Clinical Study Protocol

Drug Substance	AZD5363
Study Code	D3610C00004
Edition Number	2
Date	[redacted]

A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD5363 under Adaptable Dosing Schedules in Japanese Patients with Advanced Solid Malignancies

Sponsor:

[redacted]

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

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

Principal Investigator(s) and AstraZeneca Emergency Contact Personnel

The name and address of principal investigators are listed in the Supplement A.

For contact details of AstraZeneca personnel see Section 8.1.

INTRODUCTION & STUDY FLOW CHART

A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD5363 under Adaptable Dosing Schedules in Japanese Patients with Advanced Solid Malignancies

AZD5363 is a novel, potent, selective inhibitor of the kinase activity of AKT (also known as protein kinase B). AZD5363 acts on cancers by blocking signalling through the AKT cellular survival pathway, leading to inhibition of cell proliferation and increased apoptosis.

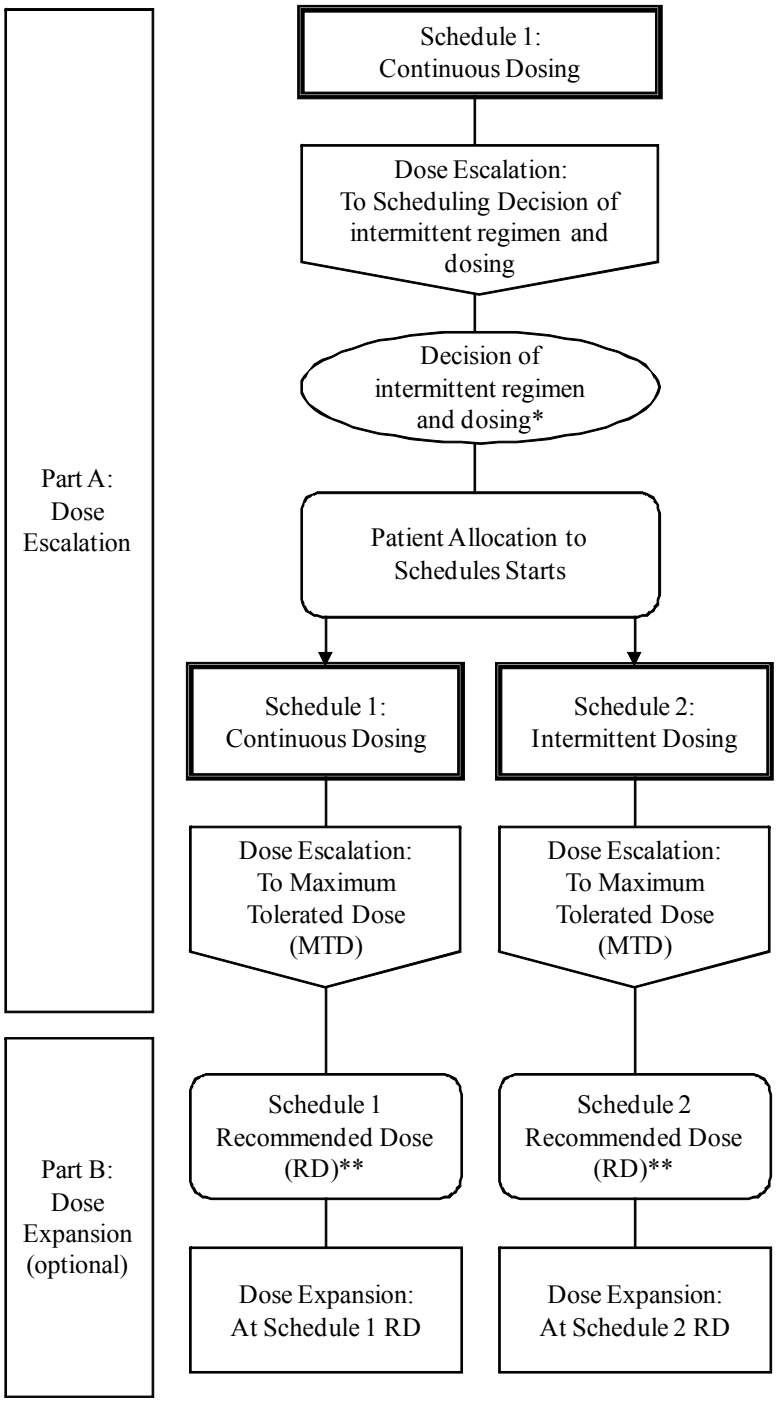
[redacted]

In this study, AZD5363 will be administered to patients with advanced solid malignancies at a starting dose [redacted] and will be escalated in separate continuous and intermittent dosing schedules to reach Recommended Doses (RDs) for further evaluation in patients as defined by dose-limiting toxicity.

Twice daily dosing of an oral formulation of AZD5363 will be used, [redacted], primarily to determine the safety and tolerability of AZD5363 in patients with advanced solid malignancies. Pharmacokinetics of AZD5363 and potential biological activity will also be investigated.

Following the dose escalation phase in each dosing schedule, additional patients will be enrolled to a dose expansion phase (optional) to explore further the safety, tolerability, pharmacokinetics and biological activity at the selected RDs.

Study flow chart. See Section 3.1



* Dose level identified by the Safety Review Committee as appropriate for commencement of the intermittent dosing schedule. See Section 3.1.

** Recommended Dose = dose level at, or below, the maximum tolerated dose (MTD) identified by the Safety Review Committee as appropriate for further evaluation. See Section 3.1.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF SUPPLEMENT

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this protocol.

Abbreviation or special term	Explanation
Ae	Cumulative amount of AZD5363 excreted unchanged in the urine
AE	Adverse Event (see definition in Section 6.4.1)
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration-time curve from zero to infinity
$AUC_{(0-12)}$	Area under the plasma concentration-time curve from zero to 12 hours
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to the time of the last measurable concentration
AUC_{ss}	Area under the concentration-time curve across the dosing interval
BP	Blood Pressure
BSL	Blood Sugar Level
CL/F	Apparent plasma clearance
CL_R	Renal clearance
C_{max}	Maximum plasma concentration
$C_{ss\ max}$	C_{max} at steady state
$C_{ss\ min}$	Minimum plasma concentration at steady state
CPD	Clinical Pharmacology, Drug Metabolism and Pharmacokinetics
CR	Complete Response
CTCAE (Ver.4)	Common Terminology Criteria for Adverse Events (Version 4)
CYP	Cytochrome
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
(e)CRF	(electronic) Case Report Form
EMEA	European Medicines Agency
FDA	Food and Drug Administration
Fe	Fractinal excretion
FSH	Follicle Stimulating Hormone

Abbreviation or special term	Explanation
GLP	Good Laboratory Practice
HDL	High Density Lipoprotein
HED	Human Equivalent Dose
hERG	human Ether-à-go-go Related Gene
HIV	Human Immunodeficiency Virus
IC_{50}	The half maximal inhibitory concentration of a drug
ICU	Intensive Care Unit
LDL	Low Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction
LWD	Last Weekly Dose (the last day that AZD5363 is received during a weekly intermittent dosing regimen)
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA	Multiple Gated Acquisition scan
NE	Not Evaluable
NSTD	Non-Seriously Toxic Dose
NTD	Non-Tolerated Dose
NTL	Non-Target Lesion
NYHA	New York Heart Association functional classification of heart failure
OAE	Other Adverse Event
PD	Progression of Disease
PK	Pharmacokinetics
PKB	Protein Kinase B
PR	Partial Response
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
QTcR	QT interval duration corrected for changes in heart rate using an individual regression method
QWBA	Quantitative Whole-Body Autoradiography
R_{ac}	Accumulation ratio
RD	Recommended Dose (see definition under Figure 2)
RECIST	Response Evaluation Criteria in Solid Tumours

Abbreviation or special term	Explanation
RNA	Ribonucleic Acid
SAE	Serious Adverse Event (see definition in Section 6.4.2)
SD	Stable Disease
SRC	Safety Review Committee
STD_{10}	Severely Toxic Dose (1/10th)
T4	Thyroxine
$t_{1/2\lambda z}$	Terminal half life
t_{max}	Time to C_{max}
$t_{ss\ max}$	t_{max} at steady state
TL	Target Lesion
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
V_Z/F	Apparent volume of distribution
WBDC	Web Based Data Capture
WHO	World Health Organisation

1. STUDY OBJECTIVES

1.1 Primary objective

To investigate the safety and tolerability of AZD5363 and to define a Recommended Dose (RD) when given orally, either as a continuous or an intermittent schedule, for further clinical evaluation when given to Japanese patients with advanced solid malignancies

1.2 Secondary objectives

To define the maximum tolerated dose (MTD) if possible or biological effective dose in Japanese patients with advanced solid malignancies.

To characterise the pharmacokinetics (PK) of AZD5363 following a single administration and after multiple dosing when given orally to Japanese patients with advanced solid malignancies.

To obtain a preliminary assessment of the anti-tumour activity of AZD5363 by evaluation of tumour response using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 in Japanese patients with advanced solid malignancies (see Appendix F).

1.3 Exploratory objectives

To assess the effect of AZD5363 on AKT activity utilizing pharmacodynamic biomakers such as total and phospho- GSK3β and total and phospho- PRAS40.

To investigate the presence and/or identity of drug metabolites of AZD5363 and, if appropriate, characterise their pharmacokinetics.

To characterise the relationship between biomarkers related to AKT activity (such as total and phospho- GSK3β and total and phospo- PRAS40, glucose, insulin and insulinc-peptide in response to emerging data) and AZD5363 plasma concentrations if a meaningful change in biomarker is observed.

To collect and store archival tumour samples and/or paired biopsies and analyse surplus blood or tissue (optional), if available, for potential future exploratory research into factors that may influence development of cancer and/or response to AZD5363 (where response is defined broadly to include efficacy, tolerability or safety). Markers may include total and phospho-AKT, p95 HER2 and somatic mutations of PIK3CA.

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 AZD5363 treatment and/or susceptibility to cancer.

2. BACKGROUND

2.1 Investigational agent

AZD5363 is a potent, selective inhibitor of the kinase activity of the serine/threonine AKT/PKB (protein kinase B) that is being developed as a potential treatment for solid and haematological malignancies.

AKT is part of the AGC family of kinases. Mammalian cells express three closely related AKT isoforms: AKT1 (PKBα), AKT2 (PKBβ) and AKT3 (PKBγ), all encoded by different genes. AKT is a node of multiple signalling pathways promoting tumorigenesis, inhibiting apoptosis, impacting on cell cycle and promoting invasion and migration.

The PI3K/AKT/PTEN pathway is frequently deregulated in cancer and drives tumour growth and cell survival (Lindsley 2010). All 3 AKT isoforms are activated in different tumour types including breast, prostate, ovarian, pancreatic and gastric cancers, and this activation is often associated with resistance to established cancer therapies as well as advanced disease and/or poor prognosis (Altomere and Testa 2005). AKT activation in tumours is largely due to input from other signalling pathways upstream of AKT (eg, mutation of oncogenesis such as Ras, Bcr-abl, mutation of receptor tyrosine kinases such as EGFR, amplification of Her2, loss of PTEN function, mutations of PI3K).

Inhibitors of AKT are anticipated to have efficacy when dosed in combination with cytotoxic chemotherapies or in combination with targeted or antihormonal agents. AZD5363 inhibits all three AKT isoforms (AKT1, AKT2 and AKT3) and therefore has the potential to provide clinical benefit over a range of therapeutic indications.

2.2 Non-clinical information and correlative studies

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

Further details are provided in the Investigators' Brochure.

3. STUDY DESIGN AND RATIONALE

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

3.1 Overall study design and flow chart

This is a phase I, open-label, multicentre study of AZD5363 administered orally in patients with advanced solid malignancies. The study design enables escalation of dose within separate continuous and intermittent dosing schedules with intensive safety monitoring to ensure the safety of the patients. The intermittent dosing schedule will be initiated, and the regimen may be subsequently changed between patient cohorts, in response to emerging safety, PK and pharmacodynamic (PDc) findings.

Approximately 40 evaluable patients with advanced solid malignancies will be enrolled in Part A/B(optional) of the study in cohorts of 3 to 6 evaluable patients (see Section 3.2). The total number of patients will depend upon the number of dose escalations investigated.

All evaluations during the twice-daily dosing regimen will be conducted as 21-day assessment cycles.

There are two parts to this study design. Part A: Dose escalation and Part B (optional): Dose expansion. Up to two different dosing schedules will be initiated in Part A, however the trial will start with Schedule 1 (continuous dosing) until the SRC deems it appropriate to initiate the other schedules (see Figure 1 and Study Design below).

