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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 Patients with Advanced Solid Malignancies

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AstraZeneca Research and Development site representative

[redacted]

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

Amendment No.	Date of Amendment	Amendment No.	Date of Amendment
1	27 August 2010	6	11 June 2013
2	24 February 2011	7	27 Jan 2014
3	1 November 2011	8	28 Jan 2015
4	27 January 2012	9	15 May 2015
5	05 March 2013	10	02 Nov 2015

[redacted]

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

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 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.

In this first time in patient study, AZD5363 will be administered to patients with advanced solid malignancies at a starting dose which has been calculated from the Non-seriously Toxic Dose in the dog (30 mg/kg/day), 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 (Part A). Differing dosing regimens may be investigated within the intermittent schedule(s) in response to emerging safety, phamacokinetic (PK) and pharmacodynamic (PDc) findings.

Twice daily dosing of an oral formulation of AZD5363 will be used, as deemed optimal in non-clinical studies, primarily to determine the safety and tolerability of AZD5363 in patients with advanced solid malignancies. PK of AZD5363 and potential biological activity will also be investigated.

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

Parts C and D, E and F will investigate the tolerability and initial signs of anti-tumour activity of AZD5363 in tumour types that are considered most likely to be sensitive to AKT inhibition, as a result of bearing a mutation of *PIK3CA, AKT1, PTEN* or other molecular aberrations leading to dysregulation of the PI3K/AKT pathway.

Part C will focus on tumours with a mutation of *PIK3CA* and will contain three separate cohorts for:

- Cohort Cb - estrogen receptor positive (ER+) or human epidermal growth factor receptor 2 positive (HER2+) breast cancer
- Cohort Cg - gynaecological cancer (ovarian, cervical, endometrial)
- Cohort Co - other advanced solid tumours (enrollment to be opened at the discretion of the SRC and AstraZeneca).

Part D will focus on tumours with mutations of *AKT1* or other molecular aberrations leading to dysregulation of the PI3K/AKT pathway, and will contain three separate cohorts for:

- Cohort Db - ER+ or HER2+ breast cancer with *AKT1* mutations
- Cohort Dg - gynaecological cancer (ovarian, cervical, endometrial) with *AKT1* mutations
- Cohort Do - breast cancer, gynaecological cancer or other advanced solid tumours with molecular aberrations leading to dysregulation of the PI3K/AKT pathway (enrollment to be opened at the discretion of the SRC and AstraZeneca).

Part E will focus on patients with advanced or metastatic ER positive breast tumours with mutations of *AKT1* and will contain two separate cohorts:

- Cohort E_R: to explore the effect of AZD5363 in combination with background fulvestrant treatment for patients whose tumours harbour *AKT1* mutations and who have exhibited prior fulvestrant resistance.
- Cohort E_D: to explore the effect of AZD5363 in combination with background fulvestrant treatment for patients whose tumours harbour *AKT1* mutations and who have not received prior fulvestrant.

Part F will focus on patients with advanced or metastatic ER positive breast tumours with alterations of *PTEN* (restricted to genomic alterations which are predicted to ablate function of the gene, e.g. alterations with known functional significance and/or of most likely therapeutic significance. For simplicity, the term mutation will be used in the rest of the protocol) and will contain two separate cohorts:

- Cohort F_R: to explore the effect of AZD5363 in combination with background fulvestrant treatment for patients whose tumours harbour *PTEN* mutations and who have exhibited prior fulvestrant resistance.

- Cohort F_D: to explore the effect of AZD5363 in combination with background fulvestrant treatment for patients whose tumours harbour *PTEN* mutations and who have not received prior fulvestrant.

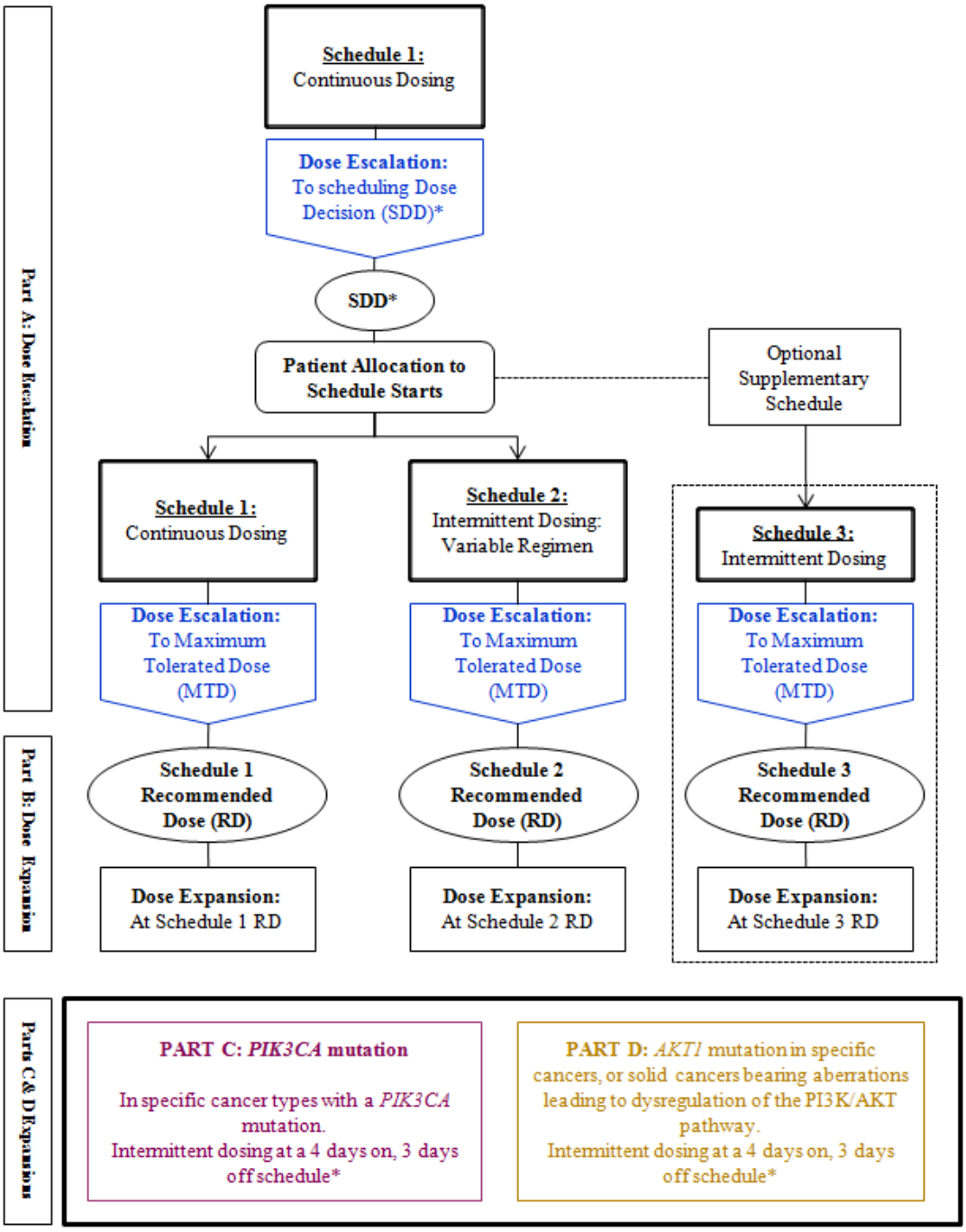
Each cohort will be conducted with a single intermittent schedule of twice-daily AZD5363 at a dose selected from Parts A and B.

Parts A, B, C, D, E and F may be conducted independently of each other. It is anticipated that recruitment and subsequent analyses of the tumour-specific cohorts in Parts C, D, E and F will be independant of each other due to the varying prevalence rates of these mutations in the various patient populations.

Parts A and B of the study will be conducted within 3 sites in the UK and Netherlands only; Parts C, D, E and F will be conducted in countries worldwide including Europe, Asia, Latin America, the US and Canada.

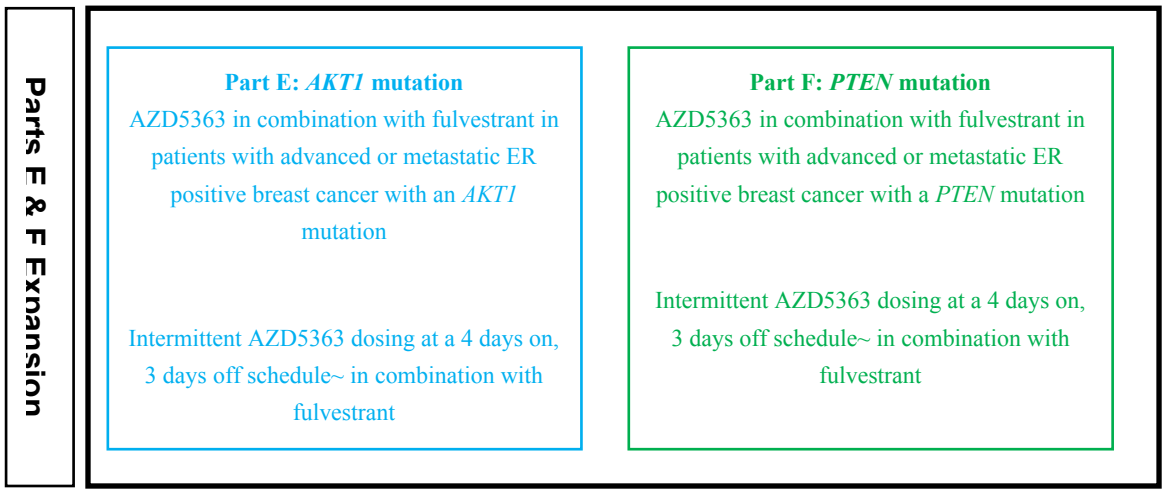
Parts A and B have been completed and have informed the recommended dose and schedule for Parts C, D, E and F.

Study flow chart. See Section 3.1. (Parts A and B have been completed)



SDD, Scheduling Dose Decision. Dose level identified by the Safety Review Committee (SRC) as appropriate for commencement of the intermittent dosing schedule (Section 3.1).
RD, Recommended Dose. Dose level at, or below, the maximum tolerated dose (MTD) identified by the SRC as appropriate for further evaluation (Section 3.1).
*The intention is to initiate Parts C and D with a twice-daily 480 mg dose in a 4 days on, 3 days off regimen. Based on emerging data the SRC and AstraZeneca may elect to use an alternative regimen of 800 mg or 640 mg in a 2 days on, 5 days off regimen.

Figure 1 continued



~ The intention is to initiate Parts E and F with a twice-daily 400mg dose in a 4 days on, 3 days off regimen. Based on emerging data the SRC and AstraZeneca may elect to use an alternative regimen in a 2 days on, 5 days off regimen.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse Event (see definition in Section 6.7.1)
AKT (also known as Protein Kinase B)	Serine/threonine specific protein kinase
AKT1, AKT2, AKT3	Oncogenic "*AKT*" genes which mutate in a range of human cancers. V-akt murine thyoma viral.
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BOR	Best objective response
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CA125	Cancer antigen 125, a marker of ovarian cancer
ctDNA	Circulating tumour DNA
C_{max}	Maximum concentration of study drug in plasma after a single dose
CR	Complete Response
CRF	Case Report Form (electronic/paper)
CSR	Clinical Study Report
$C_{ss,max}$	Maximum concentration of study drug in plasma at steady state after multiple dosing
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of response
E17K	An *AKT1* gene mutation
ECG	Electrocardiogram
EMA	European Medicines Agency
ER	Estrogen receptor
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FSH	Follicle Stimulating Hormone

Abbreviation or special term	Explanation
FTIP	First Time in Patient
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSK3β	Glycogen synthase kinase
HDL	High Density Lipoprotein
HED	Human Equivalent Dose
HER2	Human epidermal growth factor receptor 2
hERG	human Ether-à-go-go Related Gene
IC_{50}	The half maximal inhibitory concentration of a drug
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
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)
M30	Serological marker of cell death and tumour burden
M65	Serological marker of cell death and tumour burden
MedDRA	Medical Dictionary for Regulatory Activities
MSE	Mean square error
MTD	Maximum tolerated dose
MUGA	Multiple Gated Acquisition scan
NE	Not Evaluable
NSCLC	Non-small cell lung cancer
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
OCT2	Organic Cation Transporter 2
ORR	Objective response rate
OS	Overall survival
PD	Progression of Disease
PDc	Pharmacodynamics

Abbreviation or special term	Explanation
PFS	Progression-free survival
PIK3R1	An Oncogenic *PI3K* gene which mutates in a range of human cancers: phosphoinositide-3-kinase, regulatory subunit 1 (alpha)
PIK3R2	An Oncogenic *PI3K* gene which mutates in a range of human cancers: phosphoinositide-3-kinase, regulatory subunit 2 (beta)
PIK3CA	An Oncogenic *PIK3CA* gene which mutates in a range of human cancers: Phosphoinositide-3-kinase, catalytic, alpha polypeptide
PK	Pharmacokinetics
PKB	Protein Kinase B
PR	Partial Response
PRAS40	Proline-rich AKT substrate of 40 kDaltons
PSA	Prostate specific antigen
PTEN	A tumour suppressor gene mutated in a range of human cancers: Phosphatase and tensin homolog gene
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
RD	Recommended Dose. The dose level at, or below, the maximum tolerated dose (MTD) identified by the Safety Review Committee as appropriate for further evaluation.
RECIST	Response Evaluation Criteria in Solid Tumours
S6K	Ribosomal s6 kinase
SAE	Serious Adverse Event (see definition in Section 6.7.2)
SCC	Squamous cell carcinoma
SD	Stable Disease
SDD	Scheduling Dose Decision. The dose level identified by the Safety Review Committee as appropriate for commencement of the intermittent dosing schedule.
SRC	Safety Review Committee
SS	Steady state
STD10	Severely Toxic Dose ($1/10^{th}$)
T4	Thyroxine

Abbreviation or special term	Explanation
TL	Target Lesion
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBDC	Web Based Data Capture
WHO	World Health Organisation

1 STUDY OBJECTIVES

1.1 Objectives: Parts A and B (dose escalation and dose expansion) – Parts A and B have been completed.

1.1.1 Primary objective: Parts A and B

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 patients with advanced solid malignancies.

1.1.2 Secondary objectives: Parts A and B

To characterise the pharmacokinetics (PK) of AZD5363 following a single administration and after multiple dosing, when given orally.

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 (see Appendix F).

1.1.3 Exploratory objectives: Parts A and B

To assess the effect of AZD5363 on AKT activity using phospho-PRAS40 as a biomarker.

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

To characterise the relationship between biomarkers (phospho-PRAS40, total PRAS40, pAKT, pGSK3β, pS6K, M30, M65 and other exploratory markers, including glucose, insulin and insulin c-peptide, in response to emerging data) and AZD5363 plasma concentrations if a meaningful change in biomarker is observed.

To analyse circulating tumour cells for 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).

To collect and store plasma, serum and archival tumour samples or paired biopsies and analyse surplus blood or tissue, 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).

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.

1.2 Objectives: Parts C, D, E and F (PI3K/AKT pathway aberrations)

1.2.1 Primary objective: Part C

To investigate the safety and tolerability of AZD5363 in patients with advanced or metastatic estrogen receptor positive (ER+) or human epidermal growth factor receptor 2 positive (HER2+) breast cancer, gynaecological (ovarian, cervical or endometrial) cancer, or other advanced solid cancer that has a *PIK3CA* mutation.

1.2.2 Primary objective: Part D

To investigate the safety and tolerability of AZD5363 in patients with advanced or metastatic ER+ or HER2+ breast cancer, gynaecological (ovarian, cervical or endometrial) or other advanced solid cancer that has an *AKT1* mutation or other molecular aberration leading to dysregulation of the PI3K/AKT pathway.

1.2.3 Primary objective: Part E

To investigate the safety and tolerability of AZD5363 in combination with fulvestrant in patients with advanced or metastatic ER positive breast cancer that has an *AKT1* mutation.

1.2.4 Primary objective: Part F

To investigate the safety and tolerability of AZD5363 in combination with fulvestrant in patients with advanced or metastatic ER+ positive breast cancer that has a *PTEN* mutation.

1.2.5 Secondary objectives: Parts C, D, E and F

To characterise the PK of AZD5363 following multiple dosing when given orally.

To obtain a preliminary assessment of the anti-tumour activity of AZD5363 by evaluation of tumour response using RECIST version 1.1 (see Appendix F).

1.2.6 Exploratory objectives: Parts C D, E and F

To assess the effect of AZD5363 on AKT activity using phospho-PRAS40 as a biomarker.

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

To characterise the relationship between biomarkers (phospho-PRAS40, total PRAS40, pAKT, pGSK3β, pS6K, M30, M65 and other exploratory markers, including glucose and insulin, in response to emerging data) and AZD5363 plasma concentrations if a meaningful change in biomarker is observed.

To collect and store plasma, serum and archival tumour samples, paired biopsies or tumour sample on progression, and analyse surplus blood or tissue, 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).

To investigate the concordance of *PIK3CA, AKT1,*or other mutation status between per-patient analyses of blood and archival tumour tissue.

To investigate the per-patient concordance between mutations and/or other molecular aberrations in the PI3K/AKT pathway determined by local test methods, in comparison to mutations and/or other molecular aberrations confirmed by central test(s).

To obtain a preliminary assessment of the anti-tumour activity of AZD5363 by evaluation of progression-free survival (PFS) and overall survival (OS).

To collect and store 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).

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 (e.g. mutation of oncogenes 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 Background therapy (Parts E and F)

Fulvestrant is an oestrogen receptor antagonist approved and indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women, supplied as an injection for intramuscular administration. “FAKTION”, a phase 1b/2 randomised placebo controlled trial of fulvestrant +/- AZD5363 in postmenopausal women with advanced breast

cancer previously treated with a third generation aromatase inhibitor is an ongoing clinical study being conducted by Drs Howell and Jones as an investigator-sponsored study (EudraCT Number: 2013-000898-68). FAKTION has recently established a combination MTD for fulvestrant and AZD5363. Dosing fulvestrant at its licenced dose of 500 mg intramuscularly on days 1, 15, 29 and once monthly thereafter, this study established the MTD for AZD5363 to be 400mg bid po in the 4 days on – 3 days off schedule with AZD5363 dosing commencing on day 15. The adverse event profile observed in the Phase 1b part of FAKTION was consistent with the individual AE profiles of each drug and with no additional observations in relation to safety and tolerability. The randomised Phase 2 component of FAKTION commenced in March 2015 using the 400mg AZD5363 dose.

2.3 Non-clinical information and correlative studies

AZD5363 is a potent inhibitor of AKT 1, 2 and 3 (half maximal inhibitory concentration of the drug [IC_{50}] <10 nM). Non-clinical *in vitro* and *in vivo* assays have demonstrated inhibition of phosphorylation of the AKT substrates GSK3β and PRAS40, tumour cell proliferation and xenograft tumour growth models. [redacted] Chronic oral treatment of nude mice bearing a variety of established and primary xenografts with AZD5363, resulted in dose-dependent tumour growth inhibition.

[redacted]

All pivotal non-clinical safety studies were conducted to Good Laboratory Practice (GLP).

The key findings in the toxicology studies were as follows:

[redacted]

[redacted]

Further details are provided in the Investigators' Brochure.

It has recently been observed that suppression of PI3K pathway signalling results in induction of ER-dependent transcriptional activity, including increased expression of genes containing ER-binding sites and increased occupancy by the ER of promoter regions of upregulated genes. Additionally expression of ER mRNA and protein were also increased following PI3K pathway inhibition. The findings have been confirmed in animal model xenografts, patient-derived animal models, and in tumours from patients undergoing treatment with a PI3K alpha inhibitor, as well as an AKT inhibitor (AZD5363). These results suggest that PI3K pathway blockade in ER-positive breast cancer results in an ER-dependent transcriptional program that may be reversed with anti-hormonal therapies, and that simultaneous blockade of the PI3K pathway and ER signalling may be needed for optimal treatment of ER-positive breast tumours with over-activation of the PI3K pathway (Bosch et al 2015, Ribas et al 2015).

