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**Clinical Study Protocol**

Drug Substance	AZD5363
Study Code	D3610C00002
Edition Number	1
Date	24 February 2012

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**A Phase I/Ib, Multicentre, Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by *PIK3CA* Mutation Status (BEECH).**

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Sponsor:

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

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
_____	_____	_____	_____
_____	_____	_____	_____
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Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
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## PROTOCOL SYNOPSIS

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**A Phase I/Ib, Multicentre, Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by *PIK3CA* Mutation Status (BEECH).**

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### International Co-ordinating Investigator

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### Study centre(s) and number of patients planned

Number of patients planned (enrolled):

Safety Run-in. n= 40

Randomised Expansion. n= 70

Total number of study centres planned = 12

Number of patients to be recruited per site:

Maximum – not defined

Minimum: n= 2

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Study period		Phase of development
Estimated date of first patient enrolled	Q2 2012	I
Estimated date of last patient completed	Q4 2014	Ib

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## **Objectives**

### **Primary objectives.**

#### Part A. Safety run-in:

To assess the safety and tolerability of two schedules of AZD5363 (continuous and intermittent dosing) when combined with weekly paclitaxel in patients with advanced or metastatic breast cancer; and to recommend, by assessment of dose limiting toxicities and other safety, tolerability, pharmacokinetic and pharmacodynamic data, a dose and schedule of AZD5363 for further study when combined with weekly paclitaxel.

#### Part B. Randomised expansion:

To assess the relative anti-tumour activity of AZD5363 when combined with weekly paclitaxel vs. weekly paclitaxel plus placebo by comparison of change in tumour size at 12 weeks (target lesion assessment using RECIST 1.1) in the overall advanced or metastatic Estrogen Receptor positive breast cancer population and in a Phosphoinositide 3-kinase (*PIK3CA*) mutation-positive sub-population.

### **Secondary objectives (summarised)**

#### Part A. Safety run-in:

To make a preliminary assessment of the anti-tumour activity of AZD5363 when combined with paclitaxel.

#### Part B. Randomised expansion:

- To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo.
- To assess the safety and tolerability of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo.
- To investigate the effect on patients' quality of life of AZD5363 when combined with weekly paclitaxel, compared with weekly paclitaxel plus placebo.

#### Parts A and B:

- To assess the pharmacokinetics of AZD5363 when combined with paclitaxel.
- To assess the pharmacokinetics of paclitaxel alone and when combined with AZD5363.
- To assess the pharmacokinetic/pharmacodynamic relationship between AZD5363 exposure and biomarkers in blood and anti-tumour activity.

## **Study design**

This international, multicentre, study of AZD5363 when combined with paclitaxel vs paclitaxel plus placebo will be conducted in two parts:

### **Part A: Safety Run-in.**

An open-label run-in to assess the comparative safety, tolerability pharmacokinetics and pharmacodynamics of ascending doses of AZD5363 in two schedules (continuous and intermittent dosing) when combined with weekly paclitaxel; and to make a preliminary assessment of the anti-tumour activity of the combination.

The primary output of Part A will be a recommended dose and schedule of AZD5363 when combined with paclitaxel for conduct of the study Part B randomised expansion phase.

AZD5363 and paclitaxel will be given in the dosing schedules detailed below. Cohorts of 3 to 6 patients will be evaluated in escalating doses of AZD5363 to determine a recommended dose and, where applicable, a maximum tolerated dose for each schedule.

Patient assessments will continue up to cessation of both AZD5363 and paclitaxel or withdrawal of consent or death. A 28-day safety follow-up assessment should be conducted following cessation of all study therapy (AZD5363 and paclitaxel).

#### **Part A: Safety run-in - Subsidiary Japanese patient evaluation (optional)**

A subsidiary dose-escalating safety evaluation may optionally be conducted in a Japanese patient population at a starting dose, and under one schedule, determined by the Safety Review Committee. This evaluation would be conducted to determine a safe and tolerable dose of AZD5363 when combined with weekly paclitaxel in a Japanese population.

This separate Japanese safety run-in evaluation would commence following determination of the RD and dosing schedule in the Western population. It would proceed in parallel with the Part B randomised expansion, but would not inform any decision regarding the conduct of Part B. The schedule of assessments in the subsidiary Part A would be as detailed in this protocol for Part A. It is not envisaged that a Japanese population would be evaluated under study Part B.

### **Part B: Randomised Expansion**

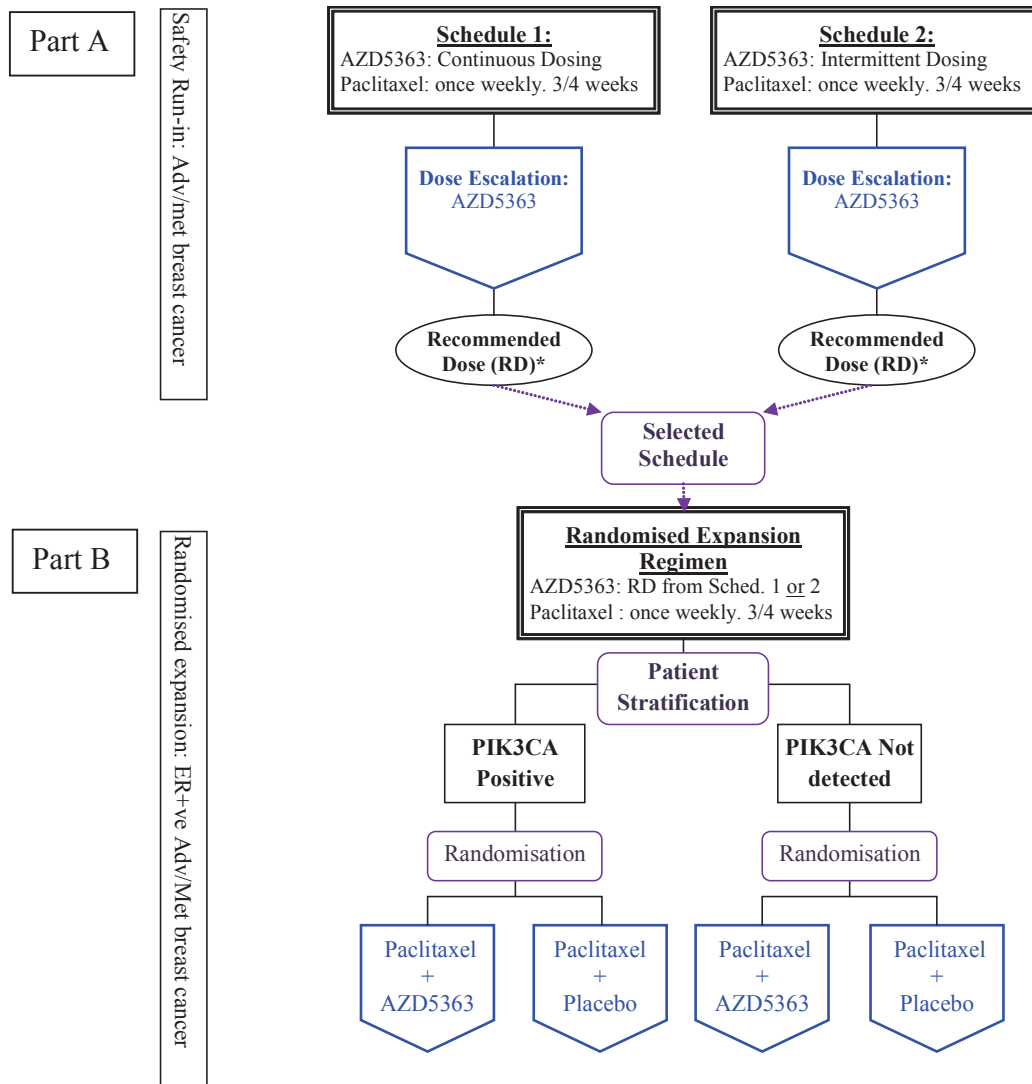
A randomised double-blind assessment of the safety, tolerability, pharmacokinetics, pharmacodynamics and anti-tumour activity of the dose and schedule of AZD5363 selected from Part A when combined with weekly paclitaxel - versus weekly paclitaxel plus placebo matched to AZD5363.

AZD5363/placebo and paclitaxel will be given in either the continuous or intermittent dosing schedule detailed below.

Patients will be assessed at screening for presence/absence of PIK3CA tumour mutations and will be stratified in to PIK3CA mutation-positive and PIK3CA mutation-not detected arms. Within each stratum, patients will be randomised to receive either paclitaxel plus AZD5363 or paclitaxel plus placebo.

Patient assessments will continue up to objective disease progression as defined by RECIST 1.1, death or withdrawal of consent. A 28-day safety follow-up assessment should be conducted following cessation of all study therapy (AZD5363/placebo and paclitaxel).

**Study Design Diagram:**



\* Recommended dose (RD) = dose level identified by the Safety Review Committee as appropriate for further evaluation in the Part B randomised expansion phase.

### **Target patient population**

Part A. Safety run-in: Female patients, 18 years or older, with advanced or metastatic breast cancer.

Part B. Randomised expansion: Female patients, 18 years or older, with ER+ve advanced or metastatic breast cancer. For inclusion in Part B, patients must not have received any prior chemotherapy in the advanced or metastatic settings.

### **Investigational product, dosage and mode of administration**

AZD5363: A twice daily regimen of an oral capsule formulation given on a continuous or intermittent weekly dosing schedule. Administration of AZD5363 will commence in Part A as detailed in section 5.5.3:

- Continuous dosing: 320 mg bd (640 mg daily) throughout a patient's participation in the study.
- Intermittent dosing (4 days of treatment followed by 3 days off-treatment): 360 mg bd (720 mg daily) each week that paclitaxel is received, and then each week following cessation of paclitaxel throughout a patient's participation in the study.

Placebo (Part B only): Oral capsule formulation, matched to AZD5363.

### **Comparator, dosage and mode of administration**

Paclitaxel: A weekly single intravenous infusion of 90 mg/m<sup>2</sup> given over approximately one hour. A 28-day treatment cycle to comprise three consecutive weeks of treatment, followed by one week off-treatment.

### **Duration of treatment**

Patients may receive study treatment, AZD5363/placebo and/or paclitaxel, to objective disease progression or withdrawal from study participation. It is anticipated that approximately 6 cycles of paclitaxel therapy will be given in the absence of disease progression or unacceptable toxicity; but further cycles can be continued at an investigator's discretion based on the patient's risk/benefit profile.

### **Outcome variable(s):**

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

#### Parts A and B:

- Safety and Tolerability.
- Tumour response as assessed by RECIST 1.1.
- AZD5363 and paclitaxel pharmacokinetics.

- Pharmacodynamic biomarkers.
- Treatment effect as assessed by quantitative change in circulating tumour cells.
- Exploratory biomarkers.
- Pharmacokinetic/pharmacodynamic investigation.

Part B. Randomised expansion:

- Treatment efficacy as assessed by progression-free survival.
- Tumour size as assessed by RECIST 1.1.
- Quality of life.

**Statistical methods**

**Part A Safety Run-in**

All Part A data will be summarised descriptively, no formal statistical analysis will be implemented on this part of the study.

The efficacy and safety analysis sets will include all patients who received at least one dose of study treatment, and patients will be assessed according to treatment actually received. Any patient who receives one or more doses of paclitaxel and does not commence dosing with AZD5363 will not be included in the assessment of safety or efficacy data.

**Part B Randomised Expansion**

The primary outcome variable of change in tumour size at 12 weeks and the secondary outcome variable of progression-free survival will be analysed formally in Part B, the randomised expansion. Each variable will be analysed for all patients and then separately in those patients with *PIK3CA* mutation-positive tumour(s). All other efficacy and safety data collected during Part B will be summarised descriptively.



All efficacy data in Part B of the study will be analysed on an intention-to-treat basis including all randomised patients and comparing treatment groups on the basis of randomised treatment, regardless of the treatment they actually received.

All patients who receive at least one dose of randomised treatment in Part B will be included in the assessment of the safety data, and patients will be assessed according to treatment actually received. Any patient who receives one or more doses of paclitaxel and does not commence dosing with investigational product (i.e. AZD5363 or placebo) will not be included in the assessment of safety data.

[REDACTED]

Progression free survival will be analysed in the Part B randomised expansion [REDACTED]

[REDACTED]

[REDACTED] Kaplan-Meier plots of progression-free survival and estimates of median progression-free survival will be presented by treatment group in the overall population and within the subgroup of patients with *PIK3CA* mutation-positive tumours.



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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
AGC kinase family	cAMP dependent, cGMP dependent & protein kinase C
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AZ	AstraZeneca
bd	'bis in die': twice daily
BOR	Best Objective Response
cAMP	cyclic adenosine monophosphate
cfDNA	circulating free plasma DNA
cGMP	cyclic guanosine monophosphate
CRF	Case Report Form (electronic/paper, e/p)
CR	Complete Response
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Terminology Criteria
CTCs	Circulating Tumour Cells
CTCAE	Common Terminology Criteria for Adverse Event
CV	Coefficient of variation
CYP	cytochrome P450 enzyme
DBP	Diastolic Blood Pressure
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)



<b>Abbreviation or special term</b>	<b>Explanation</b>
EORTC	European Organisation for the Research and Treatment of Cancer
EORTC-QLQ	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 is a core questionnaire)
ER	Estrogen Receptor
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GSK3 $\beta$	Glycogen synthase kinase
HDL	High Density Lipoprotein
HEOR	Health Economic Outcomes Research
HR	Hazard Ratio
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDL	Low Density Lipoprotein
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LVEF	Left ventricular ejection fraction
MBC	Metastatic Breast Cancer
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	mammalian Target Of Rapamycin
MUGA scan	Multi Gated Acquisition scan
NQ	Non-quantifiable
NTD	Non-Tolerated Dose
NTL	Non-Target Lesion
NYHA	New York Heart Association
OAE	Other Significant Adverse Event
OCT2	Organic Cation Transporter 2
ORR	Objective Response Rate

<b>Abbreviation or special term</b>	<b>Explanation</b>
OS	Overall Survival
PD	Progression of Disease
PK/PD	Pharmacokinetic/Pharmacodynamic
PFS	Progression Free Survival
PI3K	Phosphoinositide 3-kinase
PIK3CA	Phosphoinositide-3-kinase, catalytic, alpha polypeptide
PKA	Protein kinase A
PKB/AKT	Protein kinase B
PR	Partial Response
PR	ECG interval measured from the beginning of the P wave to the beginning of the QRS complex
PRAS40	Proline-rich AKT substrate of 40 kDaltons
PTEN	Phosphatase and Tensin Homolog
QoL	Quality of Life
QRS complex	A name for the combination of three of the graphical deflections seen on a typical electrocardiogram (ECG)
QT	ECG interval measured from onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcB	interval duration corrected for changes on heart rate using Bazett's formula
QTcF	interval duration corrected for changes on heart rate using Friderica's formula
QTcR	QT interval duration corrected for changes on heart rate using an individual regression method
QWBA	Quantitative whole-body autoradiography
RD	Recommended Dose
RECIST 1.1	Response Evaluation Criteria In Solid Tumours, version 1.1
ROCK	Rho associated protein kinase
RR	Response rate
R-R	the interval between successive Rs, where R is a point corresponding to the peak of the QRS complex of the ECG wave
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure

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<b>Abbreviation or special term</b>	<b>Explanation</b>
SD	Stable Disease
SD	Standard Deviation
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
T4	Thyroxine
TL	Target Lesion
TSH	Thyroid-Stimulating Hormone
UGT	Uridine 5' diphospho-glycosyltransferase
ULN	Upper Limit of Normal
WBDC	Web Based Data Capture
WHO	World Health Organisation

---

## 1. INTRODUCTION

### 1.1 Background

#### 1.1.1 Investigational agent

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

AKT is part of the AGC family of kinases. Mammalian cells express three closely related AKT isoforms: AKT1 (PKB $\alpha$ ), AKT2 (PKB $\beta$ ) and AKT3 (PKB $\gamma$ ), 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 Phosphoinositide 3-kinase (PI3K)/AKT/Phosphatase and Tension Homolog (PTEN) pathway is frequently deregulated in cancer and drives tumour growth and cell survival (Lindsley 2010). All 3 AKT isoforms are activated in different tumour types including breast, prostate, ovarian, pancreatic and gastric cancers, and this activation is often associated with resistance to established cancer therapies as well as advanced disease and/or poor prognosis (Altomere and Testa 2005). AKT activation in tumours is largely due to input from other signalling pathways upstream of AKT (eg, mutation of 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 when combined with cytotoxic chemotherapies or when combined 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.

A significant relationship has been found in pre-clinical studies between the presence of a phosphoinositide-3-kinase, catalytic, alpha polypeptide (*PIK3CA*) mutation and sensitivity to monotherapy AZD5363 in a panel of 182 cancer cell lines ( $p = 0.0059$ ; T test). Mutations in *PIK3CA* are common in human breast cancer; 27% of breast cancers harbour *PIK3CA* mutations. They are most common in Estrogen receptor-positive (ER+) breast tumours (35% have *PIK3CA* mutations). However, the relationship between *PIK3CA* mutation and sensitivity to AZD5363 is not absolute; some *PIK3CA* mutation-negative cell lines are also sensitive to AZD5363.

#### 1.1.2 Non-clinical information and correlative studies

AZD5363 is a potent inhibitor of AKT 1, 2 and 3 in enzyme assays and inhibits the phosphorylation of AKT substrates in cells. AZD5363 inhibits the proliferation of a range of cell lines derived from solid and haematological tumours. Breast cancer cell lines appear to be the tumour types that show the greatest sensitivity to AZD5363. AZD5363 shows dose dependent pharmacodynamic and antitumour activity in xenografts at well-tolerated doses,

and can enhance the efficacy of existing treatment (trastuzumab and docetaxel) in appropriate xenograft models.

Studies *in vitro* show AZD5363 to be a potent inhibitor of AKT 1, 2 and 3 (concentration giving 50% of the drug-induced inhibitory effect [IC<sub>50</sub>] <10 nM), and to inhibit protein kinase A (PKA) with a similar potency. AZD5363 inhibits Rho associated protein kinase (ROCK) 1 and ROCK2 with moderate potency

In cell lines, AZD5363 inhibits the phosphorylation of substrates of glycogen synthase kinase 3  $\beta$  (GSK3 $\beta$ ) and proline rich AKT substrate of 40 kilodaltons (PRAS40) with a potency of <1  $\mu$ M. AZD5363 also inhibits the kinase activity of PKA with a potency of approximately 1  $\mu$ M in a tumour cell line,

AZD5363 inhibits the proliferation of 22 tumour cell lines with a concentration causing 50% inhibition of cell growth (GI<sub>50</sub>) of <1  $\mu$ M, including the 2 tumour cell lines in which we have demonstrated inhibition of AKT substrates. Breast cancer cell lines appear to be the tumour type that show the greatest sensitivity to AZD5363 as monotherapy *in vitro*.

Further details are provided in the Investigators' Brochure.

### 1.1.3 Clinical information

At the time of preparation of this protocol, forty six patients had been recruited in two Phase I dose escalation clinical studies in Western (D3610C00001) and Japanese (D3610C00004)

populations with advanced solid malignancies, under two separate AZD5363 monotherapy dosing regimens:

- continuous dosing at 80 mg bd (n=8), 160 mg bd (n=5), 240 mg bd (n=12), 400 mg bd (n=8) and 600 mg (n=2)
- intermittent dosing (4 days on and 3 days off) at 480 mg bd (n=5) and 640 mg bd (n=6)

The most commonly reported Adverse Events (AEs), regardless of dose or causality, to date are: diarrhoea, hyperglycaemia, fatigue, maculo-papular rash, vomiting, dyspnoea, and nausea. The majority of AEs reported in patients receiving AZD5363 have been Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or Grade 2 in toxicity.

Common Terminology Criteria (CTC) Grades 3 and 4 adverse events have been associated with the use of AZD5363 in Study D3610C00001 as follows:

- diarrhoea: CTCAE grade 3 in the continuous dosing at 240 mg bd (n=1), 400 mg bd (n=1), 600 mg bd (n=1) and intermittent dosing (4 days on and 3 days off) at 640 mg bd (n=2)
- hyperglycaemia (post AZD5363 dose), CTCAE grade 3 in the continuous dosing at 240 mg bd (n=1), 400 mg bd (n=2) and intermittent dosing (4 days on and 3 days off) at 480 mg bd (n=1), 640 mg bd (n=4)
- maculo-papular rash: CTCAE grade 3 in the continuous dosing at 400 mg bd (n=1) and CTCAE grade 4 in the continuous dosing at 600 mg bd (n=2)

One dose-limiting toxicity (DLT) of CTCAE grade 3 hypoxia has been reported in a female patient with sarcoma with lung metastasis in study D3610C00004 under a continuous dosing schedule at a 240 mg bd dose.

There has been a trend for an increase in plasma glucose levels approximately 2 hours after AZD5363 dosing (single and continuous dosing), generally returning to baseline levels within 4 hours to 8 hours after AZD5363 dosing. Plasma glucose elevations have been more pronounced in the higher dose levels.

There have been no clinically significant findings identified on review of Electrocardiograms (ECGs) or left ventricular ejection fraction (LVEF) decreases attributed to AZD5363.

One female patient with cervical carcinoma (PIK3CA mutation positive) with metastasis to the lymph nodes, receiving 400 mg bd in the continuous dosing regimen, had a confirmed partial response for 20 weeks prior to disease progression. The patient had previously received adjuvant and first-line chemotherapy and radiation.

Five patients treated with the continuous dosing regimen had stable disease with duration of response (DoR) of at least 12 weeks. These were: advance cervical carcinoma (n=1), advanced osteosarcoma (n=1) at 80 mg bd; colorectal carcinoma (n=1) at 240 mg bd; urothelial carcinoma (n=1) and liposarcoma (n=1) both at 400 mg bd.

Continuous schedule doses of 80, 160, 240 and 400 mg bd have been declared tolerable, 600 mg bd has been declared non-tolerable and 480 mg bd is currently being tested.

Intermittent schedule doses of 240 and 480 mg bd have been declared tolerable and 640 mg bd is currently being tested.

Further details are provided in the Investigators' Brochure.

#### **1.1.3.1 Pharmacokinetics**



Further details are provided in the Investigators' Brochure.

## **1.2 Research hypotheses**

Part A. Safety run-in: AZD5363 when combined with paclitaxel will have an acceptable safety and tolerability profile.

Part B. Randomised expansion:

- The addition of AZD5363 to weekly paclitaxel will be more efficacious than paclitaxel alone - as demonstrated by a reduction in tumour size in patients with Estrogen-Receptor positive (ER+ve) advanced or metastatic breast cancer.
- Tumour types that have mutations in *PIK3CA* (*PIK3CA* mutation-positive) will have increased sensitivity to AZD5363 and may therefore demonstrate greater tumour size reduction and clinical response to AZD5363 when combined with paclitaxel than the overall population.

## **1.3 Rationale for conducting this study**

### **1.3.1 Breast Cancer**

Breast cancer is one of the most common malignancies in women; it is also one of the most common causes of cancer deaths in women. Although earlier detection and improving treatments have led to a decrease in the mortality rate in some countries, the overall number of

deaths from breast cancer has continued to rise in Europe (130,000 in 2004 vs 132,000 in 2006) (Ferlay et al 2007). In the US, breast cancer is the most common cancer in women with an incidence rate of 123.6 per 100,000 from 2001 to 2005.

The treatment of breast cancer is determined by the extent of the disease and a variety of other prognostic factors, including hormone receptor status. The most important factor determining response to hormonal manipulation is the presence of the ER in the target tissue (Fisher et al 2001). The choice of treatment sequence is complex and dependent on a number of factors, including prior endocrine treatments received. Irrespective of the treatment sequence received a number of patients will experience disease progression, and therefore there remains a need to identify further treatment options for those patients who progress on or shortly after endocrine therapy.

### **1.3.2 Rationale for AZD5363 in breast cancer.**

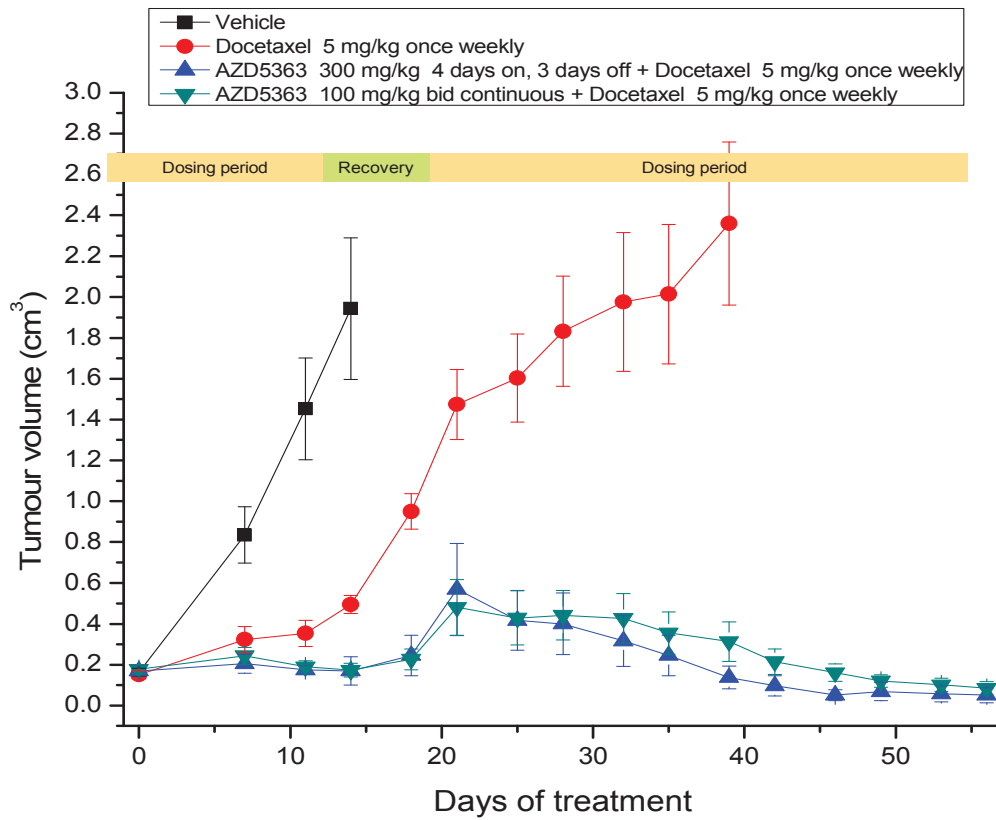
AZD5363 has been shown to greatly increase sensitivity to the taxane docetaxel (Taxotere) in several breast cancer xenograft models. For example, both continuous and intermittent schedules of AZD5363 enhanced the efficacy of docetaxel in the HCC-1187 xenograft ()

Figure 1). The sequence of administration appears to be very important; in the HCC-1187 model, administering docetaxel after an intermittent dosing schedule of AZD5363 (4 days on, 3 days off) was found to be antagonistic, whilst administering docetaxel before the intermittent schedule resulted in enhanced efficacy (Figure 2)



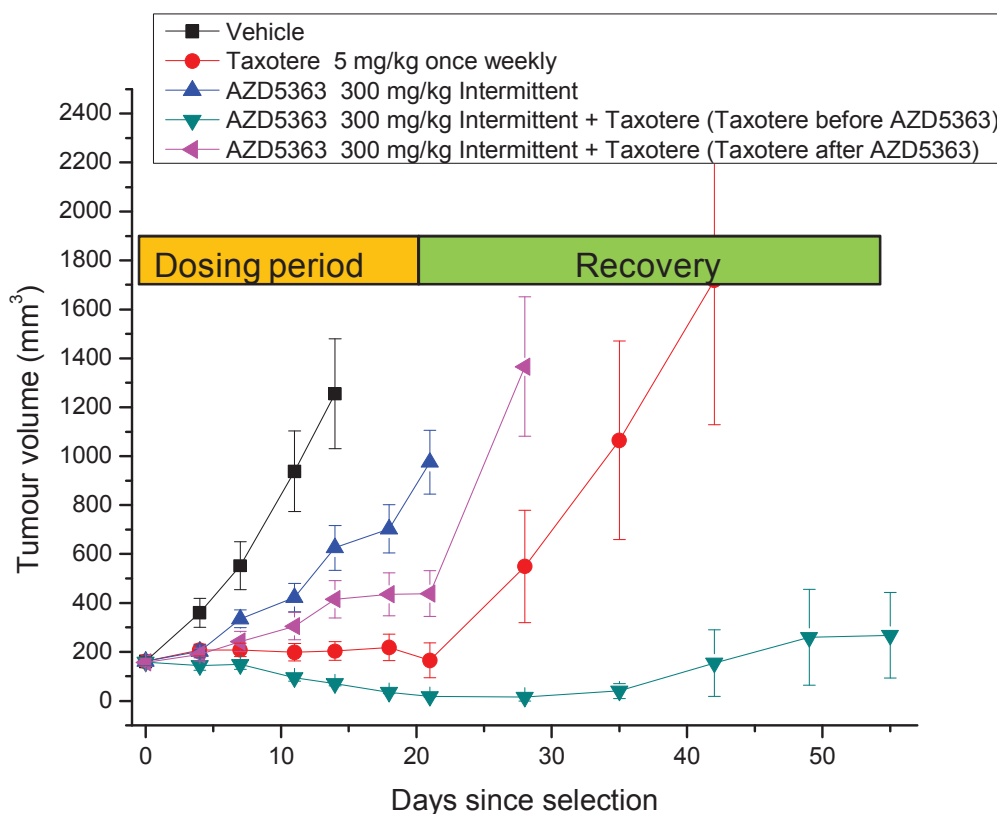
**Figure 1** AZD5363 sensitises HCC-1187 xenografts to docetaxel (Taxotere) (A)

When tumours are re-challenged after a period of recovery, both schedules (continuous and intermittent) cause sustained tumour regressions, whilst docetaxel monotherapy results in progressive tumour growth.



**Figure 2 AZD5363 sensitises HCC-1187 xenografts to docetaxel (Taxotere) (B)**

Using an intermittent dosing schedule (300 mg/kg qd, 4 days on, 3 days off), AZD5363 sensitises HCC-1187 xenografts to docetaxel provided the weekly docetaxel is administered 1-24 h before the first dose of AZD5363; the combination is antagonistic if the docetaxel is given 24 h after the AZD5363 dosing sequence



### 1.3.3 Rationale for evaluation of PIK3CA mutation sub-population.

Molecular aberrations, including *PIK3CA* activating mutations, in the PI3K/AKT pathway have been implicated in the development and progression of breast cancer and also as a mechanism of resistance to breast cancer therapy. (Gonzalez-Angulo et al 2010)

A significant relationship was found between the presence of a *PIK3CA* mutation and sensitivity to monotherapy AZD5363 (see section 1.1.1).

Activation of the PI3K-AKT-mTOR network is common in human breast cancer (27% of breast cancers have a *PIK3CA* mutation), and most common in ER+ve breast cancer (35% *PIK3CA*, 3% PTEN and 3% AKT1 mutation frequency). (Kalinsky et al 2009), (Castaneda et al 2010).

The frequency of *PIK3CA* mutations in samples has been studied performing a mutational analysis of exons 9 (HD) and 20 (KD) of the *PIK3CA* gene using tumour deoxyribonucleic acid (DNA) obtained from patients with recurrent disease. Mutations in *PIK3CA* were identified in 24.5% of patients (11.3% in HD and 13.2% in KD). *PIK3CA* mutation was significantly correlated with lower tumour grade (47% in grade 1/2 vs 8% in grade 3,  $p=0.004$ ), positive ER (35% in ER+ vs 5% in ER-,  $p=0.017$ ), and PR (37% in PR+ vs 5% in PR-,  $p=0.011$ ). Overall survival (OS) was 139.5 and 53.7 months for mutation and non-mutation carriers respectively ( $p=0.014$ ). (Ma et al 2009).

Future treatment strategies may be aligned to the presence or absence of *PIK3CA* mutations. The presence of a *PIK3CA* mutation is correlated with sensitivity to monotherapy AKT inhibition (Courtney et al 2010) – and it is therefore considered appropriate to explore AZD5363 in this setting for patients in this population.

#### **1.3.4 Rationale for study design.**

Pre-clinical data has shown that AZD5363 when given in combination with docetaxel is efficacious. This study will test the hypothesis that this pre-clinical finding is applicable to paclitaxel in the clinical setting, utilising the following design:

Part A. Safety run-in: to identify an appropriate and tolerable dose of AZD5363 and dosing schedule (continuous or intermittent), when in combination with weekly paclitaxel, to take forward to Part B.

Part B. Randomised Expansion: to make an assessment of efficacy of the combination (paclitaxel plus AZD5363) against an active control (paclitaxel alone) in a specific target patient population (ER+ve breast cancer) and to explore whether additional efficacy is likely to be present in a *PIK3CA* mutation-positive sub-group for whom it is hypothesised that there will be greater sensitivity to AZD5363.

#### **1.3.5 Rationale for Paclitaxel as combination therapy.**

Chemotherapy remains the mainstay of treatment in metastatic breast cancer (MBC) and the goals in this setting are to prolong survival, alleviate or prevent tumour-related symptoms and improve Quality of Life.

The taxanes, specifically paclitaxel and docetaxel, are amongst the most active agents in MBC (Ghersi et al 2005) and have demonstrated significant activity in MBC in terms of response rate (RR) and progression free survival (PFS) (Beslija et al 2009).

In current clinical practice, paclitaxel is used in doses ranging from 135 to 225 mg/m<sup>2</sup> administered every 3 weeks; however, its weekly administration usually at a dose of 80 mg/m<sup>2</sup> provides superior RR, PFS and overall survival (OS) (Seidman et al 2008).

The toxicity profile of paclitaxel seems to be both dose and schedule dependent. Various dosages and schedules of paclitaxel have been investigated in patients relapsing or failing after previous therapy combinations. The issue of schedule-dependent activity was addressed in several studies. In a phase I dose-finding study, 90 mg/m<sup>2</sup> was found to be the optimal dose in

breast cancer patients (Klaassen et al 1996) and has been utilised in subsequent clinical studies (eg. Miller et al).

In another phase II study, a 3-week schedule with dose densification of paclitaxel given weekly over 6 weeks consisted of a weekly 1-hour infusion of paclitaxel to a maximum dosage of 90 mg/m<sup>2</sup>/wk. Haematologic toxicity was mild, with no grade 3 or 4 toxicity up to 90 mg/m<sup>2</sup>/wk that was considered the recommended dose (RD) for single-agent treatment to be given in the outpatient setting. (Löffler et al 1996)

In this study paclitaxel 90 mg/m<sup>2</sup> will be used in a 3 weekly regimen in combination with daily AZD5363 in 28 days cycles.

## 1.4 Benefit/risk and ethical assessment

### 1.4.1 Potential benefits

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, 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).

AZD5363 is a potent inhibitor of AKT 1, 2 and 3 (IC<sub>50</sub> < 10 nM). Non-clinical *in vitro* and *in vivo* assays have demonstrated inhibition of phosphorylation of the AKT substrates GSK3 $\beta$  and PRAS40, tumour cell proliferation and xenograft tumour growth models. Further details of non-clinical data are available in the Investigators' Brochure.

This study is investigating whether AZD5363 when combined with paclitaxel has the potential to provide benefit in terms of increased efficacy in patients with ER+ advanced or metastatic with or without *PIK3CA* mutation, who have relapsed after chemotherapy or endocrinotherapy, compared to treatment with paclitaxel plus placebo.

### 1.4.2 Potential risks identified from non-clinical toxicology studies with AZD5363

 further information is in the Investigators' Brochure. The monitoring and management of potential risks are discussed below:

#### Cardiovascular effects

Standard exclusion criteria for unstable cardiac conditions and risk factors for QT prolongation are detailed in Section 4.2. Additional clarification is provided to exclude patients who have experienced coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure New York Heart Association (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 blood pressure (SBP) <90mmHg and/or diastolic blood pressure (DBP) <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 (Section 6.4.11), ECG measurements (Section 6.4.9) and Troponin (I or T), MUGA scan or echocardiogram to assess LVEF (Section 6.4.10) and electrolytes (Section 6.4.5) will be performed at the visits shown in Figure 5 and Figure 6 and as clinically indicated for management of adverse events.

### **Haematopoietic system**

Patients with inadequate bone marrow reserve as demonstrated by any of the following laboratory values (absolute neutrophil count  $<1.5 \times 10^9/L$ ; platelet count  $<100 \times 10^9/L$ ; haemoglobin  $<9 \text{ g/dL}$ ) 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 Section 6.4.5.

### **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  $>2.5x$  upper limit of normal (ULN; total bilirubin  $>1.5x$  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 6.4.5. An algorithm will be provided separately to this protocol to provide guidance for the investigation and management of patient reported symptoms of potential acute liver dysfunction and any liver transaminase results in excess of  $8x$  ULN occurring at any time during the study. This algorithm should be used in conjunction with the FDA Draft Guidance for the evaluation of Drug Induced Liver Injury (FDA 2009) See Appendix E.

### **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 6.4.5.

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 6.4.5.

[REDACTED] follicle-stimulating hormone (FSH) and oestrogen levels will be measured as detailed in Section 6.4.5.

### **Renal effects**

Patients with proteinuria (3+ on dipstick analysis or  $>500 \text{ mg/24 hours}$ ) or creatinine  $>1.5$  times ULN concurrent with creatinine clearance  $<50 \text{ ml/min}$ , 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 5](#) and [Figure 6](#). Urine microscopy (red blood cells, white blood cells, bacteria, casts and crystals) will be performed during the study 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.

Please also refer to section [1.4.4](#) for guidance regarding minimisation of risk associated with potential abnormal glucose profiles.

### **Genotoxicity**

### **Phototoxicity**

Based on the potential for phototoxicity, patients receiving AZD5363 will be advised to avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated. Use of sunbeds/tanning booths should be avoided.

### **Reproductive organs**

[REDACTED] no reproductive toxicology nor 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 should agree to use adequate contraception prior to study entry and for the duration of study participation and women who are breast feeding are excluded from the study. Patients should be fully informed of the lack of reproductive toxicity testing, and must have a negative pregnancy test prior to enrolment.

### **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. The following restrictions will therefore be put in place in the study, please refer to Appendix G 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 potentially 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, should AZD5363 pharmacokinetic outlying data be observed in the absence of confounding concomitant medications, patient genetic samples will be requested [REDACTED]

#### **1.4.3 Potential risks identified from early clinical studies with AZD5363:**

To date, the most commonly reported AEs, regardless of dose or causality, are: diarrhoea, hyperglycaemia, fatigue, maculo-papular rash, vomiting, dyspnoea and nausea. The majority of AEs reported in patients receiving AZD5363 have been CTCAE Grade 1 or Grade 2 in toxicity.

Three (DLTs) of maculo-papular rash have been reported in study D3610C00001 under a continuous dosing schedule: one in a 400 mg bd cohort (CTCAE grade 3) and two in a 600 mg bd cohort (CTCAE grade 4).

Five AEs of diarrhoea: CTCAE grade 3 in the continuous dosing at 240 mg bd (n=1), 400 mg bd (n=1), 600 mg bd (n=1) and intermittent dosing (4 days on and 3 days off) at 640 mg bd (n=2)

Seven AEs of hyperglycaemia (post AZD5363 dose), CTCAE grade 3 in the continuous dosing at 400 mg bd (n=2) and intermittent dosing (4 days on and 3 days off) at 480 mg bd (n=1), 640 mg bd (n=4)

#### **1.4.4 Risk minimisation activities for potential risks identified in early clinical studies with AZD5363:**

##### **Glucose homeostasis**

In order to reduce the potential risk of exacerbating abnormal glucose profiles, patients with Type I or Type II diabetes mellitus (irrespective of management), fasting glucose  $\geq 7$  mmol/L or glycosyated haemoglobin (HbA1c)  $\geq 8\%$  at screening will be excluded from clinical studies with AZD5363. Glucose, insulin and insulin C-peptide profiles will be performed on the first dosing day and at steady state during the first treatment cycle, at the start of each subsequent cycle and on discontinuation of AZD5363/placebo. During the first cycle, urinary glucose will be tested twice weekly after patients are discharged from the clinic, with instructions regarding clinic contact on finding a high result. Random blood glucose pre- and post-AZD5363/placebo dosing will be monitored on planned study visit days and when needed to evaluate any episodes of hyperglycaemia. 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 baseline, every 12 weeks and at discontinuation of AZD5363/placebo. A blood glucose intervention algorithm will be provided separately to this protocol to aid investigator management of elevated blood glucose.

### **Diarrhoea**

There are no standard exclusion criteria for patients with diarrhoea; however, patients with previous gastrointestinal surgery that may affect drug absorption are excluded from AZD5363 clinical studies. Diarrhoea can be managed with treatment and interruptions to AZD5363 dosing. Patient reports of diarrhoea are expected to be evaluated and treated by investigators according to local practice (eg, use of medications such as loperamide, need for IV fluid replacement). A toxicity management algorithm will be provided separately to this protocol to aid investigator management of diarrhoea.

### **Rash**

There are no standard exclusion criteria for patients with rash. Rash can be managed with treatment and interruptions to AZD5363/placebo dosing. Patient reports of rash are expected to be evaluated and treated by investigators according to local practice (eg, use of oral or topical steroids, use of oral antihistamine). A toxicity management algorithm will be provided separately to this protocol to aid investigator management of rash.

### **1.4.5 Overall benefit-risk and ethical assessment**

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 breast cancers with or without *PIK3CA* mutation. The non-clinical safety profile and emerging clinical profile from the early clinical studies have not identified risks that would preclude investigation in this setting. The study design aims to minimise potential risks, via confirmation of the optimum combination dose prior to the main randomised study. A dose modification strategy for management of toxicity and monitoring is in place for those risks deemed to be most likely or serious. Thus the benefit/risk assessment for this study supports the co-administration of AZD5363 with paclitaxel in patients with advanced or metastatic breast cancer with or without *PIK3CA* mutation.

## **2. STUDY OBJECTIVES**

### **2.1 Primary objective**

Part A. Safety run-in: To assess the safety and tolerability of two schedules of AZD5363 (continuous and intermittent dosing) when combined with weekly paclitaxel in patients with advanced or metastatic breast cancer; and to recommend, by assessment of dose limiting toxicities and other safety, tolerability, pharmacokinetic and pharmacodynamic data, a dose and schedule of AZD5363 for further study when combined with weekly paclitaxel.



**Part B. Randomised expansion:** To assess the relative anti-tumour activity of AZD5363 when combined with weekly paclitaxel vs. weekly paclitaxel plus placebo by comparison of change in tumour size at 12 weeks (target lesion assessment using Response Evaluation Criteria In Solid Tumours [RECIST 1.1]) in the overall advanced or metastatic ER+ve breast cancer population and in the *PIK3CA* mutation-positive sub-population.

## 2.2 Secondary objectives

### Part A. Safety run-in:

- To make a preliminary assessment of the anti-tumour activity of AZD5363 when combined with paclitaxel by assessment of objective response rate (ORR), and the percentage of patients without progressive disease, at 12 weeks.

### Part B. Randomised expansion:

- To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of ORR at 12 weeks.
- To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of PFS, best objective response (BOR) and DoR.
- To further assess the safety and tolerability of AZD5363 when combined with weekly paclitaxel compared with paclitaxel plus placebo.
- To investigate the effect on patients' quality of life (QoL) of AZD5363 when combined with weekly paclitaxel, compared with weekly paclitaxel alone by changes from baseline, utilising a patient-completed QoL questionnaire.

### Parts A and B:

- To assess the PK of AZD5363 when combined with paclitaxel.
- To assess the PK of paclitaxel alone and when combined with AZD5363.
- To assess the PK/PD relationship between plasma AZD5363 exposure and plasma concentrations of biomarkers (including phospho-PRAS40, total PRAS40, pAKT and pGSK3 $\beta$ ) anti-tumour activity (assessed by RECIST 1.1).

## 2.3 Exploratory objectives

### Parts A and B:

- To investigate the relationship between plasma AZD5363 exposure and plasma concentrations of exploratory biomarkers and efficacy. Biomarkers may include, but are not restricted to, somatic mutation or amplification of genes on the PI3 kinase and related pathways in circulating free plasma DNA (cfDNA).

- To obtain a preliminary assessment of AZD5363 treatment effect by quantitative change in circulating tumour cells (CTCs).
- To investigate the concordance of *PIK3CA* mutation status between per-patient analyses of blood and archival tumour tissue samples.
- To collect optional matched pre-and post- treatment tumour biopsy samples to conduct assessment of the PD effect of therapy compared to baseline.
- To collect and store archival tumour samples and analyse surplus blood or tissue, 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). Biomarkers may include, but are not restricted to, somatic mutation or amplification of genes on the PI3 kinase and related pathways, PTEN protein expression and Akt protein expression. This exploratory analysis will be reported separately.
- To obtain blood samples for DNA extraction 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. This exploratory analysis will be reported separately.

### **3. STUDY PLAN AND PROCEDURES**

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

#### **3.1 Overall study design and flow chart**

This international, multicentre study of AZD5363 when combined with paclitaxel will be conducted in two Parts- A and B:

##### **3.1.1 Part A: Safety run-in**

A multiple ascending-dose evaluation of AZD5363 in each of two schedules (continuous and intermittent dosing) when combined with weekly paclitaxel. These dose escalation schedules may commence at the same time, or one schedule may be initiated in advance of the other to facilitate ease of study initiation.

This part will assess the comparative safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of both schedules of AZD5363 when combined with weekly paclitaxel. A recommended dose and schedule of AZD5363 will be determined for conduct of Part B, the randomised expansion (see section 3.1.2)

The patient population will be female, aged 18 years or older, with advanced or metastatic breast cancer. For inclusion in Part A, patients must not have received any more than two prior courses of chemotherapy for breast cancer. Prior endocrine therapy is allowed.

Patients will be recruited in approximately 8 centres in approximately 4 countries. The number of patients enrolled will be dependent upon the number of dose escalation cohorts required, see below, but a total of approximately 40 patients is anticipated.