Dosing regimen

On commencement of their participation in the study, each patient will receive a single dose of AZD5363. Then, after 3 to 7 days washout, following review of the pre-dose liver biochemistry, twice daily dosing will be initiated and maintained (see Figure 1) under one of the treatment schedules detailed below.

Dosing schedules (twice daily regimen)

- **Schedule 1: continuous dosing** (administered every day). Patients will receive AZD5363 as twice daily dosing every day.

- **Schedule 2: intermittent dosing.** This schedule will be introduced under the direction of the SRC during Part A in response to an optimal intermittent dosing schedule identified in global FTIP study and emerging clinical data from Schedule 1 of this study. This schedule would investigate: a dose administered for a defined number of days each week, or dose escalation within an alternative weekly regimen or the appropriateness of a regimen incorporating planned drug holidays (eg, 2 weeks on, 1 week off). Prior to the initiation of Schedule 2, a protocol/IND amendment will be prepared to describe the details of the intended dosing schedule and supporting data, and share with the appropriate Institutional Review Board for each participating site (see Study Design, Part A below).

Study Design (see Figure 2)

Part A: Dose Escalation

Approximately 40 evaluable patients with advanced solid malignancies will be enrolled in Part A of the study in cohorts of 3 to 6 evaluable patients (see Section 3.2). The total number of patients will depend upon the number of dose escalations investigated.

Part A will commence under Schedule 1, continuous dosing, only. Schedule 2, intermittent dose, will be initiated after optimal intermittent dosing schedule is identified from the Global FTIP study (D3610C00001).

Dose escalation will then proceed with patients being allocated (see Section 5.1.2.1) to separate cohorts under Schedules 1 and 2.

For subsequent cohorts:

- The daily dose may be escalated, or reduced, independently for each schedule.

- The SRC may elect to change the intermittent dosing regimen for Schedule 2 between cohorts in response to safety, tolerability, PK and PDc findings and emerging clinical experience.

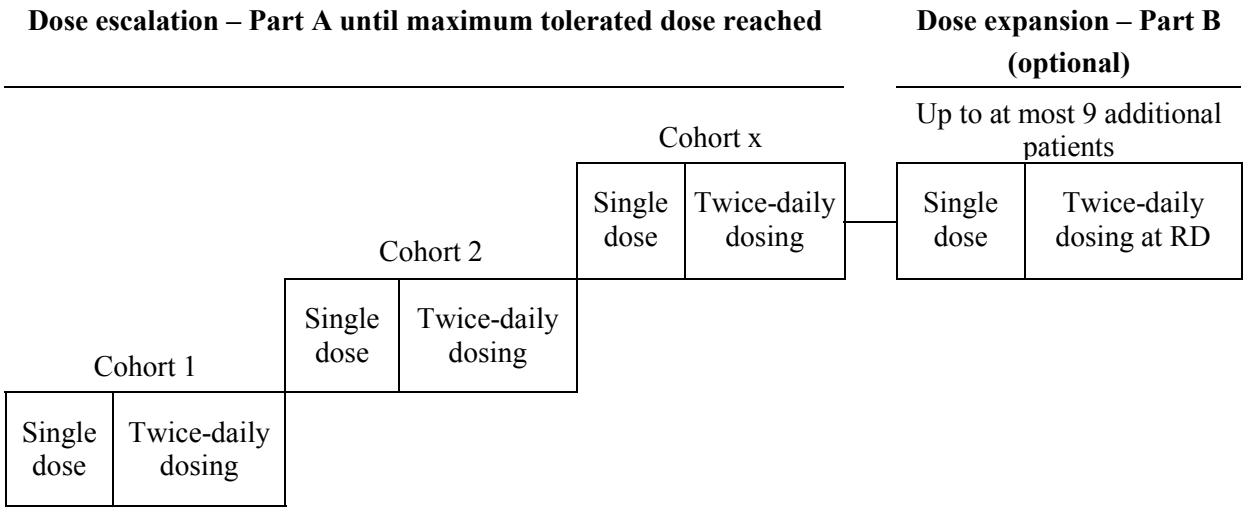
- If one schedule is temporarily suspended, recruitment to another schedule(s) may continue independently.

Dose escalation under Part A will continue until a non-tolerated dose (NTD) is attained and/or a maximum-tolerated dose (MTD) is identified (see Section 5.1.1) for each schedule. The RD to go forward to Part B (optional) will be at, or below, the MTD and will be selected by the SRC; however, no dose exceeding an MTD defined or the maximum dose in the Global FTIP study will be examined in this Japanese study.

Part B (optional)

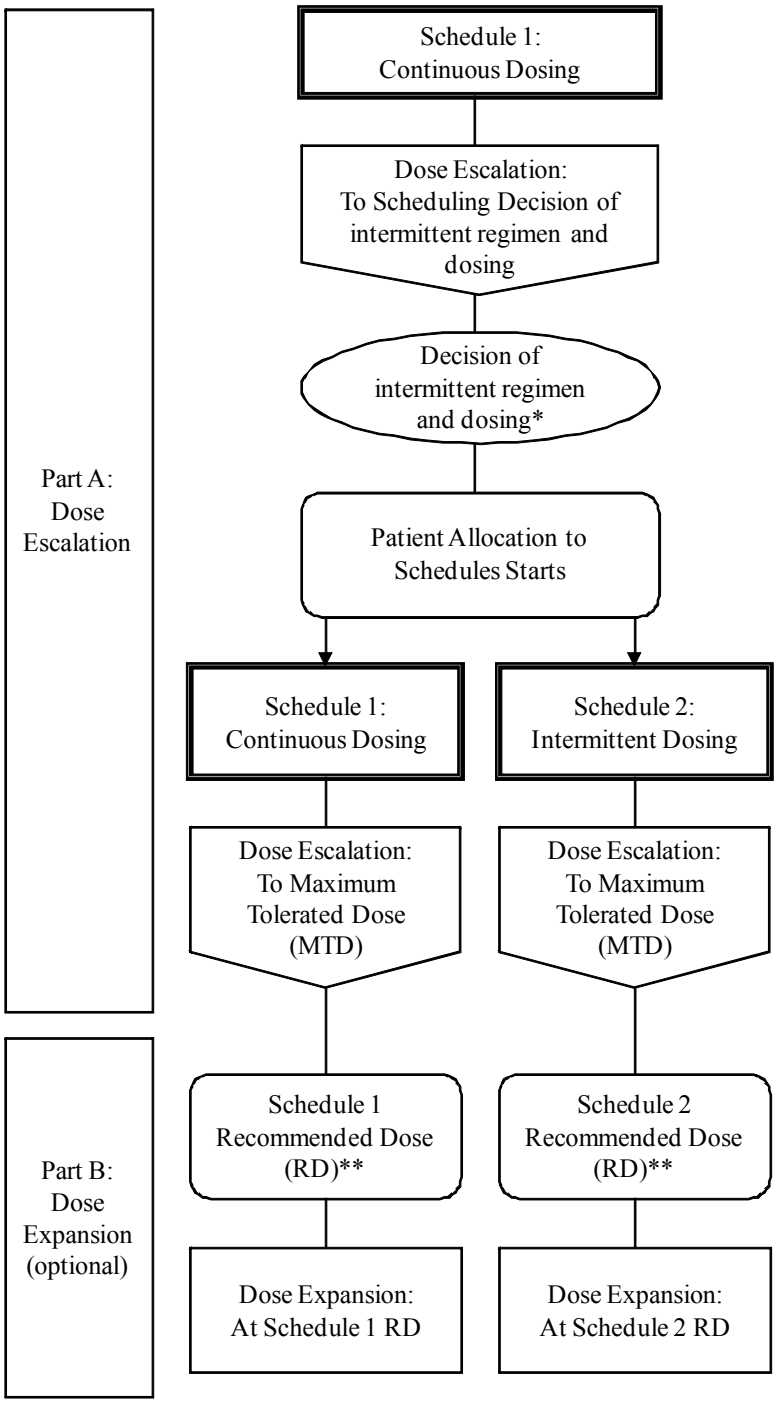
Up to 9 additional patients (dependent upon the number of eligible patients dosed at RD from part A) will be allocated to each schedule (see Section 5.1.2.1), to be dosed at the relevant RD. This is in order to ensure that the tolerability, PK and biological activity of AZD5363 has been explored in at maximum total of 12 evaluable patients (parts A and B) at the RD for each schedule evaluated.

Figure 1 Dose Escalation and Expansion



Single dose followed by washout of 3-7 days before twice-daily dosing

Figure 2 Study Flow Chart



* Dose level identified by the Safety Review Committee as appropriate for commencement of the intermittent dosing schedule.

** Recommended Dose = dose level at, or below, the maximum tolerated dose (MTD) identified by the Safety Review Committee as appropriate for further evaluation.

3.2 Rationale for conducting this study and for study design

The PI3K/AKT/PTEN pathway is frequently deregulated in cancer and drives tumour growth and cell survival. All 3 AKT isoforms are activated in different tumour types including breast, prostate, ovarian, pancreatic and gastric cancers, and this activation is often associated with resistance to established cancer therapies as well as advanced disease and/or poor prognosis. Non-clinical data suggest an AKT inhibitor has the potential to provide clinical benefit over a range of oncology indications. This is a first time in patient study primarily designed to evaluate the safety and tolerability of AZD5363, a potent AKT inhibitor, at increasing doses and in alternative dosing schedules in Japanese patients with advanced solid malignancies and for whom no standard of care exists. A Global FTIP study (D3610C00001) which is the same design as Japanese one has been preceding to this study. The study will also characterise the pharmacokinetics of AZD5363 and explore potential biological activity by assessing pharmacodynamic, exploratory biomarker and anti-tumour activity. The results from this study will form the basis for decisions for future studies.

[redacted]The study population will be patients with solid, malignant tumours that are refractory to standard therapies or for which no standard therapies exist. This is a standard population for first into patient oncology studies. [redacted]he collection of optional matched pre-and post- treatment tumour biopsies will allow assessment of the pharmacodynamic effect of therapy compared to baseline. Although patients participating in first into patient studies have advanced disease, clinical benefit may be identified in some patients, therefore RECIST assessments will be performed on patients with evaluable disease.

The starting dose, dose escalation, and cohort size are based upon accepted methodology for Phase I oncology studies as defined by ICH S9 (see Section 5.2). Careful consideration has been given to the EMEA (European Medicines Agency) guideline regarding the mitigation of risk for first-in-human clinical trials and with regard to the mode of action, the nature of the target and relevance to animal models AZD5363 is considered low risk (EMEA Guideline 2007). Part A of the study will determine the RD of AZD5363 based upon assessment of the safety, tolerability and pharmacokinetic data collected during the single dose period and the first 21 days of twice daily dosing (Cycle 1) in all schedules and dose levels evaluated. This assessment period was selected as the major toxicities leading to cessation of dose escalation in such studies (haematological, gastrointestinal, liver enzymes) are anticipated to present within this duration. However, the regular assessment of safety and tolerability will include review of all accumulated data from patients who remain on study beyond the first 21 days in order to document the emergence of any subsequent safety signals.

A washout of 3 to 7 days between patients receiving an initial single dose of AZD5363 and commencing twice-daily dosing is to allow for assessment of pharmacokinetic and safety

parameters within a period defined by a minimum of 5 half-lives ($t_{½}$ in dog model = 11 hours), while within a normally acceptable 7-day clinical schedule.

The cohort size of at least 3 and up to 6 patients ('rolling six design') has been employed to improve the rate of accrual of patients to cohorts nearer the presumed therapeutic dose by reducing the need for late replacement of patients which become non-evaluable during the 21 -day assessment period, whilst not compromising collection of safety data (Skolnik et al 2008).

Non-clinical data suggest that AZD5363 may act synergistically when administered in combination with other anti-cancer agents. Other anti-cancer agents are frequently administered on an intermittent schedule in order to mitigate against toxicity, therefore AZD5363 may also be required to be administered intermittently when given in combination: to maximise clinical benefit and to minimise additive toxicity. The investigation of the safety and tolerability profile of an intermittent AZD5363 dosing schedule in this study will enable definition of both the RD for that schedule and will assist with causality assessment for adverse events occurring in combination studies. In Part A, the study will commence with Schedule 1, continuous twice daily dosing with AZD5363, and will initiate Schedule 2, an intermittent dosing, when the intermittent dosing schedule identified from the Global FTIP study. This design, additionally incorporating evaluation of varying intermittent dosing regimens, allows for an evolutionary development of optimum doses and schedules based upon emerging findings and expanding clinical experience. In this way, it is anticipated that fewer patients would be subjected to sub-therapeutic regimens than would otherwise in parallel be necessary under additional mono-schedule arms or conduct of separate clinical studies.