Fulvestrant is an oestrogen receptor antagonist indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women, supplied as an injection for intramuscular administration.

On the basis of the biological evidence above and given the established combination dose for AZD5363 and fulvestrant, it is considered biologically and clinically appropriate to explore AZD5363 in combination with fulvestrant therapy where fulvestrant is considered to be a background therapeutic modality in ER positve advanced or metastatic breast cancer patients whose tumours harbour *AKT1* or *PTEN* mutations and who have exhibited prior fulvestrant resistance or have not received prior fulvestrant.

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 PDc findings. Where possible, population modelling and simulation methods will be used as part of the evaluation to assess relationships between emerging safety, PK and PDc.

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

There are six Parts to this study design (see Figure 1):

Part A: Dose escalation **(completed)**

Part B: Dose expansion **(completed)**

Part C: AZD5363 in patients with advanced or metastatic breast, gynaecological (ovarian, cervical or endometrial) or other advanced solid cancer that has a *PIK3CA* mutation (closed to recruitment).

Part D: AZD5363 in patients with advanced or metastatic breast, gynaecological (ovarian, cervical or endometrial) or other advanced solid cancer that has an *AKT1* mutation, or other molecular aberration leading to dysregulation of the PI3K/AKT pathway

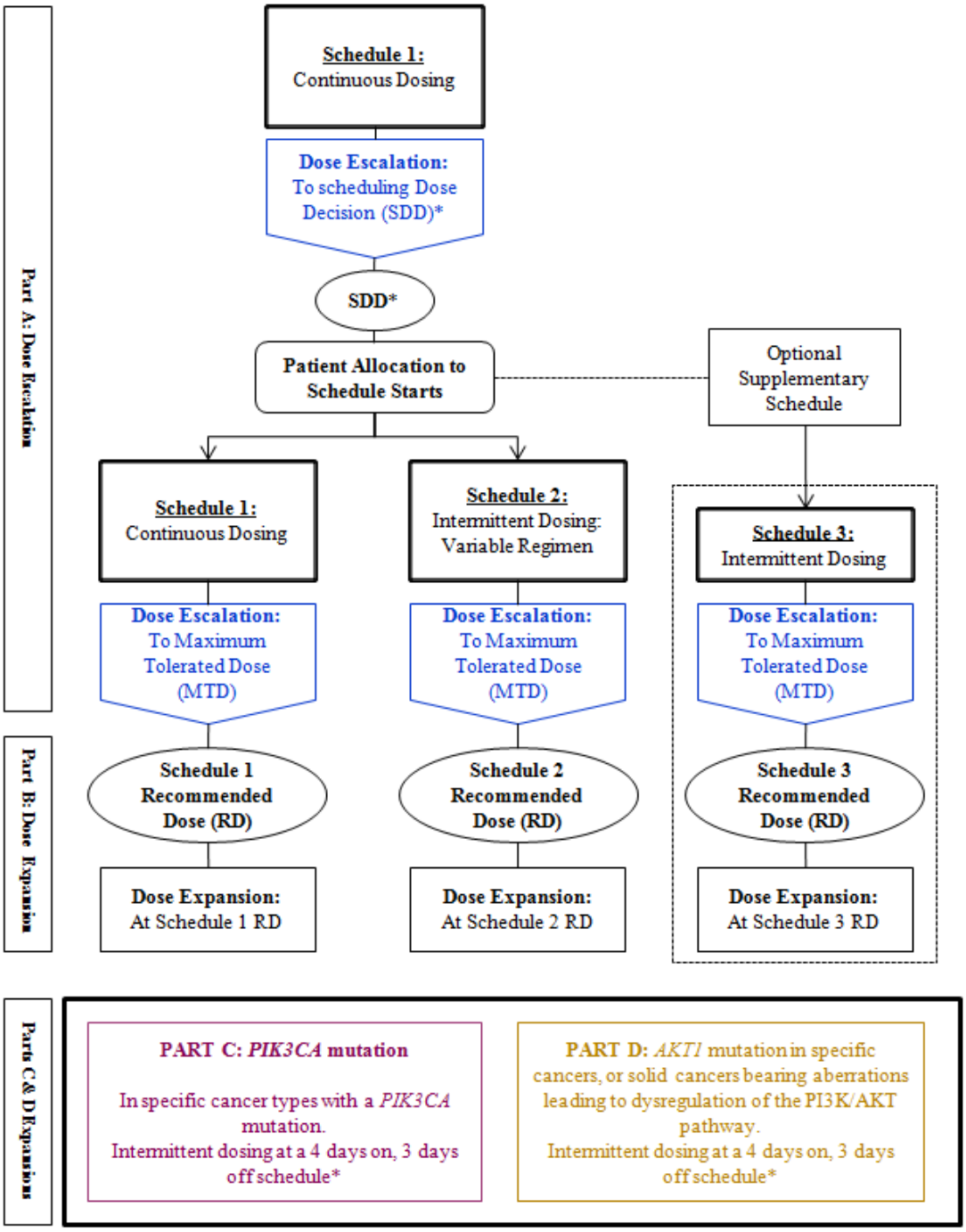
Part E: AZD5363 in combination with fulvestrant in patients with advanced or metastatic ER positive breast cancer that has an *AKT1* mutation

Part F: AZD5363 in combination with fulvestrant in patients with advanced or metastatic ER positive breast cancer that has a *PTEN* mutation

Up to three different dosing schedules will be initiated in Part A, however the trial will begin only under Schedule 1 (continuous dosing) until the Safety Review Committee (SRC) deems it appropriate to initiate the other schedules (see Sections 3.1.1 and 3.1.2).

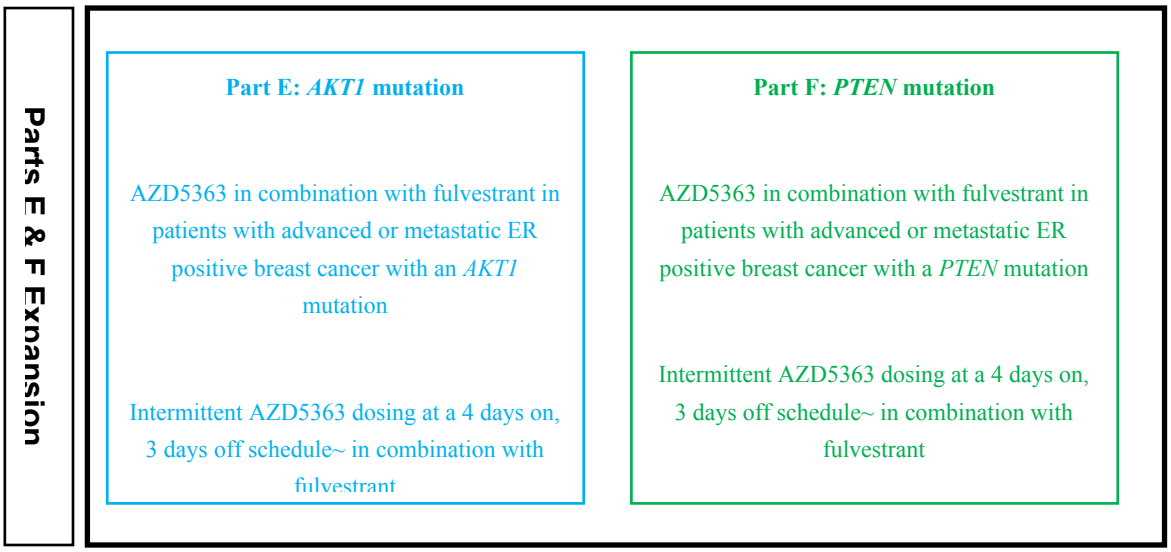
Parts A and B of the study will be conducted at 3 sites in the UK and Netherlands only Parts C, D, E and F will be conducted in countries worldwide including Europe, Asia, Latin America the US and Canada.

Figure 1 Study Flow Chart (Parts A and B have been completed)



SDD, Scheduling Dose Decision. Dose level identified by the Safety Review Committee (SRC) as appropriate for commencement of the intermittent dosing schedule (Section 3.1).
RD, Recommended Dose. Dose level at, or below, the maximum tolerated dose (MTD) identified by the SRC as appropriate for further evaluation (Section 3.1).
*The intention is to initiate Parts C and D with a twice-daily 480 mg dose in a 4 days on, 3 days off regimen. Based on emerging data the SRC and AstraZeneca may elect to use an alternative regimen of 800 mg or 640 mg in a 2 days on, 5 days off regimen.

Figure 1 continued



~ The intention is to initiate Parts E and F with a twice-daily 400mg dose in a 4 days on, 3 days off regimen. Based on emerging data the SRC and AstraZeneca may elect to use an alternative regimen in a 2 days on, 5 days off regimen.

3.1.1 Dosing regimens and schedules

3.1.1.1 Dosing regimen and schedules: Parts A and B (dose escalation and dose expansion). Parts A and B have been completed.

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 2) under one of the treatment schedules detailed below.

Parts A and B: 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 (administered for a defined number of days each week). Patients will receive a 7-day repeating regimen of twice daily dosing for periods of between 1 and 6 days, alternating with concomitant periods without dosing (such as: a regimen of 4 days on, 3 days off treatment; or every other day; or Monday and Thursday each week, or other alternative schedules may be investigated based upon emerging clinical data). This regimen may be changed between cohorts under guidance of the SRC (see Study Design, Part A below).

Schedule 3 (optional): intermittent dosing. This optional schedule may be introduced under the direction of the SRC during Part A in response to emerging clinical data, including

suspected toxicities. Schedule 3 would investigate either: dose escalation within an alternative weekly regimen or the appropriateness of a regimen incorporating planned drug holidays (eg, 2 weeks on, 1 week off). Initiation of Schedule 3 will proceed only on approval of a protocol amendment stating the intended dosing regimen and the rationale for this regimen.

3.1.1.2 Dosing schedules: Parts C, D, E and F (PI3K/AKT pathway aberrations)

It is intended that each patient will receive AZD5363 as an intermittent regimen of 480 mg twice daily for 4 days on, 3 days off dosing in Part C and Part D (see Figure 3[Part C] and Figure 4,[Part D], and as an intermittent regimen of 400mg twice daily for 4 days on, 3 days off dosing in Part E and F (see Figure 5 [Part E], and Figure 6 [Part F]). An alternative dosing schedule of twice-daily 800 mg or 640 mg dosing in a 2 days on, 5 days off regimen may be explored for one or more of the Part C, D, E or F cohorts. Exploration of this alternative dose and schedule may be conducted in parallel with, or as an alternative to, a cohort which is partially complete in respect of the twice-daily 480 mg 4 day on, 3 day off regimen. Any decision to introduce additional cohorts in order to investigate an alternative dosing regimen will be at the discretion of AstraZeneca after discussion with the SRC.

3.1.2 Study design

3.1.2.1 Study design: Part A (dose escalation)

Approximately 60 evaluable patients with advanced solid malignancies will be enrolled in Part A of the study in cohorts of 3 to 6 patients (see Section 3.2). The total number of patients will depend upon the number of dose escalations and dose schedules investigated.

Part A will commence under Schedule 1, continuous dosing, only. Dose escalation by cohort will proceed until the SRC identifies a dose of AZD5363 (Scheduling Dose Decision [SDD]) and dosing regimen deemed appropriate to initiate Schedule 2. This selection will be based upon evaluation of emerging safety, tolerability, PK, PDc profiles and if possible the relationship between them from Schedule 1 (Figure 2).

Dose escalation will then proceed with patients being allocated (see Section 5.1.4) to separate cohorts under Schedules 1 and 2. Optional Schedule 3 may be introduced at any time under the discretion of the SRC (Figure 2).

For the first cohort in each schedule, a delay of at least 7 days will be mandatory between administration of first patient first (single) dose to commencement of first (single) dose for any subsequent patients (see Section 5.1.3.1).

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.

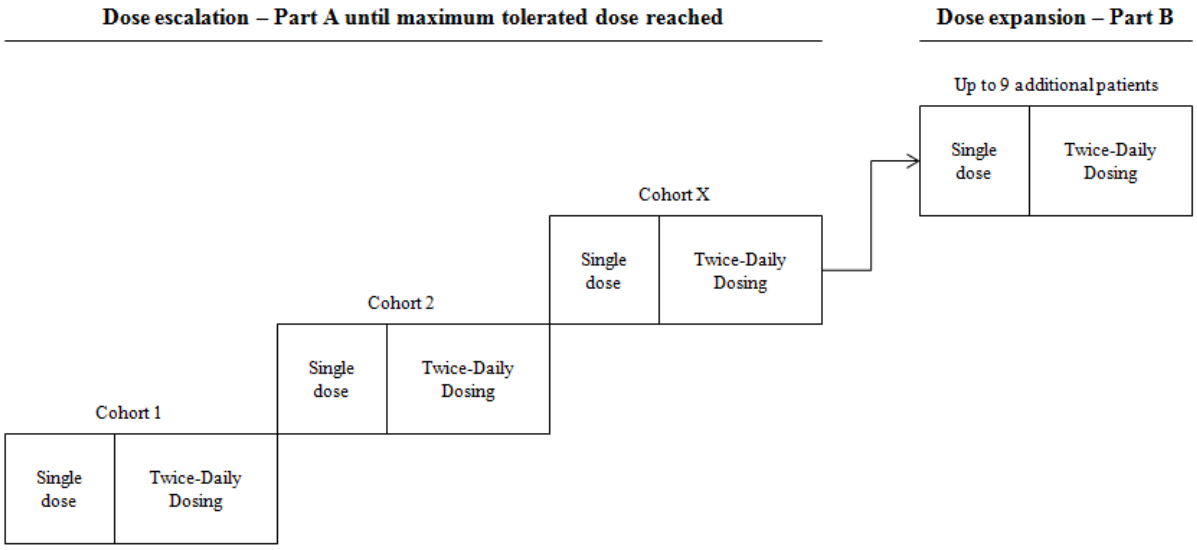
If one or more schedules are temporarily suspended, recruitment to the other schedule(s) may continue independently.

Dose escalation under Part A will continue until a non-tolerated dose (NTD) is attained and a maximum-tolerated dose (MTD) is identified (see section 5.1.3.1) for each schedule. The RD to go forward to Part B will be at, or below, the MTD and will be selected by the SRC.

3.1.2.2 Study design: Part B (dose expansion)

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 5.1.4), 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 a total of 12 evaluable patients (Parts A and B) at the RD for each schedule evaluated. If more than 2 different dosing regimens have been explored in Part A of Schedule 2, a dose expansion for each different dosing regimen maybe initiated.

Figure 2 Schedule 1, 2 and 3 Dose Escalation and Expansion (Parts A and B only – completed)



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

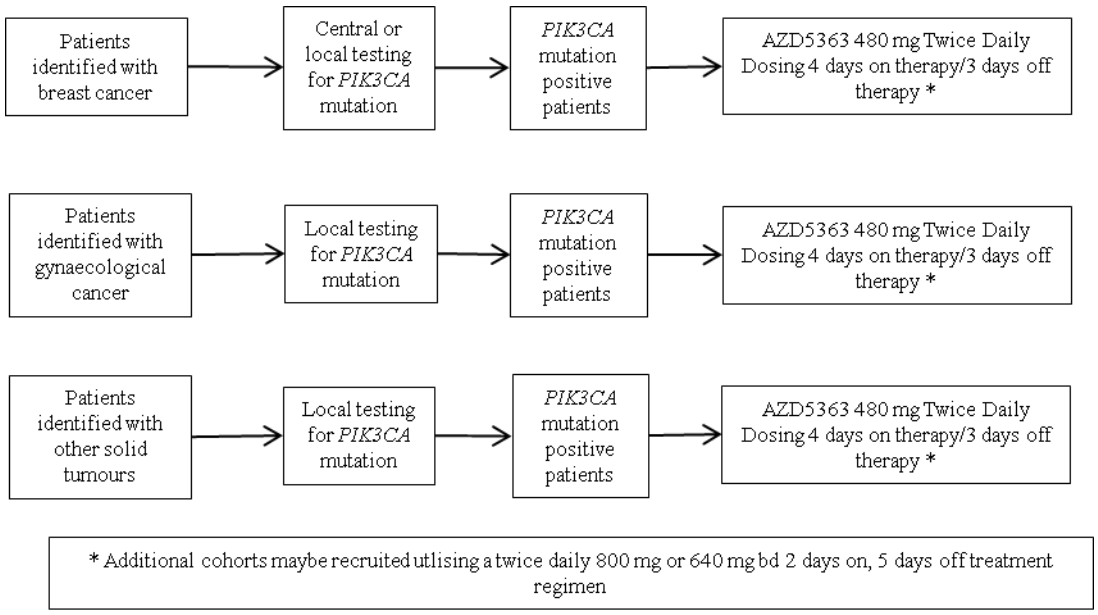
3.1.2.3 Study design: Part C (*PIK3CA* mutation)

Upon screening patients' tumours for *PIK3CA* mutations (see Section 6.5 for details), patients with advanced or metastatic ER+ or HER2+ breast, gynaecological (ovarian, cervical or endometrial) or other advanced solid cancer that are *PIK3CA* mutation positive will be recruited into part C (Figure 3). This will include three cohorts of patients with *PIK3CA* mutation-positive ER+ or HER2+ breast cancer (Cohort Cb), *PIK3CA* mutation-positive gynaecological cancer (Cohort Cg) and other solid *PIK3CA* mutation-positive cancers (Cohort Co). Cohort Co will be opened at the discretion of the SRC and AstraZeneca after the other cohorts have commenced.

Patients will be allocated to receive AZD5363 480 mg twice-daily, 4 days on 3 days off dosing. Recruitment to each cohort may continue to a maximum of 120 patients, however may be terminated based on interim reviews of the data after 20 and 40 patients have been followed for a minimum of 12 weeks (see Section 7.2 for details).

An alternative dosing schedule of twice-daily 800 mg or 640 mg dosing in a 2 days on, 5 days off regimen may be explored for one or more of the cohorts. Exploration of this alternative dose and schedule may be conducted in parallel with, or as an alternative to, a cohort which is partially complete in respect of the twice-daily 480 mg 4 days on, 3 days off regimen. Any decision to introduce additional cohorts in order to investigate an alternative dosing regimen will be at the discretion of AstraZeneca after discussion with the SRC.

Figure 3 Study flow: Part C (*PIK3CA* mutation)



Recruitment to each cohort may continue to a maximum of 120 patients, however may be terminated based on interim reviews of the data after 20 and 40 patients have been followed for a minimum of 12 weeks (see Section 7.2 for details).

*The intention is to initiate Part C with a 480 mg bd dose in a 4 days on, 3 days off regimen. Based on emerging data, the SRC and AstraZeneca may elect to use an alternative regimen of 640 mg bd in a 2 days on, 5 days off regimen.