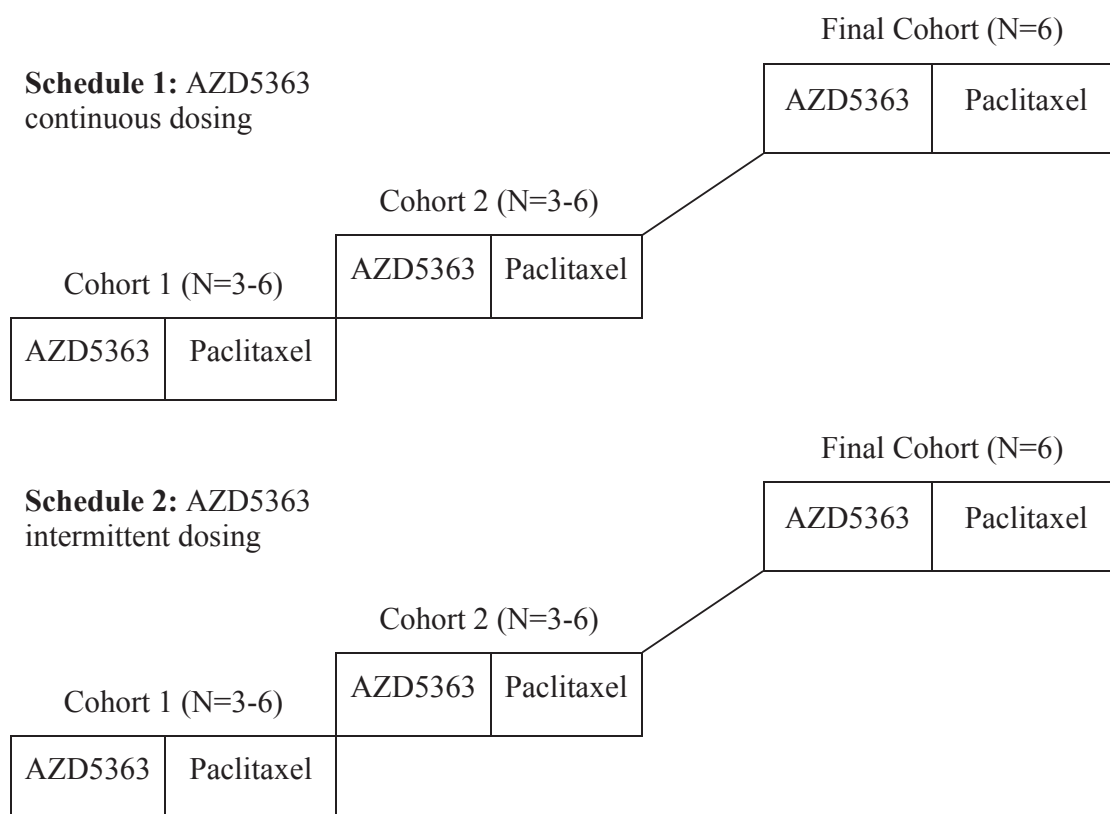
Both schedules of AZD5363 will be in combination with 90 mg/m<sup>2</sup> paclitaxel (see section 5.5.3):

- Continuous dosing: AZD5363 capsules taken orally, twice daily, each day. The starting dose for cohort 1 will be 320 mg (640 mg daily).
- Intermittent dosing: AZD5363 capsules taken orally, twice daily, for repeating weekly cycles of 4 days on treatment followed by 3 days off treatment during each week that paclitaxel is received. The starting dose for cohort 1 will be 360 mg (720 mg daily).

Dose escalating cohorts of 3 to 6 patients will be evaluated under each schedule. A total of 6 patients must be evaluated at a selected dose level for it to be confirmed as the RD. AZD5363 dose escalations and maximum doses attained will not exceed levels deemed tolerated by the Safety Review Committee (SRC) in prior first time in patient study D3610C00001.

The RD for a schedule may or may not be defined by attainment of non-tolerated dose / maximum tolerated dose (NTD / MTD) levels (see section 5.10.2). If the RD is selected prior to attaining MTD, the SRC will determine whether continued dose escalations to NTD/MTD are required.

**Safety run-in – Dose escalation:**



**Subsidiary Japanese patient evaluation (optional)**

A Part A subsidiary dose-escalating safety evaluation may be conducted optionally in a Japanese patient population at a starting dose, and under one schedule, determined by the Safety Review Committee. This evaluation would be conducted to determine a safe and tolerable dose of AZD5363 when in combination with paclitaxel in a Japanese population.

This separate Japanese safety run-in evaluation would commence following determination of the RD and dosing schedule in the Western population. It would proceed in parallel with the Part B randomised expansion, but would not inform any decision regarding the conduct of Part B. The schedule of assessments in the subsidiary Part A would be as detailed in this protocol for Part A. It is not envisaged that a Japanese population would be evaluated under study Part B.

**3.1.2 Part B: Randomised expansion**

A double-blind, stratified and randomised evaluation of AZD5363 when combined with weekly paclitaxel vs. weekly paclitaxel plus placebo. The dose and schedule of AZD5363 will be selected as an outcome from Safety run-in Part A.

The patient population will be female, aged 18 years or older, with ER+ve advanced or metastatic breast cancer, and incorporating a subgroup who have *PIK3CA* mutation-positive tumour(s). For inclusion in Part B, patients must not have received any prior chemotherapy for breast cancer in the advanced or metastatic setting. Prior (neo)adjuvant chemotherapy is allowed (if (neo) adjuvant taxane, there must have been a minimum of 12 months from completion of therapy to relapse).

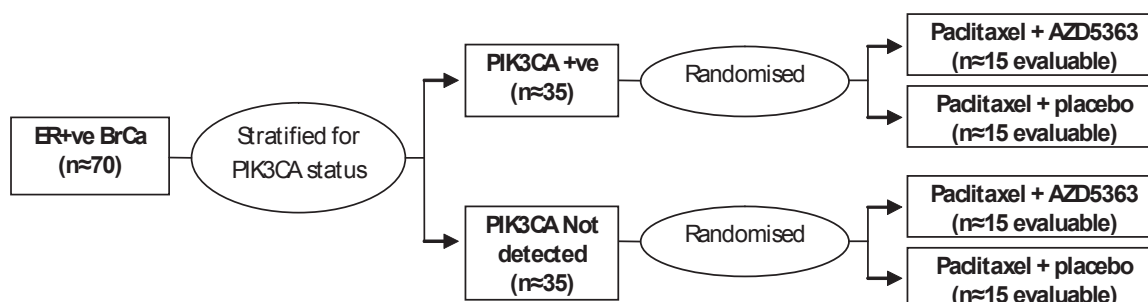
Patients will be recruited in approximately 12 centres in approximately 5 countries. Approximately 70 patients will be enrolled in this phase (to ensure that 60 are evaluable at 12 weeks), of which approximately 35 must have a tumour detectable as carrying a *PIK3CA* mutation.

To be considered evaluable for the randomised expansion primary efficacy analysis, a patient must have baseline and week 12 ( $\pm 1$  week) tumour measurements for assessment of the primary endpoint of change in tumour size, or evidence of objective progression prior to week 12, or in the absence of week 12 measurements and no evidence of objective progression, RECIST measurements available at baseline and 1 visit before or after week 12 such that a prediction for the week 12 result can be made (see section 11.1.1 for details). An overage of approximately 15% of patients is therefore planned to be randomised to allow for potential non-evaluable patients.

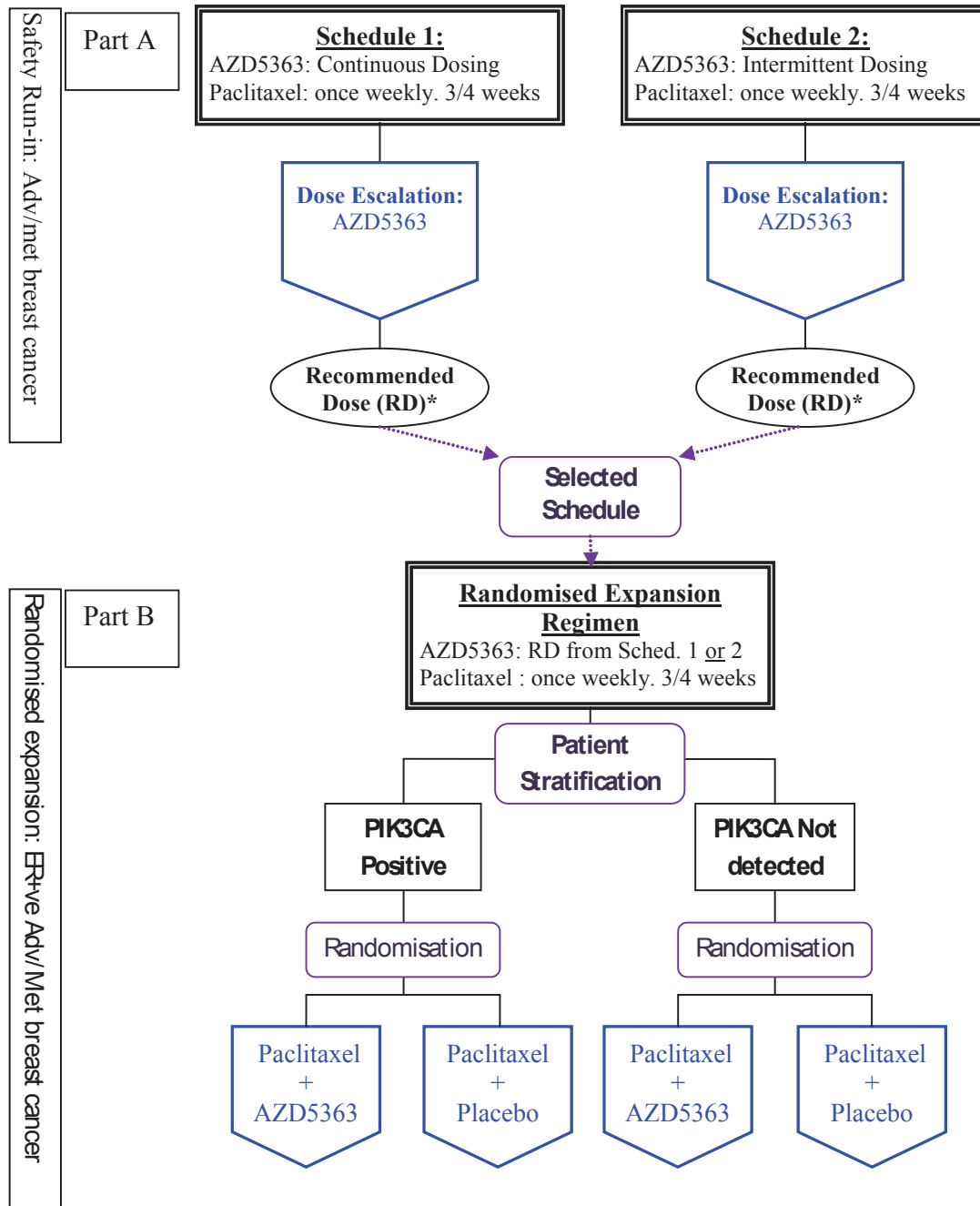
Patients will be stratified to *PIK3CA* mutation ‘positive’ and ‘not detected’ groups by prospective analysis of blood and/or tumour tissue (see sections 5.2 and 6.2.1). Patients within each stratum will be randomised to 28-day cycles (see section 5.5.3) comprising either of:

- Paclitaxel 90 mg/m<sup>2</sup> IV once weekly plus AZD5363 capsules taken orally, twice daily.
- Paclitaxel 90 mg/m<sup>2</sup> IV once weekly plus AZD5363-matching placebo capsules taken orally, twice daily.

**Figure 3 Randomised Expansion: Stratification and Randomisation**



**Figure 4 Study Flow Chart**



\* Recommended dose (RD) = dose level identified by the Safety Review Committee as appropriate for further evaluation in the Part B randomised expansion phase.

### 3.1.3 Treatment Schedules

Under both the continuous and intermittent dosing schedules, first receipt of paclitaxel will be on Cycle 1, Day 1; first receipt of AZD5363/placebo will be on Day 2.

Under the intermittent dosing schedule, weekly AZD5363 regimens thereafter will continue to start on the day after dosing with paclitaxel.

		Cycle 1				Cycle 2 onwards			
		Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
<b>Paclitaxel.</b> Dose day→		Day 1	Day 1	Day 1	None	Day 1	Day 1	Day 1	None
<b>AZD5363</b>	Continuous. Dose days →	Day 2 to Day 28				Day 1 to Day 28			
	Intermittent. Dose days →	D2 to D5	D2 to D5	D2 to D5	None	D2 to D5	D2 to D5	D2 to D5	None

Please refer to Sections 5.5.3 for further definitions and guidance for conduct of treatment cycles.

Please refer to Section 5.5.4 for guidance for conduct of dose modifications.

### 3.1.4 Assessment Schedule

Patients will undergo the assessments detailed in the schedules below, presented separately for those allocated to either the continuous or intermittent dosing schedule. Assessments are applicable to both the Safety Run-in and Randomised Expansion parts unless otherwise indicated.

**Figure 5** Schedule 1: AZD5363/placebo – Continuous Dosing.

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Paclitaxel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
Week →		1	2	3	4	1	2	3	4	1				
Week Day →	-28 to 0	1	2	3	1	2	1	1	1	1				
Paclitaxel dosed (i.v.)	X		X		X		X		X	X→				
AZD5363 dosed (bd)		X	X→	X	X→	X→	X→	X→	X→	X→				
Activity↓														
Informed consent - <i>PIK3CA</i> screen (Part B only)	X													8.4
<i>PIK3CA</i> mutation testing	X													6.2.2
Informed consent - study	X													8.4
Demography& baseline characteristics	X													6.2
Medical/surgical history	X													6.2
Previous/concomitant therapy	X													5.6
Previous cancer therapy	X													5.6
Inclusion / exclusion criteria	X													4
Physical examination	X	X			X					X	X	X	X	6.4.6
Height and weight	X	X								X	X	X	X	6.4.7
WHO performance status	X	X												6.4.8
Vital signs	X	X	X		X	X				X	X	X	X	6.4.11
12-lead ECG	X	X	X	X	X	X				X	X	X	X	6.4.9
MUGA / Echocardiogram	X									X			X	6.4.10



**Figure 5 Schedule 1: AZD5363/placebo – Continuous Dosing.**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Paclitaxel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
<b>Week →</b>		1	2	3	4	1	2	3	4	1				
<b>Week Day →</b>	-28 to 0	1	2	1	2	1	2	1	1	1				
<b>Paclitaxel dosed (i.v.)</b>	X		X		X		X		X	X→				
<b>AZD5363 dosed (bd)</b>		X	X→	X	X→	X→	X→	X→	X→	X→				
Haematology, Clinical chemistry Urinalysis	X	X	X		X		X		X	X	X			6.4.5
Glycosylated haemoglobin	X										X			6.4.12.2
Lipids	X										X			6.4.12.1
Glucose, insulin, insulin c-peptide,		X	X		X		X		X	X	X			6.4.12.3
Pregnancy test	X	X									X			6.4.5
Paclitaxel PK blood samples <sup>1</sup>		X	X		X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>						6.6.2
AZD5363 PK blood samples <sup>1</sup>		X	X		X	X	X	X						6.6.2
Pharmacodynamic blood samples <sup>1</sup>		X	X		X	X	X	X	X	X	X			6.7.1
Exploratory biomarker blood samples <sup>1</sup> (optional)	X	X	X		X		X		X	X				6.8.1.5
Exploratory biomarker hair samples (optional)		X			X									6.8.1.4
Pharmacogenetics (optional)		X												6.9.1
RECIST Tumour assessments	X													6.3.1
Archival tumour sample	X													6.8.1.2
Paired biopsy (optional)	X									X				6.8.1.3

**Figure 5 Schedule 1: AZD5363/placebo – Continuous Dosing.**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Paclitaxel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:	
		1	2	3	4	1	2	3	4						
<b>Week →</b>															
<b>Week Day →</b>	-28 to 0	1	2	3	1	2	1	1	1	1	1	1			
<b>Paclitaxel dosed (i.v.)</b>					X		X			X	X				
<b>AZD5363 dosed (bd)</b>					X	X	X	X	X	X	X				
Circulating tumour cells		X							X						6.8.1.1
Patient meal information			X		X				X						6.4.12.4
Quality of Life questionnaires (Part B only)	X											X			6.5.1
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.6
Subsequent cancer therapy												X	X	X	5.6
Adverse events	X														

1. PK, PD and Biomarker samplings are shown as cumulative timepoints. Please refer to individual study segment tables given in sections 6.6.2 (PK) and 6.8.1.6 (PD/biomarkers)

2. Part A - Safety Run-in phase only: Patients will continue to undergo paclitaxel PK measurements on these occasions.
3. RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1). Part B - Randomised expansion only: Patients will continue to undergo RECIST assessments after cessation of study therapies up to disease progression or withdrawal of consent.

**Figure 6 Schedule 2: AZD5363/placebo – Intermittent Dosing.**

Cycle →	Screen	Cycle 1					Cycle 2					Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section :	
		1	2	3	4	1	2	3	4	1	2						3
<b>Week →</b>																	
<b>Week Day →</b>	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	1	2		
Paclitaxel dosed (i.v.)		X				X				X				X→			
AZD5363 dosed (bd)		X	X→	X	X	X→	X→	X→	X→	X→	X→	X→	X→	X→			
Activity↓																	
Informed consent - <i>PIK3CA</i> screen (Part B only)	X																8.4
<i>PIK3CA</i> mutation testing	X																6.2.2
Informed consent - study	X																8.4
Demography& baseline characteristics	X																6.2
Medical/surgical history	X																6.2
Previous/concomitant therapy	X																5.6
Previous cancer therapy	X																5.6
Inclusion / exclusion criteria	X																4

**Figure 6** Schedule 2: AZD5363/placebo – Intermittent Dosing.

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section :	
		1	2	3	4	1	2	3	4						
<b>Week →</b>															
<b>Week Day →</b>	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2		
Paclitaxel dosed (i.v.)		X				X				X					
AZD5363 dosed (bd)			X	X	X	X	X	X	X	X	X	X	X		
Physical examination	X				X									X	6.4.6
Height and weight	X													X	6.4.7
WHO performance status	X														6.4.8
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.4.11
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.4.9
MUGA / Echocardiogram	X													X	6.4.10
Haematology, Clinical chemistry Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.4.5
Glycosylated haemoglobin	X													X	6.4.12.2
Lipids	X													X	6.4.12.1
Glucose, insulin, insulin c-peptide,		X	X	X	X	X	X	X	X	X	X	X	X	X	6.4.12.3
Pregnancy test	X													X	6.4.5

**Figure 6** Schedule 2: AZD5363/placebo – Intermittent Dosing.

Cycle →	Screen	Cycle 1											Cycle 2					Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section ;						
		1			2			3			4			1			2						3			4		
<b>Week →</b>		1	2	3	5	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2					
<b>Week Day →</b>	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2					
Paclitaxel dosed (i.v.)		X				X				X				X				X				X→						
AZD5363 dosed (bd)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Paclitaxel PK blood samples <sup>1</sup>		X					X <sup>2</sup>			X <sup>2</sup>					X <sup>2</sup>													6.6.2
AZD5363 PK blood samples <sup>1</sup>			X	X	X		X			X			X		X													6.6.2
Pharmacodynamic blood samples <sup>1</sup>		X		X	X		X			X			X		X							X						6.7.1
Exploratory biomarker blood samples <sup>1</sup> (optional)	X		X				X			X			X		X							X						6.8.1.5
Exploratory biomarker hair samples (optional)			X		X																							6.8.1.4
Pharmacogenetics (optional)	X																											6.9.1
RECIST Tumour assessments	X																										X <sup>3</sup>	6.3.1
Archival tumour sample	X																											6.8.1.2
Paired biopsy (optional)	X																					X						6.8.1.3

**Figure 6** Schedule 2: AZD5363/placebo – Intermittent Dosing.

Cycle →	Screen	Cycle 1										Cycle 2				Cycle 3 onward	Paclitaxel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section :
		1		2		3		4		1	2	3	4							
<b>Week →</b>																				
<b>Week Day →</b>	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	1	2	1	2	1	2	
Paclitaxel dosed (i.v.)		X				X				X				X				X→		
AZD5363 dosed (bd)			X	X→	X		X→			X→				X→				X→		
Circulating tumour cells		X												X				X <sup>3</sup>		6.8.1.1
Patient meal information			X		X		X			X			X					X		6.4.12.4
QoL questionnaires (Part B only)	X																	X <sup>3</sup>		6.5.1
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.6
Subsequent cancer therapy																			X	5.6
Adverse events	X																			

- PK, PD and Biomarker samplings are shown as cumulative timepoints. Please refer to individual study segment tables given in sections 6.6.2 (PK) and 6.8.1.6 (PD/biomarkers)
- Part A - Safety Run-in phase only: Patients will continue to undergo paclitaxel PK measurements on these occasions.
- RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1). Part B Randomised expansion only: Patients will continue to undergo RECIST assessments after cessation of study therapies up to disease progression or withdrawal of consent.

## **4. PATIENT SELECTION CRITERIA**

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

### **4.1 Inclusion criteria**

For inclusion in the study patients should fulfil the following criteria:

#### All patients:

1. Provision of informed consent prior to any study specific procedures.
2. Female patients, aged at least 18 years.
3. Histological or cytological confirmation of breast cancer (see Parts A and B inclusion criteria below).
4. World Health Organisation (WHO) performance status 0-1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks.
5. Patients must be able to swallow and retain oral medication.
6. Patients of child-bearing potential should be using adequate contraceptive measures (see Restrictions section below), should not be breast feeding and must have a negative pregnancy test prior to start of dosing.

or

Patients 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. Patients must not be breast feeding.

#### Part A. Safety Run-in:

1. Patients with histological or cytologic diagnosis of breast cancer with evidence of advanced or metastatic disease. Lesions should not be amenable to surgery or radiation of curative intent.

2. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT or MRI and is suitable for repeated assessment.

Part B. Randomised Expansion:

1. Patients with histological or cytologic diagnosis of ER+ve breast cancer with evidence of relapsed advanced or metastatic disease. Lesions should not be amenable to surgery or radiation of curative intent and must be considered unlikely to be rendered eligible for surgery by treatment with paclitaxel in this study.
2. Patients who relapsed more than 12 months after completing adjuvant endocrine therapy, or who have not had adjuvant endocrine therapy, must have received prior endocrine therapy for advanced or metastatic disease.\*

Patients who relapsed on adjuvant endocrine therapy, or within 12 months of completing adjuvant endocrine therapy, may enter the study without prior endocrine therapy for advanced or metastatic disease.\*

3. Provision of archival tumour sample for *PIK3CA* mutation testing.
4. Provision of baseline plasma sample for *PIK3CA* mutation testing.
5. At least one tumour lesion, not previously irradiated, that can be measured accurately at baseline as  $\geq 10$  mm in the longest diameter (except lymph nodes which must have short axis  $\geq 15$  mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements.

\* For guidance when evaluating inclusion criteria under item 2 above.

The following patients would be eligible for inclusion:

- Relapsed whilst on adjuvant endocrine therapy
- Relapsed  $< 12$  months after completing adjuvant endocrine therapy (with or without receiving endocrine therapy in the advanced or metastatic setting)
- Relapsed  $> 12$  months after completing adjuvant endocrine therapy and has received endocrine therapy in the advanced or metastatic setting

The following patients would not be eligible for inclusion:

- Adjuvant endocrine therapy- naive
- Relapsed  $> 12$  months after completing adjuvant endocrine therapy and has not received endocrine therapy in the advanced or metastatic setting



## 4.2 Exclusion criteria

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

### All Patients:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
2. Previous enrolment in the present study.
3. Participation in another clinical study with an investigational product (IP) during the last 30 days.
4. Receipt of any investigational drug within 30 days or 5 half-lives, whichever is longer, of the first dose of AZD5363 or matching placebo.
5. Any prior exposure to agents with primary pharmacological activity of inhibition of AKT, any inhibitor with PI3K pharmacology, including prior dosing with AZD5363 in this, or any other, study (for examples of excluded agents, please refer to Appendix H).
6. Any prior exposure to agents with PI3K, or mixed PI3K and mTOR kinase pharmacology or any mTOR kinase inhibitor. Prior exposure to rapalogs and other allosteric mTOR/mTORC1 complex inhibitors is allowed. (for examples of excluded and allowed agents, please refer to Appendix G).
7. Planned concomitant use of aromatase inhibitors or any cancer therapy, with the exception of bisphosphonates and denosumab, during the study.
8. Exposure to potent inhibitors or inducers of CYP3A4 or CYP2D6 or substrates of CYP3A4 within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort).
9. Clinically significant abnormalities of glucose metabolism as defined by any of the following:
  - Diagnosis of diabetes mellitus type I or II (irrespective of management).
  - Glycosylated haemoglobin (HbA1C)  $\geq 8.0\%$  at screening (64 mmol/mol)  
(conversion equation for HbA1C [*IFCC-HbA1C* (mmol/mol) = [*DCCT-HbA1C* (%) - 2.15] x 10.929)
  - Fasting Plasma Glucose  $\geq 7.0$  mmol/L (126 mg/dL) at screening. Fasting is defined as no caloric intake for at least 8 hours.

10. Radiotherapy with a wide field of radiation within 4 weeks or radiotherapy with a limited field of radiation for palliation within 2 weeks before the first dose of IP (AZD5363/placebo).
11. Last dose of anticancer therapy - other than for advanced or metastatic breast cancer (chemotherapy, radiation therapy, surgery, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, or tumour embolisation) must be more than 21 days (more than 6 weeks for nitrosurea or mitomycin C) prior to the first dose of study treatment. If sufficient wash-out time has not occurred due to schedule or PK properties, a longer wash-out period will be required as agreed by AZ and the investigator.
12. Major surgery (excluding placement of vascular access) within 4 weeks before the first dose of study treatment.
13. 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.
14. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.
15. Any of the following cardiac criteria:
  - Mean resting corrected QT interval (QTc) >470 msec obtained from 3 consecutive ECGs.
  - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block.
  - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, potential for torsades de pointes, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval.
  - Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA Grade 2.
  - Uncontrolled hypotension – SBP <90 mmHg and/or DBP <50 mmHg.
  - Cardiac ejection fraction outside institutional range of normal or <50% (whichever is higher) as measured by echocardiogram (or MUGA scan if an echocardiogram cannot be performed or is inconclusive).

16. With the exception of alopecia, any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting study treatment.
17. Absolute neutrophil count  $<1.5 \times 10^9/L$ .
18. Platelet count  $<100 \times 10^9/L$ .
19. Haemoglobin  $<9 \text{ g/dL}$  ( $<5.59 \text{ mmol/L}$ ). [Note: any blood transfusion must be  $>14$  days prior to the determination of a haemoglobin  $\geq 9 \text{ g/dL}$  ( $\geq 5.59 \text{ mmol/L}$ )].
20. Alanine aminotransferase (ALT)  $>2.5$  times ULN if no demonstrable liver metastases or  $>5$  times ULN in the presence of liver metastases.
21. Aspartate aminotransferase (AST)  $>2.5$  times ULN if no demonstrable liver metastases or  $>5$  times ULN in the presence of liver metastases. Elevated Alkaline phosphatase (ALP) is not exclusionary if due to the presence of bone metastasis and liver function is otherwise considered adequate in the investigator's judgement.
22. Total bilirubin  $>1.5$  times ULN if no liver metastases or  $>3$  times ULN in the presence of liver metastases.
23. Creatinine  $>1.5$  times ULN concurrent with creatinine clearance  $<50 \text{ ml/min}$  (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is  $>1.5$  times ULN.
24. Proteinuria  $>3+$  on dipstick analysis or  $>3.5 \text{ g/24 hours}$  or a urine protein/creatinine ratio  $>3.5$ .
25. Sodium or potassium outside normal reference range for site.
26. 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 / paclitaxel.
27. History of hypersensitivity to active or inactive excipients of AZD5363 or paclitaxel or drugs with a similar chemical structure or class to AZD5363 or paclitaxel.
28. 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.
29. Current disease or condition known to interfere with absorption, distribution, metabolism or excretion of drugs.

30. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
31. Evidence of dementia, altered mental status or any psychiatric condition that would prohibit understanding or rendering of informed consent.
32. Previous allogeneic bone marrow transplant.
33. Known immunodeficiency syndrome.
34. Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection will exclude patient from the optional pharmacogenetic evaluation, although the patient may enter the main study.

#### Part A. Safety Run-In:

1. More than two prior courses of chemotherapy (including taxanes) for breast cancer in the advanced or metastatic setting.
2. If patients have received prior treatment with anthracyclines or mitoxantrone, cumulative exposure must be less than 360 mg/m<sup>2</sup> for doxorubicin, 720 mg/m<sup>2</sup> for epirubicin or 72 mg/m<sup>2</sup> for mitoxantrone.

#### Part B. Randomised Expansion:

1. Any prior chemotherapy for breast cancer in the advanced or metastatic breast setting. Prior adjuvant or (neo)adjuvant chemotherapy is allowed, however, if the adjuvant or (neo)adjuvant therapy contained a taxane, at least 12 months should have elapsed since completion of the therapy before entry to this study.

For procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

## **5. STUDY CONDUCT**

### **5.1 Restrictions during the study**

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

1. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of study treatment.
2. Patients to avoid excessive sun exposure and use adequate screening protection. The use of sun-beds and tanning booths should be avoided.

3. On PK sampling days in the clinic, patients must fast (water to drink only) from at least 2 hours prior to a dose of study therapy to at least 1 hour post-dose. On all other study days patients are requested to keep to these fasting restrictions wherever possible.
4. On blood glucose assessment days (incorporating Clinical chemistry and glucose/insulin/insulin c-peptide) evaluations it is requested that patients refrain from calorific intake for a minimum of 8 hours prior to the morning dose of AZD5363 / placebo.
5. 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 or intrauterine system.
  - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
  - Male partner 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.

6. 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.

## **5.2 Patient enrolment, randomisation and initiation of investigational product**

The Principal Investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.
2. Obtain a unique enrolment number, beginning with 'E#'. The E-code is a 7-digit number comprising the centre number, the dosing schedule and the patient number within that particular centre. This number is the patient's unique identifier and is

used to identify the patient on the electronic case report form (eCRF), and should be entered in to the patient medical records. [REDACTED]

Once a candidate patient has been identified and consented, the site should obtain the enrolment number as follows:

Part A: For the safety run-in phase, the study site will notify the AstraZeneca Study Team that a patient has been consented by completion and e-mailing of a registration form. AstraZeneca will reply, providing the E- number. For Part A this will include notification of which dosing schedule the patient is allocated to.

Part B: For the randomised expansion phase, the study site will contact the Interactive Voice/Web Response System (IVRS/IWRS) by telephone or using the web to notify that a patient has consented. IVRS/IWRS will provide the E- number.

Further guidance on this process will be provided in a separate patient allocation process document.

All screened patients are assigned an E-code and will be listed on the patient enrolment and identification log irrespective of whether or not they subsequently receive study therapy. If a patient withdraws from participation in the study, their E-code will not be reused and the patient will not be allowed to re-enter the study.

For the Randomised Expansion part, if the patient is not randomised the site should notify IVRS/IWRS via a Discontinuation Call to enable the termination of the patient in the system.

3. Determine patient eligibility. See Sections 4.1 and 4.2
4. As patients become eligible for the study they will be assigned separate four digit identification codes. [REDACTED]

Part A: For the safety run-in phase, the study site will notify the AstraZeneca Study Team that a patient is eligible by completion and e-mailing of a registration form. AstraZeneca will reply, providing the identification code. [REDACTED]

**Part B:** For the randomised expansion phase, the study site will contact the IVRS/IWRS by telephone or using the web to confirm whether the patient is/is not eligible and, if eligible, to report the *PIK3CA* mutation status: 'positive' or 'not detected' (see section 5.2.1) to enable stratification. IVRS/IWRS will provide the randomised identification code. [REDACTED]

[REDACTED] The treatment randomisation will not be indicated under this system.

It is requested that sites obtain the randomised identification code on the day that the patient is ready to commence treatment.

Further guidance on this process will be provided in a separate patient allocation process document. Procedures will be provided in an IVRS/IWRS user manual that will be provided to each centre.

If a patient withdraws from participation in the study, then her identification code cannot be reused.

### **5.2.1 Procedure for identification of tumour *PIK3CA* mutation status and stratification.**

#### **Determination of *PIK3CA* mutation status**

Blood (for cfDNA) and most recent archival tumour samples should be provided at screening for determination of *PIK3CA* mutation status (see section 6.2.2)

Where possible, samples should be collected no later than two weeks prior to intended first dosing date. Samples will be analysed by Quintiles on behalf of AstraZeneca and the results reported to the study site within 7-14 days of transfer.

Patients will be designated as: '*PIK3CA* mutation positive' or '*PIK3CA* mutation not detected'. Where a sample cannot be analysed, or the analysis is flawed/indeterminate, a status of 'unknown' will be reported. The results from both the blood and tumour analyses will be utilised to derive a single 'defined' *PIK3CA* mutation status for each patient with reference to the algorithm below.

**Part A. Safety Run-In:** Defined *PIK3CA* mutation status is not a requirement for commencement of treatment, but should be recorded prior to completion of Cycle 1.

**Part B. Randomised Expansion:** Defined *PIK3CA* mutation status is required prior to commencement of treatment for stratification of patients to *PIK3CA* mutation-positive and mutation-not detected groups (see 'Patient stratification by *PIK3CA* mutation status' below).

If it is not possible to obtain one, or both, sample types at screening, the missing sample(s) must be provided no later than the end of Cycle 1.

		Sample type - Tissue		
PIK3CA mutation result→↓		Positive (+ve)	Not detected (ND)	Unknown / unavailable (U)
Sample type - Blood	Positive (+ve)	+ve	+ve	+ve
	Not detected (ND)	+ve	ND	ND
	Unknown (U)	+ve	ND	U

**Note:**

Pre-existing *PIK3CA* mutation status, where generated from a relevant tumour sample as part of local clinical practice, will also be recorded. These data may be utilised, if necessary, on study completion to assist in confirmation of mutation status where there is a discrepancy between blood and tumour *PIK3CA* mutation results from the central analysis.

Where an archival tumour sample cannot be provided in sufficient time for analysis by Quintiles to support determination of defined *PIK3CA* mutation status (Part B) or the result is ‘unknown’ (Part A or B), mutation status derived from a prior locally-conducted analysis may be utilised. This, however, will only be acceptable where the analytical methodology/kit has been approved in advance by AstraZeneca.

**Patient stratification by *PIK3CA* mutation status (Part B)**

Patients will be stratified to ‘*PIK3CA* mutation positive’ or ‘*PIK3CA* mutation not detected’ arms prior to randomisation.

Patients assigned a *PIK3CA* mutation status of ‘Unknown’ will not be eligible to participate in Part B. In cases where an archival tumour sample is not received in time to be analysed by the central laboratory during screening, defined status may be derived from the blood sample alone, or it may be applicable to utilise the status from a prior, locally-conducted tumour analysis, see above.

If a patient is initially stratified to the ‘Not detected’ arm based upon a blood sample alone, or blood sample plus locally-conducted tumour analysis, and a subsequent, delayed, tumour sample is ‘positive’ – the stratification will not be changed but the discrepancy will be noted. Any requirement to assign additional patient places to either stratification arm will be determined on an as-needed basis, dependent upon the number of discrepant patients.

**5.2.2 Procedures for allocation and randomisation**

Part A. Safety Run-In

A central coordinator at AstraZeneca is responsible for the process of allocation of patients to treatment schedules 1 or 2.



Once the eligibility of a patient for the Safety run-in phase has been confirmed, the study site should notify the AstraZeneca coordinator by completion and e-mailing of a registration form. Patients will be allocated sequentially, in the order of notification, to each open dosing schedule and will be assigned the four digit identification code.

If either schedule completes, is terminated or recruitment to it is temporarily halted due to e.g., a full quota of patients being entered to a cohort; new patients will be allocated to the other, ongoing schedule to ensure that eligible consented patients are not denied, or have delayed, access to participation in this study.

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.

#### Part B. Randomised Expansion:

The biostatistics group within AstraZeneca or representative is responsible for generating the randomisation scheme. The randomisation scheme will be produced by a computer software program that incorporates a standard procedure for generating random numbers.

Once the eligibility of a patient for the Expansion phase has been confirmed and the patient has been stratified based upon *PIK3CA* mutation status, the study site should contact the Centralized IVRS/IWRS by telephone or using the web for allocation of a randomised identification code, as described above.

Patient eligibility must be established before drug is dispensed.

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

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

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

## 5.4 Blinding and procedures for unblinding the study

This section is applicable to the Part B Randomised Expansion part only.

### 5.4.1 Methods for ensuring blinding

Study drug will be labelled using a unique Medication Identification (MedID) number, which is linked to the randomisation scheme. AZD5363 and matching placebo capsules will be identical and presented in the same packaging to ensure blinding of the study drug.

### 5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

## 5.5 Treatments

### 5.5.1 Identity of investigational product(s)

**Table 1 Dosage form and strength of investigational product.**

Investigational product	Dosage form and strength
AZD5363 (blinded and unblinded)	5 mg to 165 mg oral formulation
Matching placebo (blinded)	5 mg to 165 mg oral formulation

AstraZeneca R&D Supply Chain (or contract research organisation) will pack, label, and supply the IP for this study.

AZD5363/placebo will be packed into white high-density polythene bottles with child resistant, tamper evident closures. Study drug must be kept out of the reach of children. Patients will be supplied with sufficient amounts of study drug at each dispensing visit plus overage.

During the Randomised Expansion phase, IP will be supplied only following notification to IVRS/IWRS, and IVRS/IWRS must be contacted before dispensing a new study drug supply to the patient

### **5.5.2 Identity of combination product.**

Paclitaxel will be provided from commercially available supplies. Normally available stock will be used in keeping with the standard local practice. Generic paclitaxel may be used if available.

### **5.5.3 Doses and treatment regimens**

#### **AZD5363 / matching placebo:**

A twice daily regimen of an oral formulation given on a continuous or intermittent weekly dosing schedule.

Where possible all doses of AZD5363/placebo should be taken, at approximately the same times each day, in a fasted state (water to drink only) from at least 2 hours prior to the dose to at least 1 hour post-dose. Please also refer to Restrictions (section 5.1) for further guidance regarding patient fasting status on study assessment days.

If vomiting occurs within 30 minutes after AZD5363/placebo dosing, or later if the capsule(s) can be identified in the vomit content, the patient can re-take new capsule(s)

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 (other than to allow for receipt of Day 1 paclitaxel under the continuous dosing schedule, see Paclitaxel section below), 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/placebo capsule(s) on time.

#### **Paclitaxel:**

A weekly single intravenous (iv) infusion of 90 mg/m<sup>2</sup> given over approximately one hour (with the actual time recorded in the CRF) via a rate-controlling device. Patients will receive 3 consecutive weekly paclitaxel infusions (given on Day 1 of weeks 1, 2 and 3), followed by one week off-treatment within each 28-day treatment cycle (see below). Please also refer to local paclitaxel label.

#### **Treatment Schedules:**

Under both the continuous and intermittent dosing schedules, first receipt of paclitaxel will be on Cycle 1, Day 1; first receipt of AZD5363/placebo will be on Day 2.

Thereafter, under the intermittent dosing schedule, weekly AZD5363 regimens will continue to start on the day after receipt of paclitaxel.

		Cycle 1				Cycle 2 onwards			
		Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
<b>Paclitaxel.</b> Dose day→		Day 1	Day 1	Day 1	None	Day 1	Day 1	Day 1	None
<b>AZD5363</b>	Continuous. Dose days →	Day 2 to Day 28				Day 1 to Day 28			
	Intermittent. Dose days →	D2 to D5	D2 to D5	D2 to D5	None	D2 to D5	D2 to D5	D2 to D5	None

**Note:**

For the continuous dosing schedule; on those days in which both paclitaxel and AZD5363/placebo are to be received – **the paclitaxel infusion must be completed before the first dose of AZD5363/placebo is given.**

For the intermittent dosing schedule; AZD5363/placebo should not be taken on any week that the paclitaxel infusion is not administered – either due to a scheduled off-drug week or unscheduled omission or delay. Where paclitaxel is ceased entirely, AZD5363/placebo may be continued on a weekly schedule at the investigator’s discretion.

For the purposes of planning - a standard treatment cycle is defined as 4 weeks:- comprising three weeks of paclitaxel followed by one week off-therapy, regardless of receipt of AZD5363/placebo. Where possible, investigators are strongly urged to maintain patients to this schedule. For Part A dose cohort evaluability it is necessary for Cycle 1 to comprise three doses of paclitaxel within a four week period in the absence of a DLT (see Section 5.10.5).

For study conduct - the start of a cycle will be determined by commencement of paclitaxel following a period off-therapy of ≥1 week. After Cycle 1, a treatment cycle will be defined as receipt of a minimum of one, and a maximum of three, weeks of paclitaxel therapy followed by a period of ≥1 week off-therapy, regardless of receipt of AZD5363/placebo.

For example; if a patient completes a standard 4 week cycle (Cycle A), but then receipt of paclitaxel is delayed by a further week, the next cycle will not formally commence until next first receipt of paclitaxel (Day 1 Cycle B). Under the continuous dosing schedule - during the ‘missed’ week, the patient will continue to receive AZD5363/placebo; this period will be taken as an extension to the previous cycle (Cycle A).

Where paclitaxel has ceased, but patients continue to receive AZD5363/placebo: The start of a cycle will be the day of first receipt of AZD5363/placebo (or the day before that if the patient is on the intermittent dosing schedule). Each cycle will be 28 days.

Patients should continue on treatment with AZD5363/matching placebo bd and weekly paclitaxel until RECIST 1.1 defined objective progression or until a treatment discontinuation criterion is met. See Section 5.8

- If paclitaxel is discontinued for reasons other than disease progression, the patient may continue on AZD5363/matching placebo alone at the investigator's discretion. The patient must continue being scanned for RECIST 1.1 assessment every 12 weeks ( $\pm 1$  week) until objective disease progression (even if further anticancer therapy is administered) or withdrawal from AZD5363/matching placebo treatment
- If AZD5363/matching placebo is discontinued for reasons other than disease progression, the patient may continue on paclitaxel alone at the investigator's discretion. The patient must continue being scanned for RECIST 1.1 assessment every 12 weeks ( $\pm 1$  week) until objective disease progression (even if further anticancer therapy is administered) or withdrawal from paclitaxel.
- If a patient becomes amenable to surgery for removal of their tumour, surgery and/or adjuvant treatment with AZD5363/matching placebo/paclitaxel is permitted. The patient must continue being scanned for RECIST 1.1 assessment post-surgery until objective disease progression.

#### 5.5.4 Dose modifications

In the event of an AE which the investigator considers to be related to the administration of study treatment, supportive therapy should be given at the discretion of the investigator. In addition, the investigator may decide that dosing of study treatment should be temporarily interrupted, a subsequent treatment cycle delayed or study treatment permanently discontinued as per the guidelines outlined below. For details of dose adjustments for general toxicities and specific dose management for hyperglycemia, skin reactions and diarrhea, please refer to Appendix H.

As the intent of the study is to establish a RD of AZD5363 when combined with paclitaxel, it is recommended that, in instances where a toxicity requiring modification of study treatment cannot be associated with one of the two agents specifically, the adjustment to study treatment is made to AZD5363 and not paclitaxel. However, in instances where the investigator considers the AE of concern to be particularly associated with paclitaxel then action with respect dosing may be taken with the paclitaxel alone or paclitaxel and AZD5363 together.

#### AZD5363/placebo

It is requested that in the event of suspected toxicities associated with receipt of AZD5363/placebo, the investigator delay or temporarily suspend dosing. Dose-level reductions should not be carried out, unless in consultation and agreement with the AstraZeneca Study Delivery Team Physician.

If receipt of AZD5363/placebo is suspended for >28 continuous days, this study therapy should be permanently withdrawn. Any request to continue therapy after such a suspension must be agreed with the AstraZeneca Study Delivery Team Physician.

**During the Part A dose evaluation period (Cycle 1).** If a patient experiences a DLT or an unacceptable toxicity occurs, AZD5363 treatment will be stopped and supportive therapy administered as required. If the toxicity resolves, or reverts to CTCAE grade 0 or 1 or baseline (pre-study), levels within 28 days of onset, and the patient is showing clinical benefit, treatment with AZD5363 may be restarted at a lower dose level at the discretion of the investigator. Dose reductions should be in single or multiple increments of 80 mg bd to a minimum dose of 80 mg bd for the continuous dosing schedule and 120 mg bd for the intermittent dosing schedule.

**During the Part A post-dose evaluation period (Cycle 2 onwards) and Part B.** Any toxicity observed during the course of the study that is suspected of being related to AZD5363/matching placebo may be managed at the discretion of the investigator by dose interruption or by dose reduction. Repeat dose interruptions are to be allowed as required, for a maximum of 4 weeks (28 days) on each occasion. Dose reductions should be in single or multiple increments of 80 mg bd to to a minimum dose of 80 mg bd for the continuous dosing schedule and 120 mg bd for the intermittent dosing schedule.

All dose modifications and interruptions (including any missed doses due to AEs), and the reasons for the dose modifications/interruptions are to be recorded in the CRF.

See Appendix H for instruction regarding AZD5363/placebo dose modifications

### **Paclitaxel**

**During the Part A dose evaluation period (Cycle 1).** Paclitaxel first dose, Cycle 1, Day 1, must be administered at 90 mg/m<sup>2</sup>. Dose reductions or dose interruptions/omissions for the second and third infusions in Cycle 1 may be implemented at the discretion of the investigator to alleviate suspected toxicities. Single reductions should be in steps of no more than 20 mg/m<sup>2</sup>. Patients receiving less than 80% of the intended dose (90 mg/m<sup>2</sup> x 3) within the 28 days, and that do not experience a DLT, will not be evaluable under the dose escalation review criteria (see section 5.10.5)

Cycle 1 will comprise a 28-day evaluation period, regardless dose reductions or dose omissions, unless the patient experiences a DLT.