[redacted] Glucose and insulin profiles will be performed in this study as changes in these parameters were also observed in non-clinical safety studies and are believed to be related to the pharmacological activity of AZD5363. The timing and frequency of all assessments may be amended in light of emerging data. The collection of blood samples to allow investigation of the presence and/or identity of metabolites of AZD5363 and, if appropriate, characterise their pharmacokinetics will generate data to allow AstraZeneca to fulfil regulatory requirements in accordance with the Food and Drug Administration (FDA) Guidance on Safety Testing of Drug Metabolites 2008.

As part of the clinical drug development programme for AZD5363, 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 archival or pre- and post-treatment tumour samples, 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 AZD5363.

AstraZeneca intends to perform genetic research in the AZD5363 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD5363. [redacted]
Collection of DNA samples from populations with well described clinical characteristics may also lead to improvements in the design and interpretation of clinical studies and possibly, to genetically guided treatment strategies.

Future research may suggest other proteins, genes or gene categories as candidates for influencing not only response to AZD5363 but also susceptibility to cancer for which AZD5363 may be evaluated. Thus, this biomarker and/or genetic research may involve study of additional un-named proteins, genes or gene categories, but only as related to disease susceptibility and drug action. Should any future research be suggested, outside of the proteins or genes mentioned in the protocol, a detailed research plan will be submitted for ethics review and approval prior to any further research on these samples being initiated.

4. PATIENT SELECTION AND RESTRICTIONS

Investigators should keep a record ie, patient screening log, of patients who entered pre-study screening.

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of starting study treatment. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study, patients must fulfil all of 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 and/or genetic 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

2. Aged at least 20 years

3. Histological or cytological confirmation of a solid malignant tumour, excluding lymphoma, that is refractory to standard therapies or for which no standard therapies exist.

4. At least one lesion (measurable and/or non-measurable) that can be accurately assessed according to RECIST.

5. World Health Organisation (WHO) performance status 0-1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks

6. Females should be using adequate contraceptive measures (see Section 4.3), 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

   – Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

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

7. Patients should be willing to remain in hospital until the completion of the first cycle including cycle 0, cycle 1, and cycle 2 Day1 (as cycle 1 Day 21)

4.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled

1. Clinically significant abnormalities of glucose metabolism as defined by any of the following:

   – Diagnosis of diabetes mellitus type I or II (irrespective of management)

   – Baseline fasting glucose value of ≥7 mmol/l (126 mg/dL)

   – Glycosylated haemoglobin (HbA1C) >6.5%

2. Treatment with any of the following:

   – Nitrosourea or mitomycin C within 6 weeks of the first dose of study treatment

   – Any investigational agents or study drugs from a previous clinical study within 30 days of the first dose of study treatment

   – Any other chemotherapy, immunotherapy or anticancer agents within 3 weeks of the first dose of study treatment, except hormonal therapy with LHRH analogues for medical castration in patients with prostate cancer, which are permitted

- Potent inhibitors or inducers or substrates of CYP3A4 or substrates of CYP2D6 within the period defined by the Appendix H before the first dose of study treatment.

- AZD5363 in the present study (ie, any dosing with AZD5363 due to previous participation in this study)

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

3. With the exception of alopecia, any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE Ver.4) grade 1 at the time of starting study treatment

4. Spinal cord compression or brain metastases unless asymptomatic, treated and stable and not requiring steroids for at least 4 weeks prior to start of study treatment

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

6. 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

   - Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA Grade 2

   - Uncontrolled hypotension – Systolic BP <90 mmHg and/or diastolic BP <50 mmHg

- Left ventricular ejection fraction (LVEF) below lower limit of normal for site.

7. 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 <9 g/dL
   - Alanine aminotransferase >2.5 times the upper limit of normal (ULN)
   - Aspartate aminotransferase >2.5 times ULN
   - 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, see Section 7.3); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN
   - Proteinuria 3+ on dipstick analysis or >500 mg/24 hours
   - Sodium or potassium outside normal reference range for site

8. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD5363

9. History of hypersensitivity to active or inactive excipients of AZD5363 or drugs with a similar chemical structure or class to AZD5363

10. 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

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

In addition, the following are considered a criterion for exclusion from the exploratory genetic research:

12. Previous allogeneic bone marrow transplant

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

4.3 Restrictions

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

1. On PK sampling days in the clinic, patients must fast (water to drink only) from at least 2 hours prior to taking a dose to at least 1 hour post-dose. On all other study days patients are requested to keep to these fasting restrictions wherever possible. When on the twice daily dosing schedule, the doses should be taken at approximately the same time each morning and evening.

2. Females of child-bearing potential should use two forms of highly reliable methods of contraception from the time of screening until 4 weeks after discontinuing study treatment. Acceptable methods of contraception include:

   - Established use of oral, injected or implanted hormonal methods of contraception.
   - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
   - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
   - Partner's sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
   - True abstinence.

   It is not known whether AZD5363 has the capacity to affect the metabolism of hormonal contraceptives, so hormonal contraception should also be combined with a barrier method of contraception

3. Male patients should use barrier contraception (ie, condoms) until 6 month after discontinuing study treatment because AZD5363 showed positive result in rat bone marrow micronucleus test. It is not known whether the preclinical changes seen in the male animal reproductive organs, after treatment with AZD5363, will be fully reversible or will permanently affect the ability to produce healthy sperm following treatment. Therefore, 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

4. Patients should use sunglasses and skin cream with UVA and UVB protection SPF >30 (PA++) if exposed to sunlight and avoid long-term daylight exposure. The use of sunbeds and tanning booths should be avoided.

5. All patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to potently modulate CYP3A4 enzyme activity from the

time they enter the screening period until 2 weeks after the last dose of study treatment.

6. All patients should avoid concomitant use of drugs and herbal supplements known to be CYP3A4 or CYP2D6 substrates from the time they enter the screening period until 2 weeks after the last dose of study treatment wherever possible. If co-administration is necessary then additional monitoring for signs of toxicity related to increased exposure to the substrates is required. (see Appendix H).

For restrictions relating to concomitant medications see next Section 4.3.1.

4.3.1 Concomitant treatments

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the Case Report Form (CRF). If medically feasible patients taking regular medication, with the exception of potent inhibitors or inducers or substrates of CYP3A4 or substrates of CYP2D6 (see Section 4.2 exclusion 2 and Appendix H), should be maintained on it throughout the study period.

Other anticancer agents (with the exception of hormonal therapy with LHRH analogues for medical castration in patients with prostate cancer), investigational agents and radiotherapy should not be given while the patient is on study treatment although radiation for palliation at focal sites is permitted.

Pre-medication will be allowed after, but not before the first dose of study treatment. This includes management of diarrhoea, nausea and vomiting.

Blood transfusions are allowed at any time during the study.

Granulocyte colony stimulating factors should not be used prophylactically during Cycle 1. Use of prophylactic colony stimulating factors may be considered after Cycle 1 following discussion with the AstraZeneca Study Team Physician.

Patients may receive treatment with bisphosphonates for the treatment of bone metastases.

Patients may take warfarin or a coumarin preparation but it is recommended that they should have their anticoagulation monitored carefully and dose adjusted accordingly.

Patients may take corticosteroids, however, increased vigilance is recommended on electrolyte and/or glucose levels due to the potential for corticosteroid-related metabolic disturbance.

Supportive care and other medications that are considered necessary for the patient's well-being, may be given at the discretion of the investigator.

5. STUDY TREATMENT AND CONDUCT

5.1 Treatment

Table 1 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
AZD5363	40 – 160 mg capsules	[redacted]

AZD5363 will be administered orally, twice daily, following a single initial dose and 3 to 7 day washout (continuous dosing only).

The investigational product will be supplied by [redacted]. Additional information about the investigational product may be found in the Investigators' Brochure.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be written by [redacted].

All study drugs should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified in the document 'Handling Instruction of Investigational Product'.

Where possible all doses should be taken in a fasted state, and patients must adhere strictly to the fasting restrictions on PK sampling days, see Section 4.3.

Doses should be taken at approximately the same time each morning and evening approximately 12 hours apart (following completion of the single dose administration in the continuous dosing).

5.1.1 Starting dose, dose escalation scheme and stopping criteria

The starting dose for study part A, Schedule 1, will begin at 80 mg, and this administration must start within 7 days after randomization. Then, after 3 to 7 days washout, twice daily dosing for study part A, Schedule 1 will begin at 160 mg/day (as 80 mg per dose). A cycle of study treatment (excluding initial single dose under part A) will be defined as 21 days. Cycle1 will commence from day of receipt of first twice daily dose, and following review of the pre-dose liver biochemistry results which must be taken less than 72 hours before the administration of the first dose in Cycle 1.

Providing there are no safety concerns after completion of the first cohort, subsequent cohorts of patients will be dosed as suitable patients are identified. If ambiguous findings occur after the first cohort the SRC may choose to stagger dosing in the second cohort and likewise for subsequent cohorts.

Patients will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable patients per cohort. Dose escalation and de-escalation be determined by the SRC with reference to the following logic:

- If no dose-limiting toxicity (DLT) is observed (for definition see Section 5.1.3) in a cohort of 3-6 evaluable patients then dose escalation may occur. Dose increases will be permitted after review of data from a minimum of 3 evaluable patients has been performed.

- If one patient experiences a DLT in a group of 3 or more evaluable patients then the cohort will be expanded to include 6 evaluable patients. If only one DLT is observed in the complete cohort of 6 evaluable patients then dose escalation may occur.

- If 2 or more patients experience a DLT in a group of up to 6 evaluable patients, irrespective of the number of patients enrolled, the dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease. A lower intermediary dose (de-escalation) may be considered in order to better define the MTD.

The SRC will review all available safety data (and PK data if possible) prior to a dose escalation decision being made. Escalations will not exceed doubling of the dose. However, if no patients experience drug-related adverse events of CTCAE Grade 2 or higher at a certain dose, the SRC may increase the dose by more than 100% provided that the selected dose is not higher than a dose which has been tolerated in the preceding European Phase I study (D3610C00001). No dose exceeding an MTD defined or the maximum dose in the European study will be examined in this Japanese study.

There will be no intra-patient dose escalations.

5.1.1.1 Schedule 2

The starting dose and dosing regimen for Schedule 2, will be determined based on the Global FTIP study (D3610C00001) and emerging clinical data from Schedule 1 of this study. A cycle of study treatment (excluding initial single dose under part A) will be defined as 21 days (Study D3610C00004 protocol and IND to be amended and approved before Schedule 2 commences). Cycle1 will commence from day of receipt of first intermittent dosing, and following review of the pre-dose liver biochemistry results which must be taken less than 72 hours before the administration of the first dose in Cycle 1. The dose for subsequent cohorts or a decision to stop recruitment to any study schedule arm will be agreed by the SRC after review of the data from each relevant cohort (see Section 5.1.5).

5.1.2 Dose expansion (optional)

Once the RD (at, or below, the MTD) is defined in a dosing schedule at dose expansion phase, Part B, will begin at the RD for that schedule, in order to refine the safety, tolerability, PK and PDc of AZD5363.

Additional patients (up to 9 evaluable patients) will be enrolled to ensure at maximum total of 12 evaluable patients (in Part A + B). All assessments will be performed at the same timepoints as in Part A. There will be no specific stopping criteria for this part of the study, however, the emerging data from this expansion phase will be monitored regularly by the SRC. Individual patient stopping criteria will be as defined in Section 5.2.

5.1.2.1 Method of assigning patients to dosing schedules

Written informed consent will be obtained before enrolment, and the patients identified with an enrolment number (see Section 6.3.1).

As patients become eligible for the study they will be allocated sequentially, in the order of notification to AstraZeneca, to each open dosing schedule by the AZD5363 Centralised Registration Centre, and will be assigned separate three digit allocation identification numbers. The first digit will indicate the schedule. The second and third digits will be an escalating patient number, commencing at 01. Therefore the first patient entering schedule 1 will be numbered 101, the second will be 102 and so on. Patients assigned to Schedule 2 will be 201, 202 onwards. Under this system:

- During the initial phase of part A, dose escalation, all patients will be allocated to cohorts under Schedule 1.
- If any Schedule completes, is terminated or recruitment to it is temporarily halted due to eg a full quota of patients being entered to a cohort; new patients will be allocated to the other, ongoing, schedule(s) to ensure that eligible consented patients are not denied, or have delayed, access to participation in this study.
- Sequential allocation to schedules will continue during conduct of optional part B, dose expansion.
- In the event that all but one schedule has completed or closed, all subsequent patients will be recruited to the remaining schedule.