3.1.2.4 Study design: Part D (PI3K/AKT pathway aberrations)

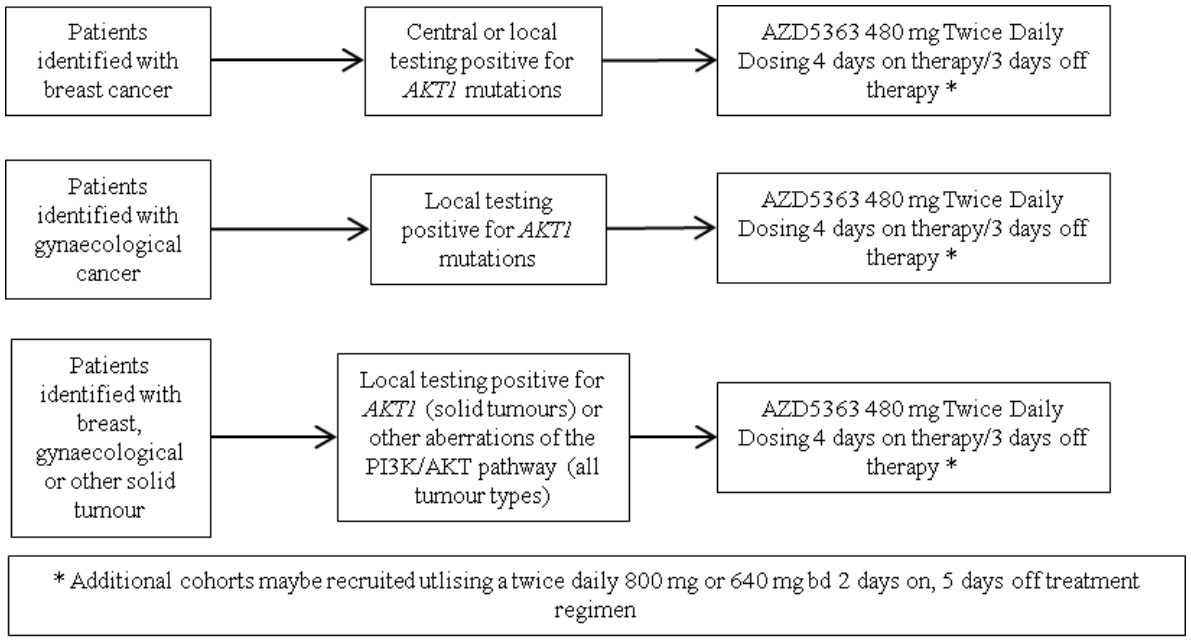
Upon screening patients' tumours for mutations (see Section 6.5 for details), patients with advanced or metastatic ER+ or HER2+ breast, gynaecological (ovarian, cervical or endometrial) or other advanced solid cancer that are positive for the *AKT1* mutation, or other molecular aberrations leading to dysregulation of the PI3K/AKT pathway, will be recruited into part D (Figure 4). This will include three cohorts of patients with *AKT1* mutation-positive ER+ or HER2+ breast cancer (Cohort Db), patients with *AKT1* mutation-positive

gynaecological cancer (Cohort Dg) and patients with breast, gynaecological or other solid cancers bearing other molecular aberrations leading to dysregulation of the PI3K/AKT pathway (Cohort Do). Cohort Do will be opened at the discretion of the SRC and AstraZeneca after the other cohorts have commenced.

Patients will be allocated to receive AZD5363 480 mg twice-daily, 4 days on 3 days off dosing. Recruitment to each cohort may continue to a maximum of 120 patients, however may be terminated based on interim reviews of the data after 20 and 40 patients have been followed for a minimum of 12 weeks (see Section 7.2 for details).

An alternative dosing schedule of twice-daily 800 mg or 640 mg dosing in a 2 days on, 5 days off regimen may be explored for one or more of the cohorts. Exploration of this alternative dose and schedule may be conducted in parallel with, or as an alternative to, a cohort which is partially complete in respect of the twice-daily 480 mg 4 days on, 3 days off regimen. Any decision to introduce additional cohorts in order to investigate the alternative dosing regimen will be at the discretion of AstraZeneca after discussion with the SRC.

Figure 4 Study flow: Part D (*AKT1* and other PI3K/AKT pathway aberrations)



Recruitment to each cohort may continue to a maximum of 120 patients, however may be terminated based on interim reviews of the data after 20 and 40 patients have been followed for a minimum of 12 weeks (see Section 7.2 for details).

The intention is to initiate Part D with a 480 mg dose in a 4 days on, 3 days off regimen. Based on emerging data, the SRC and AstraZeneca may elect to initiate Part D, or switch at a later date to, an alternative regimen of 640 mg in a 2 days on, 5 days off regimen.

3.1.2.5 Study design: Part E (*AKT1* mutation) – AZD5363 + fulvestrant combination

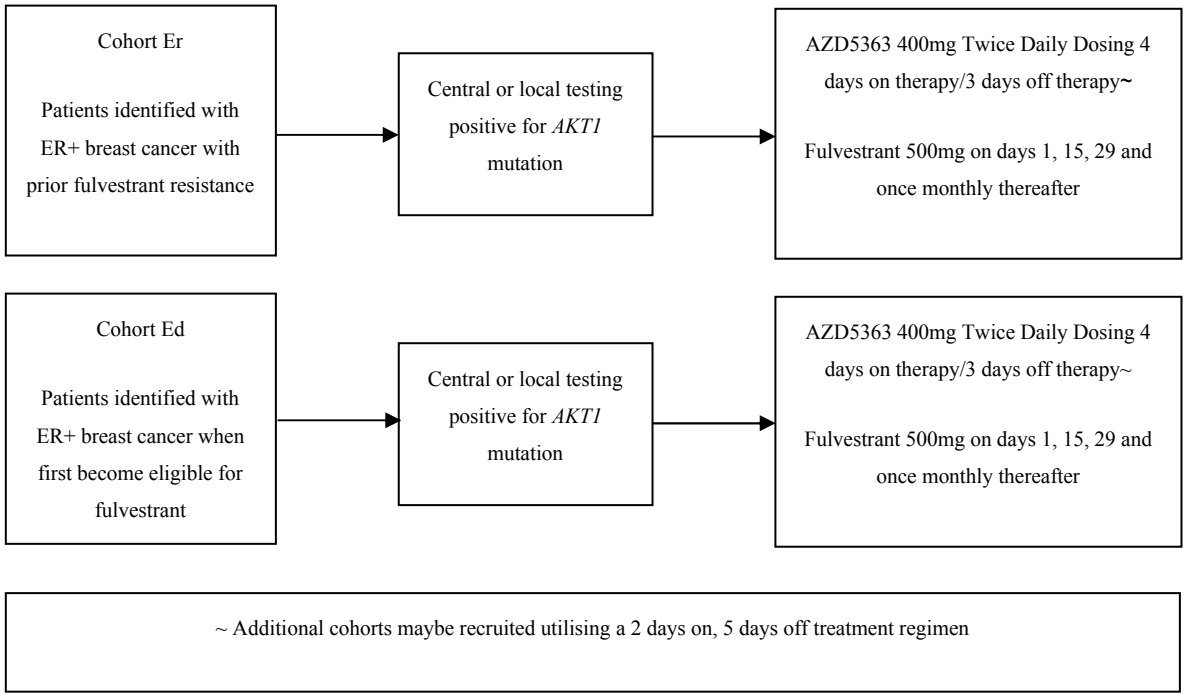
Upon screening patients' tumours for mutations (see Section 6.5 for details), patients with advanced or metastatic ER+ breast cancer that is positive for the *AKT1* mutation will be recruited into Part E (Figure 5). This will include two sub-cohorts of patients:

Cohort E_R: AZD5363 + fulvestrant combination for patients with prior fulvestrant resistance

Cohort E_D: AZD5363 + fulvestrant combination for patients whom have not received prior fulvestrant.

Patients will be allocated to receive AZD5363 400 mg twice daily, 4 days on 3 days off dosing in addition to fulvestrant at its labelled dose. Recruitment to each cohort may continue to a maximum of 24 patients, however may be terminated based on interim reviews of the data after the first 12 patients have been followed for a minimum of 24 weeks or discontinued (see Section 7.2 for details).

Figure 5 Study flow: Part E (*AKT1* mutation)



3.1.2.6 Study design: Part F (*PTEN* mutation) – AZD5363 + fulvestrant combination

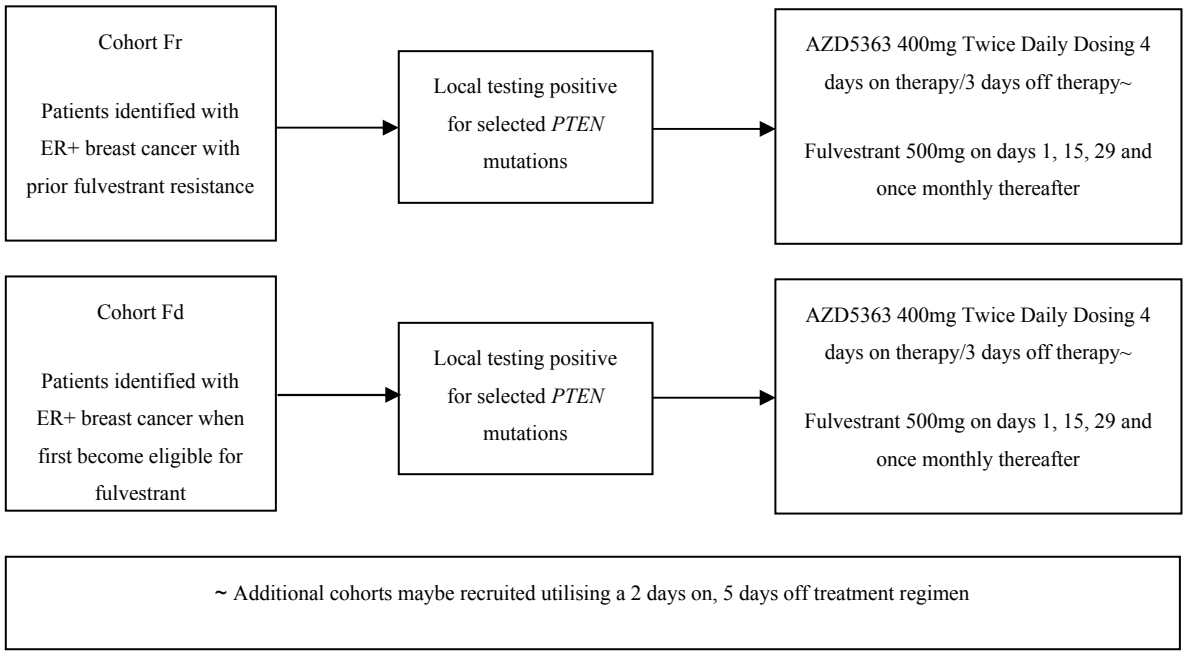
Upon screening patients' tumours for mutations (see Section 6.5 for details), patients with advanced or metastatic ER+ breast cancer that is positive for selected *PTEN* mutations will be recruited into Part F (Figure 6). This will include two cohorts of patients:

Cohort F_R: AZD5363 + fulvestrant combination for patients with prior fulvestrant resistance

Cohort F_D: AZD5363 + fulvestrant combination for patients whom have not received prior fulvestrant.

Patients will be allocated to receive AZD5363 400 mg twice daily, 4 days on 3 days off dosing in addition to fulvestrant at its labelled dose. Recruitment to each cohort may continue to a maximum of 24 patients, however may be terminated based on interim reviews of the data after the first 12 patients have been followed for a minimum of 24 weeks or discontinued (see Section 7.2 for details).

Figure 6 Study flow: Part F (*PTEN* mutation)



3.2 Rationale for conducting this study and for study design

3.2.1 Rationale for Parts A and B (dose escalation and dose expansion) (completed)

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 patients with advanced solid malignancies and for whom no standard of care exists. The study will also characterise the PK of AZD5363 and explore potential biological activity by assessing PDc, 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. Given that patients in the first few cohorts may receive AZD5363 at exposures below the anticipated efficacious level it would not be ethical to treat patients for which alternative standard therapies with demonstrated efficacy are available. The collection of optional matched pre-and post- treatment tumour biopsies will allow assessment of the PDc effect of treatment 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 European Medicines Agency (EMA) 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 (EMA Guideline 2007). Part A of the study will determine the RD of AZD5363 based upon assessment of the safety, tolerability and PK 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. [redacted] owever, 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 PK 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 continuous twice daily dosing with AZD5363, but at the direction of the SRC may explore one or two further intermittent dosing schedules. This design, additionally incorporating options for 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 be necessary under additional mono-schedule arms or conduct of separate clinical studies.

The timings of safety and PK assessments in the study have been designed on the basis of non-clinical findings. [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 PK 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 PDc and exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from archival or pre- and post-treatment tumour samples, circulating tumour cells, DNA, ribonucleic acids, 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 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 genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

3.2.2 Rationale for Part C (*PIK3CA* mutation)

Preclinical data suggest that *PIK3CA* mutations predict response to PI3K/AKT/mTOR inhibitors, including AZD5363, whereas mutations in RAS genes predict resistance (Davies et al 2012). A Phase I programme for targeted therapy with a PI3K/AKT/mTOR pathway inhibitors detected *PIK3CA* mutations in 105 (10%) of the 1,012 patients with advanced tumours: 32 (30%) had colorectal cancer, 15 (14%) breast cancer, 12 (11%) endometrial cancer, 11 (10%) ovarian cancer, 6 (6%) cervical squamous, 5 (5%) non-small cell lung cancer [NSCLC], 8 (8%) squamous cell head and neck cancer, 2 (2%) melanoma, and 28 (27%) other tumour types. Sixty-six (63%) of those patients were prospectively treated with a PI3K/AKT/mTOR inhibitor, and 11 (17%; 95% CI, 0.10–0.27) achieved a partial response (PR) and an additional 4 (6%; 95% CI, 0.02–0.15) had stable disease (SD) >6 months, strongly suggesting that tumours harbouring *PIK3CA* mutations are more sensitive to therapeutic targeting with PI3K/ AKT/mTOR pathway inhibitors (Janku et al 2012).

PIK3CA mutations are common in breast cancer (Stephens et al 2012; Banerji et al 2012), particularly in ER+ and HER2+ subtypes, where they occur with a frequency of >20%. Moreover, in breast cancer, co-incident mutations in RAS are very rare. *PIK3CA* mutations are also common in endometrial cancer, and occur in both endometrioid and serous histological subtypes with an overall frequency of ~53% (Levine, the cancer genome atlas 2nd annual scientific symposium). In ovarian cancer, mutations in *PIK3CA* are common in clear cell (frequency ~31%) and endometrioid (frequency ~13%) subtypes, but are rarely seen in high grade serous tumours (Willner et al 2007; and http://www.sanger.ac.uk/genetics/CGP/cosmic/). *KRAS* mutations also occur in 7% to 9% of clear cell and endometrioid subtypes, but the frequency of co-occurrence with *PIK3CA* mutations is unclear. However, in studies with PI3K/AKT/mTOR inhibitors in the clinic, objective responses have been seen in ovarian cancers with *PIK3CA* mutations that also carry *RAS* mutations, whereas in preclinical models and in patients with colorectal cancer, coincident *RAS* mutations appear to correlate with resistance (Janku et al 2012; Davies et al 2012). *PIK3CA* mutations are also found in 10-25% of cervical, gastric and colorectal carcinomas.

3.2.3 Rationale for Part D (*AKT1* mutation and other PI3K/AKT pathway aberrations)

AKT1 mutations are found at low frequency in a number of tumour types. The most common mutation is *E17K*, which has been shown to be transforming and increases localisation to the membrane where *AKT* is activated (Carpten et al 2007).

In a panel of 764 tumour samples the occurrence of *AKT1* (*E17K*) mutation was detected in 5.9% (16/273), 1.1% (1/88) and 0.6% (1 /155) of breast, colorectal and lung cancers, respectively (Bleeker et al 2008).

The *AKT1 E17K* mutations have been characterized in 1–8% of breast carcinomas, both ductal and lobular histotypes and are mutually exclusive with respect to the *PIK3CA E545K* or *H1047R* alleles (Carpten et al 2007). Cohen et al studied a series of 73 patients with endometrial carcinoma and detected *AKT1 E17K* mutation in 4% (3/73), mainly limited to

high grade, advanced stage tumours (G3, Stage2B, clear cellG3/; G3, Stage2B, serous and G3, Stage3A endometrioid adenocarcinomas, one each) suggesting a link of this mutation with a more aggressive cancer disease (Cohen et al 2010; Shoji et al 2009). Shoji et al found that *AKT1 (E17K)* mutant tumours do not harbour coexisting mutations in *PTEN*, *PIK3CA* or *KRAS* (Shoji et al 2009). A total of 709 NSCLC tumours from five independent studies detected *AKT1 E17K* mutation in 0.6% (4/709), and in the four studies that listed NSCLC cases with squamous cell carcinoma (SCC) histology, *AKT1 E17K* mutation was detected in 1.5% (3/193) of SCCs cases (Do et al 2010; Malanga et al 2008; Do et al 2008; Kim et al 2008).

Rare mutations in *AKT2* and *AKT3* have also been found in various cancers, although it is not known whether some of these are transforming. For example, *AKT2* mutations were found in 1/51 gastric and 2/79 lung cancers (Soung et al 2006), and in an independent study, in 2/43 non-small cell lung cancers (NSCLCs) (Parikh et al 2012). Mutations in *AKT3* have been reported in melanoma at 1.5% frequency (Davies et al 2008). In endometrial cancer, rare mutations in *AKT* and *AKT3* have been reported (Dutt et al 2009), whilst activating mutations in the regulatory subunits of *PI3K*, *PIK3R1* and *PIK3R2*, are common in endometrial cancer (Cheung et al 2011; Ulrick et al 2011).

During the course of the study new information may emerge relating to molecular aberrations that dysregulate the PI3K/AKT pathway. Provision is made in Part D for exploring the tolerability and anti-tumour activity of AZD5363 in patients whose tumours bear these aberrations as and when they are identified.

3.2.4 Rationale for Part E (*AKT1* mutation) – AZD5363 + fulvestrant combination

It has recently been observed that suppression of PI3K pathway signalling results in induction of ER-dependent transcriptional activity, including increased expression of genes containing ER-binding sites and increased occupancy by the ER of promoter regions of upregulated genes. Additionally expression of ER mRNA and protein were also increased following PI3K pathway inhibition. The findings have been confirmed in animal model xenografts, patient-derived animal models, and in tumours from patients undergoing treatment with a PI3K alpha inhibitor, as well as an AKT inhibitor (AZD5363). These results suggest that PI3K pathway blockade in ER-positive breast cancer results in an ER-dependent transcriptional program that may be reversed with anti-hormonal therapies, and that simultaneous blockade of the PI3K pathway and ER signalling may be needed for optimal treatment of ER-positive breast tumours with over-activation of the PI3K pathway (Bosch et al 2015, Ribas et al 2015).

Fulvestrant is an oestrogen receptor antagonist indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women, supplied as an injection for intramuscular administration.

On the basis of the biological evidence above and given the established combination dose for AZD5363 and fulvestrant it is considered biologically and clinically reasonable to permit the exploration of AZD5363 in combination with fulvestrant therapy where fulvestrant is considered to be a background therapeutic modality in ER positive advanced or metastatic

breast cancer patients whose tumours harbour *AKT1* or *PTEN* mutations and who have exhibited prior fulvestrant resistance or have not received prior fulvestrant. (Hyman et al 2015).

3.2.5 Rationale for Part F (*PTEN* mutation) – AZD5363 + fulvestrant combination

PTEN is one of the most frequently mutated tumour suppressor genes in human cancer and encodes a dual specific phosphatase that plays a tumour suppressor role by negatively regulating the PI3K/AKT/mTOR signalling pathways involved in cell proliferation, apoptosis, migration, genomic instability and metabolism (Salmena et al 2008). PTEN can be downregulated by various mechanisms including genetic alterations, transcription, translation, and post-translational modification and loss of PTEN function results in activation of the PI3K/AKT/mTOR pathway.

In breast cancers the prevalence of somatic *PTEN* alterations detected using next-generation sequencing is ~5% (Cancer Genome Atlas Network 2012; Jeselsohn et al 2014). A recent report on a large breast cancer cohort suggested a possible enrichment of *PTEN* alterations in ER+ve metastatic tumours compared to primaries (Yates et al 2015).

On that basis and in light of the information provided in the rationale for Part E it is considered equally important to explore the efficacy of the AZD5363 + fulvestrant combination in patients with ER positive advanced or metastatic breast cancer whose tumours harbour selected *PTEN* genomic alterations with known or predicted functional significance.

A list of *PTEN* alterations considered highly likely to be deleterious to PTEN function and therefore determining eligibility for the current clinical trial has been collated on the basis of the currently published literature for causal associations between pathogenicity and somatic or germline aberrations. These alterations together with the description of the current rule-set upon which selection of alterations has been based, will be provided in the study lab manual. The list of selected *PTEN* alterations encompasses any aberration which ablates function of the gene, e.g. point or multi-nucleotide substitutions, insertions and deletions, rearrangements and loss of part of or the entire gene locus, coding or non-coding variants. The evidence that these alterations are associated with loss of PTEN function could include the functional characterization of these alterations according to reports in the scientific literature as biochemical evidence (in vitro experiments). That is the variations alter the function of the protein. They might also be derived from predicted functional information determined by bioinformatics analysis or computational modelling. An assessment based upon the pathogenic significance of *PTEN* alterations in familial disorders as described in the literature was also employed. This list may be updated on the basis of emerging data on the functional impact of specific mutations and subject to agreement between AZ and the PI.