**During the Part A post-dose evaluation period (Cycle 2 onwards) and Part B.** At the discretion of the investigator, reduced doses may be administered in subsequent cycles to alleviate suspected toxicities according to local clinical practice. In the event of suspected neutropenia, guidance regarding paclitaxel dose modifications is provided in Appendix H.

If receipt of paclitaxel is suspended for ≥28 continuous days, this study therapy should be permanently withdrawn. Any request to continue therapy after such a suspension must be agreed with the AstraZeneca Study Delivery Team Physician.

### **5.5.5 Safety Run-In: Starting dose and dose escalation scheme**

For Study Part A; administration of AZD5363 will commence, when combined with paclitaxel, at cohort 1 of each schedule at doses of:

- Continuous dosing: 320 mg bd (640 mg daily).
- Intermittent dosing (4 days of treatment followed by 3 days off-treatment: 360 mg bd (720 mg daily).

These starting doses are below the AZD5363 monotherapy doses of: 400 mg bd (continuous dosing schedule) and 480 mg bd (intermittent dosing schedule) deemed tolerable in the ongoing Phase I multiple-ascending dose study (D3610C00001) in patients with advanced solid malignancies at the time of initiating Part A.

Patients will be enrolled to ensure a minimum of three and a maximum of six evaluable patients per dose escalation cohort. For procedures and definitions associated with dose escalation, see Section 5.10.

### **5.5.6 Randomised expansion: Selected Dose**

Study Part B will be conducted at a dose and schedule of AZD5363, when combined with paclitaxel, selected from Part A.

### **5.5.7 Labelling**

AZ will provide AZD5363/matching placebo capsules to the study sites in bottles with child-resistant, tamper-evident closures. Bottle 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.

The label will include the following information:

- Name of sponsor (AstraZeneca).
- IP/study drug dosage form, route of administration, and quantity of dosage units.
- Storage conditions.
- Study code.
- Study Part (i.e., Safety run-in/randomised).
- Enrolment code.
- Directions for use.

- MedID for Part B Randomised phase of study.

### **5.5.8 Storage**

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

## **5.6 Concomitant and post-study treatment(s)**

Information on any treatment received by the patient, with reasons for its provision, will be recorded in the eCRF from 4 weeks prior to starting study treatment up to 28 days after the last dose of AZD5363/placebo or until objective progression, whichever is the latest. 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 8 and Appendix G), should be maintained on it throughout the study period.

Other anticancer agents, investigational agents and radiotherapy should not be given while the patient is on study treatment although radiation for palliation at focal sites is permitted.

Pre-medication will be allowed after, but not before the first dose of study treatment. This includes management of diarrhoea, nausea and vomiting. Pre-medication required for paclitaxel therapy is allowed as per local standards and label.

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 or after Cycle 2.

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 Delivery Team Physician.

Patients may receive bisphosphonates for the treatment of bone metastases.

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

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

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

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



### **5.6.1 Use of metformin**

Metformin is currently recommended for the management of hyperglycaemia occurring in patients participating in studies of AZD5363 (see section 1.1.2, last paragraph). 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 administered (the half-life of AZD5363 is approximately 8-15 hours), and should be withdrawn when treatment with AZD5363 is withdrawn, unless otherwise clinically indicated.

[REDACTED] when taking both AZD5363 and metformin concurrently patients should attend the clinic for monitoring of serum creatinine at least once per week for the first 3 weeks after initiation of metformin, then every 3 weeks thereafter.

### **5.6.2 Prohibited medications**

Patients are not eligible to enter the study if they have received any of the medications specified in the exclusion criteria or are unable to meet the cautions and restrictions for prohibited therapies. Refer to Section 4.2 and Appendix G.

## **5.7 Treatment compliance**

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the eCRF.

When patients are at the clinic, compliance will be assured by supervised administration of AZD5363/matching placebo by the investigator or his/her delegate. Paclitaxel will be administered in the clinic therefore compliance is not an issue.

Patients will be asked to return all unused AZD5363/matching placebo capsules at each visit (if treatment is continuing). Compliance will be assessed by means of counts of returned unused AZD5363/matching placebo at each clinic visit. Compliance will be checked during and at the end of the study, by the site staff and study monitor.

### **5.7.1 Accountability**

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

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

- Deliveries of such products from AZ are correctly received by a responsible person.
- Such deliveries are recorded.

- Study treatments are handled and stored safely and properly as stated on the label.
- AZD5363/matching placebo is only dispensed to study patients in accordance with the protocol.
- Patients return all unused medication and empty containers to the investigator.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the AZD5363/matching placebo was dispensed, the quantity and date of dispensing and unused AZD5363/matching placebo returned to the investigator. This record is in addition to any drug accountability information recorded on the CRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained in the investigator site file.

All unused or returned medication, after drug accountability, should be destroyed according to local AZ procedures, this can be at site or in the marketing company wherever possible. In the event that this is not possible, the medication should be returned to the local distribution centre for destruction.

AZD5363/matching placebo and label accountability records will be maintained by the study site personnel. These will be used in conjunction with the handling and preparation worksheets for recording all drug and label use.

## **5.8 Discontinuation of investigational product**

Patients may be discontinued from IP at any time, without prejudice to further treatment. If a patient discontinues IP for reasons other than death, then they should still continue in the study up to objective disease progression assessed by RECIST 1.1, unless they withdraw consent from the study.

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event.
- Severe non-compliance to study protocol in the judgement of the investigator and/or AstraZeneca.
- Confirmed objective disease progression assessed by RECIST 1.1.
- Patients incorrectly initiated on IP (see Section 5.3).
- Patient becomes pregnant.

- Patient experiences CTC grade 4 hyperglycaemia.
- Patient experiences:
  - ALT or AST >8x ULN.
  - or, ALT or AST >5x ULN for more than 2 weeks.
  - or, ALT or AST >3x ULN and (total bilirubin >2x ULN or INR >1.5).
  - or, ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

### **5.8.1 Procedures for discontinuation of a patient from investigational product**

A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s) (See [Figure 5](#) and [Figure 6](#) for assessments to be performed). Adverse events will be followed up (See Sections [6.4.3](#) and [6.4.4](#)); diary cards, questionnaires and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section [5.9](#).

It is important to determine the wishes of the patient – to differentiate between discontinuation from IP or complete withdrawal from the study when consent is withdrawn.

## **5.9 Withdrawal from study**

Patients are at any time free to withdraw from study (IP 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 and assessed by an investigator. Adverse events will be followed up (See Sections [6.4.3](#) and [6.4.4](#)); diary cards, questionnaires and all study drugs should be returned by the patient.

Part A. Safety Run-in: Patients that are withdrawn from the study but are evaluable per the definition in Section [5.10.5](#) will not be replaced. Any patient that is withdrawn and is not evaluable will be replaced to ensure a minimum number of evaluable patients.

Part B. Randomised Expansion: Patients that are withdrawn will not be replaced

At the point of withdrawal, no further study procedures or follow up assessments will be performed and no further data will be collected. A call should be made to the IVRS system to discontinue the patient.

The reason for withdrawal from the study should be recorded on the eCRF. Patients will be considered to have withdrawn from the study only due to one of the following reasons:

- Patient decision (patients withdraws consent from participating in the study).

- Eligibility criteria not fulfilled.
- Adverse Event.
- Severe non-compliance to protocol.
- Condition under investigation worsened.
- Death.
- Patient lost to follow up.

Patients may withdraw from any aspects of the voluntary exploratory research (see Section 6.8.1) 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 of consent for donated biological samples are outlined in Section 7.5.

#### **5.9.1 Screening failures**

Screening failures are patients who do not fulfil the eligibility criteria for the study and are therefore not enrolled. These patients should have their reason for study withdrawal recorded as 'Eligibility Criteria not fulfilled' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screening failures (not enrolled patients).

### **5.10 Conduct of Part A: Safety Run-in Phase.**

#### **5.10.1 Starting dose**

Dose administration of AZD5363 will commence at cohort 1 of each schedule as detailed in section 5.5.5.

#### **5.10.2 Safety Review Committee and Dose Escalation Process**

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

The SRC will consist of:

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

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

- Patient Safety Physician or delegate.
- Medical Science Director or delegate.

- Senior physician from another project.

The Study Pharmacokineticist, Study Statistician, Patient Safety Scientist, and Study Delivery Team Leader may also be invited as appropriate. The SRC 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 Patient 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 pharmacodynamic data to make a decision on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into account.

The decision may be to:

1. Proceed with dose escalation – refer to Section 5.10.3.
2. Expand the cohort to a maximum of 6 evaluable patients.
3. Reduce 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 RD (and NTD/MTD where applicable). To define a RD or the MTD, 6 evaluable patients must be assessed at that dose level. The SRC may elect to assess up to a further 6 evaluable patients at the identified MTD to confirm the dose selection. To determine the NTD 2 patients, of up to 6 patients, must experience DLTs at that dose level.
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.

### **5.10.3 Criteria to conduct dose escalation and reduction**

#### **Dose Escalation: Parameters.**

Dose escalation and reduction per cohort will be determined by the SRC with reference to the following logic:

- If no DLT is observed (for definition see Section 5.10.6) 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 (reduction) may be considered in order to better define the MTD.

The dose may initially be increased up to a level the SRC declare is safe and appropriate based on clinical PK and/or safety data. The SRC will determine the dose escalation/reduction based on the above criteria at the end of each dose group.

Based on emerging data, including available PK and/or safety data and/or pre-clinical data, the SRC can consider alternative treatment schedules, including once-daily dosing of AZD5363, in consultation with AZ.

When an NTD is defined, dose escalation/ will be stopped. All patients receiving the NTD should have their dose reduced to a tolerated dose or discontinue AZD5363 if a tolerated dose has not been defined. An interim dose (ie, one between the NTD and the last dose tested before NTD) may be assessed to determine the MTD and the SRC will decide this upon review of the data. The MTD will be defined as the last dose assessed below the NTD.

If dose reductions or delays greater than those allowed under this protocol (see section 5.5.4) occur during the DLT evaluation period, the patient will be considered either as not evaluable or as having attained a DLT (see Section 5.10.6 for definition of DLT).

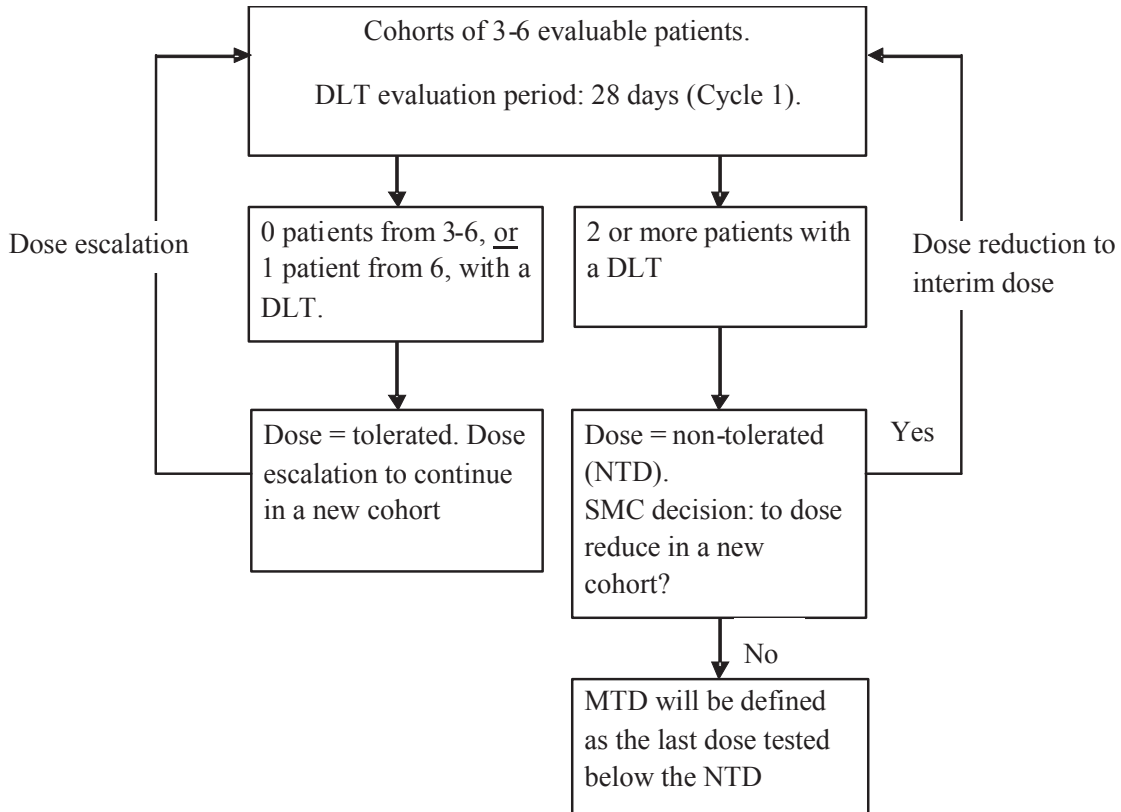
The DLT evaluation period ends following the completion of all assessments on the last day of the first cycle (Day 28).

Escalations will not exceed doubling of the dose of the prior cohort.

Intra-patient dose escalation is not permitted.

The dose for subsequent cohorts or a decision to stop recruitment to any study schedule arm will be agreed by the SRC after review of the data from each relevant cohort (see Section 5.10.2).

**Figure 7 Safety run-in dose escalation decision tree**



For the first cohort in each schedule, a delay of at least 7 days will be mandatory between administration of first patient first dose to administration of first 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 pharmacokinetic 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.

#### **5.10.4 Definition of maximum tolerated dose**

A primary objective of the Part A Safety Run-in phase is to determine a RD to take forward to the Expansion phase. It may not be necessary to escalate to NTD/MTD to establish the RD. Where it is necessary, or where the SRC deems it appropriate to do so, the following criteria will apply for determination of NTD/MTD.

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 that dose level. Once the NTD is defined the MTD will be confirmed at the previous dose-level below the NTD or a dose between the NTD and the last tolerated dose may be investigated. Six evaluable patients are required to determine the MTD.

#### **5.10.5 Definition of evaluable patient for Part A**

An evaluable patient is defined as one that, during Cycle 1: Weeks 1 to 4 has:

- Completed the minimum safety evaluation requirements and has received:
  - At least 80% of the total intended dose of AZD5363 within the 28 day cycle.
  - 3 doses of paclitaxel, comprising at least 80% of the total specified dose (where total dose is  $3 \times 90 \text{ mg/m}^2 = 270 \text{ mg/m}^2$ )\*, within the 28 day cycle\*\*.

**or**

has experienced a DLT prior to fulfilling the above criteria.

#### **Note:**

\* Cycle 1, Day 1, paclitaxel first dose must be administered at a dose of  $90 \text{ mg/m}^2$ . Dose reductions for the second and third infusions in Cycle 1 may be implemented, if required under the investigator's discretion for suspected toxicities. Single reductions can be in increments of no more than  $20 \text{ mg/m}^2$  to a minimum dose of  $60 \text{ mg/m}^2$ .

\*\* A dose delay to the second and/or third paclitaxel infusion during Cycle 1 is permissible, providing that the total delay is no more than 7 days. All three doses must be received within the 28 day cycle.

#### **5.10.6 Definition of dose-limiting toxicity**

A DLT is defined as:

- An AE or laboratory abnormality considered to be related to paclitaxel, that commences at any time during the DLT evaluation period (Cycle 1) and meets either of the following criteria:



1. Requires a dose reduction or omission to <60% of the intended Cycle 1 total paclitaxel dose (90 mg/m<sup>2</sup> x 3).
  2. Any delay to the administration of weekly paclitaxel chemotherapy on D1 of Cycle 2 by ≥7 days as a consequence of paclitaxel induced toxicity
- An AE or laboratory abnormality considered to be related to AZD5363, that commences at any time during the DLT evaluation period (Cycle 1) and meets any of the following criteria:
    1. Haematological toxicity:
      - CTCAE grade 4 haematological toxicity of any duration.
      - Febrile neutropenia (CTCAE grade ≥3 with temperature ≥38.5°C which is unresponsive to antipyretics).
      - CTCAE grade ≥3 neutropenia requiring hospitalisation.
      - CTCAE grade ≥3 thrombocytopenia associated with non-traumatic bleeding (but not applicable to patients on therapeutic anticoagulation).
    2. Clinical chemistry toxicity:
      - CTCAE ≥ 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, when combined with doubling of bilirubin from baseline, and AZD5363 is considered the most likely cause.
    3. Cardiovascular toxicity:
      - QTc (Fridericia's or Bazett's correction) interval >500msec or QTc increase >60msec from baseline on two ECGs at least 30 minutes apart, that cannot be attributed to another cause.
      - Symptomatic congestive cardiac failure (NYHA class III/IV) and a drop in LVEF which cannot be attributed to another cause. Note: Concomitant use of vasotonic drugs, adrenergic blockers, negative inotropic agents and anti-hypertensives should be taken into consideration when assigning causality.

- A decrease in LVEF of  $\geq 20\%$  to a level below the institution's lower limit of normal range.
  - CTCAE grade  $\geq 3$  hypotension which cannot be attributed to another cause.
4. Other toxicities:
- Clinically significant rash that despite optimal treatment remains CTCAE grade  $\geq 3$  for 5 days or longer and that cannot be attributed to another cause.
  - CTCAE grade  $\geq 3$  nausea, vomiting or diarrhoea, despite optimal anti-emetic or anti-diarrhoeal therapy, and which cannot be attributed to another cause.
  - Any other CTCAE grade  $\geq 3$  toxicity which, in the opinion of the investigator, is clinically significant and related to AZD5363.
  - Any delay to the administration of weekly paclitaxel chemotherapy on Day 1 of Cycle 2 by  $\geq 7$  days as a consequence of AZD5363 induced toxicity.
  - 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.

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.

The National Cancer Institute (NCI) CTCAE version 4.1 will be used whenever applicable to characterise DLTs. However, pre defined stopping criteria will supersede the CTCAE criteria.

Where a criterion for a DLT is reached, any subsequent delays in dosing or dose reductions of paclitaxel or AZD5363 due to toxicity are considered to occur after the DLT evaluation period.

If patients present with a potential DLT, the patient should be promptly investigated to define the aetiology of the symptoms. The use of appropriate (ie, non-restricted) medications in prophylactic or therapeutic management of toxicities are permitted.

The decision to interrupt dosing or to stop a patient from receiving further dosing will be taken by the principal or co-investigator, in consultation with the AZ Study Delivery Team

Physician, based on the clinical significance of the observed toxicity. If the toxicity is subsequently determined by the SRC to not be a DLT, this patient will be replaced.

The principal investigator, in consultation with the AZ Study Delivery Team Physician, may request replacement of patients who develop DLTs that are attributed to confounding factors and concomitant medications started during the DLT assessment period. Confounding medications for the specific DLT may be prohibited for the new patient(s) recruited to that dose group

## 6. COLLECTION OF STUDY VARIABLES

### 6.1 Recording of data

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

The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

### 6.2 Data collection at enrolment and follow-up

#### 6.2.1 Enrolment procedures

Written informed consent must be obtained prior to conduct of any study specific assessments. Procedures that are part of standard care may occur before informed consent is obtained.

A list of procedures and assessments described in the Study Plans ([Figure 5](#): Continuous dosing; [Figure 6](#): Intermittent dosing) for the screening visit must be completed within 4 weeks (-28 days) of enrolment. At screening, consenting patients will be assessed to ensure that they meet inclusion and exclusion criteria ([Sections 4.1 and 4.2](#)).

Demographic data and other characteristics will be recorded at screening and will include: date of birth, gender, race, menstrual status and smoking history.

Part B. Randomised Expansion: Each patient's *PIK3CA* mutation status must be determined at screening from a blood and archival tumour sample to enable the patient to be stratified as *PIK3CA* mutation positive or not detected prior to randomisation (see [section 5.2.1](#)):

- Patients will be stratified to the *PIK3CA* mutation positive arm where either one of the sample-type analyses is positive. Patients will be stratified to the not-detected arm where both sample type analyses are negative.
- It is requested that all efforts are made to ensure that archival tumour tissue is provided for this stratification analysis. Where tissue cannot be made available in a

timely manner, *PIK3CA* mutation stratification may be conducted on the blood sample analysis alone. In this event, tumour tissue must be provided for retrospective *PIK3CA* mutation analysis prior to completion of treatment Cycle 1.

- Where a patient has been assigned to the not-detected arm from blood sample analysis alone but the retrospective tumour tissue analysis is *PIK3CA* mutation positive - the patient will remain stratified to the not-detected arm. The discrepancy will be noted and an additional patient allocation may be made for this arm.
- In the event that one stratification arm (*PIK3CA* mutation positive or not-detected) completes recruitment before the other, new candidate patients will be requested to provide separate, initial, informed consent to obtain a blood and/or tumour tissue sample to screen for *PIK3CA* mutation status. Patients with status appropriate for entry to the open stratification arm will be invited to provide informed consent for entry to the study.

### **6.2.2 *PIK3CA* Mutation Status**

Patient response to treatment will be assessed against the tumour *PIK3CA* mutation status to determine whether the mutation confers any increased tumour sensitivity to AZD5363.

Blood and most recent archival tumour samples will be collected at screening (see [Figure 5](#) and [Figure 6](#)) with reference to the criteria and restrictions detailed in section 5.2.1. The *PIK3CA* mutation assay(s) will genotype for a set of mutations that will cover the majority of, but not all, mutations in the *PIK3CA* gene that have been thus far identified in breast cancer patients. Therefore, there may be patients carrying either a rare mutation, not included in the assay(s) used, or who have a level of mutation in cfDNA or tumour tissue DNA beyond the range of sensitivity of the selected assay(s). In this case, their mutation will not be identified under the protocolled testing. In acknowledgment of this, patients who are shown not to be 'mutation positive' in either cfDNA or tumour tissue DNA will be categorised as 'mutation not detected', rather than a more definitive 'mutation negative'.

During Study Part B, *PIK3CA* mutation status will be utilised to stratify patients to 'positive' and 'not detected' arms (see section 5.2.1).

### **6.2.3 Follow-up procedures**

Patients will be followed up as detailed below unless prior withdrawal from the study or death:

Part A. Safety Run-in: Patients will be followed to discontinuation of study drug / completion of the 28-day safety follow-up.

Part B. Randomised Expansion: Patients will be followed to objective disease progression.

### **6.2.3.1 Study Drug Discontinuation**

The discontinuation visits for AZD5363/matching placebo and paclitaxel should take place at the time of the last dose of the applicable study drug, or as soon as possible following confirmation that no further dosing will take place.

### **6.2.3.2 28-Day Safety follow-up**

For safety follow-up as a minimum, telephone contact should be made with the patient 28 days following the discontinuation of both AZD5363/matching placebo and paclitaxel, to follow up on any SAE/AE's, surgery, concomitant medications, concomitant procedures, radiotherapy and subsequent cancer therapy. Any SAEs will be followed to resolution where possible.

### **6.2.3.3 Progression follow-up**

Part B. Randomised Expansion only. Patients who discontinue AZD5363/matching placebo for reasons other than progression will continue RECIST 1.1 assessments every 12 weeks (from Cycle 1 Day 1)  $\pm 7$  days up to objective disease progression. This schedule of RECIST 1.1 assessments should be maintained even if study treatment cycles have been delayed. Only new SAEs due to study procedures should be collected.

## **6.3 Efficacy**

### **6.3.1 Tumour assessments**

RECIST 1.1 criteria will be used to assess patient response to treatment by determining change in tumour size at 12 weeks, percentage of patients without progressive disease, at 12 weeks, overall response rate (ORR), BoR, DoR and PFS. The RECIST 1.1 guidelines for measurable, non-measurable, target, and non-target lesions (NTL) and the objective tumour response criteria (CR, PR, stable disease [SD], or progressive disease [PD]) are presented in Appendix F.

RECIST assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis. Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. 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 of tumour burden used at baseline (CT or MRI scans of the chest, abdomen and pelvis) must be used at each subsequent follow-up assessment.

Follow-up assessments will be performed every 12 weeks ( $\pm 7$  days) after start of treatment (Cycle 1 day 1) until objective disease progression as defined by RECIST 1.1. For the Safety Run-in phase (Part A), tumour assessments will stop after cessation of study drug where prior to progression. For the Randomised Expansion phase (Part B), if a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient

should still continue to be followed until objective disease progression as defined by RECIST 1.1.

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

For Part A, for patients with non-measurable disease only at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: complete response (CR), PD (progression of disease) and Non CR/Non PD.

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

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

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

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in [Figure 5](#) and [Figure 6](#).

The primary analysis for this study will be based on the tumour assessments recorded on the eCRF.

Radiological examinations performed in the conduct of this study for RECIST response assessments must be retained at site as source data and a copy anonymised for personal identifiers, e.g. name, initials, be available for collection by the Sponsor to support any future regulatory requests.

## **6.4 Safety**

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

#### **6.4.1 Definition of adverse events**

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. AEs will be graded according to CTCAE version 4.1.

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

#### **6.4.2 Definitions of serious adverse event**

A serious adverse event (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/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

#### **6.4.3 Recording of adverse events**

##### **Time period for collection of adverse events**

Adverse Events will be collected from time of signature of informed consent, throughout the treatment period up to, and including, the follow-up period. The follow-up period is defined as 28 days after study treatment (both AZD5363/placebo and paclitaxel) is discontinued.

For the Randomised Expansion phase, SAEs occurring after the 28-day follow-up, that are considered related to study procedures, should continue to be recorded while patients are followed-up for disease progression.

If the investigator learns of any SAE(s), 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.

### **Follow-up of unresolved adverse events**

Any AEs that are unresolved at the patient's last visit in the study will be 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)/SAE(s) at the end of the study, if judged necessary.

### **Variables**

The following variables will be collect for each AE;

- AE (verbatim).
- The date when the AE started and stopped.
- Whether the AE is serious or not.
- Investigator causality rating against the IP (yes or no).
- Investigator causality rating against paclitaxel (yes or no).
- Action taken with regard to IP.
- Action taken with regard to paclitaxel.
- Outcome.

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

- Date AE met criteria for serious AE.
- Date Investigator became aware of serious AE.
- AE is serious due to (specify reason).
- Where applicable:
  - Date of hospitalisation.
  - Date of discharge.
  - Probable cause of death.
  - Date of death.



- Autopsy performed.
- Causality assessment in relation to Study procedure(s).
- Causality assessment in relation to Other medication.
- Description of AE.

The grading scales found in the revised National Cancer Institute CTCAE version 4.1 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 4.1 can be downloaded from the Cancer Therapy Evaluation Program website (<http://ctep.cancer.gov>).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

### **Causality collection**

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

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

A guide to the interpretation of the causality question is found in Appendix B to the 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 and vital signs will be summarised in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated

laboratory values, vital signs, ECGs and other safety assessments, should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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.

### **Hy's Law**

Cases where a patient shows an AST **or** ALT  $\geq 3x$  ULN **or** total bilirubin  $\geq 2x$  ULN may need to be reported as SAEs, please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

### **Disease progression**

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP 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, which are unequivocally due to disease progression, should not be reported as an AE during the study.**

### **Deaths**

All deaths (both cancer-related and other) that occur during the study and within 28 days after the last dose of AZD5363 must be reported as follows:

- Death clearly resulting from unequivocal disease progression should be reported to the study monitor at the next monitoring visit and should be documented on the relevant eCRF but should not be reported as an AE or SAE.
- When death is not due to progression of disease under study, the AE causing death must be reported to the study monitor as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

In the event of death, the patient will be considered as having completed 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 administration of study treatment and have been identified after inclusion of the patient into the clinical study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE as they are considered to be disease progression.

### **6.4.4 Reporting of serious adverse events (SAEs)**

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

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

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

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

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

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

The reference document for definition of expectedness/listedness is Section 5.4 of the Investigators' Brochure for AZD5363, and the EU Summary of Product Characteristics (SPC) for paclitaxel.

### **6.4.5 Laboratory safety assessment**

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the following timepoints:

- Screening
- Continuous Dosing schedule:
  - Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose; Weeks 2, 3 and 4: Day 1 pre-dose.
  - Cycle 2: Weeks 1, 2, 3 and 4: Day 1 pre-dose.
  - Cycle 3+: Week 1, Day 1 pre-dose up to discontinuation of both study therapies.
- Intermittent dosing schedule:
  - Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose; Day 5 pre-dose; Weeks 2, 3 and 4: Day 2 pre-dose.
  - Cycle 2: Week 1: Day 2 pre-dose; Weeks 2, 3 and 4: Day 1 pre-dose.
  - Cycles 3+: Week 1: Day 2 pre-dose up to discontinuation of both study therapies.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.
- Urine pregnancy test to be completed at: Screening, Cycle 1 Week 1 Day 1 and on discontinuation of study therapies.

Serum/Plasma glucose to be additionally measured, for evaluation of potential abnormalities of glucose metabolism, from **one sample taken between 2 to 4 hours following receipt of the morning dose of AZD5363** at the following timepoints:

- Continuous dosing schedule:
  - Cycle 1: Week1: Day 2; Weeks 2, 3 and 4: Day 1.
  - Week 1, Day 1, of every Cycle thereafter up to discontinuation of AZD5363.
- Intermittent dosing schedule:
  - Cycle 1: Week 1: Day 2; Day 5; Weeks 2, 3 and 4: Day 2.
  - Day 2 of every Cycle thereafter up to discontinuation of AZD5363.

If screening laboratory assessments are performed within 3 days prior to Cycle 1, Week 1, Day 1, these do not need to be repeated at Week 1, Day 1. Eligibility criteria should be reviewed once screening laboratory results are available (refer to Section 4.2).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator / delegate. The date, time of collection and results will be recorded on the appropriate eCRF.

The clinical chemistry, haematology, and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. For total blood volumes see Section 7.1.

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

S/P-Potassium

S/P-Total Protein

S/P Free T4

S/P TSH

S/P Troponin I or T

S/P-Sodium

S/P-Urea nitrogen

**Haematology**

Blood (B)-Haemoglobin

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

**NB.** In case a patient shows an AST **or** ALT  $\geq 3$ x ULN **or** total bilirubin  $\geq 2$ x ULN please refer to Appendix E ‘Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy’s Law’, for further instructions.

#### **Urinalysis – supplementary evaluations:**

- 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.

#### **6.4.6 Physical examination**

A complete physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

Physical examinations will be conducted at the times indicated in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the following timepoints:

- Screening.
- Cycle 1: Week 1 and 2: Day 1 pre-dose.
- Intermittent dosing schedule only. Cycle 1: Week1: Day 5 pre-dose.
- Cycles 2+: Week 1: Day 1 pre-dose.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.

#### **6.4.7 Height and weight**

The patient’s height (cm) and weight (kg) will be measured at the times indicated in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the following timepoints:

##### **Height:**

- Screening.

##### **Weight:**

- Screening.

- Each Cycle: Week 1: Day 1 at any time of the day.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.

#### **6.4.8 WHO Performance status**

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

- 0 = Fully active, able to carry out all pre-disease activities without restrictions.
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature eg, light housework, office work.
- 2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.

#### **6.4.9 Resting ECG**

ECG measurements will be conducted at the study site or other local institution as applicable.

At each timepoint, at approximately the same time of day, a standard 12-lead ECG should be performed after the patient has been resting in a semi-supine position for at least 5 minutes. A paper speed of 25mm/second, covering at least 6 sequential beats, is recommended. Three ECGs per timepoint should be conducted within a 5-minute period.

ECG measurements should be conducted as indicated in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the following timepoints:

- Screening.
- Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose, 1, 2, 6 and 24 hours post-dose; Week 2: Day 1 pre-dose.
- Intermittent dosing schedule only. Cycle 1: Week1: Day 5 post-dose.
- Cycle 2: Week 1: Day 1 post-dose.
- Cycles 3+: Week 1: Day 1 at any time of the day.
- Discontinuation of AZD5363/placebo: at any time of the day.

- Discontinuation of paclitaxel: at any time of the day.

**ECG parameters:** The following parameters will be recorded for each ECG: date and time of ECG, heart rate (beats/min), PR, R-R, QRS, QT (ms), QTc (ms), sinus rhythm (yes/no), and overall evaluation (normal/abnormal).

The ECG will be evaluated by suitably qualified personnel and entered as “Normal” or “Abnormal” in the eCRF. If the ECG is evaluated as “Abnormal” the abnormality should be further specified. Any clinically significant abnormal findings observed and recorded on ECG during the treatment period will be reported as AEs (for details on AE recording refer to Section 6.4.3).

For each ECG, one original ECG printout, initialled and dated by the Investigator, will be kept in the medical records, ensuring a copy is maintained in the source documents for the study.

#### **6.4.10 Muga scan / Echocardiogram**

A MUGA scan or echocardiogram to assess LVEF will be conducted at the times indicated in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the following timepoints:

- Screening.
- Cycle 2: Week 1: Day 1 ( $\pm 1$  week).
- Every 12 weeks from baseline thereafter: at any time of the day.
- Where clinically indicated.
- Discontinuation of AZD5363/placebo: at any time of the day.

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.

#### **6.4.11 Vital signs: Pulse and blood pressure**

Supine blood pressure and pulse rate will be measured after 10 minutes rest.

Assessments will be conducted at the times indicated in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the following timepoints:

- Screening
- Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose; 1, 2, and 6 hours post-dose; Weeks 2, 3 and 4: Day 1 pre-dose.
- Intermittent dosing schedule only. Cycle 1 Week 1: Day 5 post-dose.



- Cycle 2: Week 1: Day 1 pre-dose; Weeks 2, 3 and 4: Day 1 post-dose.
- Cycles 3+: Week 1: Day 1 at any time of the day.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.

#### **6.4.12 Other safety assessments**

##### **6.4.12.1 Lipids**

Blood samples for determination of triglycerides, HDL, LDL and cholesterol will be taken at the times indicated in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the following timepoints:

- Screening.
- Every 12 weeks from baseline: at any time of the day. Up to cessation of AZD5363/placebo.
- Discontinuation of AZD5363/placebo: at any time of the day.

##### **6.4.12.2 Glycosylated haemoglobin**

Blood samples for determination of glycosylated haemoglobin (HbA1c), will be taken taken at the times indicated in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the following timepoints:

- Screening.
- Every 12 weeks from baseline: at any time of the day.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.

##### **6.4.12.3 Glucose, insulin and insulin c-peptide**

Blood samples for determination of glucose, insulin and insulin c-peptide, will be taken taken at the times indicated in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the following timepoints:

- Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose; 2, 4, 6 and 8 hours post-dose.
- Continuous dosing schedule only:
  - Cycle 1: Week 2: Day 1 pre-dose, 2, 4, 6 and 8 hours post-dose; Weeks 3 and 4: Day 1 pre-dose.
  - Cycles 2+: Week 1 Day 1 pre-dose and between 2 to 4 hours post-dose.

- Intermittent dosing schedule only:
  - Cycle 1: Week 1: Day 5 pre-dose, 2, 4, 6 and 8 hours post-dose; Weeks 2, 3 and 4: Day 2 pre-dose.
  - Cycles 2+: Week 1: Day 2 pre-dose and between 2 to 4 hours post-dose.
- Discontinuation of AZD5363/placebo: at any time of the day.

#### **6.4.12.4 Patient meal information.**

The times and types of meals (tickbox) received by patients will be recorded on the days that the patient attends the study site and received AZD5363/placebo at the following timepoints:

- Cycle 1: Week 1: Day 2.
- Continuous dosing schedule only:
  - Cycle 1: Weeks 2, 3 and 4: Day 1.
  - Cycles 2+: Week 1 Day 1.
- Intermittent dosing schedule only:
  - Cycle 1: Week 1: Day 5; Weeks 2, 3 and 4: Day 2.
  - Cycles 2+: Week 1 Day 2.

### **6.5 Patient reported outcomes (PRO)**

#### **6.5.1 Quality of Life: EORTC QLQ C-30 and BR-23 questionnaires (Part B: Randomised expansion only).**

These questionnaires were developed to assess and monitor changes from baseline in global health status / quality of life and disease-related symptoms. Validated translations of the questionnaires will be administered as appropriate.

The European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire, EORTC QLQ-C30, is a 30-item generic instrument designed specifically to assess quality of life (QoL) in patients with cancer, and is applicable across a range of cancer types, treatments, and cultural settings. The instrument incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), a global health scale, 5 single items assessing common physical symptoms of cancer (dyspnea, loss of appetite, insomnia, constipation, and diarrhoea), and a single item assessing the financial effect of cancer. Per the EORTC scoring manual, all raw scores obtained from the QLQ-C30 will be transformed to a scale of 0–100; higher scores in the functioning and global QoL scales indicating better functioning, and higher scores in the symptom scales indicating more problems with the particular symptom being assessed. A

change of  $\geq 10$  points from baseline will indicate a meaningful increase or decrease in the specific health related QoL (HEQOL) scale.

The QLQ-C30 assessment will be supplemented with the BR-23 breast cancer-specific questionnaire. This EORTC-developed questionnaire includes 23 questions to assess the symptoms and side effects of treatment (surgery, chemotherapy, radiation therapy, and hormone), body image, sexuality, and future perspective.

During the Randomised Expansion phase only; patients will be requested to complete both questionnaires at the times indicated in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the following timepoints:

- Screening.
- Cycle 1: Week 1: Day 1: pre-dose.
- Every 12 weeks from baseline: at any time of the day and after cessation of study therapies up to disease progression or withdrawal of consent.
- Discontinuation of AZD5363/placebo: at any time of the day.

#### **6.5.2 Administration of EORTC QLQ C-30 and BR-23 questionnaires**

Each centre must allocate the responsibility for the administration of the questionnaires to a specific individual (eg, a research nurse, study coordinator) and if possible assign a back-up to cover absence. The AZ Study Delivery Team (or delegate) will provide relevant training in administration of the questionnaires. The paper questionnaire should be administered and completed, where possible, at the clinic. Where this will not be possible, patients will be provided with paper copies of the questionnaire to complete at home, and return to the site by post.

It is important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the questionnaires are as follows:

- They must be completed prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions.
- It must be completed in private by the patient.
- The patient should be given sufficient time to complete at their own speed.
- The patient should not receive help from relatives, friends or clinic staff to answer the questionnaire. However, if the patient is unable to read the questionnaire the questionnaire may be read out by trained clinic staff and responses recorded.

- On completion of the questionnaire it should be handed back to the designated responsible person who should check for completeness.
- Only one answer should be recorded for each question.

Data from the questionnaires will be transcribed at site onto the eCRF. Information on compliance with completion of the questionnaires will be collected throughout the study.

## 6.6 Pharmacokinetics

### 6.6.1 Collection of samples

Venous blood samples (4 mL) for each determination of concentrations of AZD5363, its metabolites, and paclitaxel in plasma will be taken at the times presented in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the timepoints shown below and will be analysed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D. Where AZD5363/placebo or paclitaxel are not received to schedule, post-dose PK sampling will not be applicable.

Samples will be collected, labelled stored and shipped as detailed in Laboratory Manual. Samples will be disposed of as detailed in Section [7.2.1](#). The exact date and time of each PK sample must be recorded in the CRF.

### 6.6.2 Pharmacokinetic sampling schedule

Code:

P = Samples for paclitaxel PK.

A = Samples for AZD5363 PK

**Table 2: PK sampling schedule: Safety Run-in Phase.**

Continuous dosing schedule

Time relative to first dose in cycle	Cycle 1						
	Week 1			Week 2		Week 3	Week 4
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 1	Day 1
Predose	P	P A	A	P A	P A	P A	A
2 hours	P	A		P A			
4 hours	P	A		P A			

Time relative to first dose in cycle	Cycle 1						
	Week 1			Week 2		Week 3	Week 4
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 1	Day 1
8 hours	P	A		P A			

Intermittent dosing schedule:

Time relative to first dose in cycle	Cycle 1						
	Week 1				Week 2	Week 3	Week 4
	Day 1	Day 2	Day 3	Day 5	Day 2	Day 2	Day 2
Predose	P	P A	A	A	P A	P A	A
2 hours	P	A					
4 hours	P	A					
8 hours	P	A					

**Table 3: PK sampling schedule: Randomised Expansion Phase.**

Continuous dosing schedule

Time relative to first dose in cycle	Cycle 1						
	Week 1			Week 2		Week 3	Week 4
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 1	Day 1
Predose	P	P A	A	A	A	A	A
2 hours	P	A					
4 hours	P	A					

Time relative to first dose in cycle	Cycle 1						
	Week 1			Week 2		Week 3	Week 4
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 1	Day 1
8 hours	P	A					

#### Intermittent dosing schedule

Time relative to first dose in cycle	Cycle 1						
	Week 1				Week 2	Week 3	Week 4
	Day 1	Day 2	Day 3	Day 5	Day 2	Day 2	Day 2
Predose	P	P A	A	A	A	A	A
2 hours	P	A					
4 hours	P	A					
8 hours	P	A					

### 6.6.3 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using appropriate bioanalytical methods. The lower limits of quantification (LLOQ) for AZD5363 and paclitaxel in plasma are 1.0ng/mL and 10ng/mL respectively. 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 (AZD5363 and paclitaxel) at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the pharmacokinetic samples may be subjected to further analyses in order to investigate the presence and/or identity of metabolites of AZD5363. This may involve pooling of samples if required. Any results from such analyses will be reported separately from the CSR.

## **6.7 Pharmacodynamics**

### **6.7.1 Collection of pharmacodynamic markers**

Venous blood samples (8.1 mL) to provide platelet-rich plasma will be taken for assessment of pharmacodynamic (PD) markers at the times presented in the Study Plan (see [Figure 5](#) and [Figure 6](#)) at the timepoints shown in [Table 4](#) and [Table 5](#).

Samples will be collected, labelled stored and shipped as detailed in Laboratory Manual. The exact date and time of each PD sample must be recorded in the CRF. Samples will be disposed of after a maximum of 25 years following the Last Patient's Last Visit in the study.

## **6.8 Exploratory research**

### **6.8.1 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.

Archival tumour samples will be collected for identification of patient *PIK3CA* mutation status (see sections [5.2.1](#) and [6.2.2](#)) and, where a patient consents, optional paired biopsies (see section [6.8.1.3](#)) may also be analysed 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 CSR.

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

#### **6.8.1.1 Collection of circulating tumour cells**

A whole blood sample (10 mL) for analysis of CTCs will be taken at the times presented in the Study Plan (see [Figure 5](#) and [Figure 6](#)) on each of the following timepoints:

- Cycle 1: Week 1: Day 1 pre-dose.
- Cycle 2: Week 1: Day 1 pre-dose.
- Cycle 3: Week 1: Day 1 pre-dose.
- Thereafter: every 12 weeks from baseline: at any time of the day up to cessation of study therapies.

The date and time of collection will be recorded in the CRF. Samples will be utilised within days of collection and will not be stored beyond the completion of the study.

Samples of CTCs 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.

#### **6.8.1.2 Collection of archival tumour samples**

All patients will be asked to provide consent to supply a sample of their most recently obtained archival tumour block (tissue derived from the diagnostic tumour or a metastatic site) for transfer to the AstraZeneca biobank.

The tumour sample preferably will be in the form of a formalin-fixed paraffin embedded block. If this is not possible, 10-20 slides of freshly prepared unstained 5 micron sections from the archival tumour block may be provided.

It is anticipated that, where consent is given, remaining tissue samples or slides collected for PIK3CA mutation analysis (see section 6.2.2) will be transferred to the biobank. Samples will be disposed of, or returned to the study site dependent upon local requirements, after a maximum of 25 years following the Last Patient's Last Visit in the study.

#### **6.8.1.3 Collection of paired tumour biopsies (optional)**

All patients will be asked to provide consent for collection of tumour biopsies. Where consent is given, these samples should be collected at the times presented in the Study Plan (see [Figure 5](#) and [Figure 6](#)): at screening or at pre-dose on Day 1 of Cycle 1 and on Day 1 of Cycle 2 ( $\pm$  1 week).

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. Samples will be disposed of after a maximum of 25 years following the Last Patient's Last Visit in the study.

#### **6.8.1.4 Collection of eyebrow hairs (optional)**

Four eyebrow hairs will be taken at the times presented in the Study Plan (see [Figure 5](#) and [Figure 6](#)) on each of the timepoints presented in [Table 4](#) and [Table 5](#) below.

The samples will be analysed for concentrations of exploratory biomarkers which may correlate with drug response. The date and time of collection will be recorded in the CRF. Samples will be disposed of after a maximum of 25 years following the Last Patient's Last Visit in the study.

#### **6.8.1.5 Collection of exploratory blood-borne biomarkers (optional)**

5mL venous blood will be taken at the times presented in the Study Plan (see [Figure 5](#) and [Figure 6](#)) on each of the timepoints presented in [Table 4](#) and [Table 5](#) below.



The samples will be analysed for a range of oncology biomarkers which may correlate with drug response. The date and time of collection will be recorded in the CRF. Samples will be disposed of after a maximum of 25 years following the Last Patient's Last Visit in the study.

**6.8.1.6 Pharmacodynamic and exploratory biomarker sampling schedule**

The following samples will be taken on each of the timepoints presented below.

Code:

- **PD** = venous blood for determination of pharmacodynamic parameters.
- **B** = venous blood for analysis of exploratory biomarkers.
- **BH** = 4 eyebrow hairs for analysis of exploratory biomarkers.