If a patient is allocated to the wrong schedule no attempt should be made to remedy the error once study material has been dispensed. The patient will continue with the allocation number and study material, and AstraZeneca should be notified as soon as the error is discovered. Admission of subsequent patients will continue using the first unallocated number in the original numbering sequence.

In the event of replacement patients being needed to maintain cohort size, that cohort will be opened for recruitment and patients will be allocated to it under the system described above until the cohort is complete.

5.1.3 Definition of dose-limiting toxicity

A DLT is defined as any toxicity related to study drug and not attributable to the disease or disease-related processes under investigation, which includes:

1. Haematological toxicity ≥ CTCAE grade 4 present for more than 4 days (including CTCAE grade 4 thrombocytopenia regardless of duration).

2. Non-haematological toxicity ≥ CTCAE grade 3 including:

   - Infection including febrile neutropenia
   - Confirmation of QTc prolongation (>500 msec) or QTc increase >60 msec from baseline
   - ≥ Grade 3 hyperglycaemia (glucose >13.9 mmol/L or 250 mg/dL) for more than 1 week, despite optimal intervention which is not attributable to another co-morbidity
   - Grade 4 hyperglycaemia (glucose >27.8 mmol/L or 500 mg/dL)
   - AST or ALT >10x ULN and AZD5363 is considered the most likely cause
   - AST or ALT >8x ULN, in combination with doubling of total bilirubin from baseline, and AZD5363 is considered the most likely cause

3. Any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable, does not respond to supportive care and results in a disruption of dosing schedule of more than 14 days

4. Any event, including significant dose reductions or omissions, judged to be a DLT by the SRC

A DLT excludes:

1. Alopecia of any grade

2. Isolated laboratory changes without clinical sequelae or clinical significance

5.1.3.1 Definition of maximum tolerated dose

A dose will be considered non-tolerated and dose escalation will cease if 2 or more of up to 6 evaluable patients experience a DLT at a dose level. Once the NTD is defined the MTD will be confirmed at the previous dose-level below the non-tolerated dose or a dose between the non-tolerated dose and the last tolerated dose may be investigated. Six evaluable patients are required to determine the MTD.

5.1.4 Definition of evaluable patient

For decisions on dose escalation, an evaluable patient is defined as a patient that has received AZD5363 and either:

- has completed minimum safety evaluation requirements and has received at least 75% of the specified dose during the Cycle 0 and 1

or

- has experienced a DLT during the Cycle 0 and 1

5.1.5 Safety Review Committee

After each dose level during the dose escalation phase of the study, a SRC will evaluate the safety and tolerability and pharmacokinetics of AZD5363 to decide the next dose.

The SRC will consist of:

- Study Team Physician, who will chair the committee, or delegate
- Principal Investigator or delegate from each investigational site

In addition, other physicians from the following may be invited:

  - Global Safety Physician or delegate
  - Medical Science Director or delegate
  - Senior physician from another project

The Study Pharmacokineticist, Study Statistician, Patient Safety Scientist, and Study Delivery Leader may also be invited as appropriate. The Safety Review Committee Remit document for this study will define the exact membership and who should be present for decisions to be made.

Further internal or external experts may be consulted by the SRC as necessary.

Once there are at least 3 evaluable patients at a dose level the SRC will review and assess all available safety data from the cohort, together with available PK and pharmacodynamic data to make a decision on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into account.

The decision may be to:

1. Proceed with dose escalation – refer to Section 5.1.1
2. Expand the cohort to a maximum of 6 evaluable patients
3. De-escalate the dose either to a previous lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level
4. Define the NTD, MTD (where 6 evaluable patients assessed) or RD

5. Stop the dose escalation part of the study

When there are other patients that are ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable.

Any patient started on treatment in error, as he/she failed to comply with all of the selection criteria but meets the criteria of an evaluable patient, will be reviewed on a case by case basis by the SRC to determine if the patient should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the investigators prior to dosing any new patients.

5.1.6 Dose modifications

If a patient experiences a clinically significant and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted or the dose reduced and supportive therapy administered as required (see Figure 3).

If the toxicity resolves or reverts to ≤ CTCAE (Ver. 4) grade 2 within 8 days of onset and the patient is showing clinical benefit, treatment with AZD5363 may be restarted without requiring AstraZeneca consultation using the rules below for dose modifications (see Figure 3). If the patient is still showing clinical benefit, but toxicity takes between 8 and 14 days to resolve or revert to ≤ CTCAE grade 2, treatment with AZD5363 may be restarted using the rules below for dose modifications only following agreement with the AstraZeneca Study Team Physician (see Figure 3). Patients in Cohort 1 who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level only once at the discretion of the Investigator. In the event that the patient experiences a clinically significant toxicity after restart of the treatment, if continuous treatment is expected to give clinical benefit to the patient under the discretion of the investigator and the toxicity is tolerable and manageable, it is allowed to continue the study following agreement with the AstraZeneca Study Team Physician (see Figure 3). The DLT assessment period should be regarded as having completed when dosing is interrupted due to a clinically significant and/or unacceptable toxicity including a DLT during Cycle 0 to the end of Cycle 1 (cycle 2 Day1). After that, the patients may be restarted from Cycle 2, provided that another written consent on continuous treatment should be obtained from patients.

For all other events, if the toxicity does not resolve to ≤ CTCAE grade 2 after 14 days, then the patient should be discontinued from treatment and observed until resolution of the toxicity.

During Cycle 1, patients will be required to carry out a urine glucose assessment by dipstick prior to breakfast two times per week. If a patient develops urinary glucose present (see Figure 6 and Section 5.3.2), confirmation of blood glucose and blood ketone should be performed and any related symptomatology should be recorded. Subsequent specific management of the hyperglycaemia will be according to local practice, however, the

principles in the blood glucose intervention plan (see Figure 4) should be followed. General advice based upon previous clinical experience with related agents suggests:

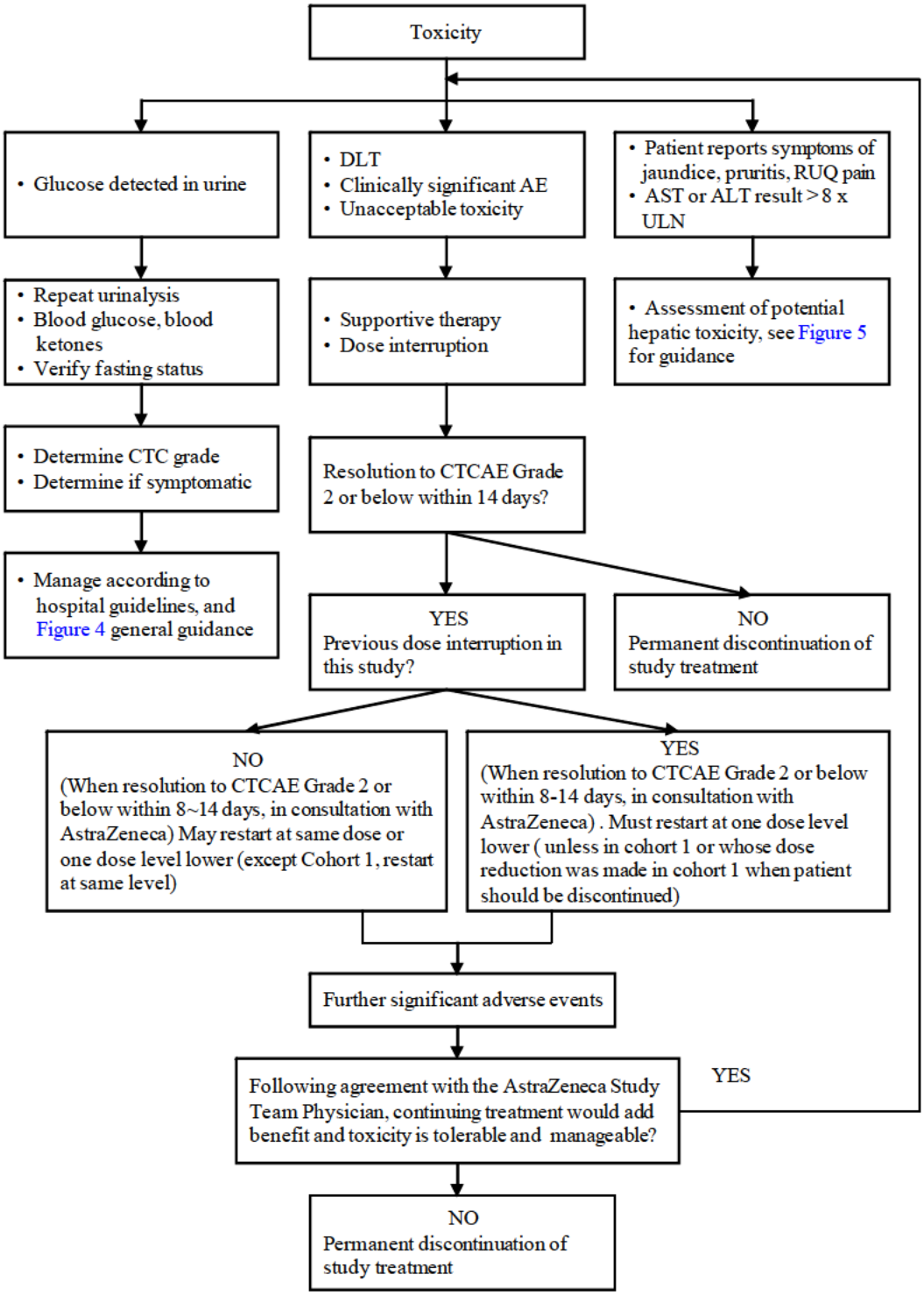
- Initial medical intervention should be an oral-antidiabetic agent eg metformin 500 mg daily

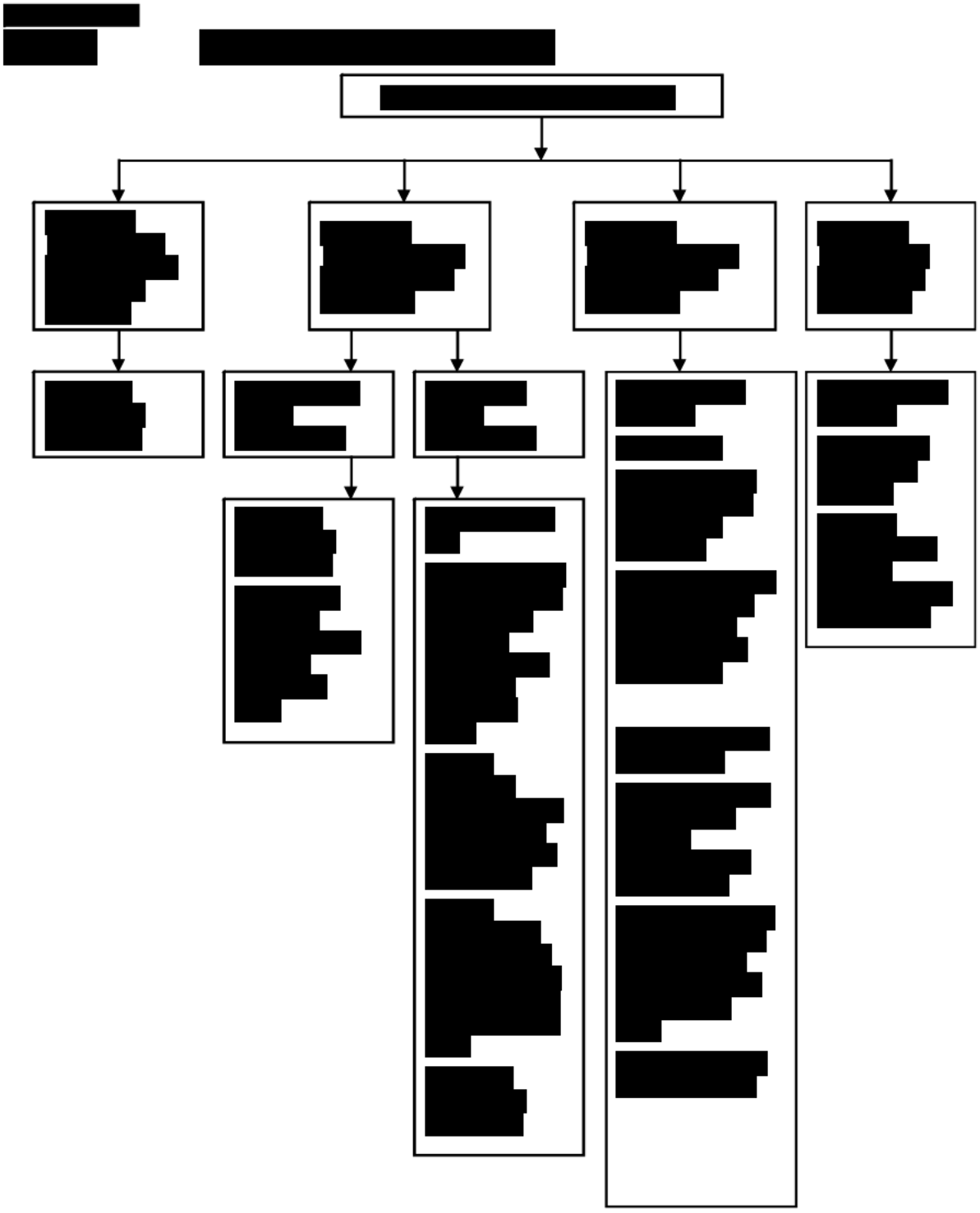
- For CTC Grade 3 or 4 hyperglycaemia, when insulin therapy is considered an insulin infusion is recommended. Avoid use of long acting insulin, avoid large boluses of short acting insulin, and observe closely for rebound hypoglycaemia

Patients experiencing CTC Grade 4 hyperglycaemia will not be permitted to restart study treatment. Refer to Section 5.3.2, glucose homeostasis for the monitoring rationale.