4 PATIENT SELECTION AND RESTRICTIONS

Investigators should keep a record i.e., 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 18 years

3. **Parts A and B only (Completed):** Histological or cytological confirmation of a solid malignant tumour, excluding lymphoma, that is refractory to standard therapies or for which no standard therapies exist.

   Part C only: Histological or cytological confirmation of ER+ or HER2+ breast cancer, ovarian, cervical or endometrial cancer, or other solid malignant tumour, excluding lymphoma, which is refractory to standard therapies or for which no standard therapies exist, and confirmation of the presence of a *PIK3CA* mutation (see Section 6.5 for specific details regarding screening procedures).

   Part D only:

   Histological or cytological confirmation of ER+ or HER2+ breast cancer, ovarian, cervical or endometrial cancer, which is refractory to standard therapies or for which no standard therapies exist, and confirmation of the presence of an *AKT1* mutation (see Section 6.5 for specific details regarding screening procedures).

   OR

   Histological or cytological confirmation of a solid malignant tumour, excluding lymphoma, which is refractory to standard therapies or for which no standard therapies exist, which bears a molecular aberration that leads to dysregulation of the PI3K/AKT pathway (see Section 6.5 for specific details regarding screening procedures).

   Part E only: Histological or cytological confirmation of ER positive+ advanced or metastatic breast cancer and confirmation of the presence of an *AKT1* mutation (see scetion 6.5 for specific details regarding screening procedures).

Part F only: Histological or cytological confirmation of ER positive+ advanced or metastatic breast cancer and confirmation of the presence of one of the mutations in *PTEN* listed in the study lab manual (see Section 6.5 for specific details regarding screening procedures).

4. **Parts A & B (Completed)** – At least one lesion (measurable and / or non-measurable) that can be accurately assessed at baseline by computerised tomography magnetic resonance imaging or plain X-ray and is suitable for repeated assessment .

   Parts C, D, E and F – At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

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

7. Male patients should be willing to use barrier contraception i.e. condoms

8. Parts C, D, E and F: Provision of a tumour and blood sample for central mutation testing.

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 (fasting is defined as no calorific intake for at least 8 hours)

- Glycosylated haemoglobin (HbA1c) >8% (64 mmol/mol) [1]

[1] conversion equation for HbA1C [IFCC-HbA1C (mmol/mol) = [DCCT-HbA1C (%) – 2.15] x 10.929]

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 2 weeks before the first dose of study treatment (3 weeks for St John's Wort). See Appendix H
   - 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 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) 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. 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 electrocardiogram (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 New York Heart Association (NYHA) Grade ≥2

- Uncontrolled hypotension – Systolic blood pressure (BP) <90mmHg and/or diastolic BP <50mmHg

- 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 < 90 g/L

- ALT > 2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases, or >5 times ULN in presence of liver metastases.

- AST > 2.5 times ULN if no demonstrable liver metastases, or >5 times ULN in presence of liver metastases.

- *Total bilirubin > 1.5 times ULN (* Patients with confirmed Gilbert's syndrome may be included in the study)

- 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. Part C: triple negative breast cancer

12. Parts C and D: where known, other solid tumours (ie, not breast or gynaecological) should be negative for mutations of *KRAS, NRAS, HRAS* and *BRAF*

13. Part C: Any prior treatment with PI3K inhibitors, mixed PI3K/mTOR inhibitors or AKT inhibitors. Prior exposure to rapalogs or pure mTOR kinase inhibitors is allowed (see Appendix H)

14. Part D, E and F: Any prior treatment with AKT inhibitors (catalytic inhibitors eg GDC0068). Prior exposure to all other agents on the pathway including allosteric AKT inhibitors (eg, MK2206) is allowed (see Appendix H).

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

15. Previous allogeneic bone marrow transplant

16. 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 (Parts A, B, C, D, E and F).

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.

- Male 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) for 16 weeks after discontinuation of study drug. 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 to avoid excessive sun exposure and use adequate screening protection. The use of sunbeds and tanning booths should be avoided.

5. During Cycle 1, following discharge from the clinic, 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 they must contact the clinic for further investigation of this result see blood glucose intervention plan, Figure 8.

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. In the case of patients with ER positive breast cancer entered in to Part

D (breast) of the study co-administration of fulvestrant may be permitted based on the following considerations:

- The patient's disease must have reached the point of formal RECIST tumour progression during the administration of AZD5363 monotherapy

- The investigator considers that the administration of fulvestrant is an appropriate course of action considering the speed and location of disease progression and any other clinical factors that might influence a decision concerning the appropriateness of administering fulvestrant in combination with AZD5363

Where fulvestrant is administered in combination with AZD5363, fulvestrant should be administered according to its approved dose of 500 mg intramuscularly on days 1, 15, 29 and once monthly thereafter and AZD5363 should be administered at a dose of 400mg bd po on a 4 days on / 3 days off schedule. Patients who had previously required dose reduction from the starting AZD5363 monotherapy dose (480mg bd po on a 4 days on / 3 days off schedule) may have AZD5363 started at a dose of 320mg bd po on a 4 days on / 3 days schedule in combination with fulvestrant at the discretion of the treating investigator and in order to maximize patient safety. In these cases of combination treatment patients will continue to be followed in accordance with the D3610C00001 schedule of assessments for safety and efficacy until subsequent progression.

In the cases of Parts E and F fulvestrant should be administered according to its approved dose of 500 mg intramuscularly on days 1, 15, 29 and once monthly thereafter and AZD5363 should be administered at a dose of 400mg bd po on a 4 days on / 3 days off schedule.

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.

Patients already receiving erythropoietin at the time of screening for the study may continue it providing they have been receiving it for more than one month at the time study treatment is started. Prophylactic erythropoietin should not be started during Cycle 1 of the study but may be started during Cycle 2 and after.

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 or RANKL inhibitors 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.

4.3.2 Use of Metformin

Metformin is recommended for the management of hyperglycaemia occurring in patients participating in studies of AZD5363. Investigators should exercise caution in the dosing and management of patients receiving the metformin/AZD5363 combination and must be vigilant for signs of renal impairment and metformin toxicity, such as lactic acidosis and hypoglycaemia, namely: lethargy, hypotension, poor urine output, drowsiness, irritation, tachypnoea, sweating, diarrhoea, and vomiting.

Metformin should only be given on the days when AZD5363 is also given (the half-life of AZD5363 is approximately 8 to15 hours), and should be withdrawn when treatment with AZD5363 is also withdrawn, unless otherwise clinically indicated.

Due to the potential interaction of metformin and AZD5363 by inhibition of OCT2, patients should attend for clinical assessment when taking both AZD5363 and metformin concurrently, including monitoring of serum creatinine. Creatinine assessments should be conducted as part of the routine clinical chemistry with additional monitoring of creatinine at the discretion of the investigator.

5 STUDY TREATMENT AND CONDUCT

5.1 Treatment

AZD5363 will be administered orally, twice daily, following a single initial dose and 3 to 7 day washout (Part A only). **Part A has been completed.**

5.1.1 Identity of investigational product

The investigational product, AZD5363, will be manufactured within a concentration range of 5 to 165 mg capsules and 80 to 320 mg tablets.

The investigational product will be supplied by AstraZeneca R&D Supply Chain (or contract research organisation) as individual patient packs. 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. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

All supplies and labelling will be prepared in accordance with GMP and local regulatory guidelines by the AstraZeneca R&D Supply Chain (or contract research organisation).

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

5.1.2 Dosing instructions

AZD5363 will be administered orally, twice daily, following a single initial dose and 3 to 7 day washout (Parts A and B only). **Part A and B have been completed.**

A twice daily regimen of AZD5363 oral formulation will be given on intermittent weekly dosing schedule .

Twice daily doses should be taken at approximately the same time each morning and evening approximately 12 hours apart (in Parts A and B this is applicable following completion of the single dose administration).

Where possible, all doses of AZD5363 should be taken, at approximately the same times each day, with water in a fasted state from at least 2 hours prior to the dose to at least 1 hour post-dose. Please also refer to Restrictions (Section 4.3) for further guidance regarding patient fasting status on study assessment days.

Should a patient miss a scheduled dose, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time the missed dose should not be taken and the patient should take their allotted dose at the next scheduled time. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the AZD5363 capsule(s) / tablets(s) on time.

5.1.3 Starting dose, dose escalation scheme and stopping criteria

5.1.3.1 Starting dose, dose escalation scheme and stopping criteria: Part A (dose escalation). (Part A has been completed)

Single dose administration for study Part A, Schedule 1, will begin at 80 mg. Twice daily dosing for study Part A, Schedule 1 will begin at 160 mg (as 80 mg per dose). A cycle of study treatment (excluding initial single dose under part A) will be defined as 21 days. Cycle 1 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.

For the first cohort in each schedule, a delay of at least 7 days will be mandatory between administration of first patient first (single) dose to administration of first (single) dose for any subsequent patients. Providing there are no serious or unexplained safety issues during this delay period, as determined by the SRC, dosing of the remainder of the cohort will continue as suitable patients are identified. However, should ambiguous findings occur, the SRC may choose to stagger the start of dosing for the remainder of the cohort of patients.

For subsequent cohorts in each schedule, the SRC may implement dose staggering, based upon emerging safety, tolerability and/or PK findings and clinical judgement. Where dose

staggering is implemented, the SRC will determine the duration of any post- first dose delay. The requirement for, and duration of, dose staggering will be a standard agenda item at each applicable SRC dose escalation meeting.

There will be a minimum of 2 days between conduct of the last patient assessment required for SRC review from one cohort and the start of dosing in the subsequent cohort.

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 5.1.5) 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 and PK data prior to a dose escalation decision being made. The planned dose escalation scheme may be amended with reference to emerging data. Escalations will not exceed doubling of the dose in principle. However, up to a quadrupling of dosing may be permitted in the first two escalations only (cohorts 1 and 2 of continuous dosing Schedule 1) – if the drug concentrations of the first or second level are not measurable or are deemed to be far from predicted drug exposure (greater than 2-fold difference) and there have been no significant safety or tolerability issues.

There will be no intra-patient dose escalations.

The dose for subsequent cohorts, the retesting of a dose (including the selection of another dose lower than the originally defined RD), 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 5.1.8).

5.1.3.2 Dose/schedule: Part B (dose expansion). (Part B has been completed)

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

Additional patients will be enrolled to ensure a total of at least 12 patients complete the first 21-day cycle of assessments at the RD and selected schedule. 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.

5.1.3.3 Dose/schedule: Parts C and D (PI3K/AKT pathway aberrations)

In both Parts C and D, patients will be allocated to receive AZD5363 480 mg twice-daily, 4 days on 3 days off dosing as capsules or as dose-equivalent tablets. A tablet formulation may be applied in all sites or in selected sites only. Recruitment to each cohort may continue to a maximum of 120 patients, however may be terminated based on interim reviews of the data after 20 and 40 patients have been followed for a minimum of 12 weeks (see Section 7.2 for details).

An alternative dosing schedule of twice-daily 800 mg or 640 mg dosing in a 2 days on, 5 days off regimen may be explored for one or more of the Part C or D cohorts. Exploration of this alternative dose and schedule may be conducted in parallel with, or as an alternative to, a cohort which is partially complete in respect of the twice-daily 480 mg 4 days on, 3 days off regimen. Any decision to introduce additional cohorts in order to investigate the alternative dosing regimen will be at the discretion of AstraZeneca after discussion with the SRC.

5.1.3.4 Dose/schedule: Parts E and F

In both Parts E and F, patients will be allocated to receive AZD5363 400 mg twice-daily, 4 days on 3 days off dosing as tablets, commencing on day 1. Fulvestrant as background therapy will be administered according to its approved dose of 500 mg intramuscularly on days 1, 15, 29 and once monthly thereafter.

5.1.4 Method of assigning patients to dosing schedules

Written informed consent will be obtained before enrolment, and the patients identified with an enrolment number. The enrolment number is a 7-digit number, ENNNNXXX, N being the centre number, and XXX being the patients' enrolment number at the centre. 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.

As patients consent for the study they will be allocated sequentially, in the order of notification to AstraZeneca, to each open dosing schedule by a central coordinator at AstraZeneca, and will be assigned separate four digit allocation identification numbers as shown in Table 1.

Table 1 Patient numbers

Part	Cancer type	Schedule	Patient numbers
A and B	Solid tumours	1 (continuous)	0101
A and B	Solid tumours	2 (intermittent)	0201
A and B	Solid tumours	3 (intermittent)	0301
C	Breast cancer *PIK3CA* mutation positive	480 mg bd 4 days on, 3 days off	1001
C	Breast cancer *PIK3CA* mutation positive	Alternative intermittent schedule[a]	1501
C	Gynaecological cancer *PIK3CA* mutation positive	480 mg bd 4 days on, 3 days off	2001
C	Gynaecological cancer *PIK3CA* mutation positive	Alternative intermittent schedule[a]	2501
C	Other solid tumours *PIK3CA* mutation positive	480 mg bd 4 days on, 3 days off	3001
C	Other solid tumours *PIK3CA* mutation positive	Alternative intermittent schedule[a]	3501
D	Breast cancer *AKT1* mutation positive	480 mg bd 4 days on, 3 days off	4001
D	Breast cancer *AKT1* mutation positive	Alternative intermittent schedule[a]	4501
D	Gynaecological cancer *AKT1* mutation positive	480 mg bd 4 days on, 3 days off	5001
D	Gynaecological cancer *AKT1* mutation positive	Alternative intermittent schedule[a]	5501
D	Breast, gynaecological and other solid tumours with PI3K/AKT pathway abberation.	480 mg bd 4 days on, 3 days off	6001
D	Breast, gynaecological and other solid tumours with PI3K/AKT pathway abberation.	Alternative intermittent schedule[a]	6501
E_R	Breast cancer *AKT1* mutation positive	400 mg bd 4 days on, 3 days off	7001
E_R	Breast cancer *AKT1* mutation positive	Alternative intermittent schedule[a]	7251
E_D	Breast cancer *AKT1* mutation positive	400 mg bd 4 days on, 3 days off	7501
E_D	Breast cancer *AKT1* mutation positive	Alternative intermittent schedule[a]	7751
F_R	Breast cancer *PTEN* mutation positive	400 mg bd 4 days on, 3 days off	8001
F_R	Breast cancer *PTEN* mutation positive	Alternative intermittent schedule[a]	8251
F_D	Breast cancer *PTEN* mutation positive	400 mg bd 4 days on, 3 days off	8501
F_D	Breast cancer *PTEN* mutation positive	Alternative intermittent schedule[a]	8751

a Alternative intermittent schedule in a 2 days on, 5 days off regimen, if required.

Therefore the first patient entering Parts A and B schedule 1 will be numbered 0101, the second will be 0102 and so on. Under this system:

During the initial phase of part A **(completed)**, dose escalation, all patients will be allocated to cohorts under Schedule 1. This will continue up to the Scheduling Dose Decision (SDD)

Following the SDD, new patients will be allocated sequentially to cohorts in Schedules 1 or 2.

If Schedule 3 is implemented, new patients will be allocated sequentially to cohorts 1, 2 or 3.

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 Part B **(completed)**, 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.

5.1.5 Part A (completed): Definition of dose-limiting toxicity

A DLT is defined as any toxicity 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

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) for more than 1 week, despite optimal intervention which is not attributable to another co-morbidity
   - Grade 4 hyperglycaemia (glucose >27.8 mmol/L)
   - AST or ALT >10x ULN and AZD5363 is considered the most likely cause
   - AST or ALT >8x ULN, in combination with doubling of 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 of any grade without clinical sequelae or clinical significance.

5.1.6 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.

5.1.7 Definition of evaluable patient

For decisions on dose escalation in Part A, 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 first 21 day cycle

or

has experienced a DLT during the first 21 day cycle.

Parts C, D, E and F will be assessed on an intent-to-treat basis (See Section 7.7).

5.1.8 Safety Review Committee

After each dose level during the dose escalation phase of the study (Part A), a SRC will evaluate the safety and tolerability and PK of AZD5363 to decide the next dose.

In the dose expansion phase (Part B) the SRC will review safety and tolerability data on an ongoing basis. At any time the SRC have the option to propose the initiation of an additional cohort (at a lower dose or a different dosing regimen).

In Parts C, D, E and F the SRC will review safety and tolerability data on an ongoing basis. At any time the SRC has the option to propose an alternative dosing schedule of twice-daily

640 mg in a 2 days on, 5 days off regimen, either within the same cohort as the first schedule tested, or as an additional cohort.

The SRC will consist of:

Study Team Physician, who will chair the committee, or delegate

Principal Investigator or delegate from each investigational site participating in Parts A and B.

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 Clinical Pharmacology Scientist, Clinical Pharmacometrician, Study Statistician, Patient Safety Scientist, and Study 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. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

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 PDc 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 5.1.3.1
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. Revise the dosing schedule for the subsequent cohort (intermittent scheduling arm only)
5. Define the NTD, MTD (where 6 evaluable patients assessed) or RD
6. 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.

5.1.9 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 7).

For Parts C, D, E and F, patients should receive dose reductions in 80 mg decrements and should have no more than 2 dose reductions. Patients who have had one or two dose reductions and who have demonstrated an acceptable response to the dose interruption may restart at their prior dose, at the discretion of the Investigator.

If the toxicity resolves or reverts to ≤ CTCAE 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 7). 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 7). Patients who are at the lowest possible dose i.e., in Cohort 1 or who have their dose previously reduced to the Cohort 1 dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

For all other events, if the toxicity does not resolve to ≤ CTCAE grade 2 after 14 days (except for rash, when a 28 day interruption is permitted), then the patient should be discontinued from treatment and observed until resolution of the toxicity.

If a patient reports urinary glucose present during home testing (see Section 4.3) the patient should be advised to attend the clinic the same day to have repeat urinalysis, confirmation of blood glucose and blood ketone results, and to determine the fasting status and any related symptomatology. Subsequent specific management of the hyperglycaemia will be according to local; however, the principles in the blood glucose intervention plan (see Figure 8) should be followed. General advice based upon previous clinical experience with related agents suggests:

Initial medical intervention should be an oral-antidiabetic agent e.g. metformin per local prescribing information, on days when AZD5363 is given, unless otherwise clinically indicated.

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

Following discharge from the clinic, any patients experiencing symptoms consistent with acute liver dysfunction such as unexplained pruritus, 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 according to local practice, however, the principles of the hepatotoxicity management algorithm (Figure 9) and the FDA Draft Guidance for evaluation of Drug-Induced Liver Injury (FDA 2009) should be followed. If a patient exhibits an AST, ALT result in excess of 10 x ULN, or AST or ALT in excess of 8 x ULN in combination with a doubling of bilirubin from baseline, which is considered to be related to study drug, they will not be permitted to restart study treatment. Refer to Section 5.3.2, liver and pancreas for the monitoring rationale.

If a patient experiences elevated blood glucose levels, guidance provided in Figure 8 should be followed.

If a patient experiences a maculo-papular rash, guidance provided in Figure 10 should be followed.