**Table 4: PD and exploratory biomarker sampling schedule: Part A Safety Run-in Phase.**

Continuous dosing schedule

Time relative to first dose in cycle	Screen	Cycle 1								Cycle 2+ Week 1	AZD5363 Disc
		Week 1			Week 2		Week 3	Week 4	Week 1		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 1	Day 1	Day 1		
Any time	B										B PD
Predose		PD	B PD BH	PD	B PD BH	PD	B PD	B PD	B PD		
2 hours			PD								
4 hours			PD BH								
8 hours			PD								

Intermittent dosing schedule

Time relative to first dose in cycle	Screen	Cycle 1								Cycle 2+ Week 1	AZD5363 Disc
		Week 1				Week 2	Week 3	Week 4	Week 1		
		Day 1	Day 2	Day 3	Day 5	Day 2	Day 2	Day 2	Day1		
Any time	B										B PD
Predose		PD	B PD BH	PD	PD BH	B PD	B PD	B PD	B PD		

Time relative to first dose in cycle	Screen	Cycle 1							Cycle 2+	AZD5363 Disc
		Week 1				Week 2	Week 3	Week 4	Week 1	
		Day 1	Day 2	Day 3	Day 5	Day 2	Day 2	Day 2	Day1	
2 hours			PD							
4 hours			PD BH							
8 hours			PD							

**Table 5. PD and exploratory biomarker sampling schedule: Part B Expansion Phase**

Continuous dosing schedule

Time relative to first dose in cycle	Screen	Cycle 1							Cycle 2+	AZD5363 Disc
		Week 1			Week 2		Week 3	Week 4	Week 1	
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 1	Day 1	Day 1	
Any time	B									B PD
Predose		PD	B PD BH	PD	B PD BH	PD	B PD	B PD	B PD	
2 hours			PD							
4 hours			PD BH							
8 hours			PD							

Intermittent dosing schedule

Time relative to first dose in cycle	Screen	Cycle 1							Cycle 2+	AZD5363 Disc
		Week 1				Week 2	Week 3	Week 4	Week 1	
		Day 1	Day 2	Day 3	Day 5	Day 2	Day 2	Day 2	Day 1	
Any time	B									B PD
Predose		PD	B PD BH	PD	PD BH	B PD	B PD	B PD	B PD	
2 hours			PD							
4 hours			PD BH							
8 hours			PD							

## **6.9 Pharmacogenetics**

### **6.9.1 Collection of pharmacogenetic samples (optional)**

All patients will be asked to provide consent for collection of a 5mL blood sample immediately prior to dosing on Cycle 1: Week 1: Day 1 for genetic research. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at this visit, it may be taken at any other 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.

The results of this pharmacogenetic research will be reported separately and will not form part of the CSR.

Samples will be disposed of after a maximum of 25 years following the Last Patient's Last Visit in the study.

## **7. BIOLOGICAL SAMPLING PROCEDURES**

### **7.1 Volume of blood**

The volume of blood that will be drawn from each patient will vary, dependent upon the dosing schedule and phase of the study:

- The volume of blood to be drawn from each patient during screening and Cycle 1 should not exceed 35 mL and 360 mL respectively
- The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 cycles of combination treatment and a discontinuation visit should not exceed 710 mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

In both phases of the study, extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments or additional PK assessment.

The maximum volume of blood to be drawn from each patient in this study is as follows:

**Table 6 Estimated Maximum volume of blood to be drawn per patient**

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Haematology	5	15	75
	Clinical chemistry	10	15	150
	Additional Glucose	2	9	18
	Lipids	5	3	15
	Glucose, insulin and insulin c-peptide	5	24	120
CTCs		10	4	40
PIK3CA mutation		10	1	10
Pharmacokinetic		4	23	92
Pharmacodynamic		8.1 (3 x 2.7)	16	129.6
Pharmacogenetics (optional)		5	1	5
Exploratory Biomarker (optional)		5	11	55
Total				709.6

Note: Maximum is taken to reflect Part A, continuous dosing schedule: 6 Cycles plus a discontinuation visit.

## 7.2 Handling, storage and destruction of biological samples

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

Biological samples for future research will be retained by AstraZeneca Alderley Park, UK for a maximum of 25 years following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the CSR but separately in a Scientific Report.

### 7.2.1 Pharmacokinetic and/or pharmacodynamic / biomarker samples

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

Key samples for investigation of exploratory biomarkers, bioanalytical validation and metabolite identification will be retained at AstraZeneca, Alderley Park, UK for a maximum of 25 years following the Last Patient's Last Visit in the study. The results from the investigation will not be reported in the CSR but separately in bioanalytical/metabolism reports.

### **7.2.2 Pharmacogenetic samples**

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, following the Last Patient's Last Visit in the study, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number, replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory 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/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

### **7.3 Labelling and shipment of biohazard samples**

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

Any samples identified as Infectious Category A materials must not be shipped and further samples must not be taken from the patient unless agreed with AstraZeneca, and appropriate labelling, shipment and containment provisions are approved.

### **7.4 Chain of custody of biological samples**

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

The Principal Investigator 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 when shipped.

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 when shipped.

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

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

## **7.5 Withdrawal of informed consent for donated biological samples**

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

As collection of the biological samples is not regarded as integral to the primary study objectives, then the patient may continue in the study.

The Principal Investigator:

- Ensures AstraZeneca is notified immediately of a patient's withdrawal of informed consent to the use of donated 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 any local laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the 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 and the action documented and returned to the study site.

## **8. ETHICAL AND REGULATORY REQUIREMENTS**

### **8.1 Ethical conduct of the study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

### **8.2 Patient data protection**

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

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

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

### **8.3 Ethics and regulatory review**

An Ethics Committee (EC) / Investigational Review Board (IRB) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

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

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, must be approved by the national regulatory authority or a notification to the national regulatory authority **must be made**, according to local regulations.

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

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

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

## **8.4 Informed consent**

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed Informed Consent Form is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an EC/IRB.

## **8.5 Changes to the protocol and informed consent form**

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

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

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

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

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

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



## **8.6 Audits and inspections**

Authorised representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

## **9. STUDY MANAGEMENT BY ASTRAZENECA**

### **9.1 Pre-study activities**

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

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

### **9.2 Training of study site personnel**

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

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

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

### **9.3 Monitoring of the study**

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.

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

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

### **9.3.1 Source data**

Refer to the CSA for location of source data.

## **9.4 Study agreements**

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

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

### **9.4.1 Archiving of study documents**

The Investigator follows the principles outlined in the CSA.

## **9.5 Study timetable and end of study**

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

The study is expected to start in Q2 2012 and to end by Q4 2014.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD5363.

## **10. DATA MANAGEMENT BY ASTRAZENECA**

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

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

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

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca. Data from external providers (e.g. central laboratories) will be validated as appropriate to ensure it is consistent with the clinical data and included in the final database. In the case of biomarker (tumour tissue or blood for exploratory analyses) data, only the original date of biopsy (historical tumour tissue sample and the actual date the sample(s) were collected) will be recorded in the eCRF and database.

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

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

## **11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA**

### **11.1 Calculation or derivation of efficacy variable(s)**

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

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

Progression of TLs will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### **11.1.1 Change in tumour size at 12 weeks**

The primary outcome variable for Part B of the study is change in tumour size at 12 weeks. This is based on RECIST measurements taken at baseline and at week 12. Tumour size is the sum of the longest diameters of the TLs that have been selected at baseline. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment. The change in tumour size will be assessed using the log (ratio) of the week 12 tumour size over the baseline tumour size for each subject. More details on TLs selection and assessment during the treatment can be found in Appendix F of the protocol.

For patients who progress before week 12, a tumour assessment should be conducted and recorded at the time of progression. The tumour size from the progression assessment will be used instead of the week 12 assessment for these patients.

Patients who discontinue study treatment (prior to 12 weeks) for reasons other than objective disease progression should have tumour assessments scans performed as scheduled in the protocol and the tumour size from the week 12 assessment will be used in this analysis.

Methods for handling data from patients with lesions that are subject to surgery prior to week 12 will be documented in the statistical analysis plan.

### **Missing Data Imputation Methods**

Whenever tumour size data for the week 12 assessment is available then this should be used in the analysis of change in tumour size at 12 weeks. A windowing rule will be applied and will follow the protocol allowed visit window; therefore, any RECIST scan performed within  $\pm 1$  week of the protocol scheduled visit will be used for the week 12 visit.

[REDACTED]

[REDACTED]

Full details of these imputation techniques will be described in the statistical analysis plan.

#### **11.1.2 Objective response rate (ORR)**

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

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

#### **11.1.3 Duration of response (DoR)**

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).

#### **11.1.4 Progression-free Survival (PFS)**

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.

#### **11.1.5 Response rate at 12 weeks and best objective tumour response**

Response rate at 12 weeks is defined as the percentage of patients who have a week 12 visit response of CR or PR (as defined by RECIST 1.1), regardless of whether the responses are confirmed or not.

Best objective tumour response will be based on RECIST measurements taken throughout the whole study and will classify patients as confirmed complete and partial responses as well as unconfirmed complete and partial responses, stable disease, progressive disease and not evaluable. ORR is defined as the percentage of patients who have at least one visit response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1).

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

The denominator for response rate calculations will be: all patients dosed for study Part A and all randomised patients for study Part B, with the exception of the *PIK3CA* mutation - positive subgroup where the denominator will be all patients dosed / randomised whose tumours test positive for the *PIK3CA* mutation.

### **11.1.6 Proportion of patients without progressive disease at 12 weeks**

The proportion of patients without progressive disease at 12 weeks is defined as the percentage of patients with a 12 week visit response of CR, PR or SD (as defined by RECIST 1.1) with no evidence of previous progression.

The denominator for patients without progressive disease at 12 weeks will be: all patients dosed for study Part A and all randomised patients for study Part B.

## **11.2 Calculation or derivation of safety variable(s)**

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

### **ECG Changes**

QTc will be calculated by the Data Management Centre, on behalf of AstraZeneca, using both Bazett's and Fridericia's formulae.

### **Creatinine Clearance**

Estimated creatinine clearance (mL/min) will be calculated using the Cockcroft and Gault formula below, from creatinine:

For creatinine values in mol/L

Men:  $[(140 - \text{age}) \times \text{weight (kg)} \times 1.23] / \text{creatinine } (\mu\text{mol/L})$

Women:  $[(140 - \text{age}) \times \text{weight (kg)} \times 1.04] / \text{creatinine } (\mu\text{mol/L})$

### **Corrected Calcium**

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

Corr. Calcium (mmol/L) = Total Calcium (mmol/L) +  $[(40 - \text{Albumin (g/L)}) \times 0.02]$

### **11.2.1 Other significant adverse events (OAE)**

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as a SAE and/or a Discontinuation of Investigational Product due to Adverse Event. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory, vital signs and ECG data will be performed for identification of OAEs.

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

### 11.3 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma concentration data for AZD5363 and paclitaxel will be performed by AstraZeneca. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using population pharmacokinetic modelling.

Where possible, appropriate PK parameters will be reported

The PK variables for the patients with sparse PK sampling will be estimated using a population PK approach. Details will be included in a separate PK analysis plan.

### 11.4 Calculation or derivation of pharmacodynamic variable(s)

#### 11.4.1 Population analysis of pharmacokinetic/pharmacodynamic variables

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

### 11.5 Calculation or derivation of health related quality of life variables (Part B: Randomised expansion only)

Health related quality of life (HRQoL) and disease-related symptom data will be collected using the EORTC QLQ-C30 and BR-23 patient reported outcome (PRO) instruments.

The QLQ-C30 instrument is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

The principle for scoring these scales is the same in all cases.

**Table 7 Scoring the QLQ C30 version 3**

	Scale	Number of items	Item range*	Version 3.0 item numbers	Function scales
<b>Global health status/QoL</b>					
Global health status/QoL (revised) †	QL2	2	6	29,30	
<b>Functional scales:</b>					
Physical functioning (revised) †	PF2	5	3	1-5	F



Role functioning (revised) †	RF2	2	3	6,7	F
Emotional functioning	EF	4	3	21-24	F
Cognitive functioning	CF	2	3	20,25	F
Social functioning	SF	2	3	26,27	F
<b>Symptom scales/items</b>					
Fatigue	FA	3	3	10,12,18	
Nausea and vomiting	NV	2	3	14,15	
Pain	PA	2	3	9,19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

\* *Item range* is the difference between the possible maximum and the minimum response to individual items;  
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated by a suffix “2” – for example, PF2.

The BR-23 instrument comprises 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy and hormonal treatment), body image, sexual functioning and future perspective. The module incorporates five multi-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning. In addition, single items assess sexual enjoyment, hair loss and future perspective. The scoring approach for the QLQ-BR23 is identical in principle to that for the function and symptom scales / single items of the QLQ-C30.

**Table 8 Scoring BR-23**

	Scale	Number of items	Item range*	QLQ-BR23 item numbers	Function scales
<b>Functional scales</b>					
Body image	BRBI	4	3	9-12	F
Sexual functioning †	BRSEF	2	3	14,15	†
Sexual enjoyment †	BRSEE	1	3	16	†
Future perspective	BRFU	1	3	13	F
<b>Symptom scales/items</b>					
Systemic therapy side effects	BRST	7	3	1-4,6,7,8	

Breast symptoms	BRBS	4	3	20-23
Arm symptoms	BRAS	3	3	17,18,19
Upset by hair loss	BRHL	1	3	5

\* “Item range” is the difference between the possible maximum and the minimum response to individual items.

† Items for the scales marked † are scored positively (i.e. “very much” is best) and therefore use the same algebraic equation as for symptom scales; however, the Body Image scale uses the algebraic equation for functioning scales.

The raw score will be calculated based on the average of the items that contribute to the subscale. A linear transformation will then be applied to the raw score so that visit scores range from 0 to 100 (as per the standard coding provided in EORTC scoring manual).

For missing items within a subscale, if there are >50% of the items in the subscale completed then the missing items will be assumed to have values that are equal to the average of the items completed. Otherwise the visit score will be set to missing.

If there are cases in which more than one questionnaire has been completed on the same day, and provide different answers, the questionnaire with the highest overall score will be used.

### Method of categorising visit scores into visit response

Osoba et al 1998 suggested that in patients with breast and small-cell lung cancer, changes (from baseline to various study time points) in scores of 5-10 on a 1-100 scale represented a small difference, 10-20 represented a moderate difference, and those above 20 represented large differences. King 1996 used a variety of clinical classifications as anchors and found similar results across various studies and cancer sites. Based on these 2 studies, mean differences of 10 points or more are widely viewed as being clinically significant when interpreting the results and hence a cut-off of a change of 10 points has been used in this study to define visit responses of improvements and worsenings. Visit scores will be categorised into visit responses as defined in Table 9.

**Table 9**                      **Categorisation of visit scores into visit responses**

Score	Change from baseline	Visit response
Symptom scales / items	≤-10	Improved
	>-10, <10	No change
	≥10, or missing questionnaire due to “Subject too sick, other than disease under investigation” or “Subject too affected by symptoms of disease under investigation”	Worsened

**Table 9**                      **Categorisation of visit scores into visit responses**

<b>Score</b>	<b>Change from baseline</b>	<b>Visit response</b>
	Missing for reasons other than those above	Not evaluable
Functional scales, Global health status	≥10	Improved
	>-10, <10	No change
	≤-10, or missing questionnaire due to “Subject too sick, other than disease under investigation” or “Subject too affected by symptoms of disease under investigation”	Worsened
	Missing for reasons other than those above	Not evaluable

**Method of calculating best overall response**

Visit scores will be combined to calculate best overall response as defined in table 10.

**Table 10**                      **Calculation of best overall response**

<b>Score</b>	<b>Definition</b>	<b>Best overall response</b>
Any	Two visit responses of “improved” a minimum of 21 days apart without an intervening visit response of “worsened”	Improved
	Does not qualify for overall score response of “improved”. Two visit responses of either “no change”, or “improved” and “no change” a minimum of 21 days apart without an intervening visit response of “worsened”	No change

Does not qualify for overall score response of “improved” or “no change”. Either (1) A visit response of “worsened” without a response of “improved” or “no change” within 21 days; or (2) Died within 12 weeks of last evaluable PRO assessment.	Worsened
Does not qualify for one of the above	Not evaluable

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A deterioration is defined as a visit response of worsened without a visit response of no change or improved within 21 days. If there are no further visit responses available then this will still count as deterioration. Death in the absence of PRO deterioration will also count as deterioration if it occurs within 12 weeks of the last evaluable PRO assessment. Time to deterioration is calculated as the time from randomisation to the date of the first assessment at which deterioration began. Subjects that have not deteriorated at the time of data cut off will be censored at the time of the last evaluable assessment for that PRO.

Any subject who cannot possibly worsen compared to baseline will be censored for time to worsening at time 0.

## **12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA**

### **12.1 Description of analysis sets**

#### **12.1.1 Efficacy analysis set**

All efficacy data in Part B of the study (change in tumour size at 12 weeks, PFS, ORR, DoR and percentage of patients without progression at 12 weeks) will be analysed on an intention-to-treat basis (ITT). This will include all randomised patients, wherever possible, and compare treatment groups on the basis of randomised treatment, regardless of the treatment they actually received.

To be considered 'evaluable' for the primary efficacy analysis, a patient must have:

- Baseline and week 12 ( $\pm 1$  week) tumour measurements; or
- Evidence of progression prior to week 12; or

- In the absence of the week 12 measurements and no evidence of progression, RECIST measurements at baseline and 1 visit after or prior to the week 12 visit such that a prediction for the week 12 result can be made (see section 11.1.1 for details)

For the Part A safety run-in, the efficacy analysis set will include all patients who received at least one dose of study treatment.

### 12.1.2 Safety analysis set

All patients who receive at least one dose of AZD5363 in Part A, or randomised treatment in Part B, will be included in the assessment of the safety data. Any patient who only receives one or more doses of paclitaxel and does not commence dosing with IP will not be included in the assessment of safety data.

Throughout the safety results sections, erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

## 12.2 Methods of statistical analyses

A comprehensive statistical analysis plan (SAP) will be prepared prior to enrolment of patients in the study.

The primary outcome variable for Part B of change in tumour size at 12 weeks, and the secondary outcome variable of PFS, will be analysed formally. All Part A data, other Part B efficacy and safety data will be summarised descriptively.

For the primary and secondary analysis the null hypothesis is that there is no treatment effect, i.e., there is no difference in terms of change in tumour size at 12 weeks between patients treated with AZD5363 + paclitaxel and patients treated with matching placebo + paclitaxel.

No adjustments for multiplicity will be made.

Details of sensitivity analyses and imputation methods for missing data will be fully documented in the SAP.

There are potentially a number of different analysis points for the study. The table below details which data will be analysed at each time point.

<b>Analysis</b>	<b>Trigger</b>	<b>Data type included</b>
End of safety run-in	All patients in Part A followed up for at least 12 weeks	Safety, efficacy (week 12 response rate, best response), PK, PD
Randomised expansion interim analysis	40 patients randomised and completed 12 week follow up period (or progressed prior to 12	Change in tumour size, response rate at 12 weeks, best objective response (No <i>PIK3CA</i> mutation

	weeks)	subgroup analysis)
Randomised expansion primary analysis	60 patients randomised and completed 12 weeks follow up period (or progressed prior to 12 weeks)	All efficacy other than PFS (including <i>PIK3CA</i> mutation subgroup analyses), safety, PK, PD
Randomised expansion progression free survival analysis	Recruitment to Part B complete and 45 progression events occurred	PFS (overall and in <i>PIK3CA</i> mutation - positive subgroup), RR and duration, safety
Safety update	When last patient discontinues study treatment	Reduced set of safety outputs

PFS analysis and safety update will be combined if last patient has discontinued by the time the PFS events are reached.

Randomisation in Part B of the study will be stratified by *PIK3CA* mutation status determined by analysis of tumour tissue (or result from a prior tumour analysis) and a blood sample (see sections 5.2.1 and 6.2.2).

A mutation detected in either the blood or tissue samples will result in a patient being classified as being in the mutation-positive group for this analysis. Concordance between tumour tissue and blood sample mutation results will be explored. In the event of conflicting results in a substantial number of patients, the impact of the different methods on the efficacy analyses will be explored.

### 12.2.1 Change in tumour size at 12 weeks

The primary endpoint for Part B, of change in tumour size at week 12 (or progression if prior to week 12), will be assessed in all patients in this part and separately within the *PIK3CA* mutation-positive subgroup of patients. Change in tumour size will be assessed as the log of the ratio of week 12 tumour size over the baseline tumour size measurement for each patient as these data have been assumed to be log-normally distributed (see section 11.1.1).

The effect of AZD5363 on change in tumour size will be estimated in the overall population and also within the *PIK3CA* mutation-positive subgroup from analysis of covariance (ANCOVA) models including covariates for treatment, baseline tumour size (log transformed) and *PIK3CA* mutation status (mutant or not detected, only included in the overall analysis model).

[REDACTED]

[REDACTED]

The number and percentage of subjects in each treatment

group whose 12-week data is imputed, will be presented on the footnote to the table of output from this analysis.

The distribution of the tumour size measurement data will be assessed without knowledge of the randomised treatment assignment. If the week 12 changes in tumour size data follow a log-normal distribution, these data will be analysed as described previously. If, however, it is judged the data do not adequately follow a log-normal distribution then the use of untransformed percentage changes or a non-parametric approach could replace the log transformed analysis as the primary approach.

The week 12 change in tumour size will also be presented graphically by waterfall plots for each treatment group which present each patient's week 12 change in tumour size as a separate bar, with the bars ordered from the largest increase to the largest decrease. This plot will be repeated separately by treatment group for those patients whose tumour was *PIK3CA* mutation-positive at entry, and also for the overall analysis but flagging (by colour or pattern) whether patients are *PIK3CA* mutation-positive or not detected. Reference lines at the +20% and -30% change in tumour levels will be added to the plots, which correspond to the changes in sum of TLs that would result in the TL responses of progression and partial response, respectively. In these waterfall plots (and also in the listings) the patients whose week 12 change in tumour size is based on an imputation due to missing TL data but known to be progressors will be clearly identified (by different coloured bars for the waterfall plots and a flag in the listings).

Change in tumour size will be presented descriptively for patients in Part A of the study with summary tables and waterfall plots.

Frequencies of NTL progressions and new lesions at week 12 will be presented together with the change in tumour size results in order to put the change in tumour size results into perspective.

### **12.2.2 Progression Free Survival**

The secondary endpoint of PFS will be analysed for the patients in Part B when recruitment to Part B has completed and approximately 45 PFS events in the overall population have occurred. Waiting until recruitment has completed to this part of the study will ensure that as many as possible of the PFS events included in the analysis come from a mixture of *PIK3CA* mutation positive and not detected patients. This aims to safeguard against the possibility that the progression events could be largely from the mutation not detected patients if that stratum recruits substantially quicker than the other. PFS will not be presented for patients in Part A of the study. PFS will be analysed for the overall population and for the subgroup of *PIK3CA* mutation patients, using separate Cox proportional-hazards models allowing for the effect of treatment and including a term for *PIK3CA* mutation status in the overall analysis (mutation positive or not detected).

The hazard ratios in the overall population and in the *PIK3CA* mutation subgroup (HR; AZD5363 + paclitaxel: placebo + paclitaxel) for treatment will be estimated together with

their

Kaplan-Meier plots of PFS and estimates of median PFS, and proportion of patients progression-free at 6 months and 1 year will be presented by treatment group for the overall analysis and in the analysis of *PIK3CA* mutation-positive patients.

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

Full details of any sensitivity analyses for PFS will be fully documented in the SAP.

### **12.2.3 Response rate at 12 weeks and best objective tumour response**

Response rate at 12 weeks and best response during the study will be tabulated by randomised treatment (AZD5363 + paclitaxel or placebo + paclitaxel) in Part B and by dose and schedule for the Part A patients. These will present frequencies of confirmed complete responses and partial responses in addition to unconfirmed complete and partial responses, stable disease, progressive disease and not evaluable. In addition, the proportion of patients known to be progression-free at 12 weeks will be presented. This is defined as the number of patients with complete response, partial response or stable disease at 12 weeks (do not have to be confirmed).

These data will not be analysed formally.

A tabulation of response rate at 12 weeks, best response during the study and proportion progression free at 12 weeks by treatment group by *PIK3CA* mutation status will also be presented to assess if the response rate is different in the *PIK3CA* mutation-positive and *PIK3CA* mutation-not detected subgroups.

### **12.2.4 Duration of response (DoR)**

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 for patients in Part B and appropriate descriptive summary statistics will be presented (number of responses, number of responses that have progressed, median, quartile, minimum and maximum DoR in the responders using the Kaplan-Meier estimate). 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.

### **12.2.5 Safety**

Safety data will not be analysed formally. All patients who receive at least 1 dose of study treatment will be included in the assessment of the safety profile (safety analysis set). Safety and tolerability data will be presented by treatment received for patients in Part B and by dose



and schedule for patients in Part A. For Part B, the main set of safety tables will consist of the overall population in the randomised expansion, but a reduced set of key safety outputs will also be repeated on patients with *PIK3CA* mutation positive tumours (as according to stratification levels determined at randomisation) to assess if the safety profile remains consistent within these patients.

### **Adverse Events**

Data from all cycles of initial treatment will be combined in the presentation of the safety data. AEs will be listed individually by patient and treatment group (dose and schedule group for the safety run-in phase). For patients who undergo 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 (AEs, SAEs, AE with outcome death, CTCAE grade  $\geq 3$ , AEs leading to permanent discontinuation) will be summarised by treatment group, and events in each category will be further summarised by MedDRA system organ class and preferred term, by treatment group. An additional table of all preferred terms sorted by decreasing frequency will be produced to show most frequent AEs regardless of system order class.

Any AE occurring before the first dose of IP (i.e., before Cycle 1 Week 1 Day 2) 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 study therapy (AZD5363/placebo and/or paclitaxel) will be included in the AE listings and summaries. AEs occurring after the 28-day follow-up period after discontinuation of IP will be listed separately, but not included in the summaries.

### **Laboratory parameters, vital signs and physical examination data**

Laboratory parameters will be listed and summarised over time in terms of absolute values and change from baseline.

Corrected calcium will be derived by AstraZeneca.

CTCAE grades will be calculated for laboratory parameters, where possible. Where CTCAE grading is available, a table of 1-grade shift, 2-grade shifts, 3-grade shifts and 4-grade shifts, in maximum CTC grade will be produced for each laboratory parameter, to summarise the overall worst CTCAE grade over the course of the study compared to the baseline CTCAE grade. Where possible, the direction of the shift will be reported to put the shift into context of an event such as hyper- or hypo- clinical event. Box and whisker plots of lab parameters against time will also be produced.

Vital signs (SBP, DBP and pulse) will be listed and box plots of change from baseline in SBP, DBP and pulse will be presented.

Physical exam data will be listed and summarised by initial dose received.

### **ECG parameters and echocardiogram data**

ECG parameters (PR, QRS, RR and QT) will be summarised over time in terms of absolute values and change from baseline. QTcB and QTcF derived from these variables by AZ will be presented in the same way.

Echocardiogram findings will be listed and summarised over time in terms of absolute values and change from baseline. Box and whisker plots of LVEF against time will be presented.

## **12.2.6 Pharmacokinetics**

### **Part A Safety Run-in AZD5363 and paclitaxel pharmacokinetics**

Plasma concentrations of AZD5363 and paclitaxel will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by dose level and schedule. Plasma concentrations at each time point will be summarised according to dose and schedule by the following summary statistics:

- The geometric mean (gmean, calculated as  $\exp[\mu]$ , where  $\mu$  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  $\pm$  standard deviation (calculated as  $\exp[\mu \pm s]$ )
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

In the calculation of plasma concentration summary statistics, plasma concentrations below the lower limit of quantification (LLOQ) will be set to zero at pre-dose. Summary statistics will be presented according to the following rules:

- If, at a given time point, 50% or less of the plasma concentrations are non-quantifiable (NQ), the geometric mean (gmean), CV, gmean  $\pm$  standard deviation (SD), arithmetic mean, SD and median will be calculated by substituting the LLOQ for values which are NQ. The minimum at that time point will be reported as NQ.

- [REDACTED]
- [REDACTED]
- [REDACTED]

### **Part B Randomised expansion**

The plasma concentrations determined using the sparse PK sampling scheme, at sampling timepoints, will be listed but not summarised.

#### **12.2.7 Pharmacodynamics and PK/PD relationships**

Biomarker levels at various time points in addition to changes from baseline will be plotted and summarized appropriately; by treatment group for Part B, and by dose and schedule for Part A.

The relationship between biomarkers, PK parameters and clinical efficacy endpoints may be explored by graphical presentations and modelling techniques, the details of which will be documented in a separate analysis plan.

#### **12.2.8 Health related quality of life (HR QoL) data (Part B only)**

As it is not known in advance how complete the HR QoL dataset will be in this early phase study, the analysis of the data will primary consist of descriptive summaries and graphical data presentations. If sufficient data are collected, further statistical analyses may be considered.

Descriptive summaries and figures will include the following, which will be produced by randomised treatment group:

- Summary of compliance of subjects to the PRO instruments.
- Percentage of subjects in each category for best overall response for each score.
- Percentage of subjects in each category by visit for each score.
- Summary statistics for scores and change from baseline in scores by visit for each score.
- Plots of mean change from baseline in scores over time with indicators of number of subjects at each time point (e.g. n and error bars) for each score.

- Summary statistics of time to deterioration for each score using Kaplan-Meier estimates

If sufficient data is collected to warrant further statistical analyses, analysis of time to deterioration of PRO scores will be considered by a log rank test to estimate hazard ratios and confidence intervals for the effect of treatment on each of the scores. Kaplan-Meier plots and estimates of median time to deterioration will also be produced. Likewise, if there is sufficient data and initial explorations warrant further exploration with statistical analyses, the use of repeated-measure analysis of variance models will be considered treating each of the scores as continuous endpoints and estimating the effect of treatment on the changes in scores over time.

### **12.2.9 Exploratory biomarkers and pharmacogenetics**

The number of patients that will agree to participate in the exploratory biomarker and genetic research is unknown. Therefore, it is not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation, or whether only descriptive statistics will be generated.

### **12.3 Interim analyses**

An interim analysis will be performed when 40 patients have been recruited to Part B and followed up for 12 weeks (or progressed prior to 12 weeks). The analysis will be primarily based on changes in tumour size at 12 weeks, but additional summaries of response rate at 12 weeks, proportion progression-free at 12 weeks and best objective response during the study will support the change in tumour size data at the interim analysis. The analysis and data presentations will be performed on the overall population, no *PIK3CA* mutation subgroup analysis will be performed as the number of patients expected to be recruited with a *PIK3CA* mutation positive tumour by that stage is likely to be low.

The purpose of the interim analysis is to provide the opportunity for an early trigger to commence setting up a phase IIb study, if the results are strong enough, such that once the primary analysis is completed to confirm the interim result, the phase IIb study could commence with minimal delay. Therefore, as safety data will be analysed on the full dataset at the primary analysis, it is proposed not to include safety data at the interim analysis. It is not considered necessary to adjust the significance level to account for this additional analysis of the data, given that this analysis will not form the basis of any stop or acceleration decisions. In addition, the results obtained will be interpreted with caution, bearing in mind the increased risk of false positive results that this additional analysis introduces.

### **12.4 Determination of sample size**

#### **Part B - Randomised expansion**

The primary endpoint of change in tumour size at week 12 will be assessed by calculating the log of the ratio of the week 12 ( $\pm 1$  week) tumour size measurement over the baseline tumour

size measurement for each patient. If the patient has documented evidence of objective disease progression prior to week 12, then this will be used as the week 12 measurement.

The primary analysis of change in tumour size will occur when week 12 tumour size data (or evidence of progression prior to week 12) are available for all patients. Analysis of change in tumour size at week 12 in the *PIK3CA* mutation patients will also occur at this time.

Approximately 70 patients will be randomised overall, 35 to each of the *PIK3CA* mutation-positive and *PIK3CA* mutation- not detected subgroups. This is to ensure that approximately 60 patients have evaluable tumour size data at baseline and week 12 (or progress prior to week 12) and approximately 30 have evaluable data within the *PIK3CA* subgroups.

[REDACTED]

[REDACTED]

[REDACTED]

### **Part A – Safety run-in**

The primary objective of Part A is to assess the safety and tolerability of two schedules of AZD5363 in combination with weekly paclitaxel, and to recommend a dose and schedule of AZD5363 to be used in combination with weekly paclitaxel for further investigation. Hence, the number of patients has been based on the desire to obtain adequate tolerability, safety, PK and pharmacodynamic data while exposing as few patients as possible to the IP and procedures.

For 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 to fulfil the primary objective.

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Date 24 February 2012

## **12.5 Data monitoring committee**

Not applicable

## 13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

### 13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

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

Name	Role in the study	Address & telephone number
[REDACTED]	Study Delivery Team Leader responsible for the protocol at central R&D site	AstraZeneca, [REDACTED] UK [REDACTED]
[REDACTED]	Study Delivery Team Physician responsible for the protocol at central R&D site	AstraZeneca, [REDACTED] UK [REDACTED]
[REDACTED]	Patient Safety Physician responsible for the protocol at central R&D site	AstraZeneca, [REDACTED] UK [REDACTED]

### 13.2 Overdose

There is no known antidote to AZD5363. Investigators should be advised that any patient who receives a higher dose than 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 is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose of AZD5363/placebo occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives **within one day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

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

For overdoses with associated SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 28 days.

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

### 13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

#### 13.3.1 Maternal exposure

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

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

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 28 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.



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Date 24 February 2012

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**Clinical Study Protocol Amendment**

Amendment Number	1
Drug Substance	AZD5363
Study Code	D3610C00002
Date	17 May 2012
Protocol Dated	24 February 2012

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**A Phase I/Ib, Multicentre, Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by *PIK3CA* Mutation Status (BEECH).**

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This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

**Sponsor:**

AstraZeneca AB, 151 85 Södertälje, Sweden.

**Centres affected by the Amendment:**

All centres within the study.

**The protocol for the study is to be amended as detailed below:**

It was identified that standard AstraZeneca protocol text describing reporting times for Serious Adverse Events (SAEs) had become non-compliant under European Directive 2011/C 172/01 (CT-3) 'Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use' section 4.3.1 paragraph 29.

Protocol Edition 1 stated SAE reporting time from the Investigator to the Sponsor as: 'immediate but no later than the end of the next business day'.

The European Directive states: 'Immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made by the investigator within a very

short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event.’.

The Study D3610C00002 protocol will therefore be amended to revise the criterion of ‘no later than the end of next business day’ to ‘within 24 hours’. This criterion will be applied to reporting of SAEs, overdose and maternal exposure:

**The protocol for the study is to be amended as follows (revised text in bold):**

**Section of protocol affected:**

6.4.4. Reporting of serious adverse events. Paragraph 2.

**Previous text:**

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

**Revised text:**

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

**Reason for Amendment:**

Incorporation of revised SAE reporting timelines.

**Persons who initiated the Amendment:**

 Study Leader

**Section of protocol affected:**

6.4.4. Reporting of serious adverse events. Paragraph 4.

**Previous text:**

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE **within one calendar day ie, immediately but no later than the end of the next business day** of when he or she becomes aware of it.

**Revised text:**

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

**Reason for Amendment:**

Incorporation of revised SAE reporting timelines.

**Persons who initiated the Amendment:**

 Study Leader

**Section of protocol affected:**

13.2. Overdose. Paragraph 3

**Previous text:**

If an overdose of AZD5363/placebo occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives **within one day, ie, immediately but no later than the end of the next business day** of when he or she becomes aware of it.

**Revised text:**

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

**Reason for Amendment:**

Incorporation of revised SAE reporting timelines.

**Persons who initiated the Amendment:**

 Study Leader

**Section of protocol affected:**

13.3.1. Maternal exposure. Paragraph 3

**Previous text:**

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

**Revised text:**

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

**Reason for Amendment:**

Incorporation of revised SAE reporting timelines.

**Persons who initiated the Amendment:**

 Study Leader



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**Clinical Study Protocol Amendment**

Amendment Number	2
Drug Substance	AZD5363
Study Code	D3610C00002
Date	24 April 2013
Protocol Dated	18 May 2012

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**A Phase I/Ib, Multicentre, Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by *PIK3CA* Mutation Status (BEECH).**

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This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

**Sponsor:**

AstraZeneca AB, 151 85 Södertälje, Sweden.

**Centres affected by the Amendment:**

This amendment affects all centres in the study.

**The protocol for the study is to be amended as follows:**

Changed or additional text is indicated in **bold**, where applicable. Deleted text is indicated as scored ~~through~~.

Administrative changes - due to, for example, correction of typographical errors or renumbering of subsequent sections following addition of new sections - have been amended as applicable and have been included in the revised protocol but will not be listed separately in this amendment.

The protocol amendments defined within this document primarily relate to the following areas:



1. **Study Title and phase of development:** Part B of this study had been re-categorised from Phase Ib to Phase II in reflection of an increase in the size of the study and change to progression-free survival as primary endpoint; as detailed in item 3 below.
2. **Study Part A. Replacement of AZD5363 continuous dosing schedule with an intermittent dosing schedule:** The original design of Part A of this study comprised two dosing schedules of AZD5363 in combination with paclitaxel: Schedule 1 - AZD5363 continuous dosing, and Schedule 2 - AZD5363 intermittent dosing [weekly - 4 days on-therapy followed by 3 days off].

Schedule 1 was not initiated in response to findings from associated clinical trial D3610C00001 - that an AZD5363 monotherapy continuous dosing schedule may not present a sufficiently favourable tolerability profile. It is proposed to now replace the Schedule 1 continuous regimen with an AZD5363 intermittent dosing regimen [weekly - 2 days on-therapy followed by 5 days off] following a strong pre-clinical positive evidence of efficacy of this schedule and an adequate clinical safety and tolerability profile as monotherapy in study D3610C00001.

3. **Study Part B. Increase of total patient number enrolled from 60 to 100 and change of primary endpoint to progression-free survival:** The original design of Part B was to provide statistical power to detect a difference in change of tumour size in the overall population and in the *PIK3CA* tumour mutation-positive subgroup. The study was also powered to detect a difference in progression-free survival (PFS) in the overall population, but not in the *PIK3CA* tumour mutation-positive subgroup.

Given the hypothesis that patients with a *PIK3CA* tumour mutation are the most likely to benefit from study therapy, it is proposed to increase the total number of patients to ensure sufficient statistical power to detect a potential difference in PFS in the *PIK3CA* tumour mutation-positive subgroup as well as in the overall population. This would provide for a more robust evaluation of AZD5363 combined with weekly paclitaxel, compared with weekly paclitaxel plus placebo, upon which to develop subsequent studies.

As a result of this change, the primary objective for Part B has been revised from assessment of relative anti-tumour activity (endpoint variable - change in tumour size at 12 weeks) to assessment of relative efficacy (endpoint variable - progression-free survival). Assessment of relative anti-tumour activity has become a secondary objective.

4. **Study Part B. Addition of overall survival as a secondary endpoint:** Overall survival has been added as a secondary endpoint in this study to provide an initial assessment of the survival time after treatment with AZD5363 combined with weekly paclitaxel compared with weekly paclitaxel plus placebo. This will provide essential guidance to inform the design of subsequent studies.

5. **Study Part B. Extension of WHO performance status evaluations:** Further performance status assessments at visits from first receipt of study drug up to progression will be performed. This has been implemented following guidance received from the UK National Institute for Health and Care Excellence (NICE) for studies of similar design.
6. **Study Part B. Introduction of an independent Safety Review Committee:** The inclusion of an SRC, with membership that is independent of participation in Study D3610C00002, is being implemented to enable periodic review of coded randomised trial data outputs. The SRC will assess safety and tolerability findings and will provide recommendations regarding continuation, adjustment or cessation of the dose and schedule of AZD5363/placebo.
7. **Study Part B. Provision for a change in AZD5363/placebo formulation:** Allowance will be made for a potential switch in AZD5363/placebo formulation from capsules to tablets prior to the start of, or during, Part B. The implementation of a tablet formulation would allow data to be generated from patients who have received a dosage form consistent with that of the likely on-market formulation. Such a change would be made only following the generation of data from study D3610C00001 demonstrating that PK exposure from the new tablet formulation is comparable to that of the original capsule formulation. Any such change would also be subject to the agreement of the SRC.
8. **Study Part B. Revision of statistical analysis plans:** The scheduling and conduct of statistical analyses will be revised to reflect the increase in patient numbers, change in primary objective and addition of overall survival evaluation under the scope of this protocol amendment
9. **Study Parts A and B. Inclusion of a Japanese patient population:** Under the original protocol it was not envisaged that Japan would participate in Part B, but that an optional dose escalation evaluation in Japanese patients could be conducted under Part A if indicated. It is now anticipated that Japanese patients will participate in Part B and be treated with the same doses of AZD5363 and paclitaxel as those in the West. This is based on the observation that Japanese patients are known to tolerate the required dose of paclitaxel and that no significant differences in PK and tolerability of AZD5363 have been observed between the Western and Japanese patients who have participated in AZD5363 Studies D3610C00001 and D3610C00004 respectively. In the event that emerging findings from Part B indicate a difference between the two populations in terms of tolerability, the Japanese dose escalation subsidiary Part A may be conducted at the request of the Safety Review Committee. In this case, enrolment of Japanese patients to Part B would be suspended.

**Section of protocol affected:**

Multiple.

**General Revisions**

1. References to a ‘continuous’ dosing schedule have been replaced by ‘intermittent’ or ‘intermittent 2-on 5-off’ throughout the amended protocol (please see amendment rationale number 2). Where these occur as solitary text changes only, they are not listed separately in this amendment.
2. References to AZD5363/placebo ‘capsule’ formulation for study Part B have been replaced by ‘capsule or tablet’ throughout the amended protocol (please see amendment rationale number 7). Where these occur as solitary text changes only, they are not listed separately in this amendment.
3. References to suspension of AZD5363/placebo dosing being permitted for single periods of up to 28 days due to suspected toxicities have been replaced by up to 14 days throughout the amended protocol and Appendix H (Instructions for study drug dose modification). After which time study therapy should be withdrawn. This change aligns with a more stringent approach to management of toxicities implemented across the AZD5363 clinical studies. Where these replacements occur as solitary text changes only, they are not listed separately in this amendment.
4. In the original protocol - Common Terminology Criteria for Adverse Events (CTCAE) version 4.1 was referenced in error. This has been corrected to version 4.0 throughout the amended protocol. Where these replacements occur as solitary text changes only, they are not listed separately in this amendment.
5. References to retention of samples by AstraZeneca for a maximum of 25 years for conduct of bioanalytical research have been revised to a maximum of 15 years throughout the amended protocol. This amendment has been made following a change in AstraZeneca’s Maximum Retention Period for Human Biological Samples policy. Where these replacements occur as solitary text changes only, they are not listed separately in this amendment.

**Section of protocol affected:**

Study Title on protocol front sheet and Synopsis.

**Previous text:**

A Phase I/II, Multicentre, Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus

Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by *PIK3CA* Mutation Status (BEECH).

**Revised text:**

A Phase I/II, Multicentre, Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by *PIK3CA* Mutation Status (BEECH).

**Reason for Amendment:**

Please see amendment rationale number 1.

**Section of protocol affected:**

Protocol Synopsis: Study centre(s) and number of patients planned

**Previous text:**

Number of patients planned (enrolled):

Safety Run-in. n= 40

Randomised Expansion. n= ~~70~~

Total number of study centres planned = ~~12~~

Number of patients to be recruited per site:

Maximum – not defined

Minimum: n= 2

<b>Study period</b>	<b>Phase of development</b>	
Estimated date of first patient enrolled	Q2 2012	I
Estimated date of last patient completed	Q4 <del>2014</del>	<del>II</del>

**Revised text:**

Number of patients planned (enrolled):

Safety Run-in. n= 40

Randomised Expansion. n= **100**

Total number of study centres planned = **25**

Number of patients to be recruited per site:

Maximum – not defined

Minimum: n= 2

<b>Study period</b>		<b>Phase of development</b>
Estimated date of first patient enrolled	Q2 2012	I
Estimated date of last patient completed	Q4 2016	II

**Reason for Amendment:**

Change to patient and site numbers – Please see amendment rationale number 3.

Change to estimated date of last patient completed is related to extension of study timings associated with follow-up for overall survival - Please see amendment rationale number 4.

Change to phase of development - Please see amendment rationale number 1.

**Section of protocol affected:**

Protocol Synopsis – Primary objectives

**Previous text:**

Part B. Randomised expansion:

~~To assess the relative anti-tumour activity of AZD5363 when combined with weekly paclitaxel vs. weekly paclitaxel plus placebo by comparison of change in tumour size at 12 weeks (target lesion assessment using RECIST 1.1) in the overall advanced or metastatic Estrogen Receptor positive breast cancer population and in a Phosphoinositide 3-kinase (*PIK3CA*) mutation-positive sub-population.~~

**Revised text:**

Part B. Randomised expansion:

**To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of progression-free survival in the overall advanced or metastatic Estrogen Receptor positive breast cancer population and in a Phosphoinositide 3-kinase (*PIK3CA*) mutation-positive sub-population.**

**Reason for Amendment:**

Please see amendment rationale number 3.

**Section of protocol affected:**

Protocol Synopsis – Secondary objectives

**Previous text:**

**Part B. Randomised expansion:**

- To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo.
- To assess the safety and tolerability of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo.
- To investigate the effect on patients' quality of life of AZD5363 when combined with weekly paclitaxel, compared with weekly paclitaxel plus placebo.

**Revised text:**

**Part B. Randomised expansion (objectives applicable to all randomised patients and to the *PIK3CA* tumour mutation-positive sub-population alone):**

- To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo **by assessment of best objective response and duration of response.**
- **To assess the relative anti-tumour activity of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo.**
- To assess the safety and tolerability of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo.
- To investigate the effect on patients' quality of life of AZD5363 when combined with weekly paclitaxel, compared with weekly paclitaxel plus placebo.
- **To compare overall survival in patients treated with AZD5363 in combination with weekly paclitaxel compared with weekly paclitaxel plus placebo.**

**Reason for Amendment:**

To clarify that the objectives relate to evaluation of the overall patient population and additionally to evaluation of the *PIK3CA* tumour-mutation positive sub-population alone.