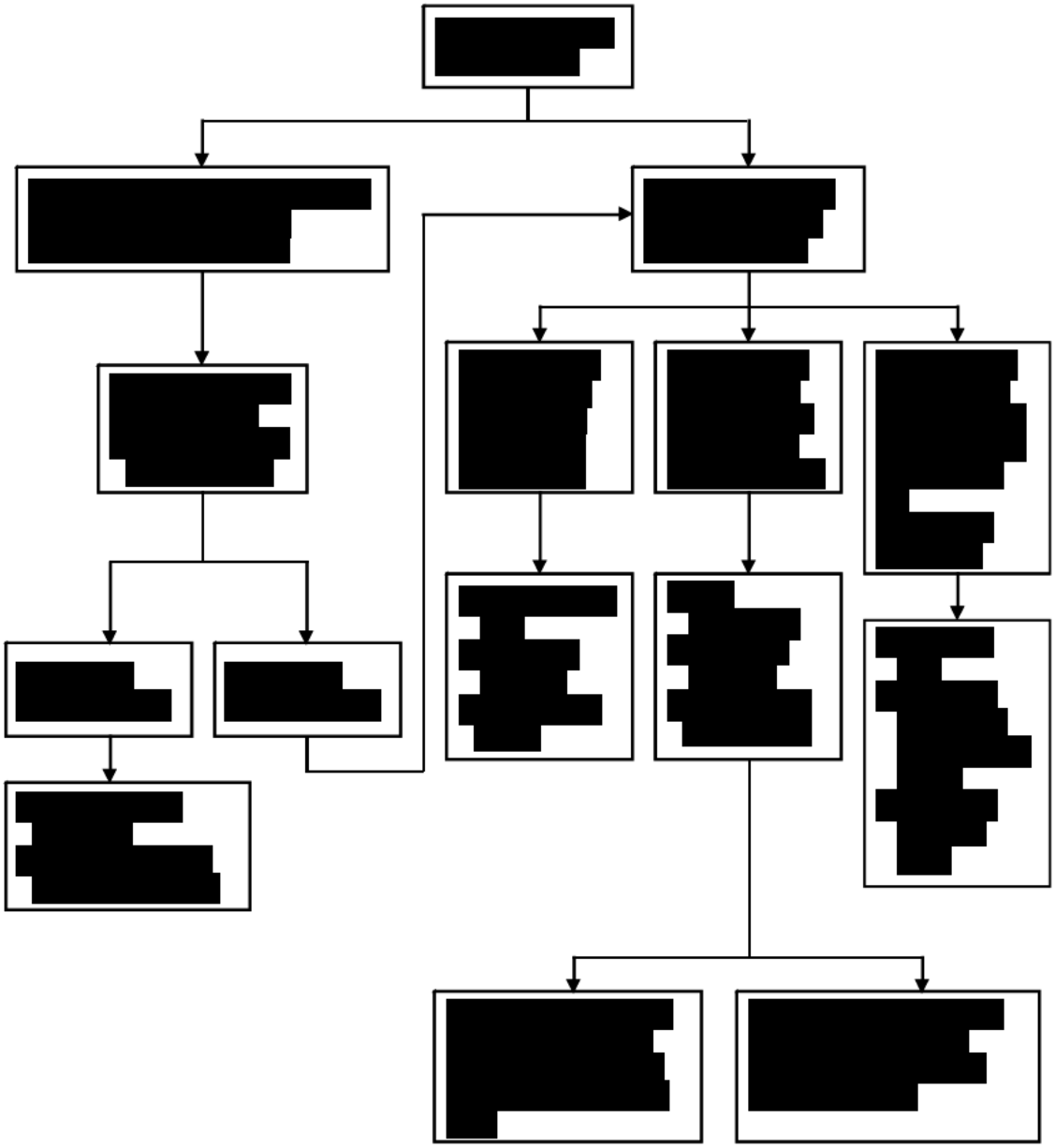
During the study, any patients experiencing symptoms consistent with acute liver dysfunction such as unexplained pruritis, jaundice or right upper quadrant pain will be advised to temporarily stop study treatment and promptly contact the clinic for clinical assessment and liver biochemistry testing. Investigation and management of these patients and any patients with AST or ALT results >8 x ULN identified at any time during the study will be at the investigator's discretion. It is recommended that the investigator should refer to the FDA Guidance for evaluation of Drug-Induced Liver Injury (FDA 2009), and the principles of the hepatotoxicity management algorithm (Figure 5). If a patient exhibits an aspartate aminotransferase (AST), alanine aminotransferase (ALT) result in excess of 10 x ULN, or AST or ALT in excess of 8 x ULN in combination with a doubling of total bilirubin from baseline, treatment should be stopped permanently and no re-start will be permitted. Refer to Section 5.3.2, liver and pancreas for the monitoring rationale.

Figure 3 Toxicity management algorithm





[redacted]



Assessment timings if dosing is interrupted

If a patient misses any doses of AZD5363 during the 21-day evaluation period of Cycle 1 please contact the AstraZeneca Study Team for advice regarding the evaluability of the patient and appropriate timing of the 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.

5.1.7 Duration of therapy

Patients may continue to receive AZD5363 as long as they are continuing to show clinical benefit without safety concern, as judged by the investigator, and in the absence of discontinuation criteria, provided that another written consent on continuous treatment should be obtained from patients before the start of Cycle 2. After Cycle 1, the Day 1 for subsequent Cycle must be initiated within 3 days after Day 21 of previous Cycle.

5.1.8 Treatment compliance and accountability

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca.

The investigational product should only be used as directed in this protocol. Details of treatment with investigational product for each patient will be recorded in the Case Report Form (CRF).

The unused drugs and empty containers are returned to the AZKK and not destroyed. And the details are shown in 'Handling instruction of Investigational Product' that AZKK provides to sites.

The study personnel at the investigational site will account for all drugs dispensed and for appropriate return. Certificates of delivery and return should be signed.

5.2 Rationale for dose regimens, dose escalation scheme and stopping criteria

[redacted]

The dose escalation scheme will not exceed doubling of the dose in principle. However, if no patient had drug-related adverse events of CTCAE Grade 2 or higher at a certain dose, the SRC may increase the dose by more than 100% provided that the selected dose is not higher than a dose which has been tolerated in the preceding European Phase I study (D3610C00001). No dose exceeding an MTD defined or the maximum dose in the European study will be examined in this Japanese study.

For every patient, there must be review of the Day 1 Cycle 1 pre-dose liver biochemistry results prior to the initiation of twice daily dosing in Cycle 1 to ensure that there is no signal for acute liver dysfunction. If ambigous safety or tolerability findings occur after the first cohort, the staggered dosing may be performed again in the second cohort and likewise for subsequent cohorts.

There will be a minimum of 2 days between completion of the last assessment of patient evaluability from one cohort and the start of dosing in the subsequent cohort in order for the SRC meeting to be called, and minutes of the dose escalation decisions to be distributed to all participating sites (see Section 5.1.1).

There are no specific individual patient pharmacokinetic stopping criteria proposed in this study. Specific stopping criteria from a safety perspective are as follows:

- If a patient enrolled in the study becomes pregnant as no formal reproductive toxicology studies have yet been performed the possible outcome is unknown.
- CTC grade 4 hyperglycaemia (glucose >27.8 mmol/L or 500 mg/dL) for urgent management of clinically significant disturbance of glucose metabolism.
- AST or ALT result >10 x ULN, or, AST or ALT result >8 x ULN in combination with doubling in total bilirubin from baseline levels, for urgent assessment of potential disease progression or acute liver dysfunction.

5.3 Benefit/risk and ethical assessment

5.3.1 Potential benefits

The PI3K/AKT/PTEN pathway is frequently deregulated in cancer and drives tumour growth and cell survival. Non-clinical data suggest that the main biological effect resulting from inhibition of AKT-mediated signalling is tumour growth inhibition. Therefore AZD5363 may have the potential to provide benefit in patients with a variety of advanced solid and haematological malignancies that are AKT-dependent to some degree. However, this benefit may not be substantial in this study where many patients are expected to have highly advanced, treatment refractory disease.

5.3.2 Potential risks identified non-clinically with AZD5363

This section highlights potential risks based upon non-clinical toxicity studies with AZD5363 in rats and dogs, and *in vitro* experiments. Details of the results of these studies are provided in Section 2.2 of this protocol, and further information is in the Investigator Brochure. The monitoring and management of the potential risks is discussed below:

[redacted]

[redacted]

[redacted]

5.3.3 Overall benefit-risk assessment for the study (Study D3610C00004)

In the advanced cancer setting that has been chosen for the initial study with AZD5363, prolonged survival rates are very low and there is a huge unmet clinical need for novel therapeutic agents. Although there can be no certainty of clinical benefit to patients, non-clinical data with AZD5363 support the hypothesis that AKT inhibition may be a valid target for the treatment of tumours driven via this pathway. The non-clinical safety profile has not identified any risks that would preclude investigation in this setting, and monitoring is in place for those risks deemed to be most likely or serious.

AstraZeneca believe the investigation of AZD5363 in this patient population is justified, based upon the non-clinical safety profile, the lack of effective alternative treatments available to patients, the limited life expectancy due to malignant disease, and the strength of the scientific hypothesis under evaluation. Thus the benefit/risk assessment for this phase I study support the oral administration of AZD5363 to patients with advanced cancer, according to the proposed study design.

5.4 Discontinuation of investigational product and withdrawal from study

Patients may be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to withdraw his/her participation in the study, without prejudice
- Adverse events
- Severe non-compliance to this protocol as judged by the investigator and/or AstraZeneca
- Confirmed disease progression
- Patients incorrectly initated on investigational product (Section 5.4.1)
- Patient becomes pregnant
- Patient experiences CTC grade 4 hyperglycaemia
- Patient experiences drug related AST or ALT result >10 x ULN, or, AST or ALT >8 x ULN in combination with doubling in total bilirubin result from baseline level

Any patient who permanently discontinues investigational product will be withdrawn from the study (Section 5.4.2).

Patients that are withdrawn from the study but are evaluable per the definition in Section 5.1.4 will not be replaced. Any patient that is withdrawn and is not evaluable will be replaced to ensure a minimum number of evaluable patients.

Patients may withdraw from any aspects of the voluntary exploratory research (see Section 6.7) 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 6.8.5.

5.4.1 Procedures for handling patients incorrectly initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be initiated on investigational product. There can be no exceptions to this rule.

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

5.4.2 Procedures for withdrawal from study

A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The investigator(s) will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient (see Section 6.3.9). Adverse events will be followed up (see Sections 6.4.3 and 6.4.4) and study drug should be returned by the patient. They will also immediately inform AstraZeneca of the withdrawal.

5.5 Study timetable and end of study

[redacted]

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

Planned duration of the study:

[redacted]

There will be an interim data cut-off defined as the earlier of 6 months after the last patient recruited starts investigational product or 30 days after the final patient discontinues investigational product. Data analysis will be performed and a Clinical Study Report written based on this data set.