Figure 7 Toxicity management algorithm

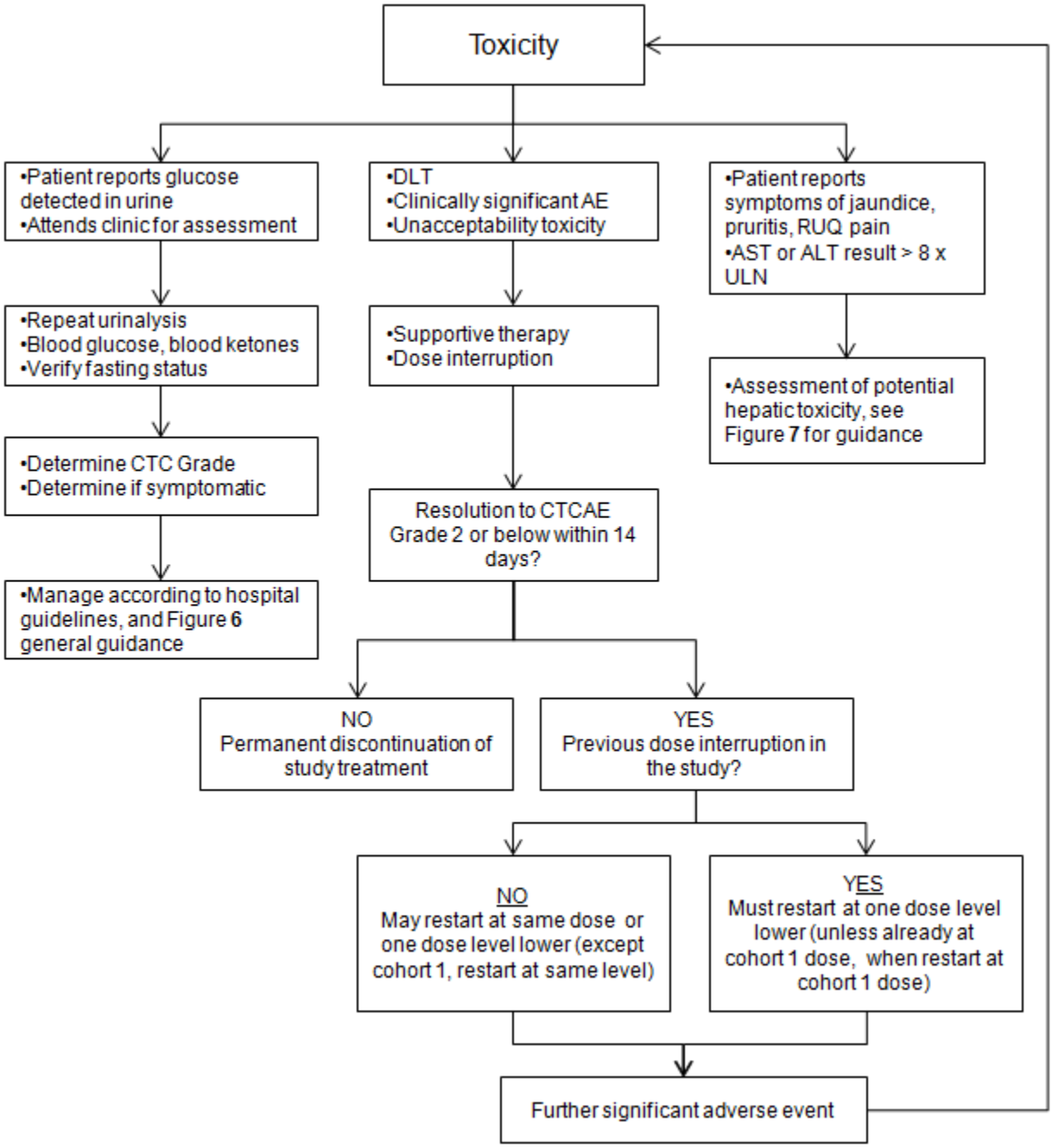
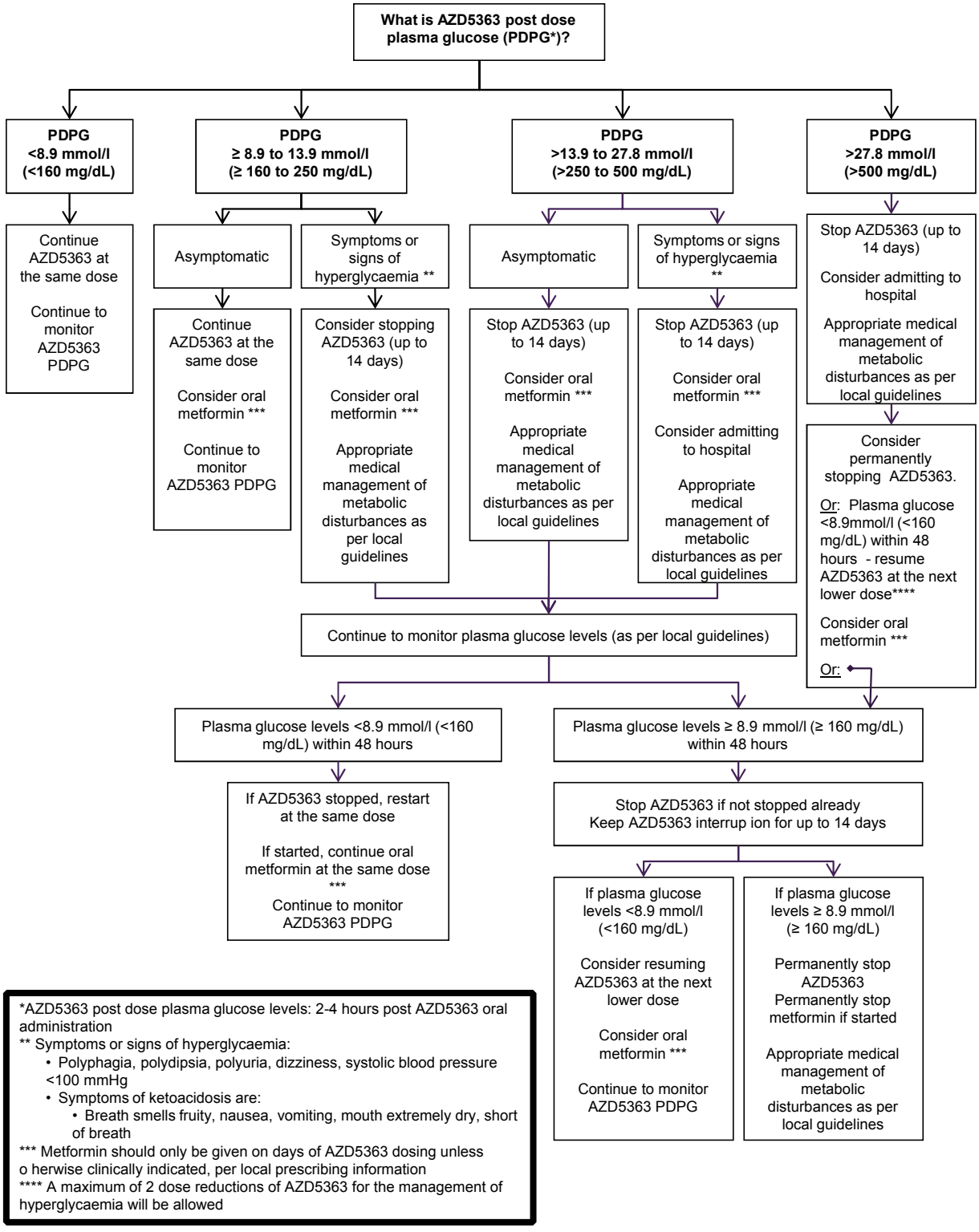


Figure 8 Blood glucose intervention plan



*AZD5363 post dose plasma glucose levels: 2-4 hours post AZD5363 oral administration
** Symptoms or signs of hyperglycaemia:
- Polyphagia, polydipsia, polyuria, dizziness, systolic blood pressure <100 mmHg
- Symptoms of ketoacidosis are:
  - Breath smells fruity, nausea, vomiting, mouth extremely dry, short of breath

*** Metformin should only be given on days of AZD5363 dosing unless o herwise clinically indicated, per local prescribing information
**** A maximum of 2 dose reductions of AZD5363 for the management of hyperglycaemia will be allowed

Figure 9 Hepatotoxicity management algorithm

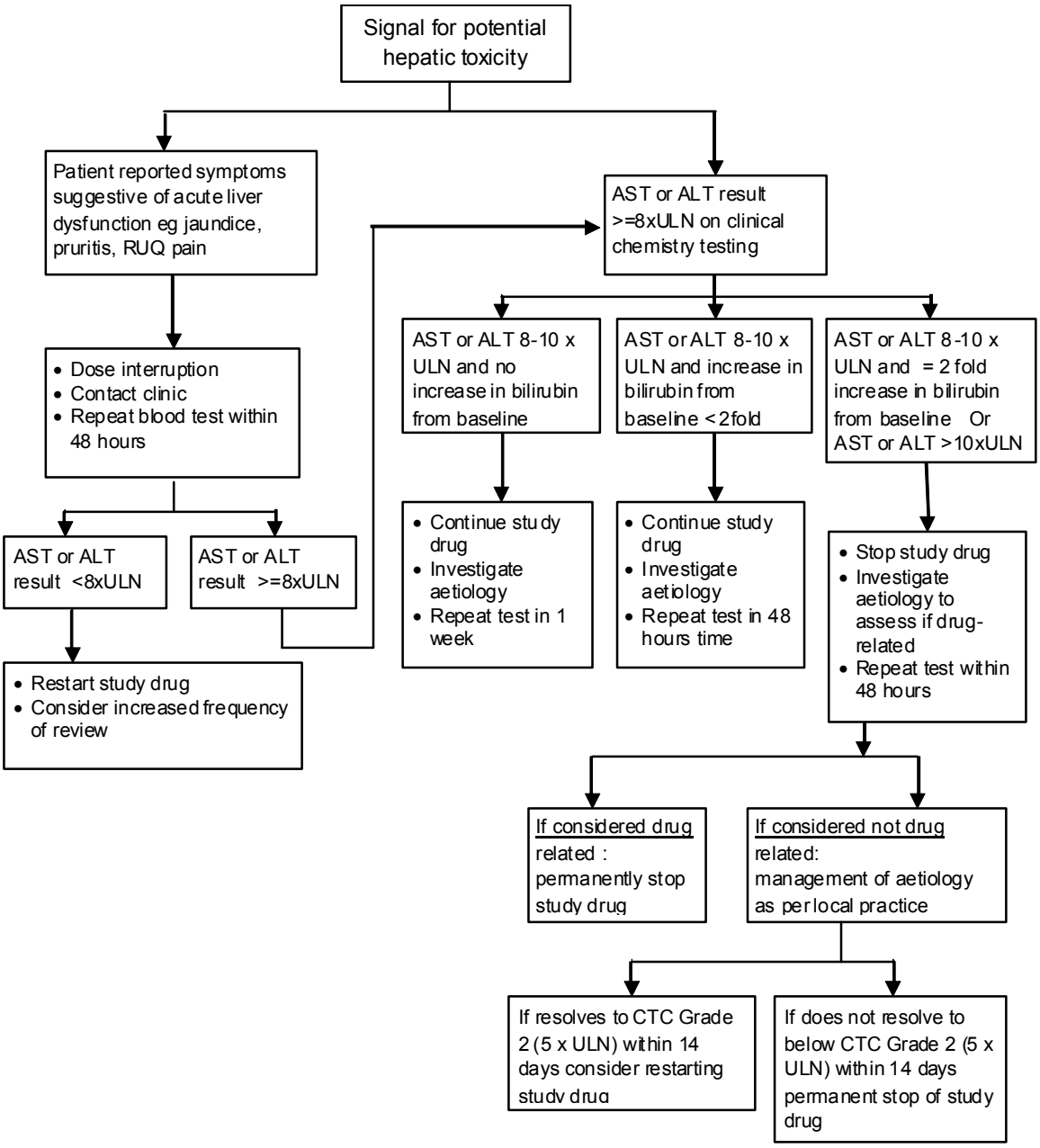
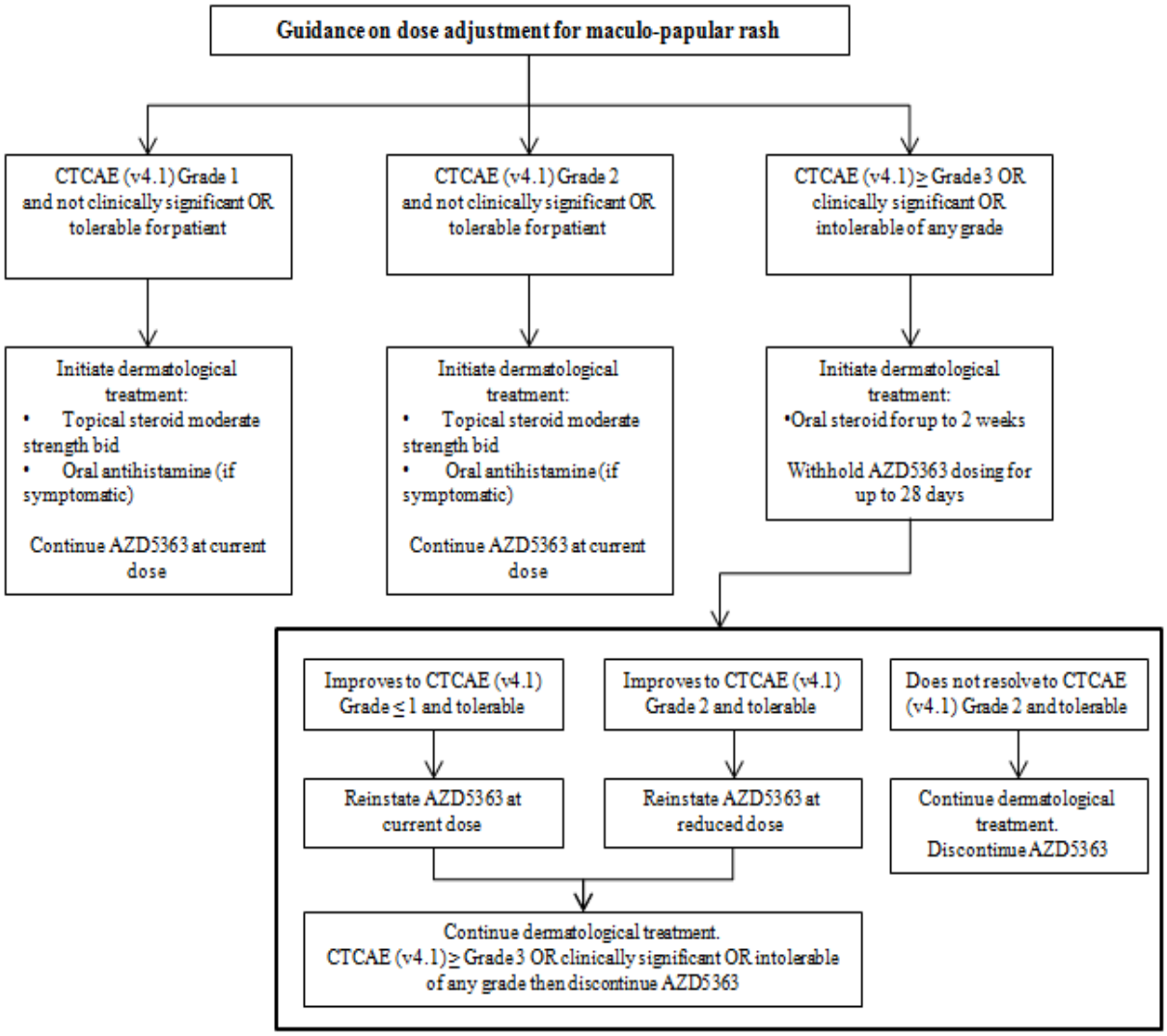


Figure 10 Maculo-Papular Rash management guidance



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.

5.1.10 Duration of therapy

Patients may continue to receive AZD5363 (plus fulvestrant if applicable) as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria.

5.1.11 Treatment compliance and accountability

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 CRF.

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

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

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

5.2.1 Rationale for the dosing regimen, dose escalation scheme and stopping criteria: Parts A and B (dose escalation and dose expansion) – Parts A and B have been completed.

A dose of 160 mg daily, administered as 80 mg two times a day (80 mg once for the initial single dose during Part A), is proposed as the starting dose in this FTIP study in patients with advanced cancer.

The dose escalation scheme will not exceed doubling of the dose in principle. However, up to a quadrupling of dosing may be permitted in the first two escalations only (Cohorts 1 and 2 of Schedule 1), if the drug concentrations of the first or second level are not measurable or are deemed to be far from predicted drug exposure. This will ensure that the fewest possible cohorts are exposed to AZD5363 below the presumed therapeutic dose. Non-clinical modelling provides only an approximate prediction of human PK, therefore the planned dose escalation scheme has the flexibility to be amended in light of emerging data.

As this is the first administration of this AKT inhibitor agent in humans, in the first cohort the administration of the first dose is separated by at least 7 days for the first 2 patients (see Section 5.1.3.1). This will ensure that any acute toxic effects of the administration will have sufficient time to be identified before additional patients are exposed. In addition, 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 ambiguous 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. The rate of enrolment to Phase I oncology studies is historically significantly slower than healthy volunteer studies, and it is unlikely that there will be rapid recruitment of the remaining 5 patients into a cohort after this initial period.

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 5.1.3.1).

There are no specific individual patient PK 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) 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 bilirubin from baseline levels, for urgent assessment of potential disease progression or acute liver dysfunction.

5.2.2 Rationale for the dosing regimen: Parts C and D (PI3K/AKT pathway aberrations)

Emerging data from the continuous and intermittent doses schedules parts of studies D3610C00001 (Western) and D3610C00004 (Asia) showed the following data:

AZD5363 320 mg bd continuous dosing regimen was considered not tolerated by the SRC in study D3610C00004 (Asia) as 2 out of 5 patients presented DLTs of diarrhoea. In Study D3610C00001 (Western), 3 out of 11 patients presented DLTs of maculo-papular rash. This dose and schedule will not be continued further.

AZD5363 480 mg bd given for 4 days on and 3 days off dosing in a weekly based regimen was considered tolerated by the SRC in both D3610C00001 and D3610C00004 as no patients presented any DLTs out of the 11 patients dosed in this cohort level.

AZD5363 640 mg bd given for 2 days on and 5 days off in a weekly based regimen, being only tested in D3610C00001 (Western), was considered tolerated by the SRC. The 800 mg bd dose level cohort reported 1 DLT (hyperglycaemia) out of 6 patients and is being expanded.

This part of the study will start with AZD5363 480 mg bd 4 days on 3 days off in a weekly based regimen, however the SRC may elect to test AZD5363 800 mg or 640 mg bd in a 2 days on and 5 days off regimen, based on the emergent safety, tolerability and efficacy data from the AZD5363 ongoing studies.

5.2.3 Rationale for the dosing regimen: Parts E and F

"FAKTION", a phase 1b/2 randomised placebo controlled trial of fulvestrant +/- AZD5363 in postmenopausal women with advanced breast cancer previously treated with a third generation aromatase inhibitor is an ongoing clinical study being conducted by Drs Howell and Jones as an investigator-sponsored study (EudraCT Number: 2013-000898-68). FAKTION has established a combination MTD for fulvestrant and AZD5363. Dosing fulvestrant in FAKTION was at its licenced dose of 500 mg intramuscularly on days 1, 15, 29 and once monthly thereafter, and this study established the MTD for AZD5363 to be 400mg bid po in the 4 days on – 3 days off schedule with AZD5363. The adverse event profile observed in the Phase 1b part of FAKTION was consistent with the individual AE profiles of each drug and with no additional observations in relation to safety and tolerability. The randomised double-blind Phase 2 component of FAKTION commenced in March 2015 using the 400mg AZD5363 dose.

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 FTIP 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:

Glucose homeostasis

In order to reduce the potential risk of exacerbating abnormal glucose profiles, patients with type I or II diabetes mellitus (irrespective of management), fasting glucose ≥7mmol/L or HbA1C>8% at screening will be excluded from the study. Blood and urine sampling for

glucose and insulin profiles will be performed at the visits and times shown in Figure 11, Figure 12 and Sections 6.6.6, 6.6.8, and 6.6.9 **(Part A & B- now complete)** 6.6.10, (Part C & D). During the first cycle, urinary glucose will be tested at home twice weekly after patients are discharged from the clinic, with instructions regarding clinic contact on finding a high result. An algorithm for the management of hyperglycaemia is provided in Section 5.1.9, see Figure 8. In addition, because of the pharmacological activity of AZD5363 on glycolysis and insulin signalling, fasting lipid profiles (triglycerides, high density lipoprotein [HDL], low density lipoprotein [LDL] and cholesterol) will also be monitored at the times shown in Section 6.6.7. **(Part A & B – now complete)** and 6.6.11 (Part C, D, E and F).