To define the inclusion of assessment of anti-tumour activity and overall survival as secondary objectives; and to clarify the separation of assessment of relative efficacy by outcome measures. Please see amendment rationale numbers 3 and 4.

**Section of protocol affected:**

Protocol Synopsis – Part A: Safety run-in - Subsidiary Japanese patient evaluation (optional).

**Previous text:**

A subsidiary dose-escalating safety evaluation may optionally be conducted in a Japanese patient population at a starting dose, and under one schedule, determined by the Safety Review Committee. This evaluation would be conducted to determine a safe and tolerable dose of AZD5363 when combined with weekly paclitaxel in a Japanese population.

This separate Japanese safety run-in evaluation would commence following determination of the RD and dosing schedule in the Western population. ~~It would proceed in parallel with the Part B randomised expansion, but would not inform any decision regarding the conduct of Part B.~~ The schedule of assessments in the subsidiary Part A would be as detailed in this protocol for Part A. ~~It is not envisaged that a Japanese population would be evaluated under study Part B.~~

**Revised text:**

A subsidiary dose-escalating safety evaluation may optionally be conducted in a Japanese patient population at a starting dose, and under one schedule, determined by the Safety Review Committee. This evaluation would be conducted to determine a safe and tolerable dose of AZD5363 when combined with weekly paclitaxel in a Japanese population.

**At the time of preparation of amended protocol 3, it is not anticipated that this subsidiary safety run-in will be required, however it may be commenced if emerging findings from Japanese patients enrolled in the Part B randomised expansion prompt the need for supplementary assessment of the dose of AZD5363 in combination with paclitaxel in Japanese patients. In this case, further enrolment of Japanese patients to Part B would then be suspended.** The schedule of assessments in the subsidiary Part A would be as detailed in this protocol for Part A.

**Reason for Amendment:**

Please see amendment rationale number 9.

**Section of protocol affected:**

Protocol Synopsis – Study design; Part B: Randomised Expansion. Last paragraph.

**Previous text:**

Patient assessments will continue up to ~~objective disease progression as defined by RECIST 1.1,~~ death or withdrawal of consent. A 28-day safety follow-up assessment should be conducted following cessation of all study therapy (AZD5363/placebo and paclitaxel).

**Revised text:**

Patient assessments will continue up to death or withdrawal of consent. A 28-day safety follow-up assessment should be conducted following cessation of all study therapy (AZD5363/placebo and paclitaxel). **Patients who discontinue treatment for reasons other than progression, death or withdrawal of consent will continue to be followed for objective disease progression status as defined by RECIST 1.1.**

**Reason for Amendment:**

Please see amendment rationale number 4.

**Section of protocol affected:**

Protocol Synopsis – Investigational product, dosage and mode of administration.

**Previous text:**

AZD5363: A twice daily regimen of an oral capsule formulation given on ~~a continuous or~~ intermittent weekly dosing schedule. Administration of AZD5363 will commence in Part A as detailed in section 5.5.3:

- ~~Continuous dosing: 320 mg bd (640 mg daily)~~ throughout a patient's participation in the study.
- Intermittent dosing (4 days of treatment followed by 3 days off-treatment): 360 mg bd (720 mg daily) each week that paclitaxel is received, and then each week following cessation of paclitaxel throughout a patient's participation in the study.

Placebo (Part B only): Oral capsule formulation, matched to AZD5363.

**Revised text:**

AZD5363: A twice daily regimen of an oral formulation given on **one of two** intermittent weekly dosing schedules. Administration of AZD5363 will commence in Part A as detailed in section 5.5.3:



- **An intermittent dosing schedule of 2 days on-treatment followed by 5 days off-treatment: 560 mg bd (1120 mg daily) each week that paclitaxel is received, and then each week following cessation of paclitaxel throughout a patient's participation in the study.**
- **An intermittent dosing schedule of 4 days of treatment followed by 3 days off-treatment: 360 mg bd (720 mg daily) each week that paclitaxel is received, and then each week following cessation of paclitaxel throughout a patient's participation in the study.**

Placebo (Part B only): Oral formulation, matched to AZD5363.

**Reason for Amendment:**

Change to dosing schedule - please see amendment rationale number 2.

AZD5363/placebo matched formulation - please see amendment rationale number 7.

**Section of protocol affected:**

Protocol Synopsis – Outcome variables;

**Previous text:**

Part B. Randomised expansion:

- Treatment efficacy as assessed by progression-free survival.
- Tumour size as assessed by RECIST 1.1.
- Quality of life.

**Revised text:**

Part B. Randomised expansion:

- Treatment efficacy as assessed by progression-free survival.
- Tumour size as assessed by RECIST 1.1.
- Quality of life.
- **Overall survival.**

**Reason for Amendment:**

Please see amendment rationale number 4.

**Section of protocol affected:**

Protocol Synopsis – Statistical methods.

**Previous text:**

**Part B Randomised Expansion**

The primary outcome variable of ~~change in tumour size at 12 weeks~~ and the secondary ~~outcome~~ variable of ~~progression-free survival~~ will be analysed formally in Part B, the randomised expansion. Each variable will be analysed for all patients and then separately in those patients with *PIK3CA* mutation-positive tumour(s). All ~~other efficacy and~~ safety data collected during Part B will be summarised descriptively.

[Redacted text block]

All efficacy data in Part B of the study will be analysed on an intention-to-treat basis including all randomised patients and comparing treatment groups on the basis of randomised treatment, regardless of the treatment they actually received.

All patients who receive at least one dose of randomised treatment in Part B will be included in the assessment of the safety data, and patients will be assessed according to treatment actually received. Any patient who receives one or more doses of paclitaxel and does not commence dosing with investigational product (i.e. AZD5363 or placebo) will not be included in the assessment of safety data.

[Redacted text block]

Progression free survival will be analysed in the Part B randomised expansion [Redacted text]

[Redacted text block]

[REDACTED]

Kaplan-Meier plots of progression-free survival and estimates of median progression-free survival will be presented by treatment group in the overall population and within the subgroup of patients with *PIK3CA* mutation-positive tumours.

**Revised text:**

The primary outcome variable of **progression-free survival** and the secondary **efficacy** variables will be analysed formally in Part B, the randomised expansion. Each variable will be analysed for all patients and then separately in those patients with *PIK3CA* mutation-positive tumour(s). All safety data collected during Part B will be summarised descriptively.

Progression free survival will be analysed in the Part B randomised expansion [REDACTED]

[REDACTED]

Kaplan-Meier plots of progression-free survival and estimates of median progression-free survival will be presented by treatment group in the overall population and within the subgroup of patients with *PIK3CA* mutation-positive tumours.

[REDACTED]

[REDACTED]

All efficacy data in Part B of the study will be analysed on an intention-to-treat basis including all randomised patients and comparing treatment groups on the basis of randomised treatment, regardless of the treatment they actually received.

All patients who receive at least one dose of randomised treatment in Part B will be included in the assessment of the safety data, and patients will be assessed according to treatment actually received. Any patient who receives one or more doses of paclitaxel and does not commence dosing with investigational product (i.e. AZD5363 or placebo) will not be included in the assessment of safety data.

In Part B, the effect of AZD5363 + paclitaxel on change in tumour size will be estimated from an analysis of covariance model including covariates for baseline tumour size (log transformed), *PIK3CA* mutation status and treatment. Change in tumour size in patients that have *PIK3CA* mutation-positive tumours will be estimated from an analysis of covariance model with baseline tumour size and treatment as covariates. Estimates of the treatment effects (ratio of glsmeans, AZD5363 + paclitaxel: placebo + paclitaxel) will be calculated together with their 2-sided 80% confidence intervals. Waterfall plots showing the percentage change in tumour size for individual patients will also be presented.

**Reason for Amendment:**

The last paragraph, detailing progression-free survival, in the original protocol has been moved to the position of paragraph 2 in the amended version. This is with reference to PFS as the revised primary outcome variable. Please see amendment rationale number 3.

Sample size description in paragraphs 3 and 4 has been revised and separated to describe and clarify the evaluation of patient subsets under the increased total number of 100 to be recruited. Please see amendment rationale number 3.

**Section of protocol affected:**

Section 1.1.2. Non-clinical information and correlative studies.

**Additional text (following paragraph 6):**

**The key findings in the toxicology studies were as follows:**

- [REDACTED]
- [REDACTED]
- [REDACTED]

[Redacted]

- [Redacted]
- [Redacted]

[Redacted]

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]

**Reason for Amendment:**

Addition of key findings from toxicology studies added to enhance the understanding of non-clinical reference background information for investigators.

**Section of protocol affected:**

Section 1.1.3. Clinical information.

**Previous text:**

[Redacted text block]

- [Redacted list item]

[Redacted text block]

[Redacted text block]

[Redacted text block]

- [Redacted list item]

[Redacted text block]

- [Redacted list item]

[Redacted text block]

[Redacted text block]

[Redacted text block]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Further details are provided in the Investigators' Brochure.

**Revised text:**

**At the time of preparation of amended protocol 2, AZD5363 has been administered as monotherapy to patients in two studies (D3610C00001 [Western] and D3610C00004 [Japan]). 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]

**11.3.1 Dose-limiting toxicities**

**AZD5363 Continuous dosing:**

[REDACTED]

[REDACTED]

[Redacted]

[Redacted]

[Redacted]

**AZD5363 Intermittent, 4 days on 3 days off, dosing:**

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

**11.3.2 Early evidence of anti-tumour activity**



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Further details are provided in the Investigators' Brochure.

**Based on the accumulated anti-tumour and safety data, both intermittent schedules: 4 days on and 3 days off and 2 days on and 5 days off are being investigated in the Part A of this study.**

**No significant safety, tolerability or pharmacokinetic (see section 1.1.3.3) differences have been observed with use of AZD5363 between Western and Japanese population (Studies D3610C00001 and D3610C00004 respectively). Population differences are not anticipated when AZD5363 is combined with weekly paclitaxel.**

**Reason for Amendment:**

Revised information has been provided to give updated details of clinical findings from concurrent AZD5363 studies for the reference of investigators. Additional information had

been added with reference to conduct of AZD5363 dosing as a 2 days-on, 5 days-off schedule (please see amendment rationale number 2).

The structure of this section has been revised to align with a new common reporting format across AZD5363 clinical studies; allowing for more effective, standardised, updates to be provided where required in future documents.

**Section of protocol affected:**

Section 1.2. Research hypothesis

**Previous text:**

**Part B. Randomised expansion:**

- The addition of AZD5363 to weekly paclitaxel will be more efficacious than paclitaxel alone - as demonstrated by ~~a reduction in tumour size~~ in patients with Estrogen-Receptor positive (ER+ve) advanced or metastatic breast cancer.
- Tumour types that have mutations in *PIK3CA* (*PIK3CA* mutation-positive) will have increased sensitivity to AZD5363 and may therefore demonstrate greater tumour size reduction and clinical response to AZD5363 when combined with paclitaxel than the overall population.

**Revised text:**

**Part B. Randomised expansion:**

- The addition of AZD5363 to weekly paclitaxel will be more efficacious than paclitaxel alone - as demonstrated by **an increase in duration of progression-free survival (PFS)** in patients with Estrogen-Receptor positive (ER+ve) advanced or metastatic breast cancer.
- Tumour types that have mutations in *PIK3CA* (*PIK3CA* mutation-positive) will have increased sensitivity to AZD5363 and may therefore demonstrate greater tumour size reduction and clinical response to AZD5363 when combined with paclitaxel than the overall population.

**Reason for Amendment:**

Please see amendment rationale number 3.

**Section of protocol affected:**

Section 1.3.2. Rationale for AZD5363 in breast cancer

**Previous text:**

AZD5363 has been shown to greatly increase sensitivity to the taxane docetaxel (Taxotere) in several breast cancer xenograft models. For example, both continuous and intermittent schedules of AZD5363 enhanced the efficacy of docetaxel in the HCC-1187 xenograft (Figure 1). The sequence of administration appears to be very important; in the HCC-1187 model, administering docetaxel after an intermittent dosing schedule of AZD5363 (4 days on, 3 days off) was found to be antagonistic, whilst administering docetaxel before the intermittent schedule resulted in enhanced efficacy (Figure 2).

**Revised text:**

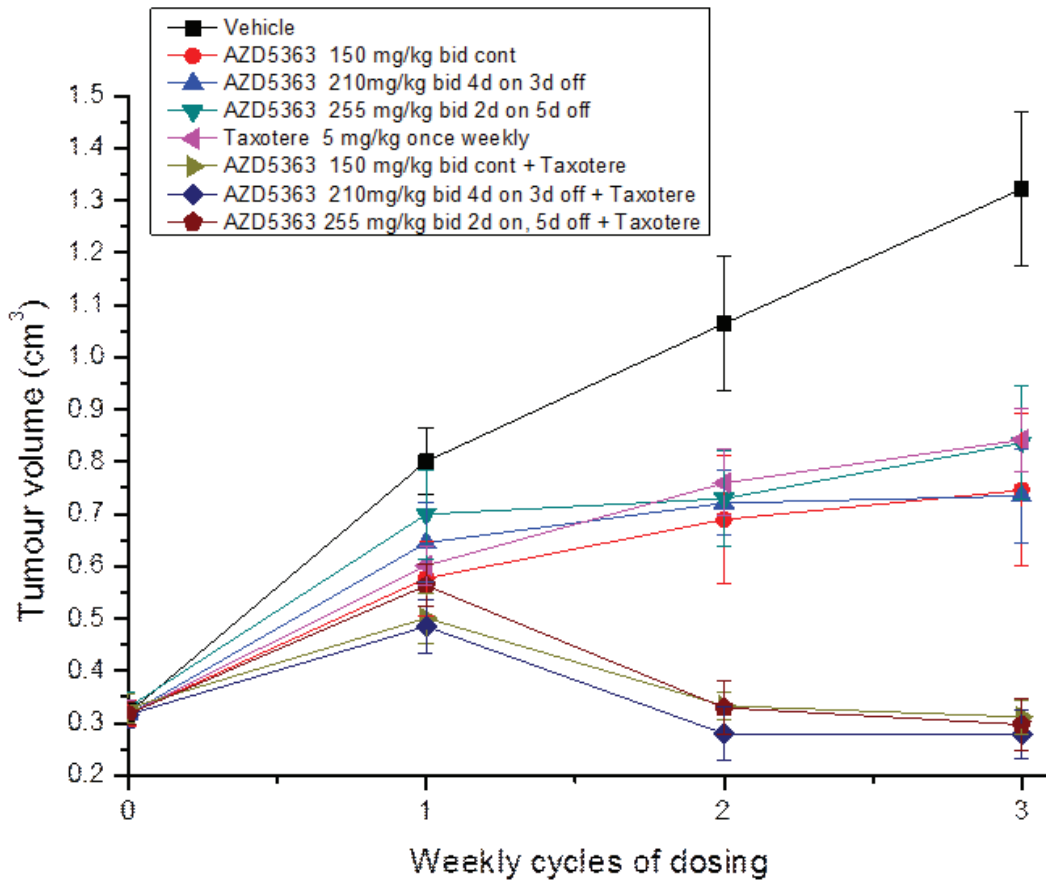
AZD5363 has been shown to greatly increase sensitivity to the taxane docetaxel (Taxotere) in several breast cancer xenograft models. For example, both continuous and intermittent schedules of AZD5363 enhanced the efficacy of docetaxel in the HCC-1187 xenograft (Figure 1). The sequence of administration appears to be very important; in the HCC-1187 model, administering docetaxel after an intermittent dosing schedule of AZD5363 (4 days on, 3 days off) was found to be antagonistic, whilst administering docetaxel before the intermittent schedule resulted in enhanced efficacy (Figure 2).

**Efficacy equivalence has been shown for AZD5363 combined with Taxotere under continuous, 4 days-on, 3 days-off and 2 days-on 5 days-off schedules at adjusted dose levels (Figure 3).**

**Additional Figure:**

**Figure 3 Different dosing schedules of AZD5363 deliver equivalent efficacy, as monotherapy or in combination with taxotere, in the BT474c xenograft model.**

**In this model, a dose of 255 mg/kg bd of AZD5363 combined with Taxotere given in a 2 days on 5 days off intermittent schedule delivers equivalent efficacy to that obtained from a combination of Taxotere with either 150mg/kg bd of AZD5363 given in a continuous schedule and 210mg /kg bd of AZD5363 given in a 4 days on, 3 days off schedule.**



**Reason for Amendment:**

Additional pre-clinical information is provided with reference to the rationale for selection of the AZD5363 2 days-on, 5 days-off dosing schedule for evaluation in Study Part A. Please see amendment rationale number 2.

**Section of protocol affected:**

Section 1.4.3. Potential risks identified from early clinical studies with AZD5363

**Previous text:**



[REDACTED]

[REDACTED]

[REDACTED]

**Revised text:**

[REDACTED]

**Further details are provided in the Investigators' Brochure.**

**Reason for Amendment:**

This summary of the occurrence of adverse events in Study D3610C00001 has been removed following provision of expanded clinical information in section 1.1.3. Investigators are also directed to the Investigator's Brochure as the primary source of safety and tolerability information derived from ongoing AZD5363 clinical studies.

**Section of protocol affected:**

Section 2.1. Primary objective

**Previous text:**

Part B. Randomised expansion: To assess the relative ~~anti-tumour activity of AZD5363 when combined with weekly paclitaxel vs. weekly paclitaxel plus placebo by comparison of change in tumour size at 12 weeks (target lesion assessment using Response Evaluation Criteria In Solid Tumours [RECIST 1.1])~~ in the overall advanced or metastatic ER+ve breast cancer population and in the *PIK3CA* mutation-positive sub-population.

**Revised text:**

Part B. Randomised expansion: To assess the relative **efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of PFS** in the overall advanced or metastatic ER+ve breast cancer population and in the *PIK3CA* mutation-positive sub-population.

**Reason for Amendment:**

Please see amendment rationale number 3.

**Section of protocol affected:**

Section 2.2. Secondary objectives

**Previous text:**

**Part B. Randomised expansion:**

- ~~• To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of ORR at 12 weeks.~~
- To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of PFS, best objective response (BOR) and DoR.
- To further assess the safety and tolerability of AZD5363 when combined with weekly paclitaxel compared with paclitaxel plus placebo.
- To investigate the effect on patients' quality of life (QoL) of AZD5363 when combined with weekly paclitaxel, compared with weekly paclitaxel alone by changes from baseline, utilising a patient-completed QoL questionnaire.

**Revised text:**

**Part B. Randomised expansion (objectives applicable to all randomised patients and to the *PIK3CA* tumour mutation-positive sub-population alone):**

- **To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of ORR at 12 weeks, best objective response (BOR) and DoR.**
- **To assess the relative anti-tumour activity of AZD5363 when combined with weekly paclitaxel vs. weekly paclitaxel plus placebo by comparison of change in tumour size at 12 weeks (target lesion assessment using Response Evaluation Criteria In Solid Tumours [RECIST 1.1]).**
- **To compare overall survival (OS) in patients treated with AZD5363 in combination with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of time to death.**
- To further assess the safety and tolerability of AZD5363 when combined with weekly paclitaxel compared with paclitaxel plus placebo.

- To investigate the effect on patients' quality of life (QoL) of AZD5363 when combined with weekly paclitaxel, compared with weekly paclitaxel alone by changes from baseline, utilising a patient-completed QoL questionnaire.

**Reason for Amendment:**

Please see amendment rationale numbers 3 and 4.

**Section of protocol affected:**

Section 2.3. Exploratory objectives

**Additional text (new bullet point in position 4):**

- **To explore changes in WHO performance status in patients treated with AZD5363 in combination with weekly paclitaxel compared with weekly paclitaxel plus placebo.**

**Reason for Amendment:**

Please see amendment rationale number 5.

**Section of protocol affected:**

Section 3.1.1. Part A: Safety run-in

**Previous text:**

~~A multiple ascending-dose evaluation of AZD5363 in each of two schedules (continuous and intermittent dosing) when combined with weekly paclitaxel. These dose escalation schedules may commence at the same time, or one schedule may be initiated in advance of the other to facilitate ease of study initiation.~~

This part will assess the comparative safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of both schedules of AZD5363 when combined with weekly paclitaxel. A recommended dose and schedule of AZD5363 will be determined for conduct of Part B, the randomised expansion (see section 3.1.2).

The patient population will be female, aged 18 years or older, with advanced or metastatic breast cancer. For inclusion in Part A, patients must not have received any more than two prior courses of chemotherapy for breast cancer. Prior endocrine therapy is allowed.

Patients will be recruited in approximately 8 centres in approximately 4 countries. The number of patients enrolled will be dependent upon the number of dose escalation cohorts required, see below, but a total of approximately 40 patients is anticipated.

Both schedules of AZD5363 will be in combination with 90 mg/m<sup>2</sup> paclitaxel (see section 5.5.3):

- ~~Continuous dosing: AZD5363 capsules taken orally, twice daily, each day. The starting dose for cohort 1 will be 320 mg (640 mg daily).~~
- ~~Intermittent dosing: AZD5363 capsules taken orally, twice daily, for repeating weekly cycles of 4 days on treatment followed by 3 days off treatment during each week that paclitaxel is received. The starting dose for cohort 1 will be 360 mg (720 mg daily).~~

Dose escalating cohorts of 3 to 6 patients will be evaluated under each schedule. A total of 6 patients must be evaluated at a selected dose level for it to be confirmed as the RD. AZD5363 dose escalations and maximum doses attained will not exceed levels deemed tolerated by the Safety Review Committee (SRC) in prior first time in patient study D3610C00001.

The RD for a schedule may or may not be defined by attainment of non-tolerated dose / maximum tolerated dose (NTD / MTD) levels (see section 5.10.2). If the RD is selected prior to attaining MTD, the SRC will determine whether continued dose escalations to NTD/MTD are required.

#### **Revised text:**

A multiple ascending-dose evaluation of AZD5363 in each of two **intermittent dosing** schedules when combined with weekly paclitaxel.

This part will assess the comparative safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of both schedules of AZD5363 when combined with weekly paclitaxel. A recommended dose and schedule of AZD5363 will be determined for conduct of Part B, the randomised expansion (see section 3.1.2). **Determination of the Part B dose and schedule may not require completion of both Part A schedules; a decision to progress to Part B may be made on findings from one schedule in advance of completion of the other where this is deemed appropriate by the Safety Review Committee (SRC).**

The patient population will be female, aged 18 years or older, with advanced or metastatic breast cancer. For inclusion in Part A, patients must not have received any more than two prior courses of chemotherapy for breast cancer. Prior endocrine therapy is allowed.

Patients will be recruited in approximately 8 centres in approximately 4 countries. The number of patients enrolled will be dependent upon the number of dose escalation cohorts required, see below, but a total of approximately 40 patients is anticipated.

Both schedules of AZD5363 will be in combination with 90 mg/m<sup>2</sup> paclitaxel (see section 5.5.3). **AZD5363 will be taken orally, twice daily, as detailed below, on each week that paclitaxel is received. AZD5363 will not be taken on any week that paclitaxel is not scheduled. AZD5363 may be taken each week following withdrawal of paclitaxel, at the discretion of the investigator, throughout a patient's participation in the study:**



- **Schedule 1: A weekly intermittent AZD5363 dosing schedule of 2 days on-treatment followed by 5 days off-treatment. The starting dose for cohort 1 will be 560 mg bd (1120 mg daily).**
- **Schedule 2: A weekly intermittent AZD5363 dosing schedule of 4 days on-treatment followed by 3 days off-treatment. The starting dose for cohort 1 will be 360 mg (720 mg daily).**

Dose escalating cohorts of 3 to 6 patients will be evaluated under each schedule. A total of 6 patients must be evaluated at a selected dose level for it to be confirmed as the RD. AZD5363 dose escalations and maximum doses attained will not exceed levels deemed tolerated by the SRC in prior first time in patient study D3610C00001.

The RD for a schedule may or may not be defined by attainment of non-tolerated dose / maximum tolerated dose (NTD / MTD) levels (see section 5.10.2). If the RD is selected prior to attaining MTD, the SRC will determine whether continued dose escalations to NTD/MTD are required.

**Reason for Amendment:**

Please see amendment rationale number 2.

**Section of protocol affected:**

Section 3.1.1. Part A: Safety run-in. Subsidiary Japanese patient evaluation (optional)

**Previous text:**

A Part A subsidiary dose-escalating safety evaluation may be conducted optionally in a Japanese patient population at a starting dose, and under one schedule, determined by the Safety Review Committee. This evaluation would be conducted to determine a safe and tolerable dose of AZD5363 when in combination with paclitaxel in a Japanese population.

~~This separate Japanese safety run-in evaluation would commence following determination of the RD and dosing schedule in the Western population. It would proceed in parallel with the Part B randomised expansion, but would not inform any decision regarding the conduct of Part B. The schedule of assessments in the subsidiary Part A would be as detailed in this protocol for Part A. It is not envisaged that a Japanese population would be evaluated under study Part B.~~

**Revised text:**

A Part A subsidiary dose-escalating safety evaluation may be conducted optionally in a Japanese patient population at a starting dose, and under one schedule, determined by the Safety Review Committee. This evaluation would be conducted to determine a safe and tolerable dose of AZD5363 when in combination with paclitaxel in a Japanese population.

**At the time of preparation of amended protocol 3, it is not anticipated that this subsidiary safety run-in will be required, however it may be commenced if emerging findings from Japanese patients enrolled in the Part B randomised expansion prompt the need for supplementary assessment of the dose of AZD5363 in combination with paclitaxel in Japanese patients. In this case, further enrolment of Japanese patients to Part B would then be suspended.** The schedule of assessments in the subsidiary Part A would be as detailed in this protocol for Part A.

**Reason for Amendment:**

Please see amendment rationale number 9.

**Section of protocol affected:**

Section 3.1.2. Part B Randomised expansion. 3<sup>rd</sup> paragraph.

**Previous text:**

Patients will be recruited in approximately ~~12~~ centres in approximately ~~5~~ countries. Approximately ~~70~~ patients will be enrolled in this phase (~~to ensure that 60 are evaluable at 12 weeks~~), of which approximately ~~35~~ must have a tumour detectable as carrying a *PIK3CA* mutation.

**Revised text:**

Patients will be recruited in approximately **25** centres in approximately **10** countries. Approximately **100** patients will be enrolled in this phase, of which approximately **50** must have a tumour detectable as carrying a *PIK3CA* mutation.

**Reason for Amendment:**

Increased country and site numbers reflect updated estimates following feasibility reviews, and in reference to increased patient number in Part B (please see amendment rationale number 3).

**Section of protocol affected:**

3.1.3. Treatment schedules

**Previous text:**

~~Under both the continuous and intermittent dosing schedules, first receipt of paclitaxel will be on Cycle 1, Day 1; first receipt of AZD5363/placebo will be on Day 2.~~

~~Under the intermittent dosing schedule, weekly AZD5363 regimens thereafter will continue to start on the day after dosing with paclitaxel.~~

		Cycle 1				Cycle 2 onwards			
		Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
Paclitaxel. Dose day→		Day 1	Day 1	Day 1	None	Day 1	Day 1	Day 1	None
AZD5363	Continuous. Dose days →	Day 2 to Day 28				Day 1 to Day 28			
	Intermittent. Dose days →	D2 to D5	D2 to D5	D2 to D5	None	D2 to D5	D2 to D5	D2 to D5	None

**Revised text:**

**Both dosing schedules will be conducted in 4-weekly cycles; comprising 3 weeks on-treatment and 1 week off-treatment. During each week on-treatment, paclitaxel will be given on Day 1 and AZD5363 will commence on Day 2:**

		Cycle 1				Cycle 2 onwards			
		Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
Paclitaxel. Dose day→		Day 1	Day 1	Day 1	None	Day 1	Day 1	Day 1	None
AZD5363	<b>2-on 5-off</b> dose days →	<b>D2 &amp; D3</b>	<b>D2 &amp; D3</b>	<b>D2 &amp; D3</b>	<b>None</b>	<b>D2 &amp; D3</b>	<b>D2 &amp; D3</b>	<b>D2 &amp; D3</b>	<b>None</b>
	<b>4-on 3-off</b> dose days →	D2 to D5	D2 to D5	D2 to D5	None	D2 to D5	D2 to D5	D2 to D5	None

**Reason for Amendment:**

Please see amendment rationale number 2.

**Section of protocol affected:**

3.1.4. Assessment Schedule

**Previous text:**

Patients will undergo the assessments detailed in the schedules below, presented separately for those allocated to either the continuous or intermittent dosing schedule. Assessments are applicable to both the Safety Run-in and Randomised Expansion parts unless otherwise indicated

**Revised text:**

Patients will undergo the assessments detailed in the schedules below, presented separately for those allocated to either **of** the intermittent dosing schedules. Assessments are applicable to both the Safety Run-in and Randomised Expansion parts unless otherwise indicated.

**Assessment timing key:**

- **Pre: Pre-dosing;**
- **Post: Post –dosing (or the number of hours post-dosing are specified);**
- **X: At any time of the day.**

**Note: For days on which study drug is not received - ‘Pre’ and ‘Post’ indicate that assessments/samplings should be conducted at equivalent times to those carried out on dosing days, where possible**

**Reason for Amendment:**

Following feedback from study sites, daily assessment and sample timepoints (pre-, post-dosing and number of hours post-dosing where applicable) have been specified in the schedules of assessments (see items below) for clarity. This additional text describes the key used to define these timepoints in the schedule diagrams.

**Section of protocol affected:**

Figure 5. Schedule of assessments - Schedule 1

**Previous text:**

Figure 5 Schedule 1: AZD5363/placebo – Continuous Dosing.

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Paclitaxel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
Week →		1	2	3	4	1	2	3	4	1				
Week Day →	-28 to 0	1	3	1	2	1	1	1	1	1				
Paclitaxel dosed (i.v.)	X			X		X			X	X→				
AZD5363 dosed (bd)		X	X→	X	X→	X→	X	X→	X→	X→				
Activity↓														
Informed consent - <i>PIK3CA</i> screen (Part B only)	X													8.4
<i>PIK3CA</i> mutation testing	X													6.2.2
Informed consent - study	X													8.4
Demography & baseline characteristics	X													6.2
Medical/surgical history	X													6.2
Previous/concomitant therapy	X													5.6
Previous cancer therapy	X													5.6
Inclusion / exclusion criteria	X													4

Figure 5 Schedule 1: AZD5363/placebo – Continuous Dosing.

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Paclitaxel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:	
		1	2	3	4	1	2	3	4						
Week →															
Week Day →	-28 to 0	1	2	3	1	2	1	1	1	1	1	1			
Paclitaxel dosed (i.v.)					X		X			X	X				
AZD5363 dosed (bd)			X	X→	X	X→	X→	X→	X→	X→	X→				
Physical examination	X				X							X	X		6.4.6
Height and weight	X											X	X		6.4.7
WHO performance status	X														6.4.8
Vital signs	X	X	X		X	X	✘	X	X	X	X	X	X	X	6.4.11
12-lead ECG	X	X	X	X	X							X	X		6.4.9
MUGA / Echocardiogram	X											X <sup>3</sup>	X	X	6.4.10
Haematology, Clinical chemistry Urinalysis	X	X	X		✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	6.4.5
Glycosylated haemoglobin	X											X <sup>3</sup>	X	X	6.4.12.2
Lipids	X											X <sup>3</sup>	X	X	6.4.12.1
Glucose, insulin, insulin c-peptide,		X	✘		✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	6.4.12.3
Pregnancy test	X	X											X	X	6.4.5

Figure 5 Schedule 1: AZD5363/placebo – Continuous Dosing.

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Paclitaxel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
Week →		1	2	3	4	1	2	3	4	1				
Week Day →	-28 to 0	1	2	3	1	2	1	1	1	1				
Paclitaxel dosed (i.v.)		X			X			X		X→				
AZD5363 dosed (bd)		X	X→	X	X→	X→	X→	X→	X→	X→				
Paclitaxel PK blood samples <sup>1</sup>		X	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>									6.6.2
AZD5363 PK blood samples <sup>1</sup>			X	X	X	X	X	X	X					6.6.2
Pharmacodynamic blood samples <sup>1</sup>		X	X	X	X	X	X	X	X		X			6.7.1
Exploratory biomarker blood samples <sup>1</sup> (optional)	X	X	X	X	X	X	X	X	X		X			6.8.1.5
Exploratory biomarker hair samples (optional)		X	X											6.8.1.4
Pharmacogenetics (optional)		X												6.9.1
RECIST Tumour assessments	X									X <sup>3</sup>				6.3.1
Archival tumour sample	X													6.8.1.2
Paired biopsy (optional)	X								X					6.8.1.3
Circulating tumour cells		X							X					6.8.1.1
Patient meal information			X		X	X	X	X	X					6.4.12.4

Figure 5 Schedule 1: AZD5363/placebo – Continuous Dosing.

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Paclitaxel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:	
		1	2	3	4	1	2	3	4						
Week →															
Week Day →	-28 to 0	1	2	3	4	1	2	1	1	1	1				
Paclitaxel dosed (i.v.)	X		X			X			X						
AZD5363 dosed (bd)		X	X→X	X→X	X→X	X→X	X→X	X→X	X→X	X→X					
Quality of Life questionnaires (Part B only)	X										X <sup>3</sup>	X		6.5.1	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	5.6	
Subsequent cancer therapy													X	5.6	
Adverse events	X														

1. **PK, PD and Biomarker samplings are shown as cumulative timepoints. Please refer to individual study segment tables given in sections 6.6.2 (PK) and 6.8.1.6 (PD/biomarkers)**
2. **Part A - Safety Run-in phase only:** Patients will continue to undergo paclitaxel PK measurements on these occasions. RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1). **Part B - Randomised expansion only:** Patients will continue to undergo RECIST assessments after cessation of study therapies up to disease progression or withdrawal of consent.
- 3.



**Revised text:**

**Figure 6** Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:	
		1	2	3	4	1	2	3	4						
Week →															
Week Day →	-28 to 0	1	2	3	1	2	1	2	1	2	1	2	1	2	
Paclitaxel dosing		X			X				X				X→		
AZD5363 dosing		X	X		X→			X→	X→				X→		
Activity↓															
Informed consent - <i>PIK3CA</i> screen (Part B only)	X														8.4
<i>PIK3CA</i> mutation testing	X														6.2.2
Informed consent - study	X														8.4
Demography& baseline characteristics	X														6.2
Medical/surgical history	X														6.2
Previous/concomitant therapy	X														5.6
Previous cancer therapy	X														5.6
Inclusion / exclusion criteria	X														4

**Figure 6** Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off

Cycle →	Screen	Cycle 1						Cycle 2						Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:	
		1	2	3	4	1	2	3	4	1	2	3	4						1
Week →		1	2	3	4	1	2	3	4	1	2	3	4	1	2				
Week Day →	-28 to 0	1	2	3	1	2	1	2	1	2	1	2	1	2	1	2			
Paclitaxel dosing		X			X			X			X			X					
AZD5363 dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Physical examination	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X		6.4.6	
Height and weight	X	X								X					X	X		6.4.7	
WHO performance status <sup>3</sup>	X	Pre	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>		6.4.8	
Vital signs	X	Pre	Pre	Post	Pre	Pre	Pre	Pre	Pre	Pre	Post	Post	Post	Post	X	X		6.4.11	
12-lead ECG	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Post					X	X		6.4.9	
MUGA / Echocardiogram	X														X <sup>2</sup>	X		6.4.10	
Haematology, Clinical chemistry Urinalysis	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X		6.4.5	
Additional glucose		2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	4-6h	4-6h	6.4.5
Glycosylated haemoglobin	X														X <sup>2</sup>	X		6.4.12.2	
Lipids	X														X <sup>2</sup>	X		6.4.12.1	

**Figure 6** Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
Week →		1	2	3	4	1	2	3	4	1				
Week Day →	-28 to 0	1	2	1	2	1	2	1	2	1	2			
Paclitaxel dosing		X		X				X		X→				
AZD5363 dosing		X	X	X→				X→		X→				
Glucose, insulin, insulin c-peptide <sup>4</sup>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X			6.4.12.3
Pregnancy test	X										X			6.4.5
Paclitaxel PK blood samples <sup>1</sup>		Pre	Pre	Pre <sup>1</sup>	Pre <sup>1</sup>									6.6.2
AZD5363 PK blood samples <sup>1</sup>		Pre	Pre	Pre	Pre	Pre	Pre							6.6.2
Pharmacodynamic blood samples <sup>1</sup>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X				6.7.1
Exploratory biomarker blood samples <sup>1</sup> (optional)	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X				6.8.1.5
Exploratory biomarker hair samples (optional)		Pre	Pre											6.8.1.4
Pharmacogenetics (optional)	X													6.9.1

**Figure 6** Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
Week →		1	2	3	4	1	2	3	4	1				
Week Day →	-28 to 0	1	2	1	2	1	2	1	2	1	2			
Paclitaxel dosing		X		X		X		X		X				
AZD5363 dosing		X	X	X	X	X	X	X	X	X	X			
RECIST Tumour assessments	X									X <sup>2</sup>				6.3.1
Archival tumour sample	X													6.8.1.2
Paired biopsy (optional)	X					X								6.8.1.3
Circulating tumour cells	Pre					Pre				Pre <sup>2</sup>				6.8.1.1
Patient meal information		X	X		X		X		X	X				6.4.12.4
QoL questionnaires (Part B only)	X									X <sup>2</sup>	X			6.5.1
Survival status (Part B only) <sup>5</sup>												X <sup>5</sup>		6.2.3.4
Subsequent cancer therapy											X			5.6
Concomitant medication	X												↗	5.6
Adverse events	X												↗	6.4.3

i. Part A - Safety Run-in phase only: Patients will continue to undergo paclitaxel PK measurements on these occasions.

2. RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1). Part B - Randomised expansion only: Patients will continue to undergo RECIST assessments after cessation of study therapies up to disease progression or withdrawal of consent.
3. WHO performance status; Part B – Randomised expansion phase only: **Performance status will be assessed at these timepoints during part B only.**
4. Insulin c-peptide; Part A – Safety Run-in phase only: **Insulin c-peptide will not be analysed during the Part B Randomised expansion.**
5. Part B Randomised expansion phase only: **Survival status and subsequent cancer therapies will be determined at the 28 day follow-up visit and at 12-weekly intervals thereafter. These visits suggested to coincide with RECIST assessments up to disease progression, and at 12-weekly intervals thereafter to death or withdrawal.**

**Reason for Amendment:**

Please see amendment rationale number 2 regarding replacement of the schedule of assessments relevant to the AZD5363/placebo continuous dosing regimen – with a schedule relevant to the intermittent (2 days-on, 4 days-off) dosing regimen.

Addition of a survival status evaluation for study Part B has been introduced with reference to amendment rationale number 4.

Reasons for other amendments to timepoints and footnotes are described per assessment for protocol sections 6.4.5 to 6.8.1.6 detailed later in this document.

**Section of protocol affected:**

Figure 5. Schedule of assessments - Schedule 2

**Previous text:**

Figure 6 Schedule 2: AZD5363/placebo – Intermittent Dosing.

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:	
		1	2	3	4	1	2	3	4						
Week →															
Week Day →	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2		
Paclitaxel dosed (i.v.)	X					X				X					
AZD5363 dosed (bd)		X	X→	X	X	X→	X→	X→	X→	X→	X→	X→	X→		
Activity↓															
Informed consent - <i>PIK3CA</i> screen (Part B only)	X														8.4
<i>PIK3CA</i> mutation testing	X														6.2.2
Informed consent - study	X														8.4
Demography& baseline characteristics	X														6.2
Medical/surgical history	X														6.2
Previous/concomitant therapy	X														5.6
Previous cancer therapy	X														5.6

Figure 6 Schedule 2: AZD5363/placebo – Intermittent Dosing.

Cycle →	Screen	Cycle 1						Cycle 2						Cycle 3 onward	AZD5363 Discont.	Pac'xel Discont.	28-day follow-up	Details in Section:		
		1	2	3	4	1	2	3	4	1	2	3	4							
Week →																				
Week Day →	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	1	2	1	2			
Paclitaxel dosed (i.v.)		X				X										X→				
AZD5363 dosed (bd)		X	X→	X	X→	X→	X→					X→	X→			X→				
Inclusion / exclusion criteria	X																			8.4
Physical examination	X			X						X							X			6.4.6
Height and weight	X									X							X			6.4.7
WHO performance status	X																			6.4.8
Vital signs	X	X	X	X	X	X	X			X							X			6.4.11
12-lead ECG	X	X	X	X	X	X	X										X			6.4.9
MUGA / Echocardiogram	X																X			6.4.10
Haematology, Clinical chemistry Urinalysis	X	X	X	X	X	X	X			X							X			6.4.5
Glycosylated haemoglobin	X																X			6.4.12.2
Lipids	X																X			6.4.12.1
Glucose, insulin, insulin c-peptide,		X	X	X	X	X	X										X			6.4.12.3

Figure 6 Schedule 2: AZD5363/placebo – Intermittent Dosing.

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:	
		1	2	3	4	1	2	3	4						
Week →															
Week Day →	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2		
Paclitaxel dosed (i.v.)		X				X				X					
AZD5363 dosed (bd)		X	X→	X	X	X→	X→			X→	X→		X→		
Pregnancy test	X												X		6.4.5
Paclitaxel PK blood samples <sup>1</sup>		X				X <sup>2</sup>									6.6.2
AZD5363 PK blood samples <sup>1</sup>		X	X	X	X	X	X	X	X						6.6.2
Pharmacodynamic blood samples <sup>1</sup>		X	X	X	X	X	X	X	X				X		6.7.1
Exploratory biomarker blood samples <sup>1</sup> (optional)	X	X				X							X		6.8.1.5
Exploratory biomarker hair samples (optional)		X			X										6.8.1.4
Pharmacogenetics (optional)	X														6.9.1
RECIST Tumour assessments	X														6.3.1
Archival tumour sample	X														6.8.1.2
Paired biopsy (optional)	X												X		6.8.1.3



Figure 6 Schedule 2: AZD5363/placebo – Intermittent Dosing.

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Paclitaxel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:	
		1	2	3	4	1	2	3	4						
Week →															
Week Day →	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2		
Paclitaxel dosed (i.v.)	X					X				X					
AZD5363 dosed (bd)		X	X→	X	X	X→				X→			X→		
Circulating tumour cells	X														6.8.1.1
Patient meal information		X			X			X					X		6.4.12.4
QoL questionnaires (Part B only)	X												X <sup>3</sup>		6.5.1
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.6
Subsequent cancer therapy													X	X	5.6
Adverse events	X														6.4.3

1. PK, PD and Biomarker samplings are shown as cumulative timepoints. Please refer to individual study segment tables given in sections 6.6.2 (PK) and 6.8.1-6 (PD/biomarkers)
2. Part A - Safety Run-in phase only: Patients will continue to undergo paclitaxel PK measurements on these occasions.
3. RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1). Part B Randomised expansion only: Patients will continue to undergo RECIST assessments after cessation of study therapies up to disease progression or withdrawal of consent

**Revised text:**

**Figure 7** Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
Week →		1	2	3	4	1	2	3	4	1				
Week Day →	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	
Paclitaxel dosing		X				X				X				
AZD5363 dosing			X	X	X	X	X		X	X	X			
Activity ↓														
Informed consent - <i>PIK3CA</i> screen (Part B only)	X													8.4
<i>PIK3CA</i> mutation testing	X													6.2.2
Informed consent - study	X													8.4
Demography & baseline characteristics	X													6.2
Medical/surgical history	X													6.2
Previous/concomitant therapy	X													5.6
Previous cancer therapy	X													5.6
Inclusion / exclusion criteria	X													4
Physical examination	X	Pre				Pre							Pre	6.4.6
													X	
													X	

**Figure 7** Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
Week →		1	2	3	4	1	2	3	4	1				
Week Day →	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	
Paclitaxel dosing		X				X				X				
AZD5363 dosing		X	X →	X		X →		X →		X →				
Height and weight	X									X		X		6.4.7
WHO performance status	X	Pre	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>		6.4.8
Vital signs	X	Pre	Pre	Pre	Post/Pre	Pre	Pre	Post	Post	Post	Post	X		6.4.11
12-lead ECG	X	Pre	Pre	Pre	Post/Pre	Pre	Post	Pre	Post	X	X	X		6.4.9
MUGA / Echocardiogram	X									X <sup>2</sup>	X	X		6.4.10
Haematology, Clinical chemistry Urinalysis	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X		6.4.5
Additional glucose <sup>6</sup>		2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	4-6h	6.4.5
Glycosylated haemoglobin	X	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	X <sup>2</sup>	X	X		6.4.12.2
Lipids	X									X <sup>2</sup>	X	X		6.4.12.1

**Figure 7** Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
Week →		1	2	3	4	1	2	3	4	1				
Week Day →	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	
Paclitaxel dosing		X				X				X				
AZD5363 dosing		X	X	X	X	X	X	X	X	X	X	X	X	
Glucose, insulin, insulin c-peptide <sup>3</sup>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	6.4.12.3
Pregnancy test	X													6.4.5
Paclitaxel PK blood samples <sup>1</sup>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	6.6.2
AZD5363 PK blood samples <sup>1</sup>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	6.6.2
Pharmacodynamic blood samples <sup>1</sup>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	6.7.1
Exploratory biomarker blood samples <sup>1</sup> (optional)	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	6.8.1.5
Exploratory biomarker hair samples (optional)		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	6.8.1.4
Pharmacogenetics (optional)	X													6.9.1

**Figure 7** Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
Week →		1	2	3	4	1	2	3	4	1				
Week Day →	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	
Paclitaxel dosing		X				X				X				
AZD5363 dosing		X	X →	X		X →		X →		X →				
RECIST Tumour assessments	X									X <sup>2</sup>				6.3.1
Archival tumour sample	X													6.8.1.2
Paired biopsy (optional)	X						X							6.8.1.3
Circulating tumour cells		Pre					Pre			Pre <sub>2</sub>				6.8.1.1
Patient meal information		X	X			X		X		X				6.4.12.4
QoL questionnaires (Part B only)	X									X <sup>2</sup>	X			6.5.1
Survival status (Part B only) <sup>6</sup>												X <sup>6</sup>		6.2.3.4
Subsequent cancer therapy <sup>6</sup>											X	X <sup>6</sup>		5.6
Concomitant medication	X												↗	5.6
Adverse events	X												↗	6.4.3

1. Part A - Safety Run-in phase only: Patients will continue to undergo paclitaxel PK measurements on these occasions.

2. RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1). Part B Randomised expansion only: Patients will continue to undergo RECIST assessments after cessation of study therapies up to disease progression or withdrawal of consent.
3. **WHO performance status; Part B – Randomised expansion phase only**: Performance status will be assessed at these timepoints during part B only.
4. **Insulin c-peptide; Part A – Safety Run-in phase only**: Insulin c-peptide will not be analysed during Part B.
5. **Part A Safety Run-in phase only**: Patients will undergo the Cycle 2 Week 1 Day 1 MUGA / Echocardiogram assessment during Part A only. **This assessment timepoint will not be conducted during the Part B Randomised expansion.**
6. **Part B Randomised expansion only**: Survival status and subsequent cancer therapies will be determined at the 28 day follow-up visit and at 12-weekly intervals thereafter. These visits suggested to coincide with RECIST assessments up to disease progression, and at 12-weekly intervals thereafter to death or withdrawal.