Any patients still receiving investigational product at the time of this data cut-off will be able to continue to receive AZD5363 while deriving clinical benefit. Such patients will continue to be monitored and all safety assessments performed until the investigational product is discontinued. In addition, these patients should be followed up for 30 days after the last dose for any new reports of adverse events. A Clinical Study Report Addendum will be prepared to summarise the additional safety data collected between the interim data cut-off and the end of the study.

6. STUDY PLAN AND COLLECTION OF STUDY VARIABLES

6.1 Study Plan

Figure 6 Study Plan

	Screen	Single dose			Twice-daily dose				IP discontinued	30-day follow-up	Details in Section:
		Cycle 0			Cycle 1			Cycle 2, 3, …			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 9, …**			
Activity Day	**-28 to -1**	**1**	**2**	**3**	**1**	**8 / LWD**	**15 / LWD +7**	**1**			
Window (days)		**+7**				**±2**	**±2**	**+3**			
Informed consent	X							X			5.1.7, Appendix D
Demography& baseline characteristics	X										6.3.1
Medical/surgical history	X										6.3.1
Inclusion / exclusion criteria	X										4.1 and 4.2
Physical examination	X	X			X		X	X	X		6.3.2
WHO performance status	X	X									6.3.2
Vital signs	X	X	X		X	X	X	X	X		6.3.3
ECG	X	X	X		X	X		X	X		6.3.4
MUGA / Echocardiogram	X							X			6.3.5
Haematology, Clinical chemistry, Urinalysis	X	X			X	X	X	X	X		6.3.6
Fasted Lipids		X						(X)			6.3.7

Figure 6 Study Plan

	Screen	Single dose			Twice-daily dose				IP discontinued	30-day follow-up	Details in Section:
		Cycle 0			Cycle 1			Cycle 2, 3, …			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 9, …**			
Activity Day	**-28 to -1**	**1**	**2**	**3**	**1**	**8 / LWD**	**15 / LWD +7**	**1**			
Window (days)		**+7**				**±2**	**±2**	**+3**			
Glucose, insulin, insulin c-peptide		X				X	X	X	X		6.3.8
Pregnancy test	X								X		6.3.6
PK blood samples		X	X	X	X	X	X				6.5.1
PK urine collection		X	X	X							6.5.1
PDc blood samples		X			X			X	X		6.7
Exploratory biomarker (hair samples)		X									6.7
Pharmacogenetics (optional)		X									6.7.1
RECIST Tumour assessments	X							X	X		6.9.1
Archival tumour sample (optional)	X										6.7
Paired biopsy (optional)	X						X				6.7
Concomitant medication	X	X	X	X	X	X	X	X	X	X	4.3.1
Adverse events	X	→	→	→	→	→	→	→	→	→	6.4
Dispense/administer study drug		X			X	→	→	→	→		5.1

6.1.1 Schedule–specific assessment timing

The starting regimen of the intermittent dosing schedule(s) will not be known on commencement of this study, and the regimen for Schedule 2 may be subject to change during the course of the trial. Where assessments correlate to last receipt of AZD5363 during a weekly intermittent dosing regimen (ie safety, PK, PDc,), it is therefore necessary to adapt the timing of these assessments in relation to the regimen. To enable this, there are two variable days within the intermittent dosing schedule(s) study plan. These will reflect the assessments listed under continuous schedule 'Day 8' and the 'Day 15' respectively (see Figure 6) but will be conducted on days relative to the last day that AZD5363 is received during a weekly intermittent dosing regimen. For this, the term Last Weekly Dose (LWD) has beed used as an abbreviation in Figure 6 and subsequently in this protocol.

All assessments listed under Cycle 1, 'Day 8 / LWD' and 'Day 15 / LWD+7 will be performed to the following timings applicable to the dosing schedule:

- **Schedule 1**: Under the continuous dosing regimen - assessments will be conducted, as detailed in Figure 6, on Day 8 and on Day 15 of cycle 1.

- **Schedule 2**: Under the intermittent dosing regimen –

  – All 'Day 8' assessments will be conducted on the LWD day during the first week of cycle 1*.

  – All 'Day 15' assessments will be conducted on the day of last weekly dose during the following week: LWD + 7days

For clarity, a study plan applicable to the continuous dosing schedule only will be provided to all study sites prior to commencement of the trial. A study plan for the intermittent dosing schedule will then be provided following determination of the Schedule 2 starting dose and intermittent dosing regimen (Study 0004 protocol and IND to be amended and approved before Schedule 2 commences).

*: If emerging PK findings indicate that there may be carry-over of circulating AZD5363 during the off-therapy period of the intermittent dosing regimen (such that maximum exposure may not be achieved during cycle 1 week 1) LWD assessment days may be moved to either week 2 or 3 of cycle 1 (and LWD+7 correspondingly to week 3 or 4 of cycle 1) under the discretion of the SRC (this protocol and IND to be amended and approved before Schedule 2 commences).

6.2 Recording of data

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

The investigator ensures the accuracy, completeness and timeliness of the data recorded and for the provision of answers to data queries according to the appropriate information.

The investigator will sign the completed Case Report Forms. A copy of the completed Case Report Forms will be archived at the study site.

For details of data and study management see Appendix E of this Clinical Study Protocol.

The Investigator will record data on the observations, tests and assessments specified in the protocol on the CRFs provided by AstraZeneca. The CRF will be accompanied with 'Instructions for the investigator', which should be followed. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded.

6.3 Safety procedures

The timing and frequency of safety evaluations may be revised, in consultation with the SRC, in response to emerging data from the Global FTIM study.

6.3.1 Enrolment and screening

At enrolment, each potential patient will provide informed consent prior to starting any study specific procedures.

Each potential patient is assigned a unique enrolment number (E-code). If a patient withdraws from the study, the patient will not be allowed to re-enter the study, and the enrolment code cannot be reused.

The centralised registration centre will manage and keep the registration code centrally and electronically. The name and contact of centre are as follows:

Name: [redacted]
Fax: [redacted]
Office hours: [redacted]
[redacted]

The enrolment number is a 7-digit number, E000NXXX, N being the centre number, XXX being the patients enrolment number at the centre. For centre number, see Supplement A "Investigators and Study Administrative Structure". The enrolment code is the patient's unique identifier and is used to identify the patient on the eCRFs. All screened patients are assigned an E-code irrespective of whether or not they pass screening and subsequently go on to receive study treatment.

The investigator(s) will perform an enrolment medical examination after the written informed consent will be obtained, and send the "Registration Notification" to the AZD5363 Centralised Registration Centre by fax (both eligible and ineligible) after the confirmation of patient's eligibility according to the results of screening tests. The AZD5363 Centralised Registration Centre will reconfirm the patient eligibility, and if eligible, the AZD5363 Centralised Registration Centre will register the patient and send by fax the "Registration Conformation Form" to the investigator(s). If ineligible, the AZD5363 Centralised Registration Centre will send by fax the "Registration Conformation Form" that documented ineligible to the investigator(s).

Each patient will undergo screening (see Study Plan Figure 6) during the 28 days prior to admission to confirm eligibility (see Sections 4.1 and 4.2). Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided the assessments fall within the protocol specified period prior to the first dose of study treatment.

6.3.2 Physical examination

A complete physical examination will be performed at the visits as indicated in the Study Plan (see Figure 6) at the following times:

- Screening
- Cycle 0: Day 1 pre-dose
- Cycle 1: Day 1 pre-dose in the morning; Day 15 pre-dose in the morning
- Cycles 2+: Day 1 pre-dose in the morning
- Discontinuation of study treatment: at any time of the day

Performance status will be assessed at screening and prior to the first dose of study treatment according to WHO criteria as follows:

0 = Fully active, able to carry out all pre-disease activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature eg, light housework, office work

2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair

6.3.3 Vital signs

Weight

Weight (Kg) will be recorded at:

- Screening.
- Each Cycle: Day 1 at any time of the day
- Discontinuation of study treatment: at any time of the day

Pulse rate and blood pressure

Supine blood pressure and pulse rate will be measured after 10 minutes rest. Assessments will be performed at the visits as shown in the Study Plan (see Figure 6) at the following times:

- Screening
- Cycle 0: Day 1 pre-dose; 1, 2, 6 and 24 hours (Day 2) post-dose
- Cycle 1: Day 1 pre-dose in the morning; Day 8 / LWD pre-dose in the morning; Day 15 / LWD+7 pre-dose in the morning
- Cycle 2: Day 1 pre-dose in the morning; 1, 2, and 6 hours post-dose
- Cycles 3+: Day 1 at any time of the day.
- Discontinuation of study treatment: at any time of the day

6.3.4 ECG

Resting 12-lead ECG

A 12-lead ECG will be performed at at the visits as shown in the Study Plan (see Figure 6) at the following times:

- Screening
- Cycle 0: Day 1 pre-dose; 1, 2, 6 and 24 hours (Day 2) post-dose
- Cycle 1: Day 1 pre-dose in the morning; Day 8 / LWD pre-dose
- Cycle 2: Day 1 pre-dose in the morning; 2, and 6 hours post-dose
- Cycles 3+: Day 1 at any time of the day. Single ECG
- Discontinuation of study treatment: at any time of the day. Single ECG

Assessments up to and including 6 hours post-dose should be performed within 15 minutes of the nominal timepoint. Assessments after 6 hours should be performed within 30 minutes of the nominal timepoint.

The timing and number of ECGs may be altered depending on the emerging PK and safety profile.

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 about 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

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 all ECGs details of intervals PR, R-R, QRS and QT and an overall evaluation will be recorded.

6.3.5 MUGA scan / Echocardiogram

A MUGA scan or echocardiogram to assess left ventricular ejection fraction (LVEF) will be conducted at screening and on Day 1 of Cycle 2 (± 1 week). Then if clinically indicated thereafter until discontinuation of study drug. 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 patients should also be examined using the same machine and operator whenever possible.

6.3.6 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the visits as indicated in the Study Plan (see Figure 6) at the following times:

- Screening
- Cycle 0: Day 1 pre-dose (Laboratory tests do not need to be repeated at baseline if the baseline visit is within 2 days of the screening sample.)
- Cycle 1: Day 1 pre-dose in the morning (Liver biochemistry results must be reviewed by the Investigator prior to first dose on Day 1, but may be taken up to 72 hours prior to Day 1); Day 8 / LWD pre-dose in the morning; Day 15 / LWD + 7 pre-dose in the morning
- Cycle 2+ : Day 1 pre-dose in the morning

- Discontinuation of study treatment: at any time of the day

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

Following review of data from a group of patients the timing of blood samples may be adjusted for subsequent groups of patient. Additional sampling times may be added if indicated by the emerging data.

Laboratory values that meet the criteria for CTCAE grade 3 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. Any AST or ALT result >8 x ULN in presence of total bilirubin increased from baseline or >10x ULN irrespective of total bilirubin result should have the blood test repeated within 48 hours and additional investigations into the aetiology should be initiated as per Figure 5 hepatotoxicity management algorithm.

The following laboratory variables will be measured:

Table 2 Clinical laboratory variables

Clinical chemistry	**Haematology**
Serum (S)/Plasma (P)-Albumin	Blood (B)-Haemoglobin
S/P-ALT	B-Leukocyte
S/P-AST	B-Absolute leukocyte differential count:
S/P-Alkaline phosphatase	Neutrophils
S/P-Bilirubin, total	Lymphocytes
S/P-Calcium, total	Eosinophils
S/P-Creatinine	B-Platelet count
S/P-FSH (females only)	
S/P-Glucose	**Urinalysis**
S/P-Magnesium	U-Glucose
S/P-Oestradiol (females only)	U-Protein
S/P-Potassium	U-Blood
S/P-Total Protein	U-Ketones
S/P Free T4	U-Microscopy (red blood cells and white blood
S/P TSH	cells, bacteria, casts and crystals) only perform if
S/P Testosterone (males only)	urinalysis is abnormal
S/P Troponin I or T	
S/P-Sodium	
S/P-Urea nitrogen	

For blood volume see Section 6.8.1.

Urinalysis – supplementary evaluations:

- An additional urine/serum sample will be collected from all female patients at screening and at treatment discontinuation for a pregnancy test.
- If 3+ proteinuria is identified by dipstick assessment, a 24-hour urine collection for formal quantification of the level of protein excretion should be performed.
- During Cycle 1, patients will be required to carry out a urine glucose assessment by dipstick prior to breakfast two times per week. If a positive result is observed, further investigation of this result is necessary (see Section 5.1.6 for glucose management algorithm).