Cardiovascular effects

Standard exclusion criteria for unstable cardiac conditions and risk factors for QT prolongation will be included in the clinical study protocol. Additional clarification is provided to exclude patients who have experienced coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA Grade ≥2 within the last six months; patients with an abnormal echocardiogram at baseline (LVEF below site lower limit of normal [LLN]); uncontrolled hypotension (systolic BP <90mmHg and/or diastolic BP <50mmHg). Patients will also be excluded if their potassium or sodium levels fall outside the normal range for the site.

In all patients, cardiac function will be monitored regularly throughout the study. Monitoring of pulse rate, systolic and diastolic blood pressure, ECG measurements and Troponin I and electrolytes will be performed at the visits and times shown in Figure 11 and Figure 12, Section 6.6.4.2 and 6.6.4.3. In addition a multiple gated acquisition (MUGA) scan or echocardiogram to assess LVEF will be conducted at the visits and times shown in Figure 11 and Figure 12, Section 6.6.5 and as clinically indicated as management of adverse events.

Haematopoietic system

Patients with inadequate bone marrow reserve as demonstrated by any of the following laboratory values (absolute neutrophil count <1.5 x 10^9/L; platelet count <100 x 10^9/L; haemoglobin <90 g/L) will be excluded from the study. Haematological parameters (including leucocytes, neutrophils, lymphocytes, haemoglobin and platelets) will be monitored as part of the standard laboratory safety assessment at the times shown in Section 6.6.6.and 6.6.10.

Liver and pancreas

In order to reduce the potential risk of acute liver necrosis, patients with evidence of severe or uncontrolled systemic liver disease including severe hepatic impairment, or abnormal liver enzymes at screening (AST or ALT >2.5 x ULN; total bilirubin >1.5 x ULN) are excluded from participating in the study. During the study, liver function tests will be monitored as part of the standard laboratory safety assessment at the times shown in Section 6.6.6. and 6.6.10. An algorithm for the investigation and management of patient reported symptoms of potential acute liver dysfunction and any liver transaminase results in excess of 8 x ULN occurring at any time during the study, is provided in Section 5.1.9, (see Figure 9) and should be used in

conjunction with the FDA Draft Guidance for the evaluation of Drug Induced Liver Injury (FDA 2009).

Hypothalamic-pituitary axis

Patients with potassium or sodium levels outside the normal range for the site will be excluded from participating in the study. During the study, sodium and potassium levels will be monitored as part of the standard laboratory safety assessment at the times shown in Section 6.6.6.and 6.6.10. In order to monitor for functional effects on the thyroid gland, thyroxine (T4) and thyroid stimulating hormone (TSH) levels will be measured as detailed in Section 6.6.6. and 6.6.10. [redacted] follicle stimulating hormone (FSH), oestrogen (females only) and testosterone (males only) levels will be will be measured as detailed in Section 6.6.6. and 6.6.10.

Renal effects

Patients with proteinuria (3+ on dipstick analysis or >500 mg/24 hours) or creatinine >1.5 times ULN concurrent with creatinine clearance <50 ml/min, will be excluded from the study. During the study, urine samples will be taken for the analysis of urinary blood, protein and glucose as part of the standard laboratory safety assessment at the visits shown in Figure 11 and Figure 12, Section 6.6.6. and 6.6.10. Urine microscopy (red blood cells, white blood cells, bacteria, casts and crystals) will be performed if urinalysis is abnormal. If 3+ proteinuria is identified by dipstick assessment, a 24-hour urine collection for quantification of protein excretion should be performed.

[redacted]

Reproductive organs

[redacted] no reproductive toxicology or teratogenic studies have been conducted with AZD5363 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation and women who are breast feeeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment. Male patients will be advised to arrange for freezing of sperm prior to the start of the study should they wish to father children at a later date.

CYP450 induction/inhibition

AZD5363 is a time dependent inhibitor of CYP3A4 which may result in increased exposure of drugs metabolized via CYP3A4 with the potential to increase the toxicity of these drugs when co-administered. AZD5363 is a substrate of CYP3A4 although data available to date suggests that glucuronidation may be the major metabolic route. Co-administration of CYP3A4 inhibitors may increase exposure to AZD5363 and hence potentially affect efficacy/toxicity and hence increase the risk of time dependent inhibition (and resultant toxicity of CYP3A4 substrates). In addition, co-administration of CYP3A4 inducers may decrease the exposure to AZD5363 and hence potentially affect efficacy. Finally, AZD5363 is a moderate inhibitor of CYP2D6. This may increase the exposure of drugs metabolized via CYP2D6 with the potential to increase the toxicity of these drugs when co-administered (Michalets 1998). The following restrictions will therefore be put in place in the study, please refer to Appendix H of this clinical study protocol for listings of relevant drugs:

Use of potent inhibitors or inducers of CYP3A4 within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort) should be avoided.

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.

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.

In addition, host genetic samples will be collected for retrospective analysis of CYP450 polymorphisms should PK outlying data be observed in the absence of confounding concomitant medications.

5.3.3 Current clinical information

To date, AZD5363 has been administered as a monotherapy to patients in two studies (D3610C00001 [Western] and D3610C00004 [Asia]). Preliminary unvalidated tolerability and anti-tumour activity data from these studies are presented in this section. The following schedules and doses have been used in the studies:

continuous dosing: 80 mg bd, 160 mg bd, 240 mg bd, 320 mg bd, 400 mg bd, 480 mg bd and 600 mg bd

intermittent dosing, 4 days on 3 days off: 480 mg bd and 640 mg bd

intermittent dosing, 2 days on 5 days off: 640 mg bd and 800 mg bd.

[redacted]

[redacted]

[redacted]

Further information on AZD5363 can be found in the Investigator's Brochure.

5.3.4 Overall benefit-risk assessment for the first-into-man study

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 either as monotherapy or in combination with fulvestrant as background therapy in these patient populations 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 FTIP phase I study support the oral administration of AZD5363 either as monotherapy or in combination with fulvestrant as background therapy 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 that in the opinion of the investigator the hyperglycaemia cannot be managed according to the principles in the blood glucose intervention plan (see Figure 8) or local clinical practice.

Patient experiences study drug related AST or ALT result >10 x ULN, or, AST or ALT >8 x ULN in combination with doubling in 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 5.1.7 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 6.10) 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 6.11.5.

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

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

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

5.4.2 Procedures for withdrawal from study

Patients are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen by an investigator and undergo the assessments and procedures scheduled for the post study assessment (see Section 6.6.12). Adverse events should be followed up (see Sections 6.7.3 and 6.7.4) and study drug should be returned by the patient.

5.5 Study timetable and end of study

The study started in Q4 2010.

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

All patients in Parts A and B have now discontinued investigational product. Data analysis for Parts A and B has been performed to allow the CSR for Parts A and B to be written.

In Parts C, D, E and F, emerging data will be kept under review by the SRC and AstraZeneca. In addition, there will be multiple interim analyses, evaluating responses within each of the individual Part C cohorts (section 3.1.2.3) and individual Part D (section 3.1.2.4), Part E (section 3.1.2.5) and Part F (section 3.1.2.6) cohorts. Analyses of data within each cohort in Part C, D, E and F may be performed separately or together.

In Parts C and D interim analyses will occur after approximately 20 and 40 patients in a specific cohort have been followed for 12 weeks or withdrawn from the study (Section 7.2.2). The data cut-off for each interim analysis will be defined as the earlier of 12 weeks (+/- 1 week) after the 20th or 40th patient evaluable for tumour assessments starts investigational product, or 28 days after the final patient discontinues investigational product.

In Parts E and F interim analyses will occur after approximately 12 patients in a specific cohort have been followed for 24 weeks or withdrawn from the study (Section 7.2.3). The data cut-off for each interim analysis will be defined as the earlier of 24 weeks (+/- 1 week) after the 12th patient evaluable for tumour assessments starts investigational product, or 28 days after the final patient discontinues investigational product.

Final analyses and reporting of all or individual cohorts in Parts C, D, E and F may be conducted separately or together. In any study Part or individual cohort in Part C and D, final analyses will be performed after the last patient recruited has been followed for 12 weeks (+/- 1 week), or following discontinuation of all subjects in Part C and/or Part D. In any study Part or individual cohort in Part E and F, final analyses will be performed after the last patient recruited has been followed for 24 weeks (+/- 1 week), or following discontinuation of all subjects in Part E and/or Part F. The CSR will be updated with separate addenda, for all or individual cohorts for Parts C, D, E and F, in line with final analyses in each study Part or individual cohort.

Any patients still receiving investigational product at the time of this final data cut-off will be able to continue to receive AZD5363 while deriving clinical benefit. Such patients will continue to be monitored and efficacy and safety assessments performed until the investigational product is discontinued. In addition, these patients should be followed up for 28 days after the last dose for any new reports of adverse events. A CSR Addendum will be prepared to summarise the additional efficacy and safety data collected between the final data cut-off and the end of the study.

6 STUDY PLAN AND COLLECTION OF STUDY VARIABLES

6.1 Study Plan: Parts A and B (dose escalation and dose expansion) – Now completed

Figure 11 Study Plan, Parts A and B only

Parts A and B	**Screen**	**Single dose**			**Twice-daily dose**				**IP disc-ontinued**	**28-day follow-up**	**Details in Section:**
		Cycle 0			**Cycle 1**			**Cycle 2-**			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Onwards**			
Activity Day	**-28 to –1**	**1**	**2**	**3**	**1**	9 **LWD**	**15 / LWD +7**	**1**			
Informed consent	X										Appendix D
Demography& baseline characteristics	X										6.6
Medical/surgical history	X										6.6
Inclusion / exclusion criteria	X										4
Physical examination	X	X			X		X	X	X		6.6.2
WHO performance status	X	X									6.6.3
Vital signs	X	X	X		X	X	X	X	X		6.6.4
ECG	X	X	X		X	X		X	X		6.6.4.3
MUGA / Echocardiogram	X							X	X		6.6.5
Haematology, Clinical chemistry, Urinalysis	X	X			X	X	X	X	X		6.6.6
Fasted Lipids		X						X	X		6.6.7
Glucose, insulin, insulin c-peptide		X				X	X	X	X		6.6.8

Figure 11 Study Plan, Parts A and B only

Parts A and B	**Screen**	**Single dose**			**Twice-daily dose**				**IP disc-ontinued**	**28-day follow-up**	**Details in Section:**
		Cycle 0			**Cycle 1**			**Cycle 2-**			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Onwards**			
Activity Day	**-28 to –1**	**1**	**2**	**3**	**1**	9 **LWD**	**15 / LWD +7**	**1**			
Glycosylated haemoglobin	X							X	X		6.6.6
Pregnancy test	X	X			X				X		6.6.6
PK blood samples		X	X	X	X	X	X				6.8
PK urine collection		X	X	X							6.8
PDc blood samples		X	X	X	X	X	X	X	X		6.10.1.5
Exploratory biomarker hair samples		X					X				6.10.1.5
Exploratory biomarker blood samples	X	X			X	X	X	X	X		6.10.1.5
Pharmacogenetics (optional)		X									6.10.2.1
RECIST Tumour assessments	X							X	X		6.12.1
Archival tumour sample (Optional)	X										6.10.1.1
Paired biopsy (optional)	X						X				6.10.1.2
Circulating tumour cells					X			X			6.10.1.5
Concomitant medication	X	X	X	X	X	X	X	X	X	X	4.3.1
Adverse events	X	→	→	→	→	→	→	→	→	→	6.7
Dispense/administer study drug		X			X	→	→	→			5.1

6.2 Study Plan: Parts C, D, E and F (PI3K/AKT pathway aberrations)

Figure 12 Study Plan, Parts C, D, E and F (4 on 3 off Intermittent Schedule)

Parts C, D, E and F	**Pre-Screen**	**Screen**	**Twice-daily dose**					**IP discontinued**	**28-day follow-up**	**Survival visits**	**Details in Section:**
			Cycle 1				**Cycle 2**				
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**onward**				
Activity/ Day **Visit Window**		**-28 to –1**	**1**	**2**	**4**	**11**	**1** **(+ or - 3 days)**				
Informed consent – molecular screen	X										Appendix D
Provision of archival tumour sample	X										6.5, 6.10.1.1
Provision of blood sample for ctDNA testing	X		X				X	X			6.5, 6.10.1.4, 6.10.1.5
Informed consent – study		X									Appendix D
Demography & baseline characteristics		X									6.6.1
Medical/surgical history		X									6.6.1
Inclusion / exclusion criteria		X									4
Physical examination		X	X		X	X	X	X			6.6.2
WHO performance status		X	X							X	6.6.3
Weight		X	X				X	X			6.6.4.1

Figure 12 Study Plan, Parts C, D, E and F (4 on 3 off Intermittent Schedule)											
Parts C, D, E and F	**Pre-Screen**	**Screen**	**Twice-daily dose**					**IP discontinued**	**28-day follow-up**	**Survival visits**	**Details in Section:**
			Cycle 1				**Cycle 2**				
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**onward**				
Activity/ Day **Visit Window**		**-28 to –1**	**1**	**2**	**4**	**11**	**1** **(+ or - 3 days)**				
Pulse Rate / Blood Pressure / ECG		X	X		X	X	X	X			6.6.4.3
MUGA / Echocardiogram		X					X	X			6.6.5
Lab safety assessments; Glucose, insulin, Clinical chemistry, Haematology,Urinalysis		X	X		X	X	X	X			6.6.10
Fasted Lipids			X				X	X			6.6.11
Glycosylated haemoglobin		X					X	X			6.6.10
Pregnancy test		X	X					X			6.6.10
PK blood samples			X			X					6.8.1
PDc blood samples			X			X					6.9.1
Pharmacogenetics (optional)			X								6.10.2.1
RECIST Tumour assessments		X					X				6.12.1
Tumour biopsy on progression (optional)								X			6.10.1.3

Figure 12 Study Plan, Parts C, D, E and F (4 on 3 off Intermittent Schedule)

Parts C, D, E and F	**Pre-Screen**	**Screen**	**Twice-daily dose**					**IP discontinued**	**28-day follow-up**	**Survival visits**	**Details in Section:**
			Cycle 1				**Cycle 2**				
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**onward**				
Activity/ Day **Visit Window**		**-28 to –1**	**1**	**2**	**4**	**11**	**1** **(+ or - 3 days)**				
Paired biopsy (optional)		X				X					6.10.1.2
Concomitant medication		X	X	X	X	X	X	X	X		4.3.1
Adverse events		X	→	→	→	→	→	→	X		6.7
Dispense/administer study drug			X	→	→	→	→	→			5.1
Survival assessments										X	6.13

6.3 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. Assessments 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 been used as an abbreviation in Parts A & B (Figure 11) and subsequently in this protocol. **(Parts A & B have completed).**

Parts C, D, E and F – The study plan in Figure 12 reflects the assessments listed under the intermittent 4 days on 3 days off schedule. If a 2 days on 5 day off schedule is studied as an alternative or in addition to the 4 days on 3 days off schedule in Parts C, D, E and F a separate schedule of assessments suitable for the 2 day dosing regimen will be provided seperately. The number and type of assessments will not place any greater burden on patients as the assessments will not be greater than those for patients receiving the 4 day regimen.

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

Parts A and B: Schedule 1: Under the continuous dosing regimen - assessments will be conducted, as detailed in Figure 11, on Day 8 and on Day 15 of Cycle 1.

Parts A and B: Schedules 2, 3: Under the intermittent dosing regimen - assessments will be conducted, as detailed in Figure 11 as follows:

- 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

Parts C, D, E and F Intermittent dosing:

Under the intermittent 4 on 3 off dosing regimen assessments will be conducted, as detailed in Figure 12.

Revised study plans will be provided following any subsequent revisions to the intermittent dosing schedule(s).

6.4 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 CRFs 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 Clinical Study Agreement.

The investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study site.

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

6.5 Confirmation of mutation status: Parts C, D, E and F only

PIK3CA and *AKT1* mutations have been associated with response to inhibitors of the PI3K/AKT pathway. Emerging data indicates mutations, and other molecular aberrations, in other genes in the PI3K/AKT pathway, such as *AKT2*, *AKT3*, *PIK3RI* and *PIK3R2* may dysregulate the PI3K/AKT pathway (see Section 3.2.3). Patient recruitment will be based on the confirmation of mutations, in *PIK3CA*, *AKT1*, *PTEN* and other genes, detected using established PCR-based technologies including allele specific amplification/discrimination, primer extension and next generation sequencing. Other molecular aberrations that lead to dysregulation of the PI3K/AKT may be identified by established methodologies such as FISH (fluorescent in situ hybridization), CISH (chromogenic in situ hybridization) and IHC (immunohistochemistry).

Cancer panel tests or other diagnostic platforms may provide the possibility of discovering other molecular aberrations in other genes in the PI3K/AKT pathway that may confer drug sensitivity. Patients whose tumours harbour such molecular aberrations in the PI3K/AKT pathway may be enrolled at the discretion of AstraZeneca.

[For patients in the United States of America, details of the testing methodology used to identify a mutation or other molecular aberration will be submitted to the US IND before the implementation of the proposed testing].

Patients with advanced or metastatic ER+ or HER2+ breast cancer or advanced or metastatic gynaecological or other advanced solid cancer

All patients enrolled into Part C, D, E and F of the study must provide pre-screening consent for mutation testing. Consent for pre-screening may be undertaken at any time. Pre-screening assessments, to determine the presence of mutations in *PIK3CA*, *AKT1, PTEN* or other molecular aberrations in the PI3K pathway, must be completed prior to main study consent and main study screening procedures.

All screening procedures agreed to as part of the main study consent are to be performed within 28 days of start of treatment as per study plan (Figure 12). The patient may re-consent if main screening procedures are not completed within the 28-day window. Re-consent may require that assessments are repeated in order to comply with the 28-day window for main study screening procedures.

Patients may complete the pre-screening consent process via one of the following scenarios;

1. **Consent to provide pre-existing local test result with subsequent central confirmatory test;** Patients may have a previously determined positive result for *PIK3CA, AKT1* or *PTEN* mutation, or other molecular aberration leading to dysregulation of the PI3K/AKT pathway.

   In this instance patients must provide;

   - Consent to access to the pre-existing local test result for mutation status of *PIK3CA , PTEN* or *AKT1*
   - Consent to the provision of a tumour sample (archival or fresh [FFPE])
   - Consent to the provision of a blood sample

   These will be collected for central confirmation of *PIK3CA, PTEN* or *AKT1* mutation, or other molecular aberration leading to dysregulation of the PI3K/AKT pathway. Where possible, the tumour sample provided for central confirmation (post randomisation) should be the same tissue sample as that used to determine mutation status locally.

2. **Consent to prospective local testing with subsequent central confirmatory test;** A patient's tumour mutation status may be determined by undertaking local testing of a blood and/ or tumour sample (archival or fresh [FFPE]) to establish a positive result for a *PIK3CA, PTEN* or *AKT1* mutation, or other molecular aberration leading to dysregulation of the PI3K/AKT pathway.

   In this instance patients must provide;

   - Consent to provide either the blood and/ or tumour sample required to perform the local testing
   - Consent to the provision of a tumour sample (archival or fresh [FFPE]) to perform central confirmatory testing
   - Consent to the provision of blood sample to perform central confirmatory testing

   These will be collected for testing of *PIK3CA, PTEN* or *AKT1* mutation, or other molecular aberration leading to dysregulation of the PI3K/AKT pathway. Where possible, the tumour sample provided for central confirmation (post randomisation) should be the same tissue sample as that used to determine mutation status locally.

3. **Consent to prospective central testing;** Prospective central testing is currently only available for patients with advanced or metastatic ER+ or HER2+ breast cancer only.