**Reason for Amendment:**

Sample timepoints (pre-, post- dosing and number of hours post-dosing where applicable) have been specified in the schedules of assessments for clarity following feedback received from study sites.

Addition of a survival status evaluation for study Part B has been introduced with reference to amendment rationale number 4.

Reasons for other amendments to timepoints and footnotes are described per assessment per protocol sections 6.4.5 to 6.8.1.6 detailed later in this document.

**Section of protocol affected:**

Section 4.2. Exclusion criteria. Bullet point 3.

**Previous text:**

3. Participation in another clinical study with an investigational product (IP) ~~during the last~~ 30 days.

**Revised text:**

3. Participation in another clinical study with an investigational product (IP) **within 30 days of the first dose of AZD5363 or matching placebo.**

**Reason for Amendment:**

For additional clarity that the exclusion timescales relates to commencement of study treatment.

**Section of protocol affected:**

Section 4.2. Exclusion criteria. Bullet point 8.

**Previous text:**

8. Exposure to potent inhibitors or inducers of CYP3A4 ~~or CYP2D6~~ or substrates of CYP3A4 within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort).

**Revised text:**

8. Exposure to potent inhibitors or inducers of CYP3A4 or substrates of CYP3A4 **or CYP2D6** within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort).

**Reason for Amendment:**

The original text was incorrect due to a typographic error in a source document. This amendment reflects that CYP2D6 is not inducible, and exposure to inhibitors of CYP2D6 should not be an exclusion. However, AZD5363 is a moderate competitive inhibitor of CYP2D6, therefore substrates of CYP2D6 are restricted.

**Section of protocol affected:**

Section 4.2. Exclusion criteria. Bullet point 11.

**Previous text:**

11. Last dose of anticancer therapy - other than for advanced or metastatic breast cancer (chemotherapy, radiation therapy, surgery, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, or tumour embolisation) ~~must be more than~~ 21 days (~~more than~~ 6 weeks for nitrosurea or mitomycin C) ~~prior to~~ the first dose of study treatment. If sufficient wash-out time has not occurred due to schedule or PK properties, a longer wash-out period will be required as agreed by AZ and the investigator.

**Revised text:**

11. Last dose of anticancer therapy - other than for advanced or metastatic breast cancer (chemotherapy, radiation therapy, surgery, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, or tumour embolisation) **within** 21 days (**within** 6 weeks for nitrosurea or mitomycin C) **before** the first dose of study treatment. If sufficient wash-out time has not occurred due to schedule or PK properties, a longer wash-out period will be required as agreed by AZ and the investigator.

**Reason for Amendment:**

To align wording to conform more precisely as an exclusion criterion.

**Section of protocol affected:**

Section 4.2. Exclusion criteria. Part A Safety Run-in. Bullet point 2.

**Previous text:**

2. If patients have received prior treatment with anthracyclines or mitoxantrone, cumulative exposure must be less than 360 mg/m<sup>2</sup> for doxorubicin, 720 mg/m<sup>2</sup> for epirubicin or 72 mg/m<sup>2</sup> for mitoxantrone.

**Revised text:**

2. If patients have received prior treatment with anthracyclines or mitoxantrone, cumulative exposure must be less than 360 mg/m<sup>2</sup> for doxorubicin, **650mg/m<sup>2</sup> for doxorubicin liposomal formulation**, 720 mg/m<sup>2</sup> for epirubicin or 72 mg/m<sup>2</sup> for mitoxantrone.

**Reason for Amendment:**

Specification of exclusion limits for liposomal doxorubicin has been provided following a question raised by a study site.

**Section of protocol affected:**

Section 5.2. Patient enrolment, randomisation and initiation of investigational product.



**Previous text:**

The Principal Investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.
2. Obtain a unique enrolment number, ~~beginning with 'E#'~~. The E-code is a 7-digit number comprising the centre number, the dosing schedule and the patient number within that particular centre. This number is the patient's unique identifier and is used to identify the patient on the electronic case report form (eCRF), and should be entered in to the patient medical records. The E-code will be in the format E000WXYZ. Where 000W= site number, X = schedule (1 = Part A ~~continuous~~, 2 = part A intermittent, 3 = Part B), Y & Z = patient number (per schedule) e.g., the first patient screened at centre 0001, to the Part A ~~continuous~~ dosing schedule would be assigned the E-code - E0001101, the second patient - E0001102; the first patient at this site in the Part A intermittent dosing schedule would be E0001201.

Once a candidate patient has been identified and consented, the site should obtain the enrolment number as follows:

Part A: For the safety run-in phase, the study site will notify the AstraZeneca Study Team that a patient has been consented by completion and e-mailing of a registration form. ~~AstraZeneca will reply, providing the E-number. For Part A this will include notification of which dosing schedule the patient is allocated to.~~

Part B: For the randomised expansion phase, the study site will contact the Interactive Voice/Web Response System (IVRS/IWRS) by telephone or using the web to notify that a patient has consented. ~~IVRS/IWRS will provide the E-number.~~

Further guidance on this process will be provided in a separate patient allocation process document.

All screened patients are assigned an E-code and will be listed on the patient enrolment and identification log irrespective of whether or not they subsequently receive study therapy. If a patient withdraws from participation in the study, their E-code will not be reused and the patient will not be allowed to re-enter the study.

For the Randomised Expansion part, if the patient is not randomised the site should notify IVRS/IWRS via a ~~Discontinuation~~ Call to enable the termination of the

3. Determine patient eligibility. See Sections 4.1 and 4.2
4. As patients become eligible for the study they will be assigned separate four digit identification codes. The first digit will indicate the schedule/phase. The second and third digits will be an escalating patient number, commencing at 001.

Part A: For the safety run-in phase, the study site will notify the AstraZeneca Study Team that a patient is eligible by completion and e-mailing of a registration form. AstraZeneca will reply, providing the identification code. The first patient entering cohort 1 of schedule 1 (~~continuous~~ dosing) will be numbered 1001, the second will be 1002 and so on. Patients assigned to schedule 2 (intermittent dosing) will be 2001, 2002 onwards.

Part B: For the randomised expansion phase, the study site will ~~contact~~ the IVRS/IWRS by telephone or using the web to confirm whether the patient is/is not eligible and, if eligible, to report the *PIK3CA* mutation status: 'positive' or 'not detected' (see section 5.2.1) to enable stratification. IVRS/IWRS will provide the ~~randomised~~ identification code. Patients that are *PIK3CA* mutation positive will be numbered 3001, 3002 onwards. Those that are *PIK3CA* mutation not detected will be numbered 4001, 4002 onwards. The treatment randomisation will not be ~~indicated under this system~~.

It is requested that sites obtain the ~~randomised~~ identification code on the day that the patient is ready to commence treatment.

Further guidance on this process will be provided in a separate patient allocation process document. Procedures will be provided in an IVRS/IWRS user manual that will be provided to each centre.

If a patient withdraws from participation in the study, then her identification code cannot be reused.

**Revised text:**

The Principal Investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.
2. Obtain a unique enrolment ('E') number – **which will be automatically generated by the RAVE system once initial patient information has been entered.** This E-code is a 7-digit number comprising the **country code**, centre number, the dosing schedule and the patient number within that particular centre. This number is the patient's unique identifier and is used to identify the patient on the electronic case report form (eCRF), and should be entered in to the patient medical records. The E-code will be in the format EAB0WXYZ. Where **AB = country code**, 0W= site number, X = schedule (1 = Part A **intermittent [2-on 5-off]**, 2 = Part A intermittent **[4-on 3-off]**, 3 = Part B), Y & Z = patient number (per schedule)

e.g., the first patient screened **in the UK (country code = 28)** at centre 01, to the Part A **intermittent 2-on 5-off** dosing schedule would be assigned the E-code – E2801101, the second patient – E2801102. The first patient at this site in the Part A intermittent **4-on 3-off** dosing schedule would be E2801201.

Once a candidate patient has been identified and consented, the site should **provide notification** as follows:

Part A: For the safety run-in phase, the study site will notify the AstraZeneca Study Team that a patient has been consented by completion and e-mailing of a registration form. AstraZeneca will reply, providing **confirmation of the dosing schedule that the patient has been assigned to. Upon entry of this into the appropriate database in the eCRF, the patient E-code will be generated automatically by the RAVE system.**

Part B: For the randomised expansion phase, the study site will contact the Interactive Voice/Web Response System (IVRS/IWRS) by telephone or using the web to notify that a patient has consented.

Further guidance on this process will be provided in a separate patient allocation process document.

All screened patients are assigned an E-code and will be listed on the patient enrolment and identification log irrespective of whether or not they subsequently receive study therapy. If a patient withdraws from participation in the study, their E-code will not be reused and the patient will not be allowed to re-enter the study.

For the Randomised Expansion part, if the patient is not randomised the site should notify IVRS/IWRS via a **Screening Failure** call to enable the termination of the patient in the system.

3. Determine patient eligibility. See Sections 4.1 and 4.2
4. As patients become eligible for the study they will be assigned separate four digit identification codes. The first digit will indicate the schedule/phase. The second and third digits will be an escalating patient number, commencing at 001.

Part A: For the safety run-in phase, the study site will notify the AstraZeneca Study Team that a patient is eligible by completion and e-mailing of a registration form. AstraZeneca will reply, providing the identification code. The first patient entering cohort 1 of schedule 1 (**intermittent 2-on 5-off** dosing) will be numbered 1001, the second will be 1002 and so on. Patients assigned to schedule 2 (intermittent **4-on 3-off** dosing) will be 2001, 2002 onwards.

Part B: For the randomised expansion phase, the study site will **notify** the IVRS/IWRS, by telephone or using the web, **that** the patient is eligible and to report the *PIK3CA* mutation status: 'positive' or 'not detected' (see section 5.2.1) to enable stratification. IVRS/IWRS will provide the **Randomisation** identification code. Patients that are *PIK3CA* **tumour**-mutation positive will be numbered 3001, 3002 onwards. Those that are *PIK3CA* **tumour**-mutation not detected will be numbered 4001, 4002 onwards. The treatment randomisation will not be **revealed to the study site.**

It is requested that sites obtain the **Randomisation** identification code on the day that the patient is ready to commence treatment.

Further guidance on this process will be provided in a separate patient allocation process document. Procedures will be provided in an IVRS/IWRS user manual that will be provided to each centre.

If a patient withdraws from participation in the study, then her **Randomisation** identification code cannot be reused.

**Reason for Amendment:**

For references to intermittent dosing schedules: 2 days-on / 5 days- off, and 4 days-on / 3 days-off, please see amendment rationale number 2.

Patient E-code numbering has been revised following implementation of AstraZeneca requirement for incorporation of country-specific codes in patient identifiers.

Other changes have been made following further guidance for accuracy and clarity in describing use of the IVRS/IWRS system.

**Section of protocol affected:**

Section 5.2.1. Procedure for identification of tumour *PIK3CA* mutation status and stratification.

**Previous text:**

Patient stratification by *PIK3CA* mutation status (Part B)

Patients will be stratified to '*PIK3CA* mutation positive' or '*PIK3CA* mutation not detected' arms prior to randomisation.

Patients assigned a *PIK3CA* mutation status of 'Unknown' will not be eligible to participate in Part B. In cases where an archival tumour sample is not received in time to be analysed by the central laboratory during screening, defined status may be derived from the blood sample alone, or it may be applicable to utilise the status from a prior, locally-conducted tumour analysis, see above.

If a patient is initially stratified to the 'Not detected' arm based upon a blood sample alone, or blood sample plus locally-conducted tumour analysis, and a subsequent, delayed, tumour sample is 'positive' the stratification will not be changed but the discrepancy will be noted. Any requirement to assign additional patient places to either stratification arm will be determined on an as-needed basis, dependent upon the number of discrepant patients.

**Revised text:**

**Patient stratification by *PIK3CA* mutation status (Part B)**

Patients will be **allocated** to ‘*PIK3CA* mutation positive’ or ‘*PIK3CA* mutation not detected’ **strata** prior to randomisation.

Patients assigned a *PIK3CA* mutation status of ‘Unknown’ will not be eligible to participate in Part B. In cases where an archival tumour sample is not received in time to be analysed by the central laboratory during screening, defined status may be derived from the blood sample alone, or it may be applicable to utilise the status from a prior, locally-conducted tumour analysis, see above.

If a patient is initially stratified to the ‘Not detected’ **stratum** based upon a blood sample alone, (or blood sample plus locally–conducted tumour analysis) **and a ‘positive’ central tumour sample analysis is received after stratification, the site will contact the IVRS/IWRS Customer Care department by telephone or using the web to provide notification of this new information. IVRS/IWRS records will be revised to show a corrected *PIK3CA* mutation status of ‘Positive’.**

**In the event of any correction to a patient’s allocated mutation status post-stratification:**

- **there will be no revision to the patient stratum allocation or numbering in RAVE.**
- **AZ will coordinate with IVRS/IWRS to ensure that the allocation of patient places per stratum is adjusted, as necessary, to ensure that the minimum number required in each will be achieved**
- **for final data analysis the corrected mutation status will be used to assign the patient to the relevant stratum.**

**Reason for Amendment:**

Clarification of patient stratification terminology – replacing ‘arm’ with ‘stratum’.

Statement of process and procedure in the event that the initially recorded *PIK3CA* tumour-mutation status of a patient is revised following subsequent tumour sample analysis.

**Section of protocol affected:**

Section 5.5.3 Doses and treatment regimens

**Previous text:**

AZD5363 / matching placebo:

A twice daily regimen of an oral formulation given on a continuous or intermittent weekly dosing schedule.

Where possible all doses of AZD5363/placebo should be taken, at approximately the same times each day, in a fasted state (water to drink only) from at least 2 hours prior to the dose to at least 1 hour post-dose. Please also refer to Restrictions (section 5.1) for further guidance regarding patient fasting status on study assessment days.

**Revised text:**

AZD5363 / matching placebo:

A twice daily regimen of an oral formulation given on **one of two** intermittent weekly dosing schedules.

**During Study Part A, patients will receive AZD5363 in capsule form only. During Study Part B, patients may receive AZD5363/placebo as capsules or as dose-equivalent tablets. A tablet formulation may be applied in all sites or in selected sites only.**

Where possible, all doses of AZD5363/placebo should be taken, at approximately the same times each day, in a fasted state (water to drink only) from at least 2 hours prior to the dose to at least 1 hour post-dose. Please also refer to Restrictions (section 5.1) for further guidance regarding patient fasting status on study assessment days.

**Reason for Amendment:**

Reference to dosing schedules - please see amendment rationale number 2.

Reference to dosing formulation - please see amendment rationale number 7.

**Section of protocol affected:**

Section 5.5.3 Doses and treatment regimens

**Previous text:**

Treatment Schedules:

Under both ~~the continuous and~~ intermittent dosing schedules, first receipt of paclitaxel will be on Cycle 1, Day 1; first receipt of AZD5363/placebo will be on Day 2.

Thereafter, ~~under the intermittent dosing schedule,~~ weekly AZD5363 regimens will continue to start on the day after receipt of paclitaxel.

		Cycle 1				Cycle 2 onwards			
		Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
Paclitaxel. Dose day→		Day 1	Day 1	Day 1	None	Day 1	Day 1	Day 1	None
AZD5363	<del>Continuous.</del> Dose days →	Day 2 to Day 28				Day 1 to Day 28			
	Intermittent. Dose days →	D2 to D5	D2 to D5	D2 to D5	None	D2 to D5	D2 to D5	D2 to D5	None

**Revised text:**

Under both intermittent dosing schedules, first receipt of paclitaxel will be on Cycle 1, Day 1; first receipt of AZD5363/placebo will be on Day 2.

Thereafter, weekly AZD5363 regimens will continue to start on the day after receipt of paclitaxel.

		Cycle 1				Cycle 2 onwards			
		Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
Paclitaxel. Dose day→		Day 1	Day 1	Day 1	None	Day 1	Day 1	Day 1	None
AZD5363	<del>2-on 5-off</del> dose days →	<del>D2 &amp; D3</del>	<del>D2 &amp; D3</del>	<del>D2 &amp; D3</del>	<del>None</del>	<del>D2 &amp; D3</del>	<del>D2 &amp; D3</del>	<del>D2 &amp; D3</del>	<del>None</del>
	<del>4-on 3-off</del> dose days →	D2 to D5	D2 to D5	D2 to D5	None	D2 to D5	D2 to D5	D2 to D5	None

**Reason for Amendment:**

Please see amendment rationale number 2.

**Section of protocol affected:**

Section 5.5.5. Safety Run-In: Starting dose and dose escalation scheme.

**Previous text:**

For Study Part A; administration of AZD5363 will commence, when combined with paclitaxel, at cohort 1 of each schedule at doses of:

- ~~Continuous dosing: 320 mg bd (640 mg daily).~~
- Intermittent dosing (4 days of treatment followed by 3 days off-treatment: 360 mg bd (720 mg daily).

These starting doses are below the AZD5363 monotherapy doses of: ~~400 mg bd (continuous dosing schedule)~~ and 480 mg bd (intermittent dosing schedule) deemed tolerable in the ongoing Phase I multiple-ascending dose study (D3610C00001) in patients with advanced solid malignancies at the time of initiating Part A.

Patients will be enrolled to ensure a minimum of three and a maximum of six evaluable patients per dose escalation cohort. For procedures and definitions associated with dose escalation, see Section 5.10.

**Revised text:**

For Study Part A; administration of AZD5363 will commence, when combined with paclitaxel, at cohort 1 of each schedule at doses of:

- **Intermittent dosing (2 days of treatment followed by 5 days off-treatment: 560 mg bd (1120 mg daily)).**
- Intermittent dosing (4 days of treatment followed by 3 days off-treatment: 360 mg bd (720 mg daily).

These starting doses are **at or** below the AZD5363 monotherapy doses of: **640 mg bd (2-on 5-off dosing schedule)** and 480 mg bd (**4-on 3-off dosing schedule**) deemed tolerable in the ongoing Phase I multiple-ascending dose study (D3610C00001) in patients with advanced solid malignancies at the time of initiating **each of the dosing schedules in** Part A.

Patients will be enrolled to ensure a minimum of three and a maximum of six evaluable patients per dose escalation cohort. For procedures and definitions associated with dose escalation, see Section 5.10.

**Reason for Amendment:**

Please see amendment rationale number 2.

**Section of protocol affected:**

Section 5.5.6 Randomised expansion: Selected Dose

**Previous text:**

Study Part B will be conducted at a dose and schedule of AZD5363, when combined with paclitaxel, selected from Part A

**Revised text:**

Study Part B will be conducted at a dose and schedule of AZD5363, when combined with paclitaxel, selected from Part A.



**During the conduct of Part B, the SRC will continue to evaluate the status of patients ongoing in Part A (see section 5.10.2). If emerging findings suggest that the AZD5363 dosing schedule that was not selected to commence Part B may present a more favourable alternative - in terms of safety, tolerability and/or efficacy – they may elect to re-start Part B under this schedule in consultation with AstraZeneca.**

**In this circumstance, recruitment to the original dose schedule for Part B would cease, and 100 patients would be recruited to the new dose schedule.**

**Reason for Amendment:**

With reference to amendment rationale number 6; this addition allows for the Part B dose and/or schedule of AZD5363/placebo to be revised under guidance from the Safety Review Committee within the parameters of assessments conducted under Part A.

**Section of protocol affected:**

Section 5.6. Concomitant and post-study treatment(s). Paragraph 1.

**Previous text:**

Information on any treatment received by the patient, with reasons for its provision, will be recorded in the eCRF from 4 weeks prior to starting study treatment up to 28 days after the last dose of AZD5363/placebo or until objective progression, whichever is the latest. 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 8 and Appendix G), should be maintained on it throughout the study period.

**Revised text:**

Information on any treatment received by the patient, with reasons for its provision, will be recorded in the eCRF from 4 weeks prior to starting study treatment up to 28 days after the last dose of AZD5363/placebo or until objective progression, whichever is the latest. **For Part B of the study, anti-cancer medications should continue to be recorded at 12-weekly intervals to death or withdrawal (see Section 6.2.3.4).** 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 8 and Appendix G), should be maintained on it throughout the study period.

**Reason for Amendment:**

Please see amendment rationale number 4.

**Section of protocol affected:**

Section 5.8. Discontinuation of investigational product. Paragraph 1.

**Previous text:**

Patients may be discontinued from IP at any time, without prejudice to further treatment. If a patient discontinues IP for reasons other than death, then they should still continue in the study up to objective disease progression assessed by RECIST 1.1, unless they withdraw consent from the study.

**Revised text:**

Patients may be discontinued from IP at any time, without prejudice to further treatment. If a patient discontinues IP for reasons other than death, then they should still continue in the study up to objective disease progression assessed by RECIST 1.1 **in Part A, and also up to death in Part B (see section 6.2.3.4)**, unless they withdraw consent from the study.

**Reason for Amendment:**

Please see amendment rationale number 4.

**Section of protocol affected:**

Section 5.10.2. Safety Review Committee and Dose Escalation Process. Paragraph 5, bullet point 5.

**Previous text (with reference to cohort dose selection in study part A):**

..... 6 evaluable patients must be assessed at that dose level. The SRC may elect to assess up to a further 6 evaluable patients at the identified MTD to confirm the dose selection. To determine the NTD 2 patients, of up to 6 patients, must experience DLTs at that dose level.

**Revised text:**

..... 6 evaluable patients must be assessed at that dose level. The SRC may elect to assess up to a further 6 evaluable patients at the identified **RD or** MTD to confirm the dose selection. To determine the NTD 2 patients, of up to 6 patients, must experience DLTs at that dose level.

**Reason for Amendment:**

This amendment allows for the Safety Review Committee in Part A to request evaluation of additional patients to confirm a recommended dose to take forward to Part B. This inclusion has been made to allow for greater surety, if required, in dose selection.

**Section of protocol affected:**

Section 5.10.6. Definition of a dose-limiting toxicity.

**Previous text:**

A DLT excludes:

1. Alopecia of any grade.
2. Isolated laboratory changes of any grade without clinical sequelae or clinical significance.

**Revised text:**

A DLT excludes:

1. Alopecia of any grade.
2. Isolated laboratory changes of any grade without clinical sequelae or clinical significance.
3. **An immune allergic reaction <CTCAE Grade 4, thought to be related to either AZD5363, paclitaxel or the combination of the two agents which is manageable and not life-threatening.**

**Reason for Amendment:**



**Section of protocol affected:**

New – Section 5.11. Conduct of Part B: Randomised Expansion Phase.

**Previous text:**

Not applicable

**New text:**

**5.11.1 Starting schedule and dose**

**Administration of AZD5363/placebo in combination with paclitaxel will commence a dose and schedule selected from Study Part A as detailed in section 5.10.2.**

**5.11.2 Safety Review Committee**

**During the Part B Randomised Phase of the study, an independent SRC will monitor safety and tolerability in the study by means of coded (A vs B) reviews of safety data at**

**approximately 3-monthly intervals. Based on this coded review, the independent SRC may recommend one of: a) continuation of recruitment without change; or b) an amendment to the dose and schedule of AZD5363/placebo eg, from a 4 days on, 3 days off schedule to a 2 days on, 5 days off schedule or to continue at the same schedule at a reduced dose of AZD5363/placebo; or c) termination of recruitment on the grounds that the combination is considered to be insufficiently well tolerated.**

**The independent SRC will consist of:**

- **AstraZeneca Physician, independent of the AZD5363 programme, who will chair the committee - or delegate**
- **AstraZeneca Global Safety Physician, independent of the AZD5363 programme.**
- **Two external Investigators independent of the study**

**The independent SRC Remit document for this study will define the exact membership and who should be present for decisions to be made.**

**The first review of coded safety data will occur when data are available from approximately 15 patients who have received at least 28 days of treatment.**

**In the event that AstraZeneca adopts the recommendation to explore an alternative dose or schedule, any patients already recruited to the study at this point will continue to receive AZD5363/placebo as per their current dose and schedule provided that they are tolerating the treatment and the investigator believes they are gaining benefit. Alternatively, the investigator may elect to change the dose/schedule of patients recruited prior to the dose change to the new dose/schedule. After a change to the schedule of AZD5363/placebo, approximately 100 new patients will be recruited to receive AZD5363/placebo as per the new schedule. There will be no more than 2 changes made to dose or schedule during the randomised phase of the study.**

**Reason for Amendment:**

Please see amendment rationale number 6.

**Section of protocol affected:**

New – Section 6.2.3.4. Survival follow-up.

**Previous text:**

Not applicable.

**New text:**

**Part B. Randomised Expansion only. Overall Survival status will be obtained for all randomised patients. Survival contacts will be made and entered into the database every 12 weeks ( $\pm$  1week) post-permanent discontinuation of study treatment and at data cut off. The patient does not have to attend the clinic for the survival assessments to be carried out; these can either be done via a telephone call, or through review of the patient's notes, or through the use of public records. If the site becomes aware that a patient has died prior to the primary analysis, the relevant eCRF on the database should be completed at that time.**

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

**Survival status will continue to be collected until 50% of randomized patients have died. Optionally, continuation until 75% of randomized patients have died may be considered.**

**Reason for Amendment:**

Please see amendment rationale number 4.

**Please note: The following amendments to sections 6.4.5 to 6.8.1.6 describe changes to patient assessments and sample collection. The primary rationale for these changes is to align samples/assessments with revised study therapy dosing timepoints due to replacement of the AZD5363/placebo continuous dosing schedule with an intermittent (2days-on, 5 days-off) schedule (see amendment rationale number 2). For clarity of review the full original/revised text has not been provided. Instead, amendments are described per section, with new items identified in bold text. Any change not associated with the schedule replacement will be outlined separately.**

**Section of protocol affected:**

Section 6.4.5. Laboratory safety assessment.

**Amendments:**

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis.

Continuous dosing schedule. Sample timepoints: Day 1 of - Cycle 1, Weeks 2, 3 and 4; Cycle 2 onwards Week 1.

*Replaced by –*

Intermittent dosing schedule (2/5). Sample timepoints: **Day 2** of - Cycle 1, Weeks 2, 3 and 4; and Cycle 2 onwards Week 1.

Serum/plasma glucose samples for additional measurements for potential abnormalities of glucose metabolism.

Continuous dosing schedule. Sample timepoints: 2-4 hours post-dose on Day 1 of - Cycle 1, Weeks 2, 3 and 4; Cycle 2 onwards Week 1.

*Replaced by –*

Intermittent dosing schedule (2/5). Sample timepoints: 2-4hours **and 4-6 hours** post-dose on **Day 2** of - Cycle 1, Weeks 2, 3 and 4; and Cycle 2 onwards Week 1.

*Additional amendment -*

Intermittent dosing schedule (4/3) Part B only. Additional **4-6 hours** post-dose sample to be taken at all timepoints.

*New text -*

**Note: It is acceptable for these additional blood glucose samples to be analysed at a hospital ward or clinical unit, where measurement can be provided in units of mg/dL, mmol/L or equivalent, rather than at the designated local laboratory.**

**Reason for Amendment:**

For general revision to timepoints, please see amendment rationale number 2.

With reference to additional blood glucose samples to be taken between 4 to 6 hours, following receipt of the morning dose of AZD5363. This change was implemented to aid review of glucose levels and management of potential abnormalities of glucose metabolism over the period of maximum concentration of circulating AZD5363 identified under pharmacokinetic analysis.

The additional note clarifies that bedside glucose measurements can be done, where appropriate, to aid in rapid evaluation of patient status.

**Section of protocol affected:**

Section 6.4.6. Physical examination.

**Amendment:**

Intermittent dosing schedule 2/5. Assessment timepoint added – **Cycle 1, Week 1, Day 3.**

**Reason for Amendment:**

This timepoint to assess patient's physical status on last day of receipt of AZD5363/placebo - to correspond with Day 5 assessment conducted for the intermittent 4/3 schedule.

**Section of protocol affected:**

Section 6.4.8. WHO performance status.

**Amendment:**

Intermittent dosing schedules 4/3 and 2/5. Part B. Assessment timepoints **added – Cycle 1, Week 1, Days 2 and 3; Weeks 2 and 3, Day 1; Week 4 Day 2. Cycle 2, Weeks 1 to 4, Day 1. Cycle 3 onwards Week 1 Day 1. At discontinuation of AZD5363/placebo and paclitaxel.**

**Reason for Amendment:**

Please see amendment rationale number 5.

**Section of protocol affected:**

Section 6.4.10. MUGA scan / Echocardiogram.

**Amendment:**

Intermittent dosing schedules 4/3 (Part B) and 2/5 (Parts A and B). Assessment timepoint **removed – Cycle 2, Week 1, Day 1.**

**Reason for Amendment:**

On review, AstraZeneca identified that this assessment timepoint did not provide sufficient value for review of patient safety to merit continuation. It will therefore be removed for all new schedules; but retained for completion of the Part A intermittent 4/3 schedule.

**Section of protocol affected:**

Section 6.4.11. Vital signs: Pulse and blood pressure.

**Amendment:**

Continuous and intermittent (4/3) dosing schedule. Assessment timepoint Cycle 1, Week 4, **Day 1.**

*Replaced by –*

Intermittent dosing schedules (2/5) and (4/3). Assessment timepoint Cycle 1, Week 4 **Day 2.**

**Reason for Amendment:**

To align all Cycle 1, Week 4, patient assessments under Day 2 – to minimise inconvenience for patients.

**Section of protocol affected:**

Section 6.4.12.3. Glucose, insulin and insulin c-peptide.

**Amendment:**

Continuous dosing schedule. Sample timepoints: **Day 1** of: Cycle 1 Weeks 2, 3 and 4; and Cycle 2 onwards Week 1.

*Replaced by –*

Intermittent dosing schedule (2/5). Sample timepoints: **Day 2** of: Cycle 1 Weeks 2, 3 and 4; and Cycle 2 onwards Week 1.



*Additional amendment -*

Insulin c-peptide measurements are removed from the Part B assessment schedules..

**Reason for Amendment:**

For realignment of sample schedule - please see amendment rationale number 2.

Removal of insulin c-peptide assessment was agreed following AstraZeneca review of critical analyses, which indicated that sufficient data on c-peptide has been generated in the AZD5363 clinical programme conducted to date.

**Section of protocol affected:**

Section 6.4.12.4. Patient meal information

**Amendment:**

Continuous dosing schedule. Sample timepoints: **Day 1** of: Cycle 1 Weeks 2, 3 and 4; and Cycle 2 onwards Week 1.

*Replaced by –*

Intermittent dosing schedule (2/5). Sample timepoints: **Day 2** of: Cycle 1 Weeks 2, 3 and 4; and Cycle 2 onwards Week 1.

*Additional amendment -*

Intermittent **doing schedule 2/5. Additional assessment timepoint** added – Cycle 1, Week 1, Day 3.

**Reason for Amendment:**

For realignment of sample schedule - please see amendment rationale number 2.

Additional timepoint to record patient's meal intake on last day of receipt of AZD5363/placebo - to correspond with Day 5 assessment conducted for the intermittent 4/3 schedule.

**Section of protocol affected:**

Section 6.6.2. Pharmacokinetic sampling schedule: Paclitaxel

**Amendment:**

Continuous dosing schedule. Paclitaxel PK sample timepoint: **Day 1** of: Cycle 1  
Week 3.

*Replaced by –*

Intermittent dosing schedule (2/5). Paclitaxel PK sample timepoint: **Day 1** of: Cycle 1  
Week 3.

*Additional amendment -*

Continuous dosing schedule. Paclitaxel PK sample timepoint: Day 1 of: Cycle 1  
Week 2 will not appear under intermittent dosing schedule (2/5).

*New text -*

**Note: Timing of paclitaxel PK sampling on Day 1 is from start of the infusion;  
e.g. if paclitaxel infusion commences at 9am, the 2, 4 and 8 hour samples should  
be taken at 11am, 1pm and 5pm respectively.**

**Reason for Amendment:**

For realignment of sample schedule - please see amendment rationale number 2.

Following a request for clarification from a study site – the additional text provides guidance  
regarding timing of paclitaxel sample timing relative to the start of paclitaxel infusion.

**Section of protocol affected:**

Section 6.6.2. Pharmacokinetic sampling schedule: AZD5363.

**Amendment:**

Continuous dosing schedule. AZD5363 PK sample timepoints: **Day 1** of - Cycle 1,  
Weeks 2, 3 and 4.

*Replaced by –*

Intermittent dosing schedule (2/5). AZD5363 PK sample timepoints: Day 2 of -  
Cycle 1, Weeks 2, 3 and 4.

**Reason for Amendment:**

Please see amendment rationale number 2.

**Section of protocol affected:**

Section 6.6.2. Pharmacokinetic sampling schedule: Tables

**Amendment:**

Separate tables defining sample timepoints under the continuous dosing schedule have been removed.

**Reason for Amendment:**

Continuous dosing schedule no longer applicable – please see amendment rationale number 2.

**Section of protocol affected:**

Sections 6.8.1 and 6.8.1.6. Exploratory biomarker research: venous blood for analysis of exploratory biomarkers.

**Amendment:**

Continuous dosing schedule. Sample timepoints: **Day 1** of - Cycle 1, Weeks 2, 3 and 4; Cycle 2 Week 1.

*Replaced by –*

Intermittent dosing schedule (2/5). Sample timepoints: **Day 2** of - Cycle 1, Weeks 2, 3 and 4; and Cycle 2 Week 1.

**Reason for Amendment:**

Please see amendment rationale number 2.

**Section of protocol affected:**

Sections 6.8.1 and 6.8.1.6. Exploratory biomarker research: eyebrow hairs for analysis of exploratory biomarkers.

**Amendment:**

Continuous dosing schedule. Sample timepoint: **Cycle 1, Week 2, Day 1.**

*Replaced by –*

Intermittent dosing schedule (2/5). Sample timepoints: **Cycle 1, Week 1, Day 3.**

**Reason for Amendment:**

Please see amendment rationale number 2; to correspond with Day 5 assessment conducted for the intermittent 4/3 schedule.

**Section of protocol affected:**

Section 6.8.1.6. Pharmacodynamic and exploratory biomarker sampling schedule: Tables

**Amendment:**

Separate tables defining sample timepoints under the continuous dosing schedule have been removed.

**Reason for Amendment:**

Continuous dosing schedule no longer applicable – please see amendment rationale number 2.

**Section of protocol affected:**

Section 7.1. Volume of blood.

**Previous text:**

The volume of blood that will be drawn from each patient will vary, dependent upon the dosing schedule and phase of the study:

- The volume of blood to be drawn from each patient during screening and Cycle 1 should not exceed 35 mL and ~~360~~ mL respectively
- The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 cycles of combination treatment and a discontinuation visit should not exceed ~~710~~ mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

In both phases of the study, extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments or additional PK assessment.

The maximum volume of blood to be drawn from each patient in this study is as follows:

**Table 6 Estimated Maximum volume of blood to be drawn per patient**

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Haematology	5	<del>15</del>	<del>75</del>
	Clinical chemistry	10	<del>15</del>	<del>150</del>
	Additional Glucose	2	<del>9</del>	<del>18</del>
	Lipids	5	<del>3</del>	<del>15</del>
	Glucose, insulin and insulin c-peptide	5	<del>24</del>	<del>120</del>
CTCs		10	4	40
PIK3CA mutation		10	1	10
Pharmacokinetic		4	<del>23</del>	<del>92</del>
Pharmacodynamic		8.1 (3 x 2.7)	16	129.6
Pharmacogenetics (optional)		5	1	5
Exploratory Biomarker (optional)		5	11	55
Total				<del>709.6</del>

Note: Maximum is taken to reflect Part A, ~~continuous~~-dosing schedule: 6 Cycles plus a discontinuation visit.

**Revised text:**

The volume of blood that will be drawn from each patient will vary, dependent upon the dosing schedule and phase of the study:

- The volume of blood to be drawn from each patient during screening and Cycle 1 should not exceed 35 mL and **380** mL respectively
- The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 cycles of combination treatment and discontinuation visits should not exceed **750** mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

In both phases of the study, extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments or additional PK assessment.

The maximum volume of blood to be drawn from each patient in this study is as follows:

**Table 5 Estimated Maximum volume of blood to be drawn per patient**

<b>Assessment</b>		<b>Sample volume (mL)</b>	<b>No. of samples</b>	<b>Total volume (mL)</b>
Safety	Haematology	5	<b>17</b>	<b>85</b>
	Clinical chemistry	10	<b>17</b>	<b>170</b>
	Additional Glucose	2	<b>20</b>	<b>40</b>
	<b>Lipids and glycosylated haemoglobin</b>	5	<b>5</b>	<b>25</b>
	Glucose and insulin	5	<b>25</b>	<b>125</b>
CTCs		10	4	40
<i>PIK3CA</i> mutation		10	1	10
Pharmacokinetic		4	<b>16</b>	<b>64</b>
Pharmacodynamic		8.1 (3 x 2.7)	16	129.6
Pharmacogenetics (optional)		5	1	5
Exploratory Biomarker (optional)		5	11	55
<b>Total</b>				<b>748.6</b>

Note: Maximum is taken to reflect Part A, 4-on 3-off dosing schedule: 6 Cycles plus discontinuation visits.

**Reason for Amendment:**

Amendments reflect: Additional glucose 4-6 hour post-dose samples, revision of the reference treatment schedule from continuous to intermittent 4 days-on, 3 days-off, AZD5363/placebo dosing - and correction of an omission under the original protocol, which had failed to include sample volumes collected during Cycles 4 to 6.

**Section of protocol affected:**

Section: 11.1. Calculation or derivation of efficacy variables.

**Amendment:**

Section 11.1.5 - Progression-free Survival (PFS) has been moved to section position 11.1.1. All subsequent section numbers have been revised accordingly.

**Reason for Amendment:**

Progression-free survival is now the primary endpoint, hence its derivation now appears as the first item in section 11.1. Please see amendment rationale number 3.

**Section of protocol affected:**

11.1.1. (originally section 11.1.5). Progression-free Survival (PFS). Paragraph 1.

**Previous text:**

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).

**Revised text:**

**The primary outcome variable for Part B of the study is PFS.** 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).

**Reason for Amendment:**

Please see amendment rationale number 3.

**Section of protocol affected:**

Section 11.1.2 (originally section 11.1.1) Change in tumour size at 12 weeks. Paragraph 1.

**Previous text:**

~~The primary outcome variable for Part B of the study is change in tumour size at 12 weeks. This is based on RECIST measurements taken at baseline and at week 12. Tumour size is the sum of the longest diameters of the TLs that have been selected at baseline. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment. The change in tumour size will be assessed using the log (ratio) of the week 12 tumour size over the baseline tumour size for each subject. More details on TLs selection and assessment during the treatment can be found in Appendix F of the protocol.~~

**Revised text:**

**Change in tumour size at 12 weeks** is based on RECIST measurements taken at baseline and at week 12. Tumour size is the sum of the longest diameters of the TLs that have been selected at baseline. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment. The change in tumour size will be assessed using the log (ratio) of the week 12 tumour size over the baseline tumour size for each subject. More details on TLs selection and assessment during the treatment can be found in Appendix F of the protocol.

**Reason for Amendment:**

Please see amendment rationale numbers 3 and 8.

**Section of protocol affected:**

New – Section 11.1.6. Overall survival.

**Previous text:**

Not applicable.

**New text:**

**11.1.6 Overall survival**

**Overall survival is defined as the interval between the date of randomisation and the date of patient death due to any cause. Patients who have not died at the time of the statistical analysis or who are lost to follow-up or withdraw consent, will be censored at the time they were last known to be alive.**

**Reason for Amendment:**

Please see amendment rationale numbers 4 and 8.

**Section of protocol affected:**

Section 12.1.1. Efficacy analysis set.

**Previous text:**

All efficacy data in Part B of the study (change in tumour size at 12 weeks, PFS, ORR, DoR and percentage of patients without progression at 12 weeks) will be analysed on an intention-to-treat basis (ITT). This will include all randomised patients, wherever possible, and compare treatment groups on the basis of randomised treatment, regardless of the treatment they actually received.

~~To be considered 'evaluable' for the primary efficacy analysis, a patient must have:~~

- ~~● Baseline and week 12 ( $\pm 1$  week) tumour measurements; or~~
- ~~● Evidence of progression prior to week 12; or~~
- ~~● In the absence of the week 12 measurements and no evidence of progression, RECIST measurements at baseline and 1 visit after or prior to the week 12 visit such that a prediction for the week 12 result can be made (see section 11.1.1 for details)~~

For the Part A safety run-in, the efficacy analysis set will include all patients who received at least one dose of study treatment.



**Revised text:**

All efficacy data in Part B of the study (**PFS, change in tumour size at 12 weeks, ORR, DoR percentage of patients without progression at 12 weeks and OS**) will be analysed on an intention-to-treat basis (ITT). This will include all randomised patients, wherever possible, and compare treatment groups on the basis of randomised treatment, regardless of the treatment they actually received.

**For the Part B randomised expansion; in the event that the dose/schedule is changed following recommendation by the SRC, and the total number of patients has been increased to compensate for patients recruited prior to the change, the primary analyses will be performed on the subset of the efficacy analysis set randomised to the new dose/schedule.**

For the Part A safety run-in, the efficacy analysis set will include all patients who received at least one dose of study treatment.

**Reason for Amendment:**

Please see amendment rationale numbers 3, 4 and 6.

**Section of protocol affected:**

Section 12.2. Methods of statistical analyses

**Previous text:**

A comprehensive statistical analysis plan (SAP) will be prepared prior to enrolment of patients in the study.

The primary outcome variable for Part B of ~~change in tumour size at 12 weeks~~, and the secondary outcome variable of ~~PFS~~, will be analysed formally. All Part A data, other Part B efficacy and safety data will be summarised descriptively.

For the primary and secondary analysis the null hypothesis is that there is no treatment effect, i.e., there is no difference in terms of ~~change in tumour size at 12 weeks~~ between patients treated with AZD5363 + paclitaxel and patients treated with matching placebo + paclitaxel.

No adjustments for multiplicity will be made.

Details of sensitivity analyses and imputation methods for missing data will be fully documented in the SAP.

There are potentially a number of different analysis points for the study. The table below details which data will be analysed at each time point.

<b>Analysis</b>	<b>Trigger</b>	<b>Data type included</b>
End of safety run-in	All patients in Part A followed up for at least 12 weeks	Safety, efficacy (week 12 response rate, best response), PK, PD
Randomised expansion interim analysis	40 patients randomised and completed 12 week follow up period (or progressed prior to 12 weeks)	Change in tumour size, response rate at 12 weeks, best objective response (No <i>PIK3CA</i> mutation subgroup analysis)
Randomised expansion <del>primary</del> analysis	<del>60 patients</del> randomised and completed 12 weeks follow up period (or progressed prior to 12 weeks)	<del>All efficacy other than PFS (including <i>PIK3CA</i> mutation subgroup analyses), safety, PK, PD</del>
Randomised expansion <del>progression-free survival</del> analysis	Recruitment to Part B complete and <del>45</del> progression events occurred	PFS (overall and in <i>PIK3CA</i> mutation - positive subgroup), <del>RR and duration</del> , safety
Safety update	When last patient discontinues study treatment	Reduced set of safety outputs

PFS analysis and safety update will be combined if last patient has discontinued by the time the PFS events are reached.

Randomisation in Part B of the study will be stratified by *PIK3CA* mutation status determined by analysis of tumour tissue (or result from a prior tumour analysis) and a blood sample (see sections 5.2.1 and 6.2.2).

A mutation detected in either the blood or tissue samples will result in a patient being classified as being in the mutation-positive group for this analysis. Concordance between tumour tissue and blood sample mutation results will be explored. In the event of conflicting results in a substantial number of patients, the impact of the different methods on the efficacy analyses will be explored.

**Revised text:**

A comprehensive statistical analysis plan (SAP) will be prepared prior to enrolment of patients in the study.

The primary outcome variable for Part B of PFS, and the secondary outcome variables, will be analysed formally. All Part A data and safety data will be summarised descriptively.

**The secondary outcome variable of OS will be formally analysed if there is sufficient data to warrant formal statistical analysis (ie enough OS events at the primary analysis to analyse OS).**

**During Part B; in the event that the SRC and AstraZeneca agrees that an alternative dose or schedule should be explored with a consequent increase in the number of patients to be enrolled, the above analyses will be performed for the patients randomised**

**after the last change in dose or schedule (for SRC roles and responsibilities reference section 5.11.2). These analyses will be considered as primary, and data from patients randomised prior to the change in dose or schedule will be summarised descriptively.**

For the primary and secondary analysis the null hypothesis is that there is no treatment effect, i.e., there is no difference in terms of **PFS** between patients treated with AZD5363 + paclitaxel and patients treated with matching placebo + paclitaxel.

No adjustments for multiplicity will be made.