6.3.7 Fasted lipids

Fasted blood samples for determination of triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL) and cholesterol will be will be taken at the visits as indicated in the Study Plan (see Figure 6) at the following schedule:

- Cycle 0: Day 1 pre-dose
- At approximately 3 and 6 months thereafter at any time of the day.

6.3.8 Glucose, insulin and insulin c-peptide

Blood samples for determination glucose, insulin and insulin c-peptide will be taken at the visits as indicated in the Study Plan (see Figure 6) at the following schedule:

- Fasting:
  - Cycle 0: Day 1 pre-dose.
  - Cycle 1: Day 8 / LWD pre-dose in the morning
- Non-fasting:
  - Cycle 0: Day 1; 2, 4, 6 and 8 hours post-dose.
  - Cycle 1: Day 8 / LWD; 2, 4, 6 and 8 hours post-dose in the morning, Day 15 / LWD+7 at any time of the day
  - Cycle 2 onwards: Day 1 at any time of the day
  - Discontinuation of study treatment: at any time of the day

Patients will be requested to record the date and time of their evening meal prior to each of the sampling days listed above. On multiple sampling days: Cycle 0 Day 1 and Cycle 1 Day

8/LWD, the data and time of all meals taken on that day prior to the 8-hour sample should be recorded. This information will be recorded in the eCRFs.

6.3.9 Follow-up

A post study assessment will be performed at the time investigational product is permanently discontinued (see Study Plan, Figure 6).

In addition patients should be followed up for 30 days after the last dose of study treatment for any new reports of adverse events. Patients should also be asked about concomitant medications at this follow-up.

6.4 Adverse events

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.

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an adverse event as far as the deterioration can be anticipated (see Disease progression).

The term adverse event is used generally to include any AE whether serious or non-serious.

6.4.2 Definitions of serious adverse events

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to adverse events), except hospitalisation that has been planned before enrolment
- Results in persistent or significant disability or incapacity
- Is or results in 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 of this Clinical Study Protocol.

For definition of other significant adverse events (OAE) see Section 7.3.1.

6.4.3 Recording of adverse events

Time period for collection of adverse events

AEs will be collected throughout the study, from informed consent until the end of the follow-up period. The follow-up period is defined as 30 days after study treatment is discontinued. SAEs occurring in the follow-up period should be reported to AstraZeneca in the usual manner (see Section 6.4.4).

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. AstraZeneca 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 AZD5363, the investigator should notify AstraZeneca.

Variables

The following variables will be collected in the CRF for each AE:

- AE diagnosis/description
- The date when the AE started and stopped
- CTCAE grade maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Outcome

For SAEs other variables will be collected including treatment given for the event.

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 investigational product and each adverse event, and answer "yes" or "no" to the question: "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

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

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

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient 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 Clinical Study Report. 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, a DLT or are the reason for discontinuation of treatment with the investigational product 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 investigational product 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 **one day**. 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 AstraZeneca 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.

Investigators and other site personnel should inform (emergency report) appropriate AstraZeneca representatives of any SAE that occurs at his or her site in the course of the study within 1 day (in this section, within 1 day is defined as "immediately but no later than the end of the next day") of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The Principal Investigator should provide detailed information to AstraZeneca in writing **within 4 calendar days** of the initial report. The Principal Investigator should notify the serious adverse events in writing to the head of the study site immediately.

Follow-up information on SAEs should also be reported to AstraZeneca by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to AstraZeneca within 1 day as described above.

The following information is required in the initial SAE report to AstraZeneca from the investigator(s): study code, site number, enrolment code, adverse event, seriousness, start date.

The following detailed information should be sent to AstraZeneca as soon as it becomes available: severity, outcome (including stop date, if available), causality (investigational product and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of adverse event, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

In addition AstraZeneca will provide details of any unexpected serious adverse drug reactions or expected fatal or life-threatening serious adverse drug reactions reported with regard to the test product in this study or other compound available overseas in which the active ingredient is known to be equivalent to the test product, to the Head of the study site, Principal Investigator and the regulatory agency. The Head of the study site should submit a written report to the IRB providing the details of all adverse event case(s) reported by AstraZeneca.

Reporting Procedure of Serious Adverse Events if using Web-based Data Capture (WBDC) system

The investigator(s) and other site personnel will access the Web Based Data Capture (WBDC) system and report SAE information by entering it into the relevant electronic CRF module. Upon entry of the SAE information, an automated email alert will be sent to the designated AstraZeneca representative. If the system is unavailable, the investigator(s) should take other appropriate measures to provide SAE report to the AstraZeneca representative immediately,

recognising that the same reporting time frames still apply. The investigator(s) is responsible for completing the electronic CRF as soon as the system becomes available again.

If initial or the subsequent reports are made by means other than WBDC, necessary information on any SAEs should finally be entered into the electronic CRF via WBDC system by the investigator(s).

6.5 Pharmacokinetics

6.5.1 Collection of pharmacokinetic samples

Venous blood samples (4 mL) for determination of concentrations of AZD5363 and possible investigation of its metabolites in plasma will be taken at the timepoints presented in Table 3 (please reference also the study plan Figure 6):

The date and time of collection of each sample will be recorded. The plasma samples will be split, one for AZD5363 and one for the metabolites.

Table 3 Pharmacokinetic sampling schedule.

Time relative to	Cycle 0			Cycle 1		
first dose in cycle	Day 1	Day 2	Day 3	Day 1	Day 8 / LWD	Day 15/ LWD+7
Pre-dose (in the morning)	X			X	X	X
30 min	X				X	
1 hour	X				X	
2 hours	X				X	
4 hours	X				X	
6 hours	X				X	
8 hours	X				X	
12 hours	X				X[a]	
24 hours		X				
48 hours			X			

[a] Sample to be taken prior to administration of the second daily dose on Day 8/LWD.

Separate urine samples (2 mL) for the determination of concentrations of AZD5363 and its metabolites will be taken during Cycle 0 at the following intervals:

Cycle 0: Pre-dose (from one sampling collected during –12 to 0 hours), and at 0-12, 12-24 and 24-48 hours post dose.

The date and time of collection and the weight of each urine collection will be recorded.

The timing of the blood and urine pharmacokinetic samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the 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 5, Section 6.8.1.

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

6.5.2 Determination of drug concentration in pharmacokinetic samples

Samples for determination of AZD5363 concentrations in plasma and urine will be analysed by PRA International, Assen, The Netherlands on behalf of AstraZeneca, using appropriate bioanalytical methods. Full details of the analytical methods used will be described in separate bioanalytical reports.

All samples still within the known stability of the analytes of interest (ie, AZD5363) at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the pharmacokinetic samples may be subjected to further analyses in order to further investigate the presence and/or identity of drug metabolites. This may involve pooling of samples if required. Any results from such analyses will be reported separately from the Clinical Study Report.

6.6 Pharmacodynamics

6.6.1 Collection of pharmacodynamic (PDc) assessments

2.7 mL venous blood (to provide platelet-rich plasma) will be taken on each of the timepoints presented in Table 4 below (please also reference the study plan, Figure 6) for PDc assessment. This will be total and phospho-GSK3β in the first instance.

The timing of the blood samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the biomarker profiles.

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

The date and time of collection of each sample will be recorded.

Table 4 Pharmacodynamic (PDc) sampling schedule.

Time relative to first dose in cycle	Cycle 0 Day 1	Cycle 1 Day 1	Cycle 2 to last Day 1	IP Discontinued
-				X
Predose	X	X	X	
1 hour	X			
4 hours	X			
8 hours	X			
12 hours	X			

6.7 Exploratory research

Exploratory biomarker research

If a patient consents, hair, paired biopsies and archived tumour may also be collected for exploratory biomarkers related to AKT activity.

For rationale and biomarkers to be analysed, see Sections 1.3 and 3.2.

The results of this exploratory biomarker research except for paired biopsies will be reported separately and will not form part of the Clinical Study Report.

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

Collection of hair samples

Eyebrow hair will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug and clinical outcomes.

Eyebrow hair determination of concentrations of exploratory biomarkers will be taken during Cycle 0 at: pre-dose (collected during –12 to 0 hours) and at 4 hours post-dose.

Collection of archival tumour samples (optional)

All patients will be asked to provide consent to supply a sample of their archival tumour blocks if a sample taken at the time of diagnosis is available.

Samples may be analysed for markers that may be predictive for response to AZD5363 such as total and phospho-AKT, p95 HER2 and somatic mutations of PIK3CA.

The tumour samples 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.

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

Collection of paired tumour biopsies (optional)

All patients will be asked to provide consent for collection of tumour biopsies. These should be collected prior to the first dose of AZD5363 (at screening or at pre-dose on Day 1 of Cycle 0) and on Day 15 of Cycle 1 (± 1 week) from consenting patients. The samples will be analysed for pharmacodynamic markers such as total and phospho-PRAS40 and total and phospho-GSK3β. Additional biomarker analysis may include markers that may influence development of cancers and/or response to AZD5363 such as total and phospho-AKT, p95 HER2 and somatic mutations of PIK3CA.

The date and time of collection will be recorded in the CRF.

6.7.1 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 pharmacogenetics research will be reported separately and will not form part of the Clinical Study Report.

6.7.1.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the patients immediately prior to dosing (single dose day, Cycle 0). 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. Such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn prior to dosing 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 details in the Laboratory Manual.

6.8 Biological sampling procedures

6.8.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study during Cycles 0 to 1, and at all subsequent cycles and on completion of study therapy is shown in Table 5. The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on AZD5363 become available.

Table 5 Volume of blood to be drawn from each patient during Screening, Cycles 0 and 1 and subsequent cycles of treatment

	Sample volume	Screening, Cycles 0 and 1		Cycle 2 Day 1		Cycles 3 Day 1 and each Cycle Day 1		IP discontinuation	
	(ml)	Number of samples	Total volume (ml)	Number of samples	Total volume (ml)	Number of samples	Total volume (ml)	Number of samples	Total volume (ml)
Safety									
Clinical chemistry	11	5	55	1	11	1	11	1	11
Haematology	2	5	10	1	5	1	5	1	5
Fasted Lipids	0.6	1	0.6	-	-	- a)	- a)	-	-
Glucose, insulin, insulin c-peptide	7	11	77	1	7	1	7	1	7
Pharmacokinetics	4	20	80	-	-	-	-	-	-
Pharmacodynamics	2.7	6	16.2	1	2.7	1	2.7	1	2.7
Pharmacogenetics	5	1	5	-	-	-	-	-	-
TOTAL			**243.8**		**25.7**		**25.7**		**25.7**

a) Fasting lipid samples to be taken at 3 and 6 months following initial dose.

6.8.2 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.

Biological samples for future research can be retained at AstraZeneca for a maximum of 25 years following the last patient's last visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in either Clinical Study Report Addendum /Scientific Report or Scientific Publication.

6.8.2.1 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.

6.8.2.2 Samples for exploratory research

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 AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory 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 AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

6.8.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (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 AstraZeneca 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 AstraZeneca designated central Contract Research Organisation.

6.8.4 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.

6.8.5 Withdrawal of informed consent for donated biological samples

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

AstraZeneca 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.

The Principal Investigator:

- Ensures AstraZeneca 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 AstraZeneca are informed about the sample disposal

As collection of the following biological samples is a voluntary part of the study then if the samples are not taken, or are withdrawn, the patient may continue in the study:

- Pharmacogenetic (blood)
- Archival tumour
- Paired tumour biopsies

6.9 Anti-tumour activity

6.9.1 Tumour assessments

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix F of this Clinical Study Protocol.

Baseline tumour 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. 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. Tumour assessment performed before Informed Consent can be used as baseline assessment if patient consents. The methods of assessment used at baseline should be used at each subsequent follow-up assessment. Follow-up assessments should be performed on Day 1 of Cycle 2 and Cycle 3 (at weeks 3 and 6 (± 1 week)), after the start of Cycle 3 treatment then at approximately 6 weekly intervals until discontinuation of study treatment or withdrawal of consent. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease).

For patients who only have non-measurable disease at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response for NTLs: CR, PD and Non CR/Non PD.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

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 NTLs is usually not sufficient to qualify for unequivocal disease progression status.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Section 6.1 and Appendix F, Section 4.1.

6.9.2 Correlative studies, special studies and functional imaging

Not Applicable

7. EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

7.1 Definition of study endpoints

To meet the objectives for this study, data for the following endpoints will be collected:

- Safety and Tolerability (Primary)
- AZD5363 Pharmacokinetics (Secondary)
- Tumour response (Secondary)
- AZD5363 Pharmacodynamics (Exploratory)
- Metabolite identification/pharmacokinetics (Exploratory)
- Exploratory biomarkers (Exploratory)
- Pharmacogenetics (Exploratory)

Derivation and calculation of safety endpoints are defined in Section 7.3, below. Analytical plans are described under 'Safety' in Section 7.9.

