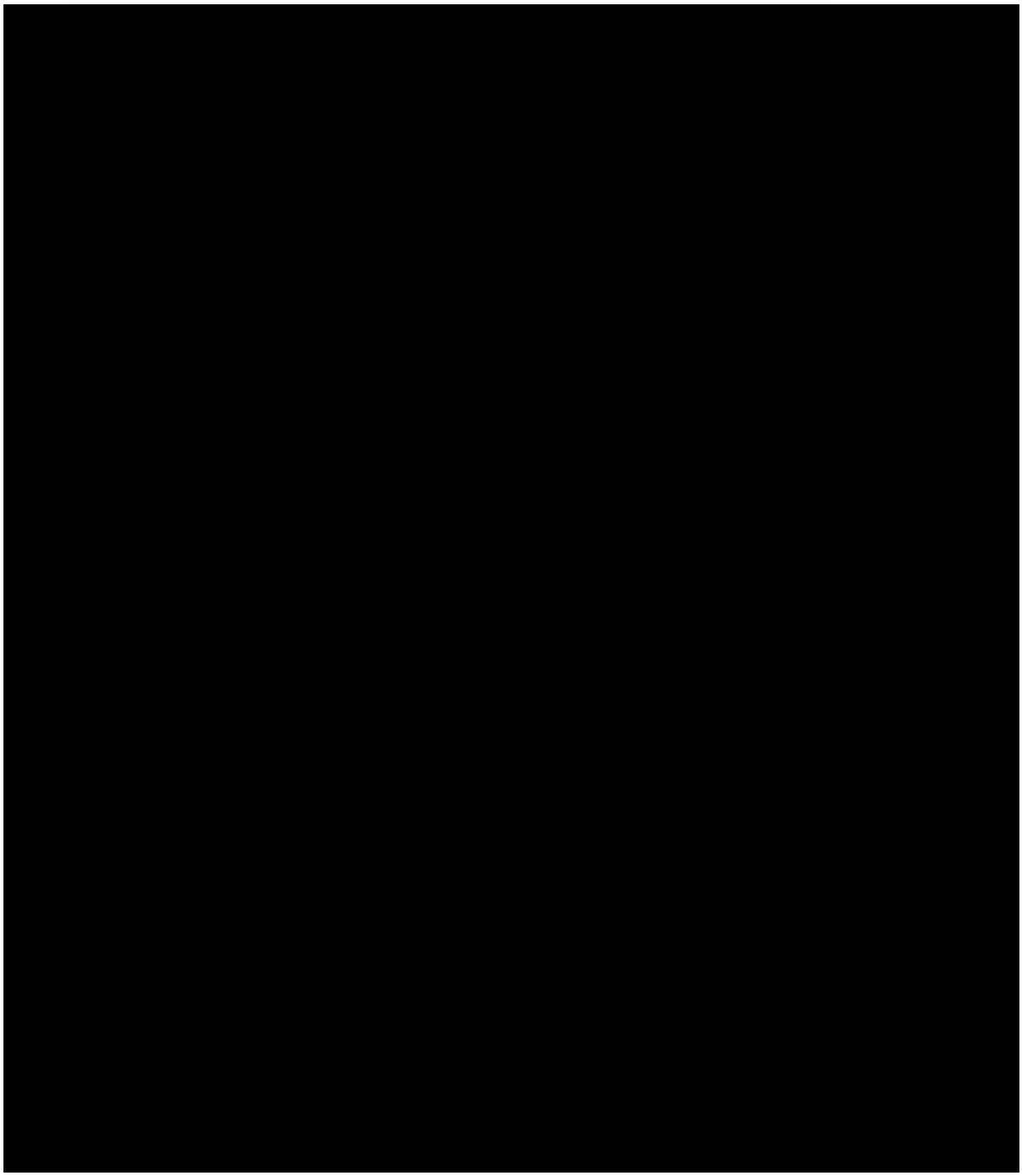
Clinical Study Protocol Appendix G

Drug Substance	AZD4547
Study Code	D2610C00004
Edition Number	2
Date	[redacted]