   For breast cancer, a patient's tumour mutation status may be determined by undertaking central testing of a blood and tumour sample (archival or fresh [FFPE]) to establish a positive *PIK3CA* or *AKT1* mutation, or other molecular aberration leading to dysregulation of the PI3K/AKT pathway. (Appendix I)

   In this instance patients must provide;

   – Consent to the provision of a tumour sample (archival or fresh [FFPE])

   – Consent to the provision of a blood sample

   This option is not currently available for patients with **advanced or metastatic gynaecological or other advanced solid cancer** but may be available in certain circumstances in the future with agreement from the global study team. If an agreement to perform prospective central testing for these patients is reached with the global team for your site, the requirements detailed in the 2 bullet points above will apply.

The central testing option is currently available for the detection of *PIK3CA* mutations and the most common mutation (E17K) in *AKT1* only. There is currently no provision for prospective central testing for alterations in *PTEN*. If an agreement to perform prospective central testing for these mutations is reached with the global team for your site, the requirements detailed in the 2 bullet points above will apply.

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

6.6 Safety procedures

The timing and frequency of safety evaluations may be revised, in consultation with the SRC, in response to emerging data and with reference to changes to intermittent dosing schedules.

6.6.1 Enrolment and screening

At enrolment, each potential patient will provide informed consent prior to starting any study specific procedures (see Appendix D of this Clinical Study Protocol for Ethics and Regulatory Requirements).

Each potential patient is assigned a unique enrolment number. If a patient withdraws from the study, then the enrolment code cannot be reused.

Demographic data and other characteristics will be recorded and will include date of birth, gender, race and smoking history.

A standard medical, medication and surgical history will be obtained with review of the selection criteria with the patient.

Each patient will undergo screening (see Study Plans Figure 11 and Figure 12) during the 28 days prior to admission to confirm eligibility (see Sections 4.1, 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.

The tumour receptor status (ER, PR and HER2) for all breast cancer patients enrolled into Parts C, D, E and F will be captured.

6.6.2 Physical examination (all Parts)

(Parts A & B - completed)

A complete physical examination will be performed at the visits as indicated in the Study Plan (see Figure 11) at the times shown in Table 2.

Table 2 Physical examination: Parts A and B only (completed)

	Screening	Cycle 0	Cycle 1		Cycle 2 Onwards	Discontinuation
		Day 1	Day 1	Day 15 / LWD + 7	Day 1	
Screening	X					
Predose		X	X	X	X	
Any time of the day						X

Physical examination (Parts C, D, E & F)

A complete physical examination will be performed at the visits as indicated in the Study Plan (see Figure 12,) at the times shown in Table 3

Table 3 Physical examination: Parts C, D, E and F only

	Screening	Cycle 1			Cycle 2 Onwards	Discontinuation
		Day 1	Day 4	Day 11	Day 1	
Screening	X					
Predose		X	X	X	X	
Any time of the day						X

6.6.3 WHO performance status (all Parts)

Performance status will be assessed at screening, prior to the first dose of study treatment and for Parts C, D, E and F only at survival visits, 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.

6.6.4 Vital signs (all Parts)

6.6.4.1 Weight (all Parts)

For Parts A, B, C, D, E and F, 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

6.6.4.2 Pulse rate, blood pressure and ECG (Parts A & B - completed)

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 11) at the times shown in Table 4

Table 4 Blood pressure and pulse: Parts A and B only (completed)

	Screening	Cycle 0	Cycle 1			Cycle 2	Cycle 3 Onwards	Discontinuation
		Day 1	Day 1	Day 8 / LWD	Day 15 / LWD+7	Day 1	Day 1	
Screening	X							
Predose		X	X	X	X	X		
1 hour		X				X		

Table 4 Blood pressure and pulse: Parts A and B only (completed)

	Screening	Cycle 0	Cycle 1			Cycle 2	Cycle 3 Onwards	Discontinuation
		Day 1	Day 1	Day 8 / LWD	Day 15 / LWD+7	Day 1	Day 1	
2 hours		X				X		
6 hours		X				X		
24 hours (Day 2)		X						
Any time of the day							X	X

ECG (Parts A & B - completed)

A 12-lead ECG will be performed at the visits as shown in the Study Plan (see Figure 11) at the times specified in Table 5.

Table 5 12-lead ECG: Parts A and B only (completed)

	Screening	Cycle 0	Cycle 1		Cycle 2	Cycle 3 Onwards	Discontinuation
		Day 1	Day 1	Day 8 / LWD	Day 1	Day 1	
Screening	X						
Predose		X	X	X	X		
1 hour		X					
2 hours		X			X		
6 hours		X			X		
24 hours (Day 2)		X					
Any time of the day						X[a]	X[a]

[a] Single ECG.

Assessments up to and including 6 hours post-dose should be performed within 10 minutes of the nominal time point. Assessments after 6 hours should be performed within 30 minutes of the nominal time point.

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, unless specifically stated as a single ECG. 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.

All ECG data will also be collected digitally and will be transferred electronically for central analysis as described in the study specific ECG manual. Heart rate, PR, R-R, QRS and QT intervals will be determined and reviewed by an external cardiologist. However, the immediate management of the patient will be based upon the local paper ECG results.

6.6.4.3 Pulse rate, blood pressure and ECG (Parts C, D, E and F)

Supine blood pressure and pulse rate will be measured after 10 minutes rest. Assessments including a 12-lead ECG will be performed at the visits as shown in the Study Plan (see Figure 12) at the times shown in Table 6.

All ECGs to be conducted as triplicate measurements, approximately 5 minutes apart, unless specifically stated as a single ECG.

Assessments up to and including 6 hours post-dose should be performed within 10 minutes of the nominal time point. Assessments after 6 hours should be performed within 30 minutes of the nominal time point.

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.

All ECG data will also be collected digitally and will be transferred electronically for central analysis as described in the study specific ECG manual. Heart rate, PR, R-R, QRS and QT intervals will be determined and reviewed by an external cardiologist. However, the immediate management of the patient will be based upon the local paper ECG results.

AstraZeneca may decide, depending on emerging data, to terminate central analysis of ECG data. In this instance, ECG's would still be performed according to locally in accordance with schedule of assessments detailed in Table 6. In this case, triplicate ECGs may not be required.

Table 6 Blood pressure, pulse and 12-lead ECG: Parts C, D, E and F only

	Screening	Cycle 1			Cycle 2	Cycle 3 Onwards	Discontinuation
		Day 1	Day 4	Day 11	Day 1	Day 1	
Screening	X						
Predose		X	X	X	X		
1 hour		X					
2 hours		X			X		
4-6 hours		X					
Any time of the day						X[a]	X[a]

[a] Single ECG (BP and pulse are not required).

6.6.5 MUGA scan / Echocardiogram (all Parts)

A MUGA scan or echocardiogram to assess LVEF will be conducted at screening, at 12 weeks (± 1 week) at any time of the day, and then only if clinically indicated thereafter. A further assessment will be required at IP discontinuation. The modality of the cardiac function assessments must be consistent within patient i.e. 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.

6.6.6 Laboratory safety assessment (Parts A & B - completed)

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 11), and in Table 7.

Table 7 Laboratory safety assessments: Parts A and B only (completed)

	Screening	Cycle 0	Cycle 1			Cycle 2 Onwards	Discontinuation
		Day 1	Day 1	Day 8 / LWD	Day 15 / LWD + 7	Day 1	
Screening	X						
Predose		X[a]	X[b]	X	X	X	
Any time of the day							X

[a] Laboratory tests do not need to be repeated at baseline if the baseline visit is within 2 days of the screening sample.

[b] 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.

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 bilirubin increased from baseline or >10x ULN irrespective of bilirubin result should have the blood test repeated within 48 hours and additional investigations into the aetiology should be initiated as per Figure 7 hepatotoxicity management algorithm.

The following laboratory variables will be measured:

Clinical chemistry

Serum (S)/Plasma (P)-Albumin

S/P-ALT

S/P-AST

S/P-Alkaline phosphatase

S/P-Bilirubin, total

S/P-Calcium, total

S/P-Creatinine[3]

S/P-FSH

S/P-Glucose[2]

S/P-Magnesium

Haematology

Blood (B)-Haemoglobin

B – Glycosylated haemoglobin (HbA1c) [1]

B-Leukocyte

B-Absolute leukocyte differential count:

- Neutrophils
- Lymphocytes
- Eosinophils

B-Platelet count

Urinalysis

U-Glucose

Clinical chemistry	**Haematology**
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 cells, bacteria, casts and crystals) only perform if urinalysis is abnormal
S/P TSH	
S/P Testosterone (males only)	
S/P Troponin I or T	
S/P-Sodium	
S/P-Urea nitrogen	

For blood volume see Section 6.11.1.

[1] Glycosylated haemoglobin (HbA1c) to be measured at the following timepoints (for Parts A & B):

Screening

Cycle 4 Day 1 predose and every 12 weeks pre-dose thereafter

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

[2] Glucose to be measured at the time points specified in Section 6.6.8.

[3] Serum Creatinine

After Cycle 2 onwards, Patients taking AZD5363 and Metformin in combination (see Section 4.3.2) should attend for weekly assessments of serum creatinine for the first 3 weeks after initiation of metformin and then at the start of every cycle.

Urinalysis – supplementary evaluations:

An additional urine/serum sample will be collected from all female patients at screening, on first day of dosing (Cycle 0 Day 1, Cycle 1 Day 1) 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, following discharge from the clinic, 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 the patient must contact the clinic for further investigation of this result (see Section 5.1.9 for patient-reported glucose management algorithm).

6.6.7 Fasted lipids (Parts A & B - completed)

Fasted blood samples for determination of triglycerides, HDL, LDL and cholesterol will be taken at the visits as indicated in the Study Plan (see Figure 11) at the following schedule:

Cycle 0: Day 1 pre-dose (Parts A and B only)

At approximately 3 and 6 months thereafter at any time of the day.

Discontinuation of study treatment: at any time of the day

6.6.8 Glucose (Parts A & B - completed)

Blood samples for determination of glucose, and urine samples for determination of glucose only, will be taken at the visits as indicated in the Study Plan (see Figure 11). All assessments are detailed in Table 8.

Table 8 Glucose assessments: Parts A and B only (completed)

	Screening	Cycle 0		Cycle 1		Cycle 2 Onwards	Discontinuation
		Day 1	Day 1	Day 8 / LWD	Day 15 / LWD + 7		
Screening	C, U						
Predose		F, C, U	C, U	F, C, U	C, U	C, U	
2 hours		N		N			
2 – 4 hours post dose		C	C	C	C	C	
4 hours		N		N			
6 hours		N		N			
8 hours		N		N			
Any time of the day					N	N	N,C,U

F = Fasting (as part of the Insulin assessments see section 6.6.9).
N = Non-Fasting (as part of the Insulin assessments see section 6.6.9).
C = Clinical Chemistry Safety (as part of the Clinical Chemistry Safety asssessments see section 6.6.6).
U = Urinalysis (as part of the Urinalysis Safety asssessments see section 6.6.6).

Patients will be requested to record the date and time of their evening meal prior to each of the sampling days listed above. On study days where samples are taken at multiple time points the date and time of meals taken prior to sampling on that day should be recorded. This information will be recorded in the eCRFs.

6.6.9 Insulin (Parts A & B - completed)

Blood samples for determination of insulin will be taken at the visits as indicated in the Study Plan (see Figure 11) at the time stated in Table 9.

Table 9 Insulin assessments: Parts A and B only (completed)

	Cycle 0	Cycle 1		Cycle 2 Onwards Day 1	Discontinuation
	Day 1	Day 8 /LWD	Day 15 / LWD+ 7		
Screening					
Predose	F	F			
2 hours	N	N			
4 hours	N	N			
6 hours	N	N			
8 hours	N	N			
Any time of the day			N	N	N

F = Fasting.
N = Non-Fasting.

6.6.10 Laboratory safety assessment (Parts C, D, E and F)

Blood and urine samples for determination of clinical chemistry, glucose, insulin, haematology, and urinalysis will be taken at the visits as indicated in the Study Plan (see Figure 12), and in Table 10.

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 bilirubin increased from baseline or >10x ULN irrespective of bilirubin result should have the blood test repeated within 48 hours and additional investigations into the aetiology should be initiated as per Figure 7 hepatotoxicity management algorithm.

The following laboratory variables will be measured:

Clinical chemistry

Serum (S)/Plasma (P)-Albumin

S/P-ALT

S/P-AST

S/P-Alkaline phosphatase

S/P-Bilirubin, total

S/P-Calcium, total

S/P-Creatinine

S/P-FSH

S/P-Glucose

S/P-Magnesium

S/P-Oestradiol (females only)

S/P-Potassium

S/P-Total Protein

S/P Free T4

S/P TSH

S/P Testosterone (males only)

S/P Troponin I or T

S/P-Sodium

S/P-Urea nitrogen

Haematology

Blood (B)-Haemoglobin

B – Glycosylated haemoglobin (HbA1c)

B-Leukocyte

B-Absolute leukocyte differential count:

Neutrophils

Lymphocytes

Eosinophils

B-Platelet count

Urinalysis

U-Glucose

U-Protein

U-Blood

U-Ketones

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

For blood volume see Section 6.11.1.

Table 10 Laboratory Safety Assessments (Glucose, Insulin, Clinical Chemistry, Haematology, Urinalysis): Parts C, D, E and F only

	Screening	Cycle 1			Cycle 2 Onwards (and all even cycles going forward)	Cycle 3 onwards (and all odd cycles going forward)	Discontinuation
		Day 1	Day 4	Day 11	Day 1	Day 1	
Screening	C^F, H^G, U, I						
Predose		$C^{2,3}$,$H^{2,3}$ $U^{2,3}$,I	C,H,U, I	C,H,U, I	C, H ,U, I	C ,H ,U,	
2 – 4 hours post dose[1]		G,I	G	G	G,I	G,	
4-6 hours post-dose[1]		G,I			G,I		
Any time of the day							C,H^G,U,I

[1] The 2-4 hour and 4-6 hour samples must be taken at least 1 hour apart.
[2] Laboratory tests do not need to be repeated at baseline if the baseline visit is within 2 days of the screening sample.
[3] 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.

C = Clinical Chemistry
C^F = Clinical Chemistry with Fasted Glucose
H= Haematology
H^G = Haematology with Glycosylated Hb (also required at cycle 5 day 1 and every 12 weeks thereafter pre dose)
U = Urinalysis
G= Glucose only
I= Insulin only

Patients will be requested to record the date and time of their evening meal prior to each of the sampling days listed above. On study days where samples are taken at multiple time points the date and time of meals taken prior to sampling on that day should be recorded. This information will be recorded in the eCRFs.

For all samples in Table 10, there is no requirement for Fasting unless specified. (Fasting is defined as no calorific intake for at least 8 hours)

Glycosylated haemoglobin

Glycosylated haemoglobin (HbA1c) to be measured at the following timepoints;

Screening

Cycle 5 Day 1 predose and every 12 weeks pre-dose thereafter

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

Serum Creatinine

After Cycle 2 onwards, Patients taking AZD5363 and metformin in combination (see Section 4.3.2) should have creatinine assessments conducted as part of the routine clinical chemistry with additional monitoring of creatinine at the discretion of the investigator.

Urinalysis – supplementary evaluations:

An additional urine/serum sample will be collected from all female patients at screening, on first day of dosing (Cycle 1 Day 1) 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, following discharge from the clinic, 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 the patient must contact the clinic for further investigation of this result (see Section 5.1.9 for patient-reported glucose management algorithm).

6.6.11 Fasted lipids (Parts C, D, E and F)

Fasted blood samples for determination of triglycerides, HDL, LDL and cholesterol will be taken at the visits as indicated in the Study Plan (see Figure 12) at the following schedule:

Cycle 1: Day 1 pre-dose

At approximately 3 and 6 months thereafter (Pre dose)

Discontinuation of study treatment: at any time of the day

6.6.12 Follow-up (all Parts)

A post study assessment will be performed at the time investigational product is permanently discontinued (see Study Plan, Figure 11 and Figure 12).

In addition patients should be followed up for 28 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.

6.7 Adverse events

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

6.7.1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a

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

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.

6.7.2 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

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.

6.7.3 Recording of adverse events

Time period for collection of adverse events

For Parts A & B **(completed)**, AEs will be collected throughout the study, from informed consent.

For Parts C, D, E and F, procedure related SAEs only will be captured after pre-screening informed consent for those patients who provide a sample for determination of *PIK3CA / AKT1 / PTEN* mutations i.e., those SAEs occurring during or as a result of tumour biopsy and/or blood draw.

Capture of all other AEs will commence from the point that the patient formally provides informed consent for the main part of the study (i.e. Adult study subject information and consent form).

AEs will be collected throughout the study until 28 days after study treatment is discontinued. SAEs occurring within this period should be reported to AstraZeneca in the usual manner (see Section 6.7.4).

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 6.7.2. 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 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes

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

6.7.4 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 eCRF.

If any SAE occurs in the course of the study, then investigators or other centre personnel inform appropriate AstraZeneca representatives immediately or **no later than 24 hours** after he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative. If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **as soon as possible, but no later than 24 hours after being aware of it.**

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other centre personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE **as soon as possible, but no later than 24 hours after being aware of it**.

The reference document for definition of expectedness is Section 5.4 of the Investigators' Brochure for AZD5363.

6.8 Pharmacokinetics

6.8.1 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 11 and Table 12 (please reference also the study plan Figure 11 and Figure 12).

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 11 PK sampling schedule: Parts A and B (completed)

Time relative to first dose in cycle	Cycle 0			Cycle 1		
	Day 1	Day 2	Day 3	Day 1	Day 8 / LWD	Day 15/ LWD+7
Predose	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	
10-12 hours	X				Xa	
24 hours		X				

Table 11 PK sampling schedule: Parts A and B (completed)

Time relative to first dose in cycle	Cycle 0			Cycle 1		
	Day 1	Day 2	Day 3	Day 1	Day 8 / LWD	Day 15/ LWD+7
Predose	X			X	X	X
48 hours			X			

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

Parts A and B only: Separate urine samples (5 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 0-4, 4-8, 8-12, 12-24 and 24-48 hours post dose.

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

Table 12 PK sampling schedule: Parts C, D, E and F

Time relative to first dose in cycle	Cycle 1	
	Day 1	Day 11
Predose up to 1 hour pre dose	X	X
2 hours plus or minus 0.5hrs	X	X
4 hours plus or minus 1 hour	X	X

The timing of the blood and urine PK 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 15, Table 16, and in Section 6.11.1.

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

6.8.2 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 PK 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.

6.9 Pharmacodynamics

6.9.1 Collection of pharmacodynamic (PDc) assessments

9 mL venous blood (to provide platelet-rich plasma) will be taken on each of the timepoints presented in Table 13 for Parts A and B and in Table 14 for Parts C, D, E and F (please also reference the study plan, Figure 11 and Figure 12) for PDc assessment.

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

6.10 Exploratory research

6.10.1 Exploratory biomarker research

Blood and 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. From approval of CSP amendment 8, blood and hair biomarker samples will no longer be collected.

If a patient consents, paired biopsies and/or archived tumour may also be optionally collected (see section 6.10.1.1 and 6.10.1.2) for exploratory biomarker analysis as outlined above.

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

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

6.10.1.1 Collection of archival tumour samples

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. In Parts A and B **(completed)** this is optional; in Parts C, D, E and F this is a mandatory requirement (see Section 6.5 for details).

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.

If an archival sample is not available a fresh biopsy (formalin fixed and paraffin embedded) may be taken if the investigator deems this to be appropriate.

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

6.10.1.2 Collection of paired tumour biopsies

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 / LWD + 7 of Cycle 1 (± 1 week) from consenting patients **(Parts A & B – Now complete).**

For Parts C, D, E and F these should be collected prior to the first dose of AZD5363 at screening or at pre-dose on Day 1 of Cycle 1 and on a day on which the patient will take study medication (optimally Day 11 but can also be taken on Day 10, 17 and 18) at 2-4 hours post dose from consenting patients. The samples will be analysed for biomarkers that may influence development of cancers and/or response to AZD5363. The date and time of collection will be recorded in the CRF.

6.10.1.3 Collection of tumour biopsy on progression

All patients will be asked to provide consent for collection of tumour biopsies. These should be collected within a week after confirmation of progression from consenting patients. The samples will be analysed for biomarkers that may influence development of cancers and/or response to AZD5363. The date and time of collection will be recorded in the CRF.