Details of sensitivity analyses and imputation methods for missing data will be fully documented in the SAP.

There are potentially a number of different analysis points for the study. The table below details which data will be analysed at each time point.

<b>Analysis</b>	<b>Trigger</b>	<b>Data type included</b>
End of safety run-in	All patients in Part A followed up for at least 12 weeks	Safety, efficacy (week 12 response rate, best response), PK, PD
Randomised expansion <b>1st</b> interim analysis	40 patients randomised and completed 12 week follow up period (or progressed prior to 12 weeks)	Change in tumour size, response rate at 12 weeks, best objective response (No <i>PIK3CA</i> mutation-positive subgroup analysis), <b>safety</b> .
Randomised expansion <b>2nd</b> interim analysis	<b>38 progression events in the overall population and 30 <i>PIK3CA</i> mutation-positive patients</b> randomised and completed 12 week follow up period (or progressed prior to 12 weeks)	<b>All efficacy other than survival for the overall population (including <i>PIK3CA</i> mutation-positive subgroup analyses for change in tumour size, response rate at 12 weeks, BOR), safety,</b>
Randomised expansion progression <b>primary</b> analysis	Recruitment to Part B complete and <b>76 progression events occurred in the overall population and 38 progression events occurred in the <i>PIK3CA</i> mutation-positive patients.</b>	<b>All efficacy, PFS (overall and in <i>PIK3CA</i> mutation - positive subgroup), safety, PK, PD.</b>
<b>Randomised expansion overall survival analysis</b>	<b>At 50% maturity. A further analysis at 75% maturity may be considered.</b>	<b>OS (overall and in <i>PIK3CA</i> mutation - positive subgroup), safety.</b>
Safety update	When last patient discontinues study treatment	Reduced set of safety outputs

PFS analysis and safety update will be combined if last patient has discontinued by the time the PFS events are reached.

Randomisation in Part B of the study will be stratified by *PIK3CA* mutation status determined by analysis of tumour tissue (or result from a prior tumour analysis) and a blood sample (see sections 5.2.1 and 6.2.2).

A mutation detected in either the blood or tissue samples will result in a patient being classified as being in the mutation-positive group for this analysis. Concordance between tumour tissue and blood sample mutation results will be explored. In the event of conflicting results in a substantial number of patients, the impact of the different methods on the efficacy analyses will be explored.

**Reason for Amendment:**

Please see amendment rationale numbers 3, 4 and 8.

**Section of protocol affected:**

Section: 12.2. Methods of statistical analyses.

**Amendment:**

Subsection 12.2.2, Progression Free Survival, has been moved to subsection position 12.2.1.

**Reason for Amendment:**

Progression-free survival is now the primary endpoint, hence its derivation now appears as the first item in section 12.2. Please see amendment rationale numbers 3 and 8.

**Section of protocol affected:**

Section 12.2.1 (originally section 12.2.2). Progression Free Survival. Paragraph 1.

**Previous text:**

The ~~secondary~~ endpoint of PFS will be analysed for the patients in Part B when recruitment to Part B has completed and approximately 45 PFS events in the overall population have occurred. Waiting until recruitment has completed to this part of the study will ensure that as many as possible of the PFS events included in the analysis come from a mixture of *PIK3CA* mutation positive and not detected patients. This aims to safeguard against the possibility that the progression events could be largely from the mutation not detected patients if that stratum recruits substantially quicker than the other. PFS will not be presented for patients in Part A of the study. PFS will be analysed for the overall population and for the subgroup of *PIK3CA* mutation patients, using separate Cox proportional-hazards models allowing for the effect of treatment and including a term for *PIK3CA* mutation status in the overall analysis (mutation positive or not detected).

**Revised text:**

The **primary** endpoint of PFS will be analysed for the patients in Part B when recruitment to Part B has completed and **76** PFS events in the overall population, **and 38 in the PIK3CA mutation-positive subgroup**, have occurred. Waiting until recruitment has completed to this part of the study will ensure that as many as possible of the PFS events included in the analysis come from a mixture of *PIK3CA* mutation positive and not detected patients. This aims to safeguard against the possibility that the progression events could be largely from the mutation not detected patients if that stratum recruits substantially quicker than the other. PFS will not be presented for patients in Part A of the study. PFS will be analysed for the overall population and for the subgroup of *PIK3CA* mutation patients, using separate Cox proportional-hazards models allowing for the effect of treatment and including a term for *PIK3CA* mutation status in the overall analysis (mutation positive or not detected).

**Reason for Amendment:**

Please see amendment rationale numbers 3 and 8.

**Section of protocol affected:**

Section 12.2.2 (originally section 12.2.1). Change in tumour size at 12 weeks. Paragraph 1.

**Previous text:**

The **primary** endpoint for Part B, of change in tumour size at week 12 (or progression if prior to week 12), will be assessed in all patients in this part and separately within the *PIK3CA* mutation-positive subgroup of patients. Change in tumour size will be assessed as the log of the ratio of week 12 tumour size over the baseline tumour size measurement for each patient as these data have been assumed to be log-normally distributed (see section 11.1.1).

**Revised text:**

The **secondary** endpoint for Part B, of change in tumour size at week 12 (or progression if prior to week 12), will be assessed in all patients in this part and separately within the *PIK3CA* mutation-positive subgroup of patients. Change in tumour size will be assessed as the log of the ratio of week 12 tumour size over the baseline tumour size measurement for each patient as these data have been assumed to be log-normally distributed (see section 11.1.1).

**Reason for Amendment:**

Please see amendment rationale number 3.

**Section of protocol affected:**

New – Section 12.2.2. Overall survival. (Note: subsequent subsections have been re-numbered accordingly).

**Previous text:**

Not applicable.

**New text:**

**12.2.2 Overall survival**

**The analysis population for OS will be the ITT population.**

**OS on AZD5363 in combination with weekly paclitaxel compared to weekly paclitaxel plus placebo will also be analysed using the same methods as for PFS. This analysis will be performed after 50% of patients have died. If fewer than 50% of patients have died at the time of the primary PFS analysis, then the OS data will only be summarized at that time.**

**A further analysis after 75% of patients have died may be considered.**

**Reason for Amendment:**

Please see amendment rationale numbers 3, 4 and 8.

**Section of protocol affected:**

12.2.4 (originally 12.2.3): Response rate at 12 weeks and best objective tumour response

**Previous text:**

Response rate at 12 weeks and best response during the study will be tabulated by randomised treatment (AZD5363 + paclitaxel or placebo + paclitaxel) in Part B and by dose and schedule for the Part A patients. These will present frequencies of confirmed complete responses and partial responses in addition to unconfirmed complete and partial responses, stable disease, progressive disease and not evaluable. In addition, the proportion of patients known to be progression-free at 12 weeks will be presented. This is defined as the number of patients with complete response, partial response or stable disease at 12 weeks (do not have to be confirmed).

~~These data will not be analysed formally.~~

A tabulation of response rate at 12 weeks, best response during the study and proportion progression free at 12 weeks by treatment group by *PIK3CA* mutation status will also be presented to assess if the response rate is different in the *PIK3CA* mutation-positive and *PIK3CA* mutation-not detected subgroups.

**Revised text:**

Response rate at 12 weeks and best response during the study will be tabulated by randomised treatment (AZD5363 + paclitaxel or placebo + paclitaxel) in Part B and by dose and schedule

for the Part A patients. These will present frequencies of confirmed complete responses and partial responses in addition to unconfirmed complete and partial responses, stable disease, progressive disease and not evaluable. In addition, the proportion of patients known to be progression-free at 12 weeks will be presented. This is defined as the number of patients with complete response, partial response or stable disease at 12 weeks (do not have to be confirmed).

**Response rate will be analysed for the overall population and for the subgroup of *PIK3CA* mutation-positive patients using separate logistic regression models allowing for the effect of treatment and including a term for *PIK3CA* mutation status in the overall analysis.**

A tabulation of response rate at 12 weeks, best response during the study and proportion progression free at 12 weeks by treatment group by *PIK3CA* mutation status will also be presented to assess if the response rate is different in the *PIK3CA* mutation-positive and *PIK3CA* mutation-not detected subgroups.

**Reason for Amendment:**

Please see amendment rationale numbers 3 and 8.

**Section of protocol affected:**

12.3. Interim analyses

**Previous text:**

~~An~~ interim analysis will be performed when 40 patients have been recruited to Part B and followed up for 12 weeks (or progressed prior to 12 weeks). The analysis will be primarily based on changes in tumour size at 12 weeks, but additional summaries of response rate at 12 weeks, proportion progression-free at 12 weeks and best objective response during the study will support the change in tumour size data at the interim analysis. The analysis and data presentations will be performed on the overall population, no *PIK3CA* mutation subgroup analysis will be performed as the number of patients expected to be recruited with a *PIK3CA* mutation positive tumour by that stage is likely to be low.

The purpose of the interim analysis is to provide the opportunity for an early trigger to commence setting up a phase IIb study, if the results are strong enough, such that once the primary analysis is completed to confirm the interim result, the phase IIb study could commence with minimal delay. ~~Therefore, as safety data will be analysed on the full dataset at the primary analysis, it is proposed not to include safety data at the interim analysis.~~ It is not considered necessary to adjust the significance level to account for this additional analysis of the data, given that this analysis will not form the basis of any stop or acceleration decisions. In addition, the results obtained will be interpreted with caution, bearing in mind the increased risk of false positive results that this additional analysis introduces.

**Revised text:**

**The 1<sup>st</sup> interim analysis will be performed when 40 patients have been recruited to Part B and followed up for 12 weeks (or progressed prior to 12 weeks). The analysis will be primarily based on changes in tumour size at 12 weeks, but additional summaries of response rate at 12 weeks, proportion progression-free at 12 weeks and best objective response during the study will support the change in tumour size data at the interim analysis. The analysis and data presentations will be performed on the overall population, no *PIK3CA* mutation subgroup analysis will be performed as the number of patients expected to be recruited with a *PIK3CA* mutation positive tumour by that stage is likely to be low.**

**A 2<sup>nd</sup> interim analysis will be conducted when at least 38 PFS events across both *PIK3CA* mutation subgroups have been achieved and 30 *PIK3CA* mutation-positive patients have completed 12 week follow up period (or progressed prior to 12 weeks).**

**The 2<sup>nd</sup> interim analysis will be conducted upon all efficacy outputs other than survival for the overall population (including *PIK3CA* mutation-positive subgroup analyses for change in tumour size, response rate at 12 weeks, BOR) and safety.**

The purpose of the interim analyses is to provide the opportunity for an early trigger to commence setting up a phase IIb study, if the results are strong enough, such that once the primary analysis is completed to confirm the interim result, the phase IIb study could commence with minimal delay. It is not considered necessary to adjust the significance level to account for this additional analysis of the data, given that this analysis will not form the basis of any stop or acceleration decisions. In addition, the results obtained will be interpreted with caution, bearing in mind the increased risk of false positive results that this additional analysis introduces.

**Reason for Amendment:**

Please see amendment rationale numbers 3 and 8.

**Section of protocol affected:**

12.4. Determination of sample size

**Previous text:**

Part B - Randomised expansion

~~The primary endpoint of change in tumour size at week 12 will be assessed by calculating the log of the ratio of the week 12 ( $\pm 1$  week) tumour size measurement over the baseline tumour size measurement for each patient. If the patient has documented evidence of objective disease progression prior to week 12, then this will be used as the week 12 measurement.~~



~~The primary analysis of change in tumour size will occur when week 12 tumour size data (or evidence of progression prior to week 12) are available for all patients. Analysis of change in tumour size at week 12 in the *PIK3CA* mutation patients will also occur at this time.~~

~~Approximately 70 patients will be randomised overall, 35 to each of the *PIK3CA* mutation-positive and *PIK3CA* mutation-not detected subgroups. This is to ensure that approximately 60 patients have evaluable tumour size data at baseline and week 12 (or progress prior to week 12) and approximately 30 have evaluable data within the *PIK3CA* subgroups.~~

[Redacted text block]

[Redacted text block]

[Redacted text block]

**Revised text:**

The primary endpoint will be PFS. A sample size is determined for each *PIK3CA* mutation status and irrespective of *PIK3CA* status (i.e. overall).

**Overall sample size:**

[Redacted text block]

**Sample size within *PIK3CA* mutation positive group**



**Reason for Amendment:**

Please see amendment rationale number 3.

**Section of protocol affected:**

Appendix G. Guidance Regarding Cautions and Restrictions for Prior and Concomitant Medications

**Amendment:**

In Appendix G, reference is made to exclusion of potent inhibitors or inducers of CYP3A4 or CYP2D6, or substrates of CYP3A4 within 2 weeks prior to first dose of study treatment.

This has been corrected (Appendix edition 2) to state: exclusion potent inhibitors or inducers of CYP3A4 ~~or CYP2D6~~, or substrates of CYP3A4 **or CYP2D6** within 2 weeks prior to first dose of study treatment.

**Reason for Amendment:**

The original text was incorrect due to a typographic error in a source document. This amendment reflects that CYP2D6 is not inducible, and exposure to inhibitors of CYP2D6 should not be an exclusion. However, AZD5363 is a moderate competitive inhibitor of CYP2D6, therefore substrates of CYP2D6 are restricted.

**Section of protocol affected:**

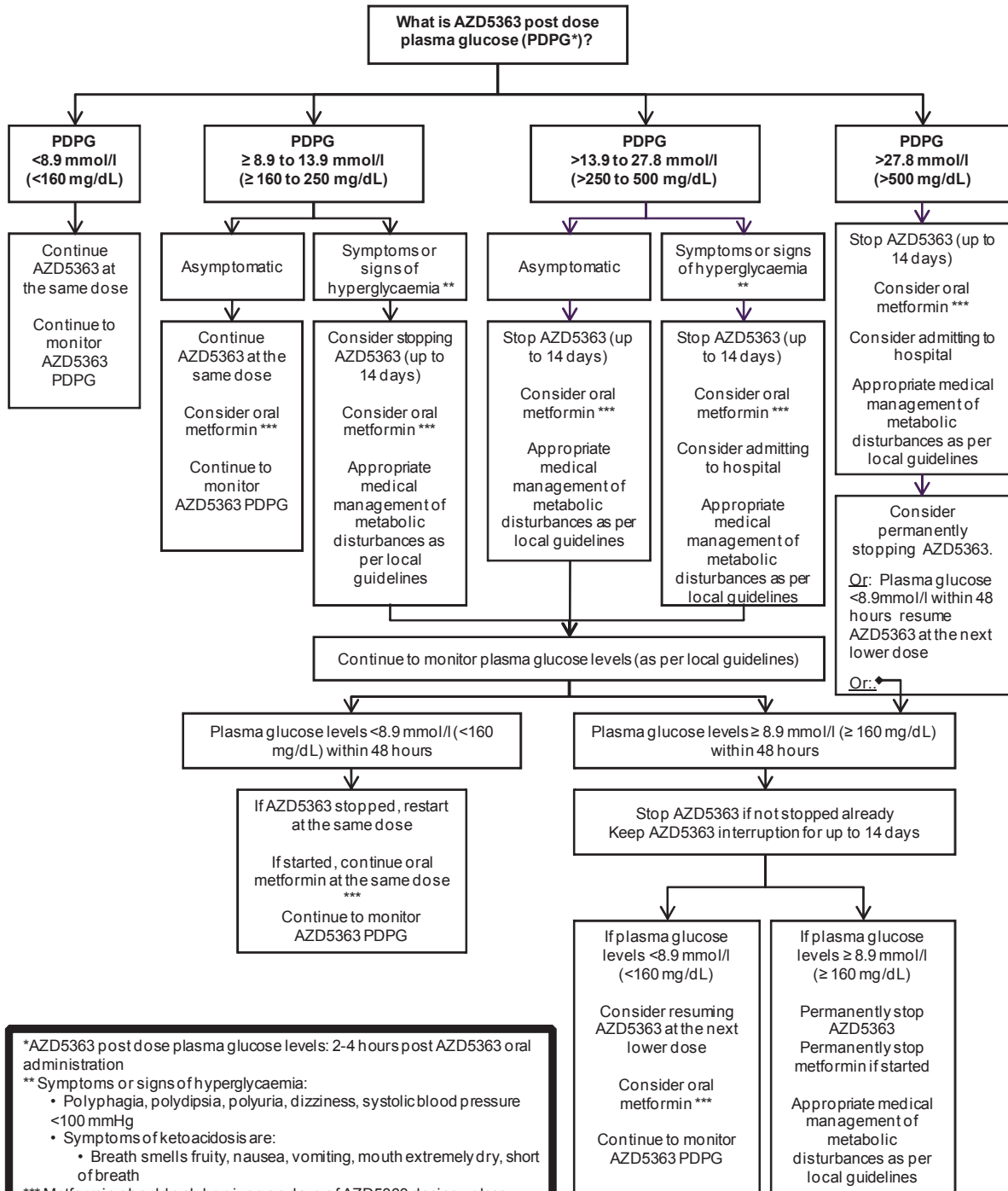
Appendix H. Instructions for Study Drug Dose Modification

**Previous text:**

Not applicable.

**New text:**

Figure 2. 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 otherwise clinically indicated, per local prescribing information  
 \*\*\*\* A maximum of 2 dose reductions of AZD5363 for the management of hyperglycaemia will be allowed

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**Reason for Amendment:**

Following investigational site feedback, this management plan for elevated plasma glucose levels (also provided separately as a study aide) has been incorporated in to Appendix H for completeness of information.



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**Clinical Study Protocol Amendment**

Amendment Number	3
Drug Substance	AZD5363
Study Code	D3610C00002
Date	09 May 2014
Protocol Dated	30 April 2013

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**A Phase I/II, Multicentre, Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by *PIK3CA* Mutation Status (BEECH).**

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This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

**Sponsor:**

AstraZeneca AB, 151 85 Södertälje, Sweden.

**Centres affected by the Amendment:**

This amendment affects all centres in the study

**The protocol for the study is to be amended as follows:**

Changed or additional text is indicated in **bold**, where applicable. Deleted text is indicated as scored ~~through~~.

Administrative changes - due to, for example, correction of typographical errors or renumbering of subsequent sections following addition of new sections - have been amended as applicable and have been included in the revised protocol but will not be listed separately in this amendment.

The protocol amendments defined within this document primarily relate to the areas detailed, with rationales, below. Other amendments are described separately in the body of this document.

1. **Part B Inclusion Criteria:**

- Addition of requirement for patients to be negative for presence of Human Epidermal Growth Factor Receptor 2 (HER2) for entry to Part B of this study. This change was to reflect that HER2 – positive patients would be *de-facto* excluded from the study due to non-allowance of anti-HER2 agents in combination, and is for the purposes of clarity rather than significantly altering the intended patient population.
- Removal of requirement for patients to have received prior endocrine therapy for entry to Part B. This change was made following Investigators' identification that this criterion prevented access to study treatment for otherwise applicable patients. On review, AstraZeneca concluded that receipt of prior endocrine therapy would not present a critical factor in the interpretation of trial outcomes and that allowing entry of patients without such prior therapies would not confer additional risks to patient safety or welfare.

2. **Part B Patient Stratification:** Allowance included for patients to be allocated to *PIK3CA* tumour mutation 'positive' or 'not detected' strata based upon central laboratory analysed and/or pre-existing local laboratory analyses. Allowance is also given for patients to be allocated to the 'not detected' stratum as a default option where no *PIK3CA* tumour mutation status results available at the time of planned start of standard care / study treatment. This change was made in response to Investigators concerns that the period required for provision and analysis of both a patient's blood and tissue samples for central determination of their *PIK3CA* tumour mutation status could result in a clinically unacceptable delay to the commencement of study and standard of care treatment (i.e would take longer than the time required to complete other screening procedures). This change therefore allows Investigators to ensure that patients may be stratified and commence study therapy without incurring delay; based upon the best available information, or in the absence of information. Additional changes to enrolment procedures are also included to ensure that appropriate numbers of patients with/without *PIK3CA* mutation of their tumour are included in the study and that randomisation balance is maintained within each of these two study strata:

- In instances where a patient may be allocated to the 'not-detected' stratum, and the *PIK3CA* tumour mutation is subsequently identified as 'positive', the patient's status will be amended accordingly in the study database and the corrected status utilised for all analyses.
- In the event that recruitment to one stratum is completed before the other, this change will provide clarity regarding a process to close the completed stratum to further recruitment and to pre-screen patients for mutation status applicable to the remaining, open, stratum

3. **Efficacy Variable:** Durable Response Rate added as new efficacy variable. This change was made to enable an assessment of the proportion of patients who had a

sustained response of at least 24 weeks. Whilst the primary outcome of the study is the standard endpoint of progression-free survival, from which a positive result may be obtained if patients benefit from an extended duration of stable disease; durable response rate allows analysis of the presence and durable effect of any anti-tumour activity arising from the combination of AZD5363 with paclitaxel chemotherapy which could not be measured by assessing only response rate.

4. **Part B Patient Assessments:** Reduction in the number of patient assessments, and the number of days on which patients are required to attend for evaluation. This change was made in response to Investigators' observations that the originally proposed schedule of assessments presented a potential burden to both patients and site staff. Whilst all assessments are acceptable and essential for the Phase I (Part A) evaluation, the data that the removed assessments would provide were - on further review- not considered fundamental for the Phase II evaluation of Part B; nor were they essential for the purposes of maintaining patient safety.

It was also noted that the schedule of assessments during Cycle 1, Week 1 – requiring patients to attend on Day 3 (and 5 for those on the 4 days-on, 3 days-off regimen) post commencement of dosing - resulted in it being necessary to initiate the study on particular days of the week in order to avoid assessments being required on non-working days. This restricted the ability of study sites to provide the most appropriate timetable for patient attendance for initiation and subsequent evaluations.

On consideration of the above, AstraZeneca has concluded that it is appropriate to remove Part B patient evaluations on Cycle 1 Week 1 Days 3 and 5 and on Week 4 of Cycles 1 and 2; with some re-assignment of specific assessments. This was based on the judgement that sufficient data will be collected during Part A at these timepoints to support study endpoints and objectives, when combined with a reduced and revised evaluation set from Part B. It was considered that anticipated benefit in ease of study conduct for sites and patients mitigated against reduction in overall data collection.

5. **Data Monitoring Committee.** Inclusion of an AstraZeneca internal Data Monitoring Committee (AZDMC). This change was made following a review of interim data analysis requirements for study Part B. From this it was identified that blinded data evaluation alone by the Safety Review Committee may be insufficient to adequately evaluate patient safety and initial efficacy indicators in the event of any outcomes that may require amendment to study conduct. In addition, the introduction of the AZDMC would ensure that the AZ personnel directly involved in the running of the study would not be involved in reviewing the data from the interim analyses and therefore limits any potential for bias in study conduct after each of the interim analyses.

The members of the AZDMC will be AstraZeneca personnel independent of the AZD5363 project team. Their remit will be to evaluate unblinded data outputs following Part B 1st and 2nd interim analyses and provide the project team with

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recommendations for action with respect to study conduct and the management of patients treated under the auspices of the study protocol.

It is the judgement of the AstraZeneca Project Team that none of the protocol changes detailed in this document present any additional risk or hazard to participating patients welfare or safety.



## Amendments

### **Section of protocol affected:**

Protocol Synopsis: Secondary objectives / Part B Randomised expansion

### **Previous text:**

To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of best objective response and duration of response.

### **Revised text:**

To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of best objective response, **durable response rate** and duration of response.

### **Reason for Amendment:**

Please refer to amendment rationale number 3.

### **Section of protocol affected:**

Protocol Synopsis: Study Design / Part B: Randomised Expansion

**Additional text** (following paragraph 2):

**Patients may be stratified based upon *PIK3CA* status determined by a central laboratory (Quintiles) and/or an existing *PIK3CA* status determined by local analysis. In instances where the period required for provision and analysis of both a patient's blood and tissue samples for central determination of their *PIK3CA* tumour mutation status would result in a clinically unacceptable delay to the commencement of study and standard of care treatment (i.e will take longer than the time required to complete other screening procedures), the patient may be stratified to the 'not-detected' arm by default in the absence of a known status. In such cases, where the *PIK3CA* tumour mutation status is subsequently identified as 'positive', the record of the patient's status will be amended accordingly in the study database and the corrected status utilised for all analyses.**

### **Reason for Amendment:**

Please refer to amendment rationale number 2.

### **Section of protocol affected:**

Protocol Synopsis: Target Population

**Previous text:**

Part B. Randomised expansion: Female patients, 18 years or older, with ER+ve advanced or metastatic breast cancer. For inclusion in Part B, patients must not have received any prior chemotherapy in the advanced or metastatic settings.

**Revised text:**

Part B. Randomised expansion: Female patients, 18 years or older, with ER+ve, **HER2-ve**, advanced or metastatic breast cancer. For inclusion in Part B, patients must not have received any prior chemotherapy in the advanced or metastatic settings.

**Reason for Amendment:**

Please refer to amendment rationale number 1.

**Section of protocol affected:**

List of Abbreviations and Definitions of Terms

**Additional text lines:**

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<b>Abbreviation or special term</b>	<b>Explanation</b>
AZDMC	AstraZeneca Data Monitoring Committee
DRR	Durable Response Rate
HER2	Human Epidermal Growth Factor Receptor 2
ISRC	Independent Safety Monitoring Committee

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**Reason for Amendment:**

Additional abbreviations associated with protocol amendment items.

**Section of protocol affected:**

Section 2.2 Secondary objectives / Part B. Randomised expansion (bullet point 2)

**Previous text:**

To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of ORR at 12 weeks, best objective response (BOR) and DoR and Durable Response Rate (DRR).

**Revised text:**

To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of ORR at 12 weeks, best objective response (BOR) ~~and~~, DoR **and Durable Response Rate (DRR)**.

**Reason for Amendment:**

Please refer to amendment rationale number 3.

**Section of protocol affected:**

Section 3.1.2 Part B: Randomised expansion (bullet point 2)

**Previous text:**

The patient population will be female, aged 18 years or older, with ER+ve advanced or metastatic breast cancer, and incorporating a subgroup who have *PIK3CA* mutation-positive tumour(s). For inclusion in Part B, patients must not have received any prior chemotherapy for breast cancer in the advanced or metastatic setting. Prior (neo)adjuvant chemotherapy is allowed (if (neo) adjuvant taxane, there must have been a minimum of 12 months from completion of therapy to relapse).

**Revised text:**

The patient population will be female, aged 18 years or older, with ER+ve, **HER2-ve**, advanced or metastatic breast cancer, and incorporating a subgroup who have *PIK3CA* mutation-positive tumour(s). For inclusion in Part B, patients must not have received any prior chemotherapy for breast cancer in the advanced or metastatic setting. Prior (neo)adjuvant chemotherapy is allowed (if (neo) adjuvant taxane, there must have been a minimum of 12 months from completion of therapy to relapse).

**Reason for Amendment:**

Please refer to amendment rationale number 1.

**Section of protocol affected:**

Section 3.1.1.4 Assessment Schedule

**Previous text:**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
<b>Week →</b>		1	2	3	4	1	2	3	4	1				
<b>Week Day →</b>	-28 to 0	1	2	1	2	1	2	1	2	1	2			
<b>Paclitaxel dosing</b>		X		X				X		X→				
<b>AZD5363 dosing</b>		X	X	X→	X→			X→	X→	X→				
<b>Activity↓</b>														
<b>Informed consent - <i>PIK3CA</i> screen (Part B only)</b>	X													8.4
<b><i>PIK3CA</i> mutation testing</b>	X													6.2.2
<b>Informed consent - study</b>	X													8.4
<b>Demography&amp; baseline characteristics</b>	X													6.2
<b>Medical/surgical history</b>	X													6.2
<b>Previous/concomitant therapy</b>	X													5.6
<b>Previous cancer therapy</b>	X													5.6

**Figure 6 Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off**

**Figure 6 Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:		
		1	2	3	4	1	2	3	4							
<b>Week →</b>		1	2	3	4	1	2	1	2	1	2	1	2			
<b>Week Day →</b>	-28 to 0	1	2	3	1	2	1	2	1	2	1	2	1	2		
<b>Paclitaxel dosing</b>		X			X				X							
<b>AZD5363 dosing</b>		X	X		X→				X→							
Inclusion / exclusion criteria	X															4.0
Physical examination	X	Pre	Pre				Pre						Pre		X	6.4.6
Height and weight	X						X						X		X	6.4.7
WHO performance status <sup>3</sup>	X	Pre	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>		X <sup>3</sup>		X <sup>3</sup>				X <sup>3</sup>		X <sup>3</sup>	6.4.8
Vital signs	X	Pre	Pre	Post	Pre		Pre		Post				X		X	6.4.11
12-lead ECG	X	Pre	Pre	Pre	Pre		Post						X		X	6.4.9
MUGA / Echocardiogram	X												X <sup>2</sup>		X	6.4.10
Haematology, Clinical chemistry Urinalysis	X	Pre	Pre	Pre	Pre		Pre		Pre				Pre		X	6.4.5
Additional glucose		2-4h	2-4h	2-4h	2-4h		2-4h		2-4h				2-4h			6.4.5
Glycosylated haemoglobin	X	4-6h	4-6h	4-6h	4-6h		4-6h		4-6h				X <sup>2</sup>		X	6.4.12.2

**Figure 6 Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:		
		1	2	3	4	1	2	3	4							
<b>Week →</b>		1	2	3	4	1	2	1	2	3	4	1				
<b>Week Day →</b>	-28 to 0	1	2	3	1	2	1	2	1	2	1	2	1	2		
<b>Paclitaxel dosing</b>	X		X		X		X		X		X		X→			
<b>AZD5363 dosing</b>		X	X		X→		X→		X→		X→		X→			
<b>Lipids</b>	X												X <sup>2</sup>	X		6.4.12.1
<b>Glucose, insulin, insulin c-peptide<sup>4</sup></b>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X		6.4.12.3
<b>Pregnancy test</b>	X													X		6.4.5
<b>Paclitaxel PK blood samples<sup>1</sup></b>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre			6.6.2
<b>AZD5363 PK blood samples<sup>1</sup></b>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre			6.6.2
<b>Pharmacodynamic blood samples<sup>1</sup></b>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X		6.7.1
<b>Exploratory biomarker blood samples<sup>1</sup> (optional)</b>	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X		6.8.1.5
<b>Exploratory biomarker hair samples (optional)</b>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre			6.8.1.4

**Figure 6 Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:		
		1	2	3	4	1	2	3	4							
<b>Week →</b>		1	2	3	4	1	2	1	2	1	2	1	2			
<b>Week Day →</b>	-28 to 0	1	2	3	1	2	1	2	1	2	1	2	1	2		
<b>Paclitaxel dosing</b>		X				X				X						
<b>AZD5363 dosing</b>		X	X			X	X			X	X					
Pharmacogenetics (optional)	X															6.9.1
RECIST Tumour assessments	X															6.3.1
Archival tumour sample	X															6.8.1.2
Paired biopsy (optional)	X															6.8.1.3
Circulating tumour cells	Pre															6.8.1.1
Patient meal information		X	X			X	X									6.4.12.4
QoL questionnaires (Part B only)	X															6.5.1
Survival status (Part B only) <sup>5</sup>																6.2.3.4
Subsequent cancer therapy																5.6
Concomitant medication	X															5.6
Adverse events	X															6.4.3

<sup>5</sup> Part A - Safety Run-in phase only: Patients will continue to undergo paclitaxel PK measurements on these occasions.

2. RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1). Part B - Randomised expansion only: Patients will continue to undergo RECIST assessments after cessation of study therapies up to disease progression or withdrawal of consent.
3. WHO performance status: Part B – Randomised expansion phase only: Performance status will be assessed at these timepoints during part B only.
4. Insulin c-peptide: Part A - Safety Run-in phase only: Insulin c-peptide will not be analysed during the Part B Randomised expansion.
5. Part B Randomised expansion phase only: Survival status and subsequent cancer therapies will be determined at the 28 day follow-up visit and at 12-weekly intervals thereafter. These visits suggested to coincide with RECIST assessments up to disease progression, and at 12-weekly intervals thereafter to death or withdrawal.

**Figure 7 Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac'xel Discort.	AZD5363 Discort.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
<b>Week →</b>		1	2	3	4	1	2	3	4	1				
<b>Week Day →</b>	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	
<b>Paclitaxel dosing</b>	X		X			X			X	X→				
<b>AZD5363 dosing</b>		X	X→	X		X→		X→		X→			X→	
<b>Activity ↓</b>														
<b>Informed consent - PIK3CA screen (Part B only)</b>	X													8.4
<b>PIK3CA mutation testing</b>	X													6.2.2
<b>Informed consent - study</b>	X													8.4
<b>Demography &amp; baseline characteristics</b>	X													6.2
<b>Medical/surgical history</b>	X													6.2



**Figure 7 Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off**

Cycle →	Screen	Cycle 1												Cycle 2						Cycle 3 onward	Pac <sup>x</sup> el Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:				
		1			2			3			4			1	2	3	4											
<b>Week →</b>		1	2	3	5	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2							
<b>Paclitaxel dosing</b>		X				X				X				X				X			X→							
<b>AZD5363 dosing</b>		X	X→	X	X	X→	X	X→	X	X→	X	X→	X	X→	X	X→	X	X→	X	X→	X	X→						
Previous/concomitant therapy	X																											5.6
Previous cancer therapy	X																											5.6
Inclusion / exclusion criteria	X																											4
Physical examination	X	Pre				Pre				Pre											Pre				X	X		6.4.6
Height and weight	X																				X				X	X		6.4.7
WHO performance status	X	Pre	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	6.4.8	
Vital signs	X	Pre	Pre	1h	2h	6h	Post	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Post	Post	Post	Post	X	X	X	6.4.11	
12-lead ECG	X	Pre	Pre	1h	2h	6h	Post	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Post	Post	Post	Post	X	X	X	6.4.9	
MUGA / Echocardiogram	X																								X	X		6.4.10



**Figure 7 Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off**

Cycle →	Screen	Cycle 1												Cycle 2				Cycle 3 onward	Pac'xel Discort.	AZD5363 Discort.	28-day follow-up	Details in Section:					
		1			2			3			4			1	2	3	4										
<b>Week →</b>		1	2	3	5	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2						
<b>Week Day →</b>	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2						
<b>Paclitaxel dosing</b>		X				X				X				X				X			X						
<b>AZD5363 dosing</b>		X	X	X	X					X	X	X	X					X	X	X	X	X					
<b>Pharmacodynamic blood samples<sup>1</sup></b>		Pre	Pre	Pre	Pre					Pre	Pre	Pre	Pre				Pre	Pre	Pre	Pre	Pre					6.7.1	
<b>Exploratory biomarker blood samples<sup>1</sup> (optional)</b>	X									Pre	Pre	Pre	Pre				Pre	Pre	Pre	Pre	Pre					6.8.1.5	
<b>Exploratory biomarker hair samples (optional)</b>																										6.8.1.4	
<b>Pharmacogenetics (optional)</b>																										6.9.1	
<b>RECIST Tumour assessments</b>	X																									6.3.1	
<b>Archival tumour sample</b>	X																									6.8.1.2	
<b>Paired biopsy (optional)</b>																										6.8.1.3	
<b>Circulating tumour cells</b>		Pre																								6.8.1.1	
<b>Patient meal information</b>			X			X				X				X				X			X					6.4.12.4	

**Figure 7 Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	Pac <sup>x</sup> el Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4					
<b>Week →</b>		1	2	3	4	1	2	3	4	1				
<b>Week Day →</b>	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	
<b>Paclitaxel dosing</b>		X				X				X				
<b>AZD5363 dosing</b>		X	X	X	X	X	X	X	X	X	X			
<b>QoL questionnaires (Part B only)</b>	X									X <sup>2</sup>				6.5.1
<b>Survival status (Part B only)<sup>6</sup></b>													X <sup>6</sup>	6.2.3.4
<b>Subsequent cancer therapy<sup>6</sup></b>												X	X <sup>6</sup>	5.6
<b>Concomitant medication</b>	X													5.6
<b>Adverse events</b>	X													6.4.3

1. Part A - Safety Run-in phase only: Patients will continue to undergo paclitaxel PK measurements on these occasions.
2. RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1). Part B Randomised expansion only: Patients will continue to undergo RECIST assessments after cessation of study therapies up to disease progression or withdrawal of consent.
3. WHO performance status: Part B – Randomised expansion phase only: Performance status will be assessed at these timepoints during part B only.
4. Insulin c-peptide: Part A - Safety Run-in phase only: Insulin c-peptide will not be analysed during Part B.
5. Part A Safety Run-in phase only: Patients will undergo the Cycle 2 Week 1 Day 1 MUGA / Echocardiogram assessment during Part A only. This assessment timepoint will not be conducted during the Part B Randomised expansion.

**Revised text:** Note 1 – the following tables now represent patient assessments as applicable to Part A of the study only. These assessments remain unchanged from protocol edition 2. All changes are therefore relevant to removal of assessments applicable to Part B alone (which are now shown in new Figure 9). For clarity of presentation, the revised schedules of assessment and footnotes are shown below without marked deletions. The individual changes are described in the relevant sections identified under the ‘Details in Section.’ column.

Note 2 - a ‘12 weekly’ column has been included to more clearly identify assessments relevant to the set of evaluations conducted at 12-weekly intervals and to delineate these from assessments conducted routinely at the start of each Cycle.

**Schedule of Assessments: Part A**

Figure 6 Part A Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off																		
Cycle →	Screen	Cycle 1					Cycle 2					Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:	
		1	2	3	4	1	2	3	4	1	2							3
Week →		1	2	3	4	1	2	3	4	1	2	3	4	1				
Week Day →	-28 to 0	1	2	3	1	2	1	2	1	2	1	2	1	2				
Paclitaxel dosing		X			X					X				X→				
AZD5363 dosing		X	X		X→			X→		X→			X→					
Activity ↓																		
<i>PIK3CA</i> mutation testing	X																	6.2.2
Informed consent - study	X																	8.4
Demography & baseline characteristics	X																	6.2
Medical/surgical history	X																	6.2
Previous/concomitant therapy	X																	5.6

**Figure 6 Part A Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off**

Cycle →	Screen	Cycle 1												Cycle 2						Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2							3	4	
Week →		1	2	3	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2						
Week Day →	-28 to 0	1	2	3	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2						
Paclitaxel dosing		X			X			X			X			X			X			X								
AZD5363 dosing		X	X		X	X		X	X		X	X		X	X		X	X		X	X							
Previous cancer therapy	X																											5.6
Inclusion / exclusion criteria	X																											4
Physical examination	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X	X				6.4.6
Height and weight	X	X																					X	X				6.4.7
WHO performance status	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre						6.4.8
Vital signs	X	Pre	Pre	Post	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X	X				6.4.11
12-lead ECG	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X	X				6.4.9
MUGA / Echocardiogram	X																								X			6.4.10
Haematology, Clinical chemistry Urinalysis	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X	X				6.4.5
Additional glucose			2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h	2-4h						6.4.5
			4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h	4-6h						

**Figure 6 Part A Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4						
Week →		1	2	3	4	1	2	3	4	1					
Week Day →	-28 to 0	1	2	1	2	1	2	1	2	1	2				
Paclitaxel dosing		X		X		X		X		X					
AZD5363 dosing		X	X	X	X	X	X	X	X	X	X				
Glycosylated haemoglobin	X											X			6.4.12.2
Lipids	X											X			6.4.12.1
Glucose, insulin, insulin c-peptide		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X			6.4.12.3
Pregnancy test	X											X			6.4.5
Paclitaxel PK blood samples		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre				6.6.2
AZD5363 PK blood samples		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre				6.6.2
Pharmacodynamic blood samples		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre				6.7.1
Exploratory biomarker blood samples (optional)	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre				6.8.1.5

**Figure 6 Part A Schedule 1: AZD5363/placebo – Intermittent Dosing: 2 days on 5 days off**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4						
Week →		1	2	3	4	1	2	3	4	1					
Week Day →	-28 to 0	1	2	1	2	1	2	1	2	1	2				
Paclitaxel dosing	X	X	X	X		X	X	X		X→					
AZD5363 dosing		X	X	X→	X→		X→	X→	X→	X→					
Exploratory biomarker hair samples (optional)		Pre 4h													6.8.1.4
Pharmacogenetics (optional)	X														6.9.1
RECIST Tumour assessments	X										X <sup>1</sup>				6.3.1
Archival tumour sample	X														6.8.1.2
Paired biopsy (optional)	X						X								6.8.1.3
Circulating tumour cells	Pre						Pre			Pre <sup>2</sup>	Pre <sup>1</sup>				6.8.1.1
Patient meal information		X	X	X	X										6.4.12.4
Subsequent cancer therapy													X	X	
Concomitant medication	X														
Adverse events	X														5.6



- RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1).
- Circulating tumour cell samples will be collected on Cycle 3 Week 1 Day 1 and then only at 12-weekly assessments thereafter (see footnote 1 above).

Figure 7 Part A Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off																
Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:	
		1	2	3	4	1	2	3	4							
Week →																
Week Day →	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2			
Paclitaxel dosing	X					X				X						
AZD5363 dosing		X	X	X	X	X	X	X	X	X	X	X	X			
Activity ↓																
PIK3CA mutation testing	X															6.2.2
Informed consent - study	X															8.4
Demography & baseline characteristics	X															6.2
Medical/surgical history	X															6.2
Previous/concomitant therapy	X															5.6
Previous cancer therapy	X															5.6
Inclusion / exclusion criteria	X															4

**Figure 7 Part A Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off**

Cycle →	Screen	Cycle 1						Cycle 2						Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:		
		1	2	3	4	1	2	3	4	1	2	3	4								
<b>Week →</b>																					
<b>Week Day →</b>	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2	1	2	1	2				
<b>Paclitaxel dosing</b>		X				X						X				X →					
<b>AZD5363 dosing</b>		X	X →	X	X →	X →	X →					X →	X →			X →					
Physical examination	X	Pre		Pre												Pre		X		6.4.6	
Height and weight	X															X		X		6.4.7	
WHO performance status	X	Pre																		6.4.8	
Vital signs	X	Pre	Pre	1h	2h	6h	Pre	Post	Pre	Pre	Pre	Post	Post	Post	Post	X		X		6.4.11	
12-lead ECG	X	Pre	Pre	1h	2h	6h	Pre	Post	Pre	Post	Pre	Post	Post	Post	Post	X		X		6.4.9	
MUGA / Echocardiogram	X																	X		X <sup>1</sup>	6.4.10
Haematology, Clinical chemistry Urinalysis	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X		X	6.4.5
Additional glucose			2-4h	4-6h		2-4h	4-6h		2-4h	4-6h		2-4h	4-6h		2-4h	4-6h				X <sup>1</sup>	6.4.5
Glycosylated haemoglobin	X																	X		X <sup>1</sup>	6.4.12.2

**Figure 7 Part A Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4						
<b>Week →</b>															
<b>Week Day →</b>	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2		
<b>Paclitaxel dosing</b>		X				X				X					
<b>AZD5363 dosing</b>		X	X→	X	X	X→	X→	X→	X→	X→	X→				
<b>Lipids</b>	X												X		6.4.12.1
<b>Glucose, insulin, insulin c-peptide</b>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X	6.4.12.3
<b>Pregnancy test</b>	X												X		6.4.5
<b>Paclitaxel PK blood samples</b>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre		6.6.2
<b>AZD5363 PK blood samples</b>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre		6.6.2
<b>Pharmacodynamic blood samples</b>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X	6.7.1
<b>Exploratory biomarker blood samples (optional)</b>	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X	6.8.1.5
<b>Exploratory biomarker hair samples (optional)</b>		Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre		6.8.1.4

**Figure 7 Part A Schedule 2: AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off**

Cycle →	Screen	Cycle 1				Cycle 2				Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	4	1	2	3	4						
<b>Week →</b>															
<b>Week Day →</b>	-28 to 0	1	2	3	5	1	2	1	2	1	2	1	2		
<b>Paclitaxel dosing</b>		X				X				X					
<b>AZD5363 dosing</b>		X	X→	X	X	X→	X→	X→	X→	X→	X→				
Pharmacogenetics (optional)		X													6.9.1
RECIST Tumour assessments	X											X <sup>1</sup>			6.3.1
Archival tumour sample	X														6.8.1.2
Paired biopsy (optional)	X								X						6.8.1.3
Circulating tumour cells	Pre								Pre			Pre <sup>1</sup>			6.8.1.1
Patient meal information		X	X	X	X	X	X	X	X			X			6.4.12.4
Subsequent cancer therapy													X		5.6
Concomitant medication	X														5.6
Adverse events	X														6.4.3

1. RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1).
2. Circulating tumour cell samples will be collected on Cycle 3 Week 1 Day 1 and then only at 12-weekly assessments thereafter (see footnote 1 above).

**Reason for Amendment:**

Revision to reflect Part A assessments only - Please refer to amendment rationale number 4.

Addition of a '12 weekly' column followed feedback received from study sites that delineation of evaluations between those to be conducted at the start of each cycle from Cycle 3 onwards and those to be conducted at 12-weekly intervals from baseline, was insufficiently clear in the original protocol versions.