Appendix G
Patient Reported Outcomes

HEALTH RELATED QUALITY OF LIFE QUESTIONNAIRE

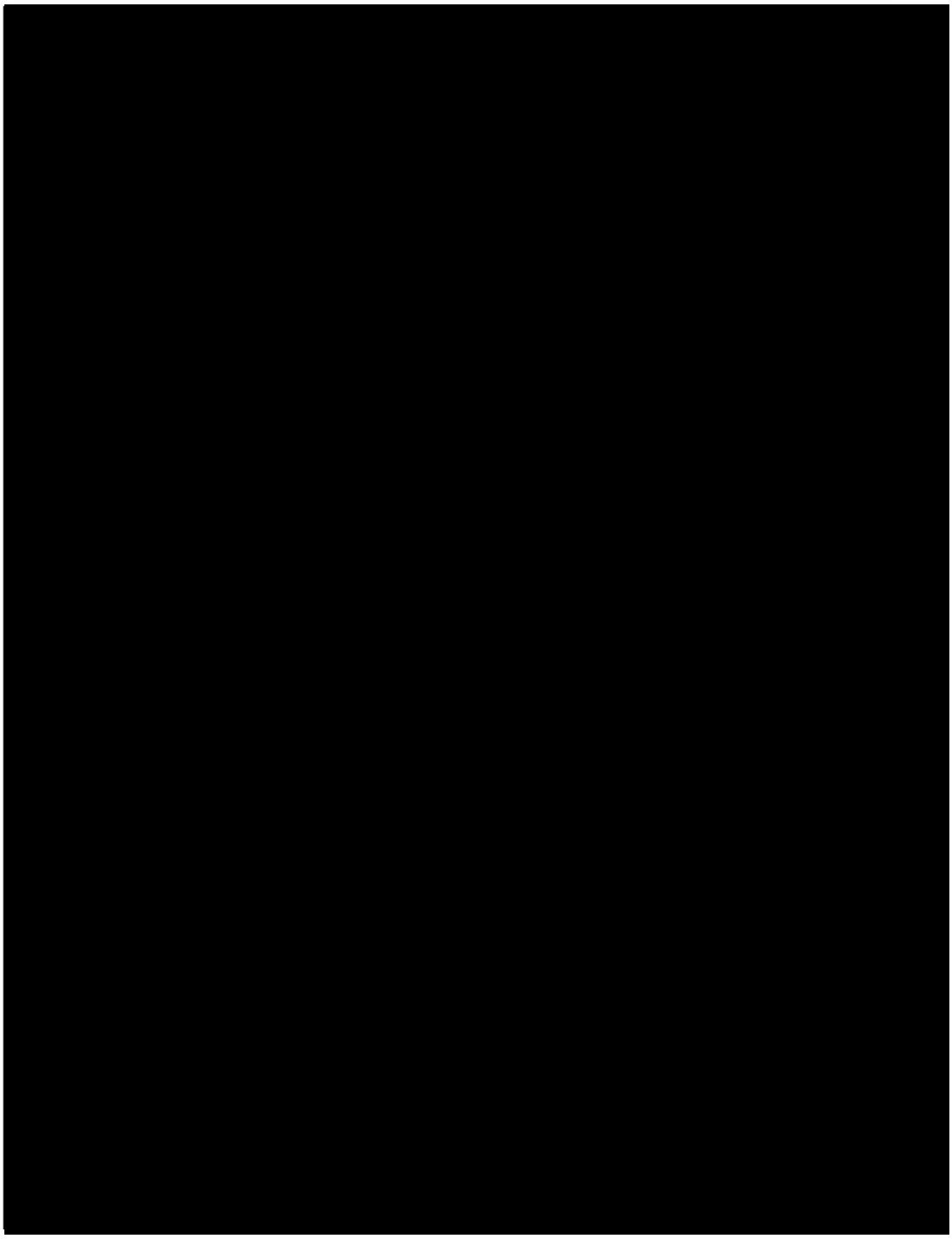
QLQ-C30 European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire core 30 (c30) - a 30 item PRO instrument developed by the EORTC to assess the health status and health-related quality of life of cancer patients



[redacted]

DISEASE RELATED SYMPTOM QUESTIONNAIRE

European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) for gastric cancer 22 (STO22) - a 22 item PRO instrument developed by the EORTC to assess the impact of disease related symptoms in patients with gastric cancer



HEALTH UTILITY QUESTIONNAIRE

The EuroQol 5 Dimension 5 Level (EQ-5D-5L) was developed by the EuroQoL Group for describing and valuing health related quality of life and evaluating the health benefits associated with different health care interventions in different therapeutic areas. It includes five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) plus a visual analogue scale (thermometer) asking the patient to rate their health today