6.10.1.4 Collection of plasma for analysis of ctDNA: Parts C, D, E and F (PI3K/AKT pathway aberrations)

All patients in Parts C, D, E and F will be requested to provide plasma samples for the extraction and analysis of circulating tumour DNA (ctDNA). The ctDNA may be used for the analysis of *PIK3CA / AKT1 / PTEN* mutations, or other aberrations leading to dysregulation of the PI3K/AKT pathway, but may also be used for the determination of the mutation status of other cancer genes associated with tumour development and/or progression.

All patients will be required to provide:

1x 10 mL blood sample for preparation of plasma at pre screening

2x 10 mL blood sample for preparation of plasma on Day 1 of every Cycle (pre-dose)

2x 10 mL blood sample for preparation of plasma at discontinuation (any time of day).

Time points for collection of ctDNA samples are presented in Table 14. Samples will be collected, labelled, stored and shipped as detailed in the laboratory manual. Residual material may be used for future exploratory biomarker research.

6.10.1.5 Collection of exploratory biomarkers

Study specific exploratory biomarker samples

5 mL venous blood (3 mL to provide serum, 2 mL to provide plasma) will be taken on each of the timepoints presented in Table 13 for Parts A and B only (please also reference the study plan, Figure 11 for analysis of exploratory biomarkers). The samples will be analysed for a range of oncology biomarkers which may correlate with drug response.

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

Table 13 Pharmacodynamic (PDc) and Biomarker (B) sampling schedule: Parts A and B (completed)

Time relative to first dose in cycle	Screen	Cycle 0			Cycle 1			Cycle 2 - last	IP Dis-continued
		Day 1	Day 2	Day 3	Day 1	Day 8 / LWD	Day 15 / LWD +7	Day 1	
	B								PDc, B
Predose		PDc, B			PDc, B	PDc, B	PDc, B	PDc, B	
1 hour		PDc							
4 hours		PDc							
8 hours		PDc							
10-12 hours		PDc							
24 hours			PDc						
48 hours				PDc					

Hair (eyebrow) determination of concentrations of exploratory biomarkers will be taken:

During Cycle 0 at pre dose (collected during –12 to 0 hours) at 4 hours post dose and Cycle 1: Day 15 / LWD + 7 pre dose (Parts A & B).

Table 14 Pharmacodynamic (PDc) and ctDNA sampling schedule; Parts C, D, E and F

Time relative to first dose in cycle	Pre screening	Cycle 1 Day 1	Cycle 1 Day11	Cycle 2 onwards (every cycle)	IP discontinued and / or progression
Pre dose (up to 1 hour pre dose)	ctDNA	ctDNA PDc	PDc	ctDNA	ctDNA
4 hours (+/- 1 hour)		PDc	PDc		

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.

Hair samples and exploratory blood biomarker samples are no longer collected in Parts C and D from Version 8 of the CSP, and will not be required for Parts E and F.

The total number of samples and the total volume of blood taken from each patient will not exceed that presented in Table 15 and Table 16 in Section 6.11.1.

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

For rationale and biomarkers to be analysed, see section 3.2.

Circulating tumour cells (Parts A and B only - completed)

A whole blood sample (10 mL) for circulating tumour cell assessment will be taken at the following timepoints:

Pre-dose, on day 1 of Cycle 1

Pre-dose, on day 1 of Cycle 2

Cycle 3 to Cycle 8: Day 1 pre-dose or at +/- 1 week of RECIST assessments

Circulating tumour cell samples will be shipped under ambient conditions on the day of acquisition so as to be received at an AstraZeneca approved laboratory within 72 hours of blood sampling. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Tumour-specific markers (Parts C, D, E and F only)

The results of local tumour-specific marker assessments (eg, prostate-specific antigen [PSA] in prostate cancer patients, and cancer antigen 125 [CA125] in ovarian cancer patients), if collected as part of the patient's normal clinical management, will be recorded on the eCRF.

6.10.2 Pharmacogenetics

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

6.10.2.1 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 (Parts A and B only), Cycle 1 Day 1 Predose [Parts C, D, E and F only]). 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 detailed in the Laboratory Manual.

6.11 Biological sampling procedures

6.11.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is shown in Table 15 (Parts A & B) and Table 16 (Parts C, D, E and F). 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 15 Parts A and B: Volume of blood to be drawn from each patient during Screening, Cycles 0 and 1 and subsequent cycles of treatment. (Parts A & B now completed)

		Screening, Cycles 0 and 1		Cycle 2 Day 1		Cycles 3+ Day 1		IP discontinuation	
	Sample volume (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	6	9	30	2	6	2	6	1	6
Clinical chemistry (Glucose 2-4 hr sample)	2	4	8	1	2	1	2		
Haematology	9	5	45	1	9	1	9	1	9
Glycosylated Haemoglobin (HbA1c)	3	1	3	-	-	1	3	1	3
Fasted Lipids	5	1	5	-	-	-*	-	1	5
Glucose, insulin, insulin c-peptide	5	11	55	1	5	1	5	1	5
Pharmacokinetics	4	20	80	-	-	-	-	-	-
Pharmacodynamics	9	10	90	1	9	1	9	1	9
Exploratory biomarker research	5	5	25	1	5	1	5	1	5
Circulating tumour cells	10	1	10	1	10	-	-	-	-
Pharmacogenetics	5	1	5	-	-	-	-	-	-
TOTAL		**356**			**46**		**39**		**42**

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

Table 16 Parts C, D, E and F: Volume of blood to be drawn from each patient during Pre screening, Screening, Cycles 1, 2 and subsequent cycles of treatment.

		Pre screening	Screening, Cycle 1		Cycle 2 Day 1		Cycles 3+ Day 1		IP discontinuation	
	Sample volume (mL)	Total volume (mL)	Number of samples	Total volume (mL)	Number of samples	Total volume (mL)	Number of samples per Cycle	Total volume (mL) per Cycle	Number of samples	Total volume (mL)
Blood sample for ctDNA analysis	10	10	2	20	2	20	2	20	2	20
Clinical chemistry	6		4	24	1	6	1	6	1	6
Clinical chemistry (Glucose only sample)	2		2	4	-	-	1[a]	2	-	-
Glucose, insulin	5		2	10	2	10	2[b]	10	-	-
Insulin	3		4	12	1	3	-	-	1	3
Haematology	9		4	36	1	9	1	9	1	9
Glycosylated Haemoglobin (HbA1c)	3		1	3	-	-	1[c]	3	1	3
Fasted Lipids	5		1	5	-	-	1[d]	5	1	5
Pharmacokinetics	4		6	24	-	-	-	-	-	-
Pharmacodynamics	9		4	36	-	-	-	-	-	-
Pharmacogenetics	5		1	5	-	-	-	-	-	-
TOTAL		**10**	**179**			**48**		**55**	**46**	

a Odd Cycles (Cycle 3, 5, 7 etc) have a Glucose only assessment at 2-4hr post-dose
b Even Cycles (Cycle 4, 6, 8, etc) have Glucose and Insulin assessments at 2-4hr and 4-6hr post-dose
c Glycosylated Haemoglobin samples to be taken approximately every 12 weeks (pre-dose)
d Fasting lipid samples to be taken at 3 and 6 months following initial dose

6.11.2 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 by AstraZeneca for a maximum of 15 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 a Clinical Study Report Addendum /Scientific Report or Scientific Publication.

6.11.2.1 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.

6.11.2.2 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 by 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.

6.11.3 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.

6.11.4 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.

6.11.5 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.

Parts A and B (completed): 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.

Parts C, D, E and F: 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)

Paired tumour biopsies

Tumour biopsy on progression.

Collection of the following biological samples is a required part of the study, but these are not regarded as integral to the primary or secondary study objectives. As such, if the samples are not taken, or are withdrawn, the patient may continue in the study:

- PDc (blood) **(ALL PARTS)**
- Exploratory biomarkers (blood and hair) **(DO NOT COLLECT FROM CSP VERSION 8)**
- PK (urine) (Parts A and B only) (completed)
- Circulating tumour cells (blood) (Parts A and B only) (completed)

As collection of blood samples for PK analysis is an integral part of the study, then the patient should be withdrawn from further participation in the study if consent for PK sampling is withdrawn.

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.

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.

6.12 Anti-tumour activity

6.12.1 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. The methods of assessment used at baseline should be used at each subsequent follow-up assessment. For Parts A and B, follow-up assessments should be performed at weeks 6 and 12 (± 1 week), after the start of treatment then at approximately 6-weekly intervals until discontinuation of study treatment or withdrawal of consent.

From approval of amendment 7, for all parts, follow-up assessments should be performed at weeks 6, 12, 18, and 24 (± 1 week), after the start of treatment then at approximately 12-weekly intervals until discontinuation of study treatment or withdrawal of consent. CT or MRI are required for the assessment of target lesions. If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression then these patients will continue to be followed until evidence of objective disease progression as defined by RECIST 1.1.

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 treatment. 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 plans in Section 6.1 and Appendix F, Section 4.1.

6.12.2 Correlative studies, special studies and functional imaging

Functional imaging may also be used to assess patients' tumour responses at the investigators discretion.

6.13 Survival assessments (Parts C, D, E and F only)

Survival status will be obtained for all patients in Parts C, D, E and F. Survival status will be collected every 3 months (±1 week) post-permanent discontinuation of AZD5363. To aid the interpretation of the survival analysis the use of subsequent anti-cancer therapies after discontinuation of study treatment will also be recorded on the eCRF for patients who have received AZD5363 in Parts C, D, E and F of this study. Survival status will continue to be collected in Parts C, D, E and F until the earlier of 12 months after the last patient is recruited into a cohort, or when 75% of the patients in the cohort have died. The patient does not have to attend the clinic for the assessment to be carried out; it can either be done via a telephone call, or through a review of the patient's notes, or through the use of public records. If the site becomes aware that a patient has died prior to the final analysis, the relevant eCRF on the database should be completed at that time.

7 EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

7.1 Definition of study endpoints

7.1.1 Study endpoints: Parts A and B (dose escalation and dose expansion) (completed)

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

Safety and Tolerability (Primary)

AZD5363 PK (Secondary)

Tumour response (Secondary)

AZD5363 PDc (Exploratory)

Metabolite identification/PK (Exploratory)

Circulating tumour cells (Exploratory)

Exploratory biomarkers: phospho-PRAS40, total PRAS40, pAKT, pGSK3β, pS6K, M30, M65, CTCs and other markers in response to emerging data (Exploratory)

Pharmacogenetics (Exploratory)

7.1.2 Study endpoints: Parts C, D, E and F (PI3K/AKT pathway aberrations)

Safety and Tolerability (Primary)

AZD5363 PK (Secondary)

Tumour response: best objective response (BOR), duration of response, durable response, percentage of patients without progressive disease at 12 weeks and clinical benefit rate (CBR Parts E and F only) (Secondary).

Metabolite identification/PK (Exploratory)

Exploratory biomarkers: phospho-PRAS40, total PRAS40, pAKT, pGSK3β, pS6K, M30, M65, and other markers in response to emerging data (Exploratory)

Concordance of status of *PIK3CA*, *AKT1* or other mutations between per-patient analyses of blood and archival tumour tissue (Exploratory).

Concordance of status of *PIK3CA, AKT1* or other molecular aberrations in the PI3K/AKT pathway between per-patient analyses of local and central tests for mutations and/or other molecular aberrations (exploratory).

Tumour response : PFS and OS (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

7.2.1 Sample size: Parts A and B (dose escalation and dose expansion) (completed)

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 PK and PDc data while exposing as few patients as possible to the investigational product and procedures.

For the dose escalation phase (Part A) 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 an additional 9 evaluable patients will be accrued at the RD for each treatment schedule arm to explore further the tolerability, PK and biological activity at these doses (Part B only).

7.2.2 Sample size: Parts C and D (PI3K/AKT pathway aberrations)

Parts C and D will recruit up to 120 patients in each of the cohorts on a specified dosing schedule. Analyses will be carried out after 20 and 40 patients have been followed for 12 weeks or withdrawn from the study. The analysis after an initial 20 patients in each of the cohorts on a specified dosing schedule will provide an adequate body of tolerability, safety,

PK and PDc data and will also give a reasonable chance of detecting any efficacy signal in this cohort, should one exist.

Patients are evaluable for tumour assessment if they have at least one post-baseline RECIST assessment. Parts C and D will enable an assessment of anti-tumour activity based on the response rate. If the true underlying response rate is 20%, with an initial 20 patients there would be a <2% chance of seeing no responses, and >90% chance of observing 2 or more responses. Confidence intervals (Clopper Pearson) will be constructed around the response rate observed in each of the cohorts to enable decisions to be made around stopping the expansion in that cohort in the current study or to enable decisions to be made around the likely success of future studies in each of these cohorts. For example with the first 20 patients, if the following response rates were observed, the 80% confidence intervals around those response rates would be:

50% (10/20), the 2-sided 80% confidence interval would be (33.8%, 66.2%)

70% (14/20), the 2-sided 80% confidence interval would be (53.3%, 83.4%).

If a cohort shows evidence of anti-tumour activity, a further analysis will be performed after 40 patients have been followed for 12 weeks or withdrawn. With 40 patients, if the following response rates were observed the 80% confidence intervals around those response rates would be:

43% (17/40), the 2-sided 80% confidence interval would be (30.0%, 42.0%)

63% (25/40), the 2-sided 80% confidence interval would be (51.1%, 72.9%).

If a cohort still shows evidence of anti-tumour activity after this analysis, a final analysis will be performed with all 120 patients. With 120 patients if the following response rates were observed the 80% confidence intervals around those response rates would be:

36% (43/120), the 2-sided 80% confidence interval would be (30.0%, 42.0%)

57% (68/120), the 2-sided 80% confidence interval would be (50.4%, 62.8%).

Any decision to stop recruitment in a specific cohort will be at the discretion of AstraZeneca after discussion with the SRC, and will be based on emerging safety, tolerability, anti-tumour activity, PK and PDc data.

7.2.3 Sample size: Parts E and F

Parts E and F will recruit up to 24 patients in each of the cohorts. An interim analysis in each of the cohorts will be carried out after 12 patients have been followed for 24 weeks or withdrawn from the study.

Patients are evaluable for tumour response if they have at least one post-baseline RECIST assessment. Parts E and F will enable an assessment of anti-tumour activity based on the clinical benefit rate (CBR).

For Parts E_R and F_R, if the true underlying clinical benefit rate is 40%, with 24 patients there would be a 90% chance of seeing at least 7 clinical benefit responses. Confidence intervals will be constructed around the clinical benefit rate observed in the cohort to enable decisions to be made around the likely success of future studies in patients. For example with 24 patients, if the following clinical benefit rates were observed, the 80% confidence intervals around those response rates would be:

- 25% (6/24), the 2-sided 80% confidence interval would be (14%, 40%)
- 38% (9/24), the 2-sided 80% confidence interval would be (24%, 53%)

For Parts E_D and F_D if the true underlying clinical benefit rate is 65%, with 24 patients there would be a 90% chance of seeing at least 13 responses. Confidence intervals will be constructed around the clinical benefit rate observed in the cohort to enable decisions to be made around the likely success of future studies in patients. For example with 24 patients, if the following clinical benefit rates were observed, the 80% confidence intervals around those response rates would be:

- 50% (12/24), the 2-sided 80% confidence interval would be (35%, 65%)
- 63% (15/24), the 2-sided 80% confidence interval would be (47%, 76%)

Any decision to stop recruitment in a specific cohort will be at the discretion of AstraZeneca after discussion with the SRC, and will be based on emerging safety, tolerability, anti-tumour activity, PK and PDc data.

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 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 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 –

- Men: [(140 – age) x weight (kg) x 1.23] / serum creatinine (μmol/L)]
- Females: [(140 – age) x weight (kg) x 1.04] / serum creatinine (μmol/L)])

For creatinine values in mg/dL -

- Men: [140 - age] x weight (kg) / [72 x serum creatinine (mg/dL)]
- Females: 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 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

Pharmacokinetic analysis of the plasma and urine concentration data for AZD5363 will be performed by [redacted] on behalf of, Alderley Park, AstraZeneca. 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 PK (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. Ae 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 PK, PDc, demographic, safety and tumour response data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK/PDc methods. The results of any such analyses will be reported separately from the Clinical Study Report. Details will be included in a separate data analysis plan for Pharmacometrics.

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.

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.

[redacted]

Best objective 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.

Duration of response is defined as the date of first documentation of response (CR/PR) until the date of disease progression as defined by RECIST 1.1 or death (by any cause in the absence of disease progression).

Durable response is defined as the percentage of patients who have a response (CR/PR) with a duration of at least 4 months.

Clinical benefit rate is defined as the percentage of patients with either a best response of PR or CR (a confirmed response of PR or CR), or have demonstrated Stable Disease for at least 24 weeks after first dose of study medication.

Progression-free survival (PFS) is defined as the time from start of treatment until objective disease progression as defined by RECIST 1.1 or death (by any cause in the absence of progression).

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

If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression then these patients will continue to be followed until evidence of objective disease progression as defined by RECIST 1.1 and their PFS time will be derived as defined above. The PFS time will always be derived based on scan/assessment dates not visit dates.

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

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

When censoring a subject for PFS the subject will be censored at the latest of the dates contributing to a particular overall visit assessment.

Overall survival is defined as the interval from the start of treatment until the date of death. Patients who have not died by the date of data cut-off, or who are lost to follow-up or withdraw consent will be censored at the date they were last known to be alive.

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 17.

Table 17 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 PDc research
Tumour response	Dosed patients with a baseline tumour assessment.
Tumour response 2	Dosed patients with a baseline tumour assessment and measurable lesions at baseline according to RECIST v1.1
Intent-to-treat	All dosed patients with a baseline tumour assessment
Exploratory biomarkers	All patients that provide biological samples for exploratory biomarker research

If a patient has been recruited into a cohort without the required mutation, the patient will not be included in the efficacy summaries and the efficacy data will only be listed. They will be included in all the safety summaries.

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. Patients in Parts A and B will be grouped by schedule and dose, and the *PIK3CA, AKT1, PTEN* and other PI3K/AKT pathway mutation expansion patients (Parts C, D, E and F) will be summarised together in separate groups. 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 (date of last dose minus date of first dose) 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

Safety data will not be formally analysed. 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 $\geq$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 28 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 28 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 $100 \sqrt{[\exp(s^2)-1]}$, 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 PK 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 treatment 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.

Response rates, progression-free survival (PFS) and overall survival (OS): Parts C, D, E and F only

Response rate will be tabulated for each population. These will present frequencies of confirmed CR and PR in addition to unconfirmed CR and PR, SD, PD and NE.

If there are sufficient numbers of responders, and sufficient number of responses that have progressed by the point of the analysis, Kaplan-Meier plots of DoR in the responding patients will be produced and appropriate descriptive summary statistics will be presented (n, number of responses that have progressed, median, quartile, minimum and maximum DoR, proportion with a DoR $\geq$4 months and $\geq$6 months in the responders). If there is an insufficient number of responses that have progressed by the data cut-off, DoR in the responding patients will be presented as individual line plots for each patient, with lines indicating the DoR and symbols indicating whether the response had ended (progressed) or censored at the data cut off.

The percentage of patients who have a response with a duration of at least 4 months will be summarised.

Summaries of PFS (n events, medians, quartiles, proportion progression free at 6 months and 1 year) and Kaplan Meier plots will be provided.

For patients who are dosed in Parts C, D, E and F only, summaries of OS (n, deaths, medians quartiles) and Kaplan Meier plots will be provided.

Clinical Benefit Rate (Parts E and F only)

Clinical benefit rate will be tabulated for each population. These will present the proportion of patients with a confirmed CR/PR or stable disease for at least 24 weeks.

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 6.7.4**

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

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[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 on an AstraZeneca study drug occurs in the course of the study, then investigators or other centre personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours after 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 6.7.4. For other overdoses, reporting should be done within 28 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 28 days after discontinuing investigational product, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** i.e., immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, (see Section 6.7.4) and within 28 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.

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