7.2 Determination of sample size

The primary objective of this study is to investigate the safety and tolerability and thereby identify the RD of AZD5363 and to recommend dose(s) and treatment schedule(s) for evaluation in future clinical studies. Hence the number of patients has been based on the desire to obtain adequate tolerability, safety and pharmacokinetic and pharmacodynamic data while exposing as few patients as possible to the investigational product and procedures.

For the dose escalation phase of the study, cohorts of 3-6 evaluable patients will be required. The total number of patients will depend upon the number of dose escalations necessary.

Up to at most additional 9 evaluable patients will be accrued at the RD for each treatment schedule arm to explore further the tolerability, pharmacokinetics and biological activity at these doses.

7.3 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, SAEs, deaths, laboratory data, vital signs, ECG changes and left ventricular ejection fraction (LVEF) and abnormalities of glucose metabolism. These will be collected for all patients. Appropriate summaries of these data will be presented as described in Section 7.9.

ECG Changes

QTc will be calculated by AstraZeneca using both Bazett's and Fridericia's formulae.

Creatinine Clearance

Estimated creatinine clearance will be calculated by the study site at screening using the Cockcroft and Gault formula:

- For creatinine values in µmol/L –
  - Male: [(140 – age) x weight (kg) x 1.23] / serum creatinine (µmol/L)]
  - Female: [(140 – age) x weight (kg) x 1.04] / serum creatinine (µmol/L)])
- For creatinine values in mg/dL -:
  - Male: [140 - age] x weight (kg) / [72 x serum creatinine (mg/dL)]
  - Female: 0.85 x ([140 - age] x weight (kg) / [72 x serum creatinine (mg/dL)])

7.3.1 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of investigational product. Based on the expert's judgement, adverse events of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of other significant adverse events.

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.

7.4 Calculation or derivation of pharmacokinetic variables

Bioassay of the plasma and urine concentration data for AZD5363 will be performed by [redacted]. The calculation of PK parameters will be performed by [redacted]. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where possible the following PK parameters will be determined for AZD5363.

Plasma PK parameters

Following the single dose part (Cycle 0) of the study:

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal rate constant (λ_z), terminal half life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to 12 hours ($AUC_{(0-12)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F) and apparent volume of distribution (V_z/F),

Other parameters may be included if deemed appropriate.

Following the twice-daily dose part (Cycle 1) of the study:

Maximum plasma concentration at steady state ($C_{ss\ max}$), time to $C_{ss\ max}$ ($t_{ss\ max}$), minimum plasma concentration at steady state ($C_{ss\ min}$), area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_{ss}), extent of accumulation on multiple dosing (R_{ac}), and time dependency of the pharmacokinetics (linearity factor).

The maximum plasma concentration (C_{max}), the C_{max} at steady state ($C_{ss\ max}$), the time of maximum concentration (t_{max}) and the t_{max} at steady state ($t_{ss\ max}$) will be determined by inspection of the concentration-time profiles. Where possible the terminal elimination rate constant (λ_z) will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and the terminal half-life ($t_{½\lambda z}$) will be calculated as $\ln 2/\lambda_z$. The area under the concentration-time curve up to 12 hours ($AUC_{(0-12)}$) will be calculated using the linear trapezoidal rule. Where appropriate, the $AUC_{(0-t)}$ (the area under the plasma concentration-time curve from zero to the time of the last measurable concentration) will be extrapolated to infinity using λ_z to obtain AUC. The area under the concentration-time curve across the dosing interval, AUC_{ss} will be calculated using the linear trapezoidal rule. The apparent clearance (CL/F) will be determined from the ratio of dose/AUC. The volume of distribution (V_z/F) will be determined by dividing the dose by the product of λ_z and AUC. The accumulation ratio (R_{ac}) will be calculated as the ratio of the $AUC_{(0-12)}$ after multiple and single dose. The linearity factor will be assessed by the calculation of the ratio of $AUC_{(0-12)}$ after twice-daily dose/AUC after single dose.

Other parameters may be calculated if deemed appropriate.

Urine PK parameters

The renal clearance (CL_R) will be calculated as the cumulative amount of AZD5363 excreted unchanged in the urine (Ae) divided by the appropriate AUC. Fe will be presented as a % of the dose ie, (Ae/dose) × 100.

7.5 Calculation or derivation of pharmacodynamic variables

7.5.1 Population analysis of pharmacokinetic/pharmacodynamic variables

The pharmacokinetic, pharmacodynamic, demographic, safety and tumour response data collected in this study may also be combined with similar data from other studies and explored using population pharmacokinetic and/or pharmacokinetic-pharmacodynamic methods. The results of any such analyses will be reported separately from the Clinical Study Report.

7.6 Calculation or derivation of exploratory research variables

Results from the exploratory biomarker and pharmacogenetic research will be reported separately from the Clinical Study Report for the main study. Calculation or derivation of exploratory research variable will be also reported from the same report.

7.7 Calculation or derivation of tumour response variables

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.

[redacted]

[redacted]

Objective response rate is defined as the percentage of patients who have a confirmed 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.

In the case of stable disease, measurements should have met the stable disease criteria at least once during the study, observed at least 6 weeks after the start of treatment.

When the investigator is in doubt as to whether progression of disease has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

Best overall response will be calculated as the best response recorded from date study treatment started for each patient.

Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs compared to baseline.

For further details see Appendix F of this Clinical Study Protocol.

7.8 Description of analysis sets

The analysis of data will be based on different subsets according to the purpose of the analysis. Throughout the safety results sections, erroneously treated patients (eg, those assigned to receive dose A who actually received dose B, those who failed to meet the selection criteria) will be accounted for in the actual dose group received.

Analysis sets are presented in Table 6.

Table 6 Analysis sets

Analysis Set	Definition
Safety	All patients who received at least 1 dose of AZD5363.
Pharmacokinetics	All patients who provide concentration time data for AZD5363
Pharmacodynamics	All patients that provide biological samples for pharmacodynamic research
Tumour response	Dosed patients with a baseline tumour assessment.
Exploratory biomarkers	All patients that provide biological samples for exploratory biomarker research

7.9 Methods of statistical analysis

There will be no formal analyses of endpoints in this study, appropriate summary tables and figures will be produced, grouping patients by schedule and dose where there are sufficient patients to summarise. Additional summaries and/or figures may also be produced for the recommended dose within each schedule. Examples of the types of data presentations that will be produced are described below.

Demographic data

Characteristics of the patients, including medical history and disease characteristics at baseline will be listed for each patient and summarised by dose group where appropriate.

Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation and will be summarised by dose level if appropriate.

Exposure

Exposure to investigational product ie, total amount of study drug received will be listed for all patients.

Total exposure and total time on study treatment (date of last dose minus date of first dose plus one) will be summarised by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption/dose delay and at least one dose reduction will be presented separately for the initial period of evaluability defined as 21 days and for any time following this initial period of the study.

Safety

All patients who receive at least one dose of AZD5363 will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles of initial treatment will be combined in the presentation of safety data. AEs will be listed individually by patient and dose group (dose and schedule). For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of patients with adverse events in different categories (eg, causally related, CTCAE grade ≥3 etc) will be summarised by dose group, and events in each category will be further summarised by MedDRA system organ class and preferred term, by dose group. SAEs will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of investigational product (ie, before study Day 1) will be included in the data listings but will not be included in the summary tables of adverse events.

Any AE occurring within the defined 30 day follow-up period after discontinuation of investigational product will be included in the AE summaries. Any adverse events in this period that occur after a patient has received further therapy for cancer (following discontinuation of investigational product) will be flagged in the data listings. AEs occurring after the 30 day follow-up period after discontinuation of investigational product will be listed separately, but not included in the summaries.

Haematology, clinical chemistry, urinalysis, vital signs, ECG data, LVEF, serum glucose measurement, insulin and insulin c-peptide, T4, TSH, FSH, oestradiol, testosterone, demographic data, medical histories and concomitant medications will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the CTCAE version 4.0, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used.

Details of any deaths will be listed for all patients.

Any qualitative assessments will be summarised for all patients using the number of patients with results of negative, trace or positive.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

Pharmacokinetics

Plasma concentrations of AZD5363 will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by actual dose received. Parameters following single and twice-daily dosing will be summarised separately. Plasma concentrations at each time point will be summarised according to actual dose received by the following summary statistics:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on a log scale)
- Gmean ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Maximum
- Median
- Number of observations

The following summary statistics will be presented for AUC, $AUC_{(0\text{-}12}$, $AUC_{(0\text{-}t)}$, AUC_{ss}, C_{max}, $C_{ss\ max}$ and $C_{ss\ min}$:

- Gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Maximum
- Median
- Number of observations

The following summary statistics will be presented for CL/F, volume of distribution, $t_{½\lambda z}$, R_{AC}, linearity factor, Ae and % dose excreted:

- Arithmetic mean
- Standard deviation

- Minimum
- Maximum
- Number of observation

The following summary statistics will be presented for t_{max} and $t_{max\ ss}$:

- Median
- Minimum
- Maximum
- Number of observations

The pharmacokinetic data for AZD5363 after single and twice-daily dosing will also be displayed graphically. Displays will include plasma concentration patient profiles (on the linear and log-scale) versus time and gmean concentration (+/-standard deviation) versus time, stratified by dose.

Scatter plots of PK parameters versus dose, or dose normalised PK parameters versus dose will also be considered following both single and twice-daily dose administration of AZD5363 to assess dose proportionality.

Pharmacodynamics

Absolute biomarker levels and percentage change from baseline in these biomarker levels will be summarised by visit for each schedule and dose. These results will also be displayed graphically in the form of time profile plots for individual patients and box plots over time grouping data for patients by schedule and dose.

Exploratory biomarker research and pharmacogenetics

Data will be listed and summaries will only be produced if there is sufficient data for this to be appropriate. The results of this exploratory biomarker research will be reported separately and will not form part of the Clinical Study Report.

Tumour response

Tumour response data will be listed and summarised by dose, if appropriate, using the following response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE).

In addition, the percentage of patients who have a confirmed PR or CR or have a visit response of SD that is at least 12 weeks after the first dose of study therapy will be summarised.

Waterfall plots (bar charts) indicating the percentage change from baseline in sum of the diameters of TLs may be produced by dose level depending on how much data is obtained in patients with measurable disease at baseline. These may be individual patient plots of changes in tumour size over time or dose level plots with the best percentage change per patient displayed. If there is only limited data then percentage change in tumour size will be listed only.

8. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

8.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes a 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 Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician as below.

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

8.2 Overdose

There is no known antidote to AZD5363, and there is no definition of what constitutes an overdose since this is the first study in humans with AZD5363.

Investigators should be advised that any patient who receives a higher dose 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 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.

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.

8.3 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to AstraZeneca using the appropriate forms.

8.3.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the 30 days after discontinuing investigational product, 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 for SAEs within a fixed timeline (see Section 6.4.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.2 Paternal exposure

Pregnancy of a patient's partner is not considered to be an adverse event. However, any conception occurring from the date of dosing until 16 weeks after dosing should be reported to AstraZeneca and followed up for its outcome.

9. REFERENCES

Altomere and Testa 2005
Altomere DA and Testa JR. Perturbations of the AKT signalling pathway in human cancer. Oncogene. 2005; 24: 7455-7464.

EMEA Guideline 2007
Committee for Medicinal Products For Human Use (CHMP). Guidelines on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. 2007. http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf

FDA 2009
Guidance for Industry Drug-Induced Liver Injury: Pre-marketing Clinical Evaluation. 2009 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

ICH S9
ICH Harmonised Tripartite Guideline . Nonclinical Evaluation For Anticancer Pharmaceuticals S9. http://www.ich.org/LOB/media/MEDIA5785.pdf

Lindsley 2010
Lindsley CW. The Akt/PKB family of protein kinases: A review of small molecule inhibitors and progress towards target validation: A 2009 update. Current Topics in Medicinal Chemistry. 2010; 10: 458-477.

Safety Testing of Drug Metabolites 2008
Guidance for Industry Safety Testing of Drug Metabolites. FDA February 2008. http://www.fda.gov/CDER/GUIDANCE/6897fnl.pdf

Skolnik et al 2008
Skolnik JM, Barrett JS, Jayaraman B, Patel D, Adamson PC. Shortening the timeline of paediatric Phase I trials: the rolling 6 design. Journal of Clinical Oncology 2008, 26(2): 190-195.