**Section of protocol affected:**

Section 3.1.4 Assessment Schedule

**Additional figure:**

*Note: The following table represents patient assessments applicable to Part B of the study only. This is a new entry associated with a revision to original figures 6 and 7 to represent patient assessments applicable to Part A only.*

Figure 8 Part B Schedules 1 and 2. AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off and 2 days on 5 days off																			
Cycle →	Screen	Cycle 1						Cycle 2						Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	1	2	3	1	2	3	1	2	3						
Week →																			
Week Day →	-28 to 0	1	2	1	2	1	2	1	2	1	2	1	2	1	2				
Paclitaxel dosing		X		X		X		X		X		X		X→					
AZD5363 dosing			X		X→		X→		X→		X→		X→		X→				
Activity↓																			
Informed consent - PIK3CA screen	X																		8.4 / 5.2.1
PIK3CA mutation testing <sup>1</sup>	X																		6.2.2

**Figure 8 Part B Schedules 1 and 2. AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off and 2 days on 5 days off**

Cycle →	Screen	Cycle 1						Cycle 2						Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1		2		3		1		2		3							
		1	2	1	2	1	2	1	2	1	2	1	2						
Week →																			
Week Day →	-28 to 0	1	2	1	2	1	2	1	2	1	2	1	2	1	2				
Paclitaxel dosing		X		X		X		X		X		X		X					
AZD5363 dosing			X		X		X		X		X		X		X				
Informed consent - study	X																	8.4	
Demography & baseline characteristics	X																	6.2	
Medical/surgical history	X																	6.2	
Previous/concomitant therapy	X																	5.6	
Previous cancer therapy	X																	5.6	
Inclusion / exclusion criteria	X																	4	
Physical examination	X	Pre		Pre				Pre						Pre		X		6.4.6	
Height and weight	X	X						X						X		X		6.4.7	
WHO performance status	X	Pre	X	X		X		X		X		X		X		X		6.4.8	
Vital signs	X	Pre	Pre	Pre		Pre		Pre		Post		Post		X		X		6.4.11	
			1h	2h	6h														

**Figure 8 Part B Schedules 1 and 2. AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off and 2 days on 5 days off**

Cycle →	Screen	Cycle 1			Cycle 2			Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	1	2	3						
<b>Week →</b>													
<b>Week Day →</b>	-28 to 0	1	2	1	2	1	2	1	2				
<b>Paclitaxel dosing</b>		X	X	X	X	X	X	X→	X				
<b>AZD5363 dosing</b>		X	X→	X→	X→	X→	X→	X→	X→				
<b>12-lead ECG</b>	X	Pre 1h 2h 6h	Pre		Post			X		X			6.4.9
<b>MUGA / Echocardiogram</b>	X								X <sup>2</sup>	X			6.4.10
<b>Haematology, Clinical chemistry Urinalysis</b>	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre		X			6.4.5
<b>Glycosylated haemoglobin</b>	X									X			6.4.12.2
<b>Lipids</b>	X									X			6.4.12.1
<b>Glucose, insulin,</b>		Pre 2h 4h 6h 8h	Pre 2h 4h	Pre 2h 4h	Pre 2h 4h	Pre 2h 4h	Pre 2h 4h	Pre 2-4h		X			6.4.12.3
<b>Pregnancy test</b>	X	X								X			6.4.5
<b>Paclitaxel PK blood samples</b>		Pre 2h 4h 8h	Pre										6.6.2

**Figure 8 Part B Schedules 1 and 2. AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off and 2 days on 5 days off**

Cycle →	Screen	Cycle 1						Cycle 2						Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1		2		3		1		2		3							
		1	2	1	2	1	2	1	2	1	2	1	2						
Week →																			
Week Day →	-28 to 0	1	2	1	2	1	2	1	2	1	2	1	2	1	2				
Paclitaxel dosing		X		X		X		X		X		X		X					
AZD5363 dosing			X		X		X		X		X		X		X				
AZD5363 PK blood samples		Pre		Pre		Pre		Pre		Pre		Pre		Pre					6.6.2
Pharmacodynamic blood samples		Pre		Pre		Pre	4h	Pre		Pre		Pre		Pre		X			6.7.1
Exploratory biomarker blood samples (optional)	X															X			6.8.1.5
Exploratory biomarker hair samples (optional)		Pre	4h																6.8.1.4
Pharmacogenetics (optional)		X																	6.9.1
RECIST Tumour assessments	X																		6.3.1
Archival tumour sample	X																		6.8.1.2
Paired biopsy (optional)	X								X										6.8.1.3
Circulating tumour cells		Pre							Pre										6.8.1.1
Patient meal information		X							X										6.4.12.4



**Figure 8 Part B Schedules 1 and 2. AZD5363/placebo – Intermittent Dosing: 4 days on 3 days off and 2 days on 5 days off**

Cycle →	Screen	Cycle 1			Cycle 2			Cycle 3 onward	12 weekly	Pac'xel Discont.	AZD5363 Discont.	28-day follow-up	Details in Section:
		1	2	3	1	2	3						
Week →								1					
Week Day →	-28 to 0	1	2	1	2	1	2	1	2				
Paclitaxel dosing		X	X	X	X	X	X	X→					
AZD5363 dosing		X	X→	X→	X→	X→	X→	X→					
QoL questionnaires	X	Pre							X <sup>2</sup>	X			6.5.1
Survival status <sup>4</sup>											X <sup>4</sup>		6.2.3.4
Subsequent cancer therapy <sup>4</sup>										X	X <sup>4</sup>		5.6
Concomitant medication	X											▲	5.6
Adverse events	X											▲	6.4.3

1. Note: PIK3CA mutation testing results is required for patient stratification and randomisation. The blood sample for PIK3CA mutation testing should therefore be sent to the central laboratory as soon as possible after consent. If a patient requires urgent chemotherapy, a patient may be stratified/randomised before the PIK3CA result is available provided that the blood sample has been received at the central laboratory. Please refer to section 5.2.
2. RECIST, MUGA/Echo, CTCs, Glycosylated haemoglobin, lipids and QoL to be conducted every 12 weeks from start of treatment (Cycle 1 Day 1). Patients will continue to undergo RECIST assessments after cessation of study therapies up to disease progression or withdrawal of consent.
3. Circulating tumour cell samples will be collected on Cycle 3 Week 1 Day 1 and then only at 12-weekly assessments thereafter (see footnote 2 above).
4. Survival status and subsequent cancer therapies will be determined at the 28 day follow-up visit and at 12-weekly intervals thereafter. These visits suggested to coincide with RECIST assessments up to disease progression, and at 12-weekly intervals thereafter to death or withdrawal.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 4.1 Inclusion criteria / Part B Randomised Expansion.

**Previous text:**

Part B. Randomised Expansion:

1. Patients with histological or cytologic diagnosis of ER+ve breast cancer with evidence of relapsed advanced or metastatic disease. Lesions should not be amenable to surgery or radiation of curative intent and must be considered unlikely to be rendered eligible for surgery by treatment with paclitaxel in this study.
2. Patients who relapsed more than 12 months after completing adjuvant endocrine therapy, or who have not had adjuvant endocrine therapy, must have received prior endocrine therapy for advanced or metastatic disease.\*

Patients who relapsed on adjuvant endocrine therapy, or within 12 months of completing adjuvant endocrine therapy, may enter the study without prior endocrine therapy for advanced or metastatic disease.\*

3. Provision of archival tumour sample for *PIK3CA* mutation testing.
4. Provision of baseline plasma sample for *PIK3CA* mutation testing.
5. At least one tumour lesion, not previously irradiated, that can be measured accurately at baseline as  $\geq 10$  mm in the longest diameter (except lymph nodes which must have short axis  $\geq 15$  mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements.

\* For guidance when evaluating inclusion criteria under item 2 above.

The following patients would be eligible for inclusion:

- Relapsed whilst on adjuvant endocrine therapy
- Relapsed <12 months after completing adjuvant endocrine therapy (with or without receiving endocrine therapy in the advanced or metastatic setting)
- Relapsed >12 months after completing adjuvant endocrine therapy and has received endocrine therapy in the advanced or metastatic setting

The following patients would not be eligible for inclusion:

- Adjuvant endocrine therapy- naive
- Relapsed >12 months after completing adjuvant endocrine therapy and has not received endocrine therapy in the advanced or metastatic setting

**Revised text:**

Part B. Randomised Expansion:

1. Patients with histological or cytologic diagnosis of ER+ve **and HER2-ve** breast cancer with evidence of relapsed advanced or metastatic disease. Lesions should not be amenable to surgery or radiation of curative intent and must be considered unlikely to be rendered eligible for surgery by treatment with paclitaxel in this study.
2. **Blank (inclusion criterion removed)** ~~Patients who relapsed more than 12 months after completing adjuvant endocrine therapy, or who have not had adjuvant endocrine therapy, must have received prior endocrine therapy for advanced or metastatic disease.\*~~  
~~Patients who relapsed on adjuvant endocrine therapy, or within 12 months of completing adjuvant endocrine therapy, may enter the study without prior endocrine therapy for advanced or metastatic disease.\*~~
3. Provision of archival tumour sample for *PIK3CA* mutation testing.
4. Provision of baseline plasma sample for *PIK3CA* mutation testing.
5. At least one tumour lesion, not previously irradiated, that can be measured accurately at baseline as  $\geq 10$  mm in the longest diameter (except lymph nodes which must have short axis  $\geq 15$  mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements.

~~\* For guidance when evaluating inclusion criteria under item 2 above.~~

~~The following patients would be eligible for inclusion:~~

- ~~● Relapsed whilst on adjuvant endocrine therapy~~
- ~~● Relapsed  $< 12$  months after completing adjuvant endocrine therapy (with or without receiving endocrine therapy in the advanced or metastatic setting)~~
- ~~● Relapsed  $> 12$  months after completing adjuvant endocrine therapy and has received endocrine therapy in the advanced or metastatic setting~~

~~The following patients would not be eligible for inclusion:~~

- ~~● Adjuvant endocrine therapy naive~~

- ~~Relapsed >12 months after completing adjuvant endocrine therapy and has not received endocrine therapy in the advanced or metastatic setting~~

**Reason for Amendment:**

Please refer to amendment rationale number 1.

**Section of protocol affected:**

Section 4.2 Exclusion criteria (*criterion 9*)

**Previous text:**

9. Clinically significant abnormalities of glucose metabolism as defined by any of the following:
- Diagnosis of diabetes mellitus type I or II (irrespective of management).
  - Glycosylated haemoglobin (HbA1C)  $\geq 8.0\%$  at screening (64 mmol/mol) (conversion equation for HbA1C [IFCC-HbA1C (mmol/mol) = [DCCT-HbA1C (%) - 2.15] x 10.929)
  - Fasting Plasma Glucose  $\geq 7.0$ mmol/L (126 mg/dL) at screening. Fasting is defined as no caloric intake for at least 8 hours.

**Revised text:**

9. Clinically significant abnormalities of glucose metabolism ~~as defined by any of the following~~ **including diagnosis of diabetes mellitus type I or II (irrespective of management), defined according to the American Diabetes Association Guidelines 2014 (ADA 2014) which include the criteria:**
- ~~— Diagnosis of diabetes mellitus type I or II (irrespective of management).~~
  - Glycosylated haemoglobin (HbA1C)  $\geq 6.5\%$  at screening (48 mmol/mol) (conversion equation for HbA1C [IFCC-HbA1C (mmol/mol) = [DCCT-HbA1C (%) - 2.15] x 10.929)
  - Fasting Plasma Glucose  $\geq 7.0$ mmol/L (126 mg/dL) at screening. Fasting is defined as no caloric intake for at least 8 hours.

**Reason for Amendment:**

Further clarity to description of exclusion of patients with type I or II diabetes mellitus. Re-alignment of HbA1C limit criterion to conform to current American Diabetes Association Guidelines for definition of diabetes, and as adopted by the European Diabetes Association.

**Section of protocol affected:**

Section 5.2.1 Procedure for identification of tumour PIK3CA mutation status and stratification.

**Previous text:**

Determination of PIK3CA mutation status

Blood (for cfDNA) and most recent archival tumour samples should be provided at screening for determination of *PIK3CA* mutation status (see section 6.2.2)

Where possible, samples should be collected no later than two weeks prior to intended first dosing date. Samples will be analysed by Quintiles on behalf of AstraZeneca and the results reported to the study site within 7-14 days of transfer.

Patients will be designated as: ‘*PIK3CA* mutation positive’ or ‘*PIK3CA* mutation not detected’. Where a sample cannot be analysed, or the analysis is flawed/indeterminate, a status of ‘unknown’ will be reported. The results from both the blood and tumour analyses will be utilised to derive a single ‘defined’ *PIK3CA* mutation status for each patient with reference to the algorithm below.

Part A. Safety Run-In: Defined *PIK3CA* mutation status is not a requirement for commencement of treatment, but should be recorded prior to completion of Cycle 1.

Part B. Randomised Expansion: Defined *PIK3CA* mutation status is required prior to commencement of treatment for stratification of patients to *PIK3CA* mutation-positive and mutation-not detected groups (see ‘Patient stratification by *PIK3CA* mutation status’ below).

If it is not possible to obtain one, or both, sample types at screening, the missing sample(s) must be provided no later than the end of Cycle 1.

		Sample type - Tissue		
		PIK3CA mutation result→↓	Positive (+ve)	Not detected (ND)
Sample type - Blood	Positive (+ve)	+ve	+ve	+ve
	Not detected (ND)	+ve	ND	ND
	Unknown (U)	+ve	ND	U

**Note:**

Pre-existing *PIK3CA* mutation status, where generated from a relevant tumour sample as part of local clinical practice, will also be recorded. These data may be utilised, if necessary, on study completion to assist in confirmation of mutation

status where there is a discrepancy between blood and tumour *PIK3CA* mutation results from the central analysis.

Where an archival tumour sample cannot be provided in sufficient time for analysis by Quintiles to support determination of defined *PIK3CA* mutation status (Part B) or the result is 'unknown' (Part A or B), mutation status derived from a prior locally-conducted analysis may be utilised. This, however, will only be acceptable where the analytical methodology/kit has been approved in advance by AstraZeneca.

#### Patient stratification by *PIK3CA* mutation status (Part B)

Patients will be allocated to '*PIK3CA* mutation positive' or '*PIK3CA* mutation not detected' strata prior to randomisation.

Patients assigned a *PIK3CA* mutation status of 'Unknown' will not be eligible to participate in Part B. In cases where an archival tumour sample is not received in time to be analysed by the central laboratory during screening, defined status may be derived from the blood sample alone, or it may be applicable to utilise the status from a prior, locally-conducted tumour analysis, see above.

If a patient is initially stratified to the 'Not detected' stratum based upon a blood sample alone, (or blood sample plus locally-conducted tumour analysis) and a 'positive' central tumour sample analysis is received after stratification, the site will contact the IVRS/IWRS Customer Care department by telephone or using the web to provide notification of this new information. IVRS/IWRS records will be revised to show a corrected *PIK3CA* mutation status of 'Positive'.

In the event of any correction to a patient's allocated mutation status post-stratification:

- there will be no revision to the patient stratum allocation or numbering in RAVE.
- AZ will coordinate with IVRS/IWRS to ensure that the allocation of patient places per stratum is adjusted, as necessary, to ensure that the minimum number required in each will be achieved
- for final data analysis the corrected mutation status will be used to assign the patient to the relevant stratum.

#### **Revised text:**

#### Determination of *PIK3CA* mutation status

Blood (for cfDNA) and most recent archival tumour samples should be provided at screening for determination of *PIK3CA* mutation status (see section 6.2.2). **For Part B, in the event that recruitment to one stratum is completed before the other, it will be necessary to pre-screen patients for mutation status applicable to the remaining open stratum (see section 5.2.2 and Figure 9).**

Where possible, samples should be collected no later than two weeks prior to intended first dosing date. Samples will be analysed by Quintiles on behalf of AstraZeneca and the results reported to the study site within 7-14 days of transfer.

Patients will be designated as: ‘*PIK3CA* mutation positive’ or ‘*PIK3CA* mutation not detected’. Where a sample cannot be analysed, or the analysis is flawed/indeterminate, a status of ‘unknown’ will be reported. The results from both the blood and tumour analyses will be utilised to derive a single ‘defined’ *PIK3CA* mutation status for each patient with reference to the **following** algorithm below.

		Sample type - Tissue		
		PIK3CA mutation result → ↓	Positive (+ve)	Not detected (ND)
Sample type - Blood	Positive (+ve)	+ve	+ve	+ve
	Not detected (ND)	+ve	ND	ND
	Unknown (U)	+ve	ND	U

Part A. Safety Run-In: Defined *PIK3CA* mutation status is not a requirement for commencement of treatment, but should be recorded prior to completion of Cycle 1.

Part B. Randomised Expansion: ~~Defined *PIK3CA* mutation status is required prior to commencement of treatment for stratification of patients to *PIK3CA* mutation positive and mutation not detected groups (see ‘Patient stratification by *PIK3CA* mutation status’ below).~~

~~If it is not possible to obtain one, or both, sample types at screening, the missing sample(s) must be provided no later than the end of Cycle 1.~~

		Sample type - Tissue		
		PIK3CA mutation result → ↓	Positive (+ve)	Not detected (ND)
Sample type - Blood	Positive (+ve)	+ve	+ve	+ve
	Not detected (ND)	+ve	ND	ND
	Unknown (U)	+ve	ND	U

**Note:**

~~Pre-existing *PIK3CA* mutation status, where generated from a relevant tumour sample as part of local clinical practice, will also be recorded. These data may be utilised, if necessary, on study completion to assist in confirmation of mutation status where there is a discrepancy between blood and tumour *PIK3CA* mutation results from the central analysis.~~

~~Where an archival tumour sample cannot be provided in sufficient time for analysis by Quintiles to support determination of defined *PIK3CA* mutation status (Part B) or the result is 'unknown' (Part A or B), mutation status derived from a prior locally conducted analysis may be utilised. This, however, will only be acceptable where the analytical methodology/kit has been approved in advance by AstraZeneca.~~

**Patients must be stratified to either the *PIK3CA* mutation-positive or mutation-not detected arm prior to randomisation and commencement of treatment.**

**All efforts should be made to provide plasma and tumour tissue samples for *PIK3CA* mutation analysis during the screening period\*. However, patients may be stratified in the absence of mutation status results from one or both sample types (see below) where the investigator considers this necessary to minimise delay to commencement of standard treatment with paclitaxel. Any samples not collected during screening must be provided for analysis no later than the end of Cycle 1.**

**Investigators may register a patient's *PIK3CA* tumour mutation status via IVRS/IWRS to enable stratification and randomisation - at a time appropriate to start of study therapy. *PIK3CA* tumour mutation status will be identified and stratification may be conducted under the following conditions, dependent upon availability of *PIK3CA* mutation results from either mandated central laboratory (Quintiles) analysis or pre-existing local tumour tissue analysis (please also refer to Figure 9):**

~~Patient stratification by *PIK3CA* mutation status (Part B)~~

~~Patients will be allocated to '*PIK3CA* mutation positive' or '*PIK3CA* mutation not detected' strata prior to randomisation.~~

~~Patients assigned a *PIK3CA* mutation status of 'Unknown' will not be eligible to participate in Part B. In cases where an archival tumour sample is not received in time to be analysed by the central laboratory during screening, defined status may be derived from the blood sample alone, or it may be applicable to utilise the status from a prior, locally conducted tumour analysis, see above.~~

**Patient will be identified as *PIK3CA* 'positive' in either/both of the following cases:**

- Available centrally analysed plasma and/or tumour tissue sample results are *PIK3CA* 'positive' (Note: where both sample types have been sent for central analysis, stratification may be based on the first result to be returned).



- **Locally analysed plasma and/or tumour tissue result is positive for any *PIK3CA* mutation.**

Patient will be identified as *PIK3CA* ‘not detected’ in either of the following cases\*\*:

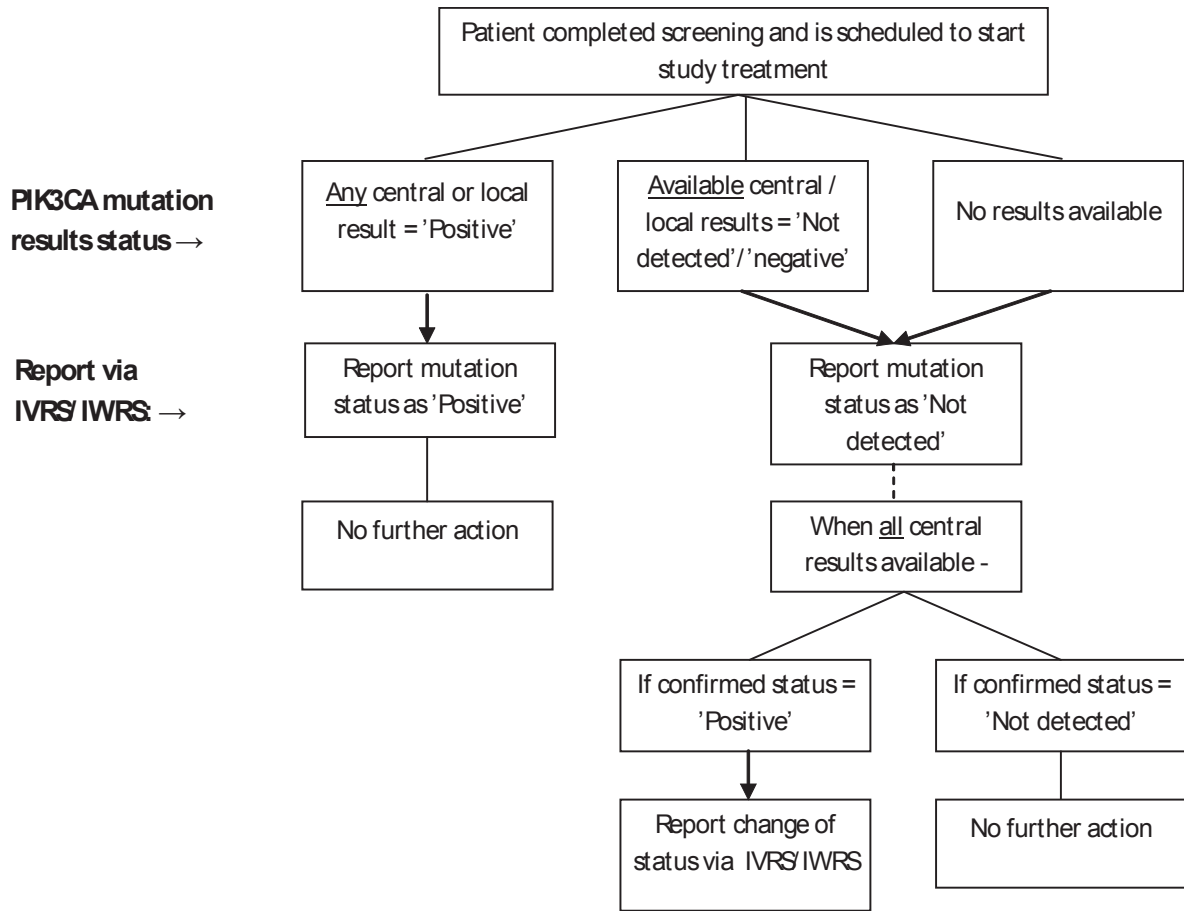
- **Available centrally analysed plasma and tumour tissue sample results are *PIK3CA* ‘not detected’ and any locally analysed tumour tissue sample result is negative for *PIK3CA* mutation.**
- **Centrally analysed plasma or tumour tissue sample results are awaited, but not yet available, and no locally analysed tumour tissue sample results are available, at the planned time of stratification. In this case the patient may be stratified to the ‘not detected’ group by default. Note - at least the plasma sample must have been received by the central laboratory before the patient may be stratified/randomised.**

**\* In the event that only one stratum is open to recruitment, see section 5.2.2 and Figure 9 scenario 2, patients will be separately evaluated for *PIK3CA* mutation status prior to screening to determine eligibility. In such a case, the status derived for eligible patients will be carried forward to be recorded under the screening assessment.**

**\*\*~~If~~ Where a patient is initially stratified to the ‘Not detected’ stratum based upon a blood sample alone, (or blood sample plus locally conducted tumour analysis) in the absence of one or more sample analyses, and a ‘positive’ central tumour sample analysis result is received after stratification, the site will contact the IVRS/IWRS Customer Care department by telephone or using the web to provide notification of this new information. IVRS/IWRS records will be revised to show a corrected *PIK3CA* mutation status of ‘Positive’.**

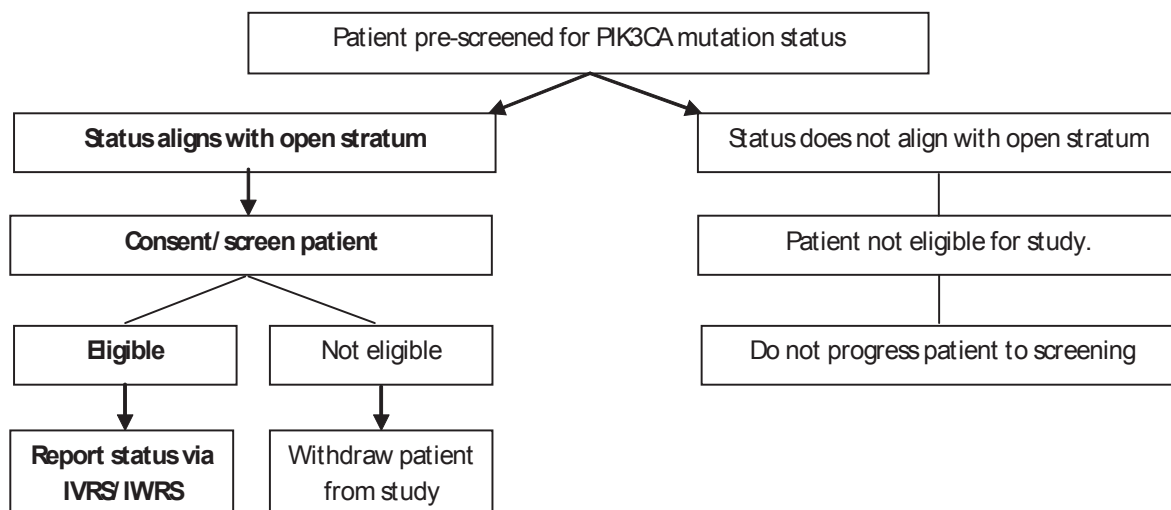
In the event of any correction to a patient’s allocated mutation status post-stratification:

- there will be no revision to the patient stratum allocation or numbering in RAVE.
- AZ will coordinate with IVRS/IWRS to ensure that the allocation of patient places per stratum is adjusted, as necessary, to ensure that the minimum number required **and randomisation balance within** each will be achieved.
- for final data analysis the corrected mutation status will be used to assign the patient to the relevant stratum.



## Figure 9 Patient stratification scenarios

### Scenario 1: Both strata open:



### Scenario 2: One stratum open:

#### Reason for Amendment:

Revision of criteria for stratification of Part B patients by PIK3CA tumour mutation status and provision of further information regarding the processes to be followed in the event that one stratum closes before the other. Provision of further process guidance for study site staff and investigators regarding both of the above. Please refer to amendment rationale number 2.

#### Section of protocol affected:

Section 5.2.2 Procedures for allocation and randomisation / Part B Randomised Expansion

#### Additional text (Final paragraphs):

**Selective recruitment of patients by PIK3CA tumour mutation status will be implemented in the event of either of the following:**

- **Recruitment to one stratum is completed (a minimum of 50 patients corrected for any post-screening revised mutation status) prior to the other.**
- **Agreed recommendation by the AstraZeneca Data Monitoring Committee (AZDMC) to cease recruitment to one stratum. See section 12.5.**

**In the event that selective recruitment is required, patients will be invited to undergo pre-screening for PIK3CA tumour mutation status. A separate candidate patient**

**consent for PIK3CA tumour mutation pre-screening assessment will be provided for this. Those patients whose mutation status aligns with the actively recruiting stratum will be invited to consent to participate in the BEECH study. Further mutation status analysis during screening will not be required in these cases see Figure 9.**

**Reason for Amendment:**

Identification of scenarios under which one Part B stratum could close before the other, and notification of the requirement for patients then to be pre-screened for PIK3CA tumour mutation status to determine eligibility to the open stratum. Please refer to amendment rationale number 2.

With reference to the AZDMC, please refer to amendment rationale number 5.

**Section of protocol affected:**

Section 5.5.3 Doses and treatment regimens / Treatment Schedules (third paragraph note)

**Previous text:**

**Note:**

AZD5363/placebo should not be taken on any week that the paclitaxel infusion is not administered – either due to a scheduled off-drug week or unscheduled omission or delay. Where paclitaxel is ceased entirely, AZD5363/placebo may be continued on a weekly schedule at the investigator's discretion.

**Revised text:**

**Note:**

AZD5363/placebo should not be taken on any week that the paclitaxel infusion is not administered – either due to a scheduled off-drug week or unscheduled omission or delay. Where paclitaxel is ceased entirely, **it is recommended that AZD5363/placebo may be is** continued on a weekly schedule at the investigator's discretion (**see section 5.5.4**).

**Reason for Amendment:**

Following Investigator comments regarding preferred clinical management of patients remaining on AZD5363/placebo after having ceased paclitaxel. This change provides further emphasis upon a recommendation to continue such patients under a weekly AZD5363/placebo treatment schedule – i.e. 4 weeks per cycle rather than 3 weeks on-treatment followed by 1 week-off.

**Section of protocol affected:**

Section 5.5.4 Dose modifications / AZD5363/placebo

**Additional text** (*new 3<sup>rd</sup> paragraph*):

**If paclitaxel is permanently ceased, and the investigator elects to continue provision of AZD5363/placebo, it is recommended that the 3 weeks-on, 1 week-off dosing schedule is changed to a weekly dosing schedule – i.e AZD5363/placebo may be taken on every week during a cycle, with no requirement for an off-treatment week. This change remains at the discretion of the investigator. Please note that irrespective of any change to the overall *inter*-weekly treatment schedule, the *intra*-weekly schedule (eg 4 days-on, 3 days-off or 2 days-on, 5 days-off) should be retained.**

**Reason for Amendment:**

Please see rationale provided for changes to Section 5.5.3 above.

**Section of protocol affected:**

Section 5.10.2 Safety Review Committee and Dose Escalation Process

**Additional text** (*new final paragraph*):

**The SRC will continue to evaluate Part A patients after the dose decision for the last cohort has been made, up to a point at which all patients have completed three treatment cycles or have withdrawn from the study prior to the end of Cycle 3. No further routine evaluations will then be performed by the Part A SRC; although members may be requested to attend ad-hoc meetings for discussion of specific safety issues that may arise.**

**Reason for Amendment:**

Following agreement with the Part A Safety Review Committee, this addition provides clarity regarding the processes and timelines for their evaluation of patient safety up to and following completion of Part A recruitment.

**Section of protocol affected:**

Section 5.11.2 Safety Review Committee (Part B)

**Previous text:**

During the Part B Randomised Phase of the study, an independent SRC will monitor safety and tolerability in the study by means of coded (A vs B) reviews of safety data at approximately 3-monthly intervals. Based on this coded review, the independent SRC may recommend one of: a) continuation of recruitment without change; or b) an amendment to the dose and schedule of AZD5363/placebo eg, from a 4 days on, 3 days off schedule to a 2 days on, 5 days off schedule or to continue at the same schedule at a reduced dose of

AZD5363/placebo; or c) termination of recruitment on the grounds that the combination is considered to be insufficiently well tolerated.

The independent SRC will consist of:

- AstraZeneca Physician, independent of the AZD5363 programme, who will chair the committee - or delegate
- AstraZeneca Global Safety Physician, independent of the AZD5363 programme.
- Two external Investigators independent of the study

The independent SRC Remit document for this study will define the exact membership and who should be present for decisions to be made.

The first review of coded safety data will occur when data are available from approximately 15 patients who have received at least 28 days of treatment.

In the event that AstraZeneca adopts the recommendation to explore an alternative dose or schedule, any patients already recruited to the study at this point will continue to receive AZD5363/placebo as per their current dose and schedule provided that they are tolerating the treatment and the investigator believes they are gaining benefit. Alternatively, the investigator may elect to change the dose/schedule of patients recruited prior to the dose change to the new dose/schedule. After a change to the schedule of AZD5363/placebo, approximately 100 new patients will be recruited to receive AZD5363/placebo as per the new schedule. There will be no more than 2 changes made to dose or schedule during the randomised phase of the study.

**Revised text:**

During the Part B Randomised Phase of the study, an independent SRC (**ISRC**) will monitor safety and tolerability in the study by means of coded (A vs B) reviews of safety data at approximately 3 to 6-monthly intervals. Based on this coded review, the ~~independent~~ ISRC may recommend one of: a) continuation of recruitment without change; or b) an amendment to the dose and schedule of AZD5363/placebo eg, from a 4 days on, 3 days off schedule to a 2 days on, 5 days off schedule or to continue at the same schedule at a reduced dose of AZD5363/placebo; or c) termination of recruitment on the grounds that the combination is considered to be insufficiently well tolerated.

The ~~independent~~ ISRC will consist of:

- AstraZeneca Physician, independent of the AZD5363 programme, who will chair the committee ~~—or delegate~~
- AstraZeneca Global Safety Physician, independent of the AZD5363 programme.
- Two external Investigators independent of the study

The ~~independent~~ ISRC Remit document for this study will define the exact membership and who should be present for decisions to be made.

The first review of coded safety data will occur when data are available from approximately 15 patients who have received at least 28 days of treatment.

In the event that AstraZeneca adopts the recommendation to explore an alternative dose or schedule, any patients already recruited to the study at this point will continue to receive AZD5363/placebo as per their current dose and schedule provided that they are tolerating the treatment and the investigator believes they are gaining benefit. Alternatively, the investigator may elect to change the dose/schedule of patients recruited prior to the dose change to the new dose/schedule. After a change to the schedule of AZD5363/placebo, approximately 100 new patients will be recruited to receive AZD5363/placebo as per the new schedule. There will be no more than 2 changes made to dose or schedule during the randomised phase of the study

**Reason for Amendment:**

Redefinition of frequency of ISRC meetings from approximately 3 monthly to 3-6 monthly. This change was made to allow flexibility of timing of ISRC reviews in response to varying patient recruitment rates at differing stages during conduct of Part B.

Removal of option for independent AZ Physician chair to appoint a delegate to attend ISRC meetings. This change was made to correspond with guidance incorporated in to the standard AZ SRC remit parameters.

**Section of protocol affected:**

Section 6.2.1 Enrolment procedures

**Previous text:**

Written informed consent must be obtained prior to conduct of any study specific assessments. Procedures that are part of standard care may occur before informed consent is obtained.

A list of procedures and assessments described in the Study Plans (Figure 6: Intermittent dosing 2-on 5-off; Figure 7: Intermittent dosing 4-on 3-off) for the screening visit must be completed within 4 weeks (-28 days) of enrolment. At screening, consenting patients will be assessed to ensure that they meet inclusion and exclusion criteria (Sections 4.1 and 4.2).

Demographic data and other characteristics will be recorded at screening and will include: date of birth, gender, race, menstrual status and smoking history.

Part B. Randomised Expansion: Each patient's *PIK3CA* mutation status must be determined at screening from a blood and archival tumour sample to enable the patient to be stratified as *PIK3CA* mutation positive or not detected prior to randomisation (see section 5.2.1):

- Patients will be stratified to the *PIK3CA* mutation positive arm where either one of the sample-type analyses is positive. Patients will be stratified to the not-detected arm where both sample type analyses are negative.
- It is requested that all efforts are made to ensure that archival tumour tissue is provided for this stratification analysis. Where tissue cannot be made available in a timely manner, *PIK3CA* mutation stratification may be conducted on the blood sample analysis alone. In this event, tumour tissue must be provided for retrospective *PIK3CA* mutation analysis prior to completion of treatment Cycle 1.
- Where a patient has been assigned to the not-detected arm from blood sample analysis alone but the retrospective tumour tissue analysis is *PIK3CA* mutation positive - the patient will remain stratified to the not-detected arm. The discrepancy will be noted and an additional patient allocation may be made for this arm.
- In the event that one stratification arm (*PIK3CA* mutation positive or not-detected) completes recruitment before the other, new candidate patients will be requested to provide separate, initial, informed consent to obtain a blood and/or tumour tissue sample to screen for *PIK3CA* mutation status. Patients with status appropriate for entry to the open stratification arm will be invited to provide informed consent for entry to the study.

**Revised text:**

Written informed consent must be obtained prior to conduct of any study specific assessments. Procedures that are part of standard care may occur before informed consent is obtained.

A list of procedures and assessments described in the Study Plans (**Part A** - Figure 6: Intermittent dosing 2-on 5-off; Figure 7: Intermittent dosing 4-on 3-off, **Part B – Figure 8**) for the screening visit must be completed within 4 weeks (-28 days) of enrolment. At screening, consenting patients will be assessed to ensure that they meet inclusion and exclusion criteria (Sections 4.1 and 4.2).

Demographic data and other characteristics will be recorded at screening and will include: date of birth, gender, race, menstrual status and smoking history.

Part B. Randomised Expansion: Each patient's *PIK3CA* mutation status ~~must~~ **should** be determined at screening from a blood and archival tumour sample to enable the patient to be stratified as *PIK3CA* mutation positive or not detected prior to randomisation (see sections 5.2.1 **and** 5.2.2):

- ~~Patients will be stratified to the *PIK3CA* mutation positive arm where either one of the sample type analyses is positive. Patients will be stratified to the not detected arm where both sample type analyses are negative.~~



- ~~● It is requested that all efforts are made to ensure that archival tumour tissue is provided for this stratification analysis. Where tissue cannot be made available in a timely manner, *PIK3CA* mutation stratification may be conducted on the blood sample analysis alone. In this event, tumour tissue must be provided for retrospective *PIK3CA* mutation analysis prior to completion of treatment Cycle 1.~~
- ~~● Where a patient has been assigned to the not detected arm from blood sample analysis alone but the retrospective tumour tissue analysis is *PIK3CA* mutation positive the patient will remain stratified to the not detected arm. The discrepancy will be noted and an additional patient allocation may be made for this arm.~~

~~In the event that one stratification arm (*PIK3CA* mutation positive or not detected) completes recruitment before the other, new candidate patients will be requested to provide separate, initial, informed consent to obtain a blood and/or tumour tissue sample to screen for *PIK3CA* mutation status. Patients with status appropriate for entry to the open stratification arm will be invited to provide informed consent for entry to the study.~~

**Reason for Amendment:**

Addition of new Figure 8, a Part B-specific assessment schedule, reflects changes to the schedules of assessments previously described in Section 3.1.4 in relation to amendment rationale number 4.

Revisions to the subset ‘Part B. Randomised Expansion’ reflect changes and additions to Sections 5.2.1 and 5.2.2 in relation to amendment rationale number 2. Deletion of text reflects that additional information, now provided in Sections 5.2.1 and 5.2.2, rendered this text, in Section 6.2.1, unnecessary.

**Section of protocol affected:**

Section 6.2.2 *PIK3CA* Mutation Status

**Previous text:**

Patient response to treatment will be assessed against the tumour *PIK3CA* mutation status to determine whether the mutation confers any increased tumour sensitivity to AZD5363.

Blood and most recent archival tumour samples will be collected at screening (see Figure 6 and Figure 7) with reference to the criteria and restrictions detailed in section 5.2.1. The *PIK3CA* mutation assay(s) will genotype for a set of mutations that will cover the majority of, but not all, mutations in the *PIK3CA* gene that have been thus far identified in breast cancer patients. Therefore, there may be patients carrying either a rare mutation, not included in the assay(s) used, or who have a level of mutation in cfDNA or tumour tissue DNA beyond the range of sensitivity of the selected assay(s). In this case, their mutation will not be identified under the protocolled testing. In acknowledgment of this, patients who are shown not to be

‘mutation positive’ in either cfDNA or tumour tissue DNA will be categorised as ‘mutation not detected’, rather than a more definitive ‘mutation negative’.

During Study Part B, *PIK3CA* mutation status will be utilised to stratify patients to ‘positive’ and ‘not detected’ arms (see section 5.2.1).

**Revised text:**

Patient response to treatment will be assessed against the tumour *PIK3CA* mutation status to determine whether the mutation confers any increased tumour sensitivity to AZD5363.

**A 10ml blood sample** and most recent archival tumour samples will be collected at screening (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) with reference to the criteria and restrictions detailed in section 5.2.1. The *PIK3CA* mutation assay(s) will genotype for a set of mutations that will cover the majority of, but not all, mutations in the *PIK3CA* gene that have been thus far identified in breast cancer patients. Therefore, there may be patients carrying either a rare mutation, not included in the assay(s) used, or who have a level of mutation in cfDNA or tumour tissue DNA beyond the range of sensitivity of the selected assay(s). In this case, their mutation will not be identified under the protocolled testing. In acknowledgment of this, patients who are shown not to be ‘mutation positive’ in either cfDNA or tumour tissue DNA will be categorised as ‘mutation not detected’, rather than a more definitive ‘mutation negative’.

During Study Part B, *PIK3CA* mutation status will be utilised to stratify patients to ‘positive’ and ‘not detected’ arms (see sections 5.2.1 **and 5.2.2 and Figure 9**).

**An optional 20mL blood sample will also be taken, subject to separate patient consent, to be utilised for evaluation of innovative *PIK3CA* mutation analysis platforms. The purpose of this evaluation is to evaluate new analytical options for enhanced specificity, accuracy and/or increased speed of sample processing.**

**Reason for Amendment:**

Clarification of blood sample volume and inclusion of an optional 20ml sample for evaluation of *PIK3CA* analytical platforms. This change was made to allow for collection of a voluntary blood sample to be used to assess new analytical technologies that may enable more rapid and/or more accurate measurement of *PIK3CA* tumour mutations. Further clarity is given regarding volumes to differentiate between this optional sample and the mandatory blood sample for screening *PIK3CA* analysis.

**Section of protocol affected:**

Section 6.2.3 Follow-up procedures

**Previous text:**

Patients will be followed up as detailed below unless prior withdrawal from the study:

Part A. Safety Run-in: Patients will be followed to discontinuation of study drug / completion of the 28-day safety follow-up.

Part B. Randomised Expansion: Patients will be followed to death.

**Revised text:**

Patients will be followed up as detailed below unless prior withdrawal from the study:

Part A. Safety Run-in: Patients will be followed to discontinuation of study drug / completion of the 28-day safety follow-up.

Part B. Randomised Expansion: Patients will be followed to death, **or to cessation of the study.**

**Reason for Amendment:**

Specification of limitation of follow-up period for study Part B.

**Section of protocol affected:**

6.3.1 Tumour assessments (*1st paragraph*)

**Previous text:**

RECIST 1.1 criteria will be used to assess patient response to treatment by determining change in tumour size at 12 weeks, percentage of patients without progressive disease, at 12 weeks, overall response rate (ORR), BoR, DoR and PFS. The RECIST 1.1 guidelines for measurable, non-measurable, target, and non-target lesions (NTL) and the objective tumour response criteria (CR, PR, SD or progressive disease [PD]) are presented in Appendix F.

**Revised text:**

RECIST 1.1 criteria will be used to assess patient response to treatment by determining change in tumour size at 12 weeks, percentage of patients without progressive disease, at 12 weeks, overall response rate (ORR), BoR, **DRR**, DoR and PFS. The RECIST 1.1 guidelines for measurable, non-measurable, target, and non-target lesions (NTL) and the objective tumour response criteria (CR, PR, SD or progressive disease [PD]) are presented in Appendix F.

**Reason for Amendment:**

Please refer to amendment rationale number 3.

**Section of protocol affected:**

6.4.5 Laboratory safety assessment

**Previous text:**

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Figure 6 and Figure 7) at the following timepoints:

- Screening
- Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose; Weeks 2, 3 and 4: Day 2 pre-dose.  
2-on 5-off schedule only: Week 1 Day 3 pre-dose  
4-on 3-off schedule only: Week 1 Day 5 pre-dose
- Cycle 2: Week 1: Day 2 pre-dose; Weeks 2, 3 and 4: Day 1 pre-dose.
- Cycles 3+: Week 1: Day 2 pre-dose up to discontinuation of both study therapies.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.
- Urine pregnancy test to be completed at: Screening, Cycle 1 Week 1 Day 1 and on discontinuation of study therapies.

Serum/Plasma glucose to be additionally measured, for evaluation of potential abnormalities of glucose metabolism, from samples taken between 2 to 4 hours, and between 4 to 6 hours, following receipt of the morning dose of AZD5363 at the following timepoints:

- Cycle 1: Week 1: Day 2; Weeks 2, 3 and 4: Day 2.  
2-on 5-off schedule only: Week 1 Day 3  
4-on 3-off schedule only: Week 1 Day 5
- Day 2 of every Cycle thereafter up to discontinuation of AZD5363.

**Revised text:**

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plans (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) at the following timepoints:

- Screening
- Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose; Weeks 2 and 3 ~~and 4~~: Day 2 pre-dose.  
**Part A only - 2-on 5-off schedule only**: Week 1 Day 3 pre-dose; **Week 4 Day 2 pre-dose.**  
**Part A only - 4-on 3-off schedule only**: Week 1 Day 5 pre-dose; **Week 4 Day 2 pre-dose.**
- Cycle 2: Week 1: Day 2 pre-dose; Weeks 2 and 3 ~~and 4~~: Day 1 pre-dose.  
**Part A only - both schedules: Week 4 Day 1 pre-dose.**
- Cycles 3+: Week 1: Day 2 pre-dose up to discontinuation of both study therapies.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.
- Urine pregnancy test to be completed at: Screening, Cycle 1 Week 1 Day 1 and on discontinuation of study therapies.

**Part A only (additional glucose assessments will not be conducted in Part B) - Serum/Plasma glucose** to be additionally measured, for evaluation of potential abnormalities of glucose metabolism, from samples taken between 2 to 4 hours, and between 4 to 6 hours, following receipt of the morning dose of AZD5363 at the following timepoints:

- Cycle 1: Week 1: Day 2; Weeks 2, 3 and 4: Day 2.  
**2-on 5-off schedule only**: Week 1 Day 3  
**4-on 3-off schedule only**: Week 1 Day 5
- Day 2 of every Cycle thereafter up to discontinuation of AZD5363.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.4.6 Physical examination

**Previous text:**

A complete physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

Physical examinations will be conducted at the times indicated in the Study Plan (see Figure 6 and Figure 7) at the following timepoints:

- Screening.
- Cycle 1: Week 1 and 2: Day 1 pre-dose.
  - 2-on 5-off schedule only: Week 1 Day 3 pre-dose
  - 4-on 3-off schedule only: Week 1 Day 5 pre-dose
- Cycles 2+: Week 1: Day 1 pre-dose.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.

**Revised text:**

A complete physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

Physical examinations will be conducted at the times indicated in the Study Plans (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) at the following timepoints:

- Screening.
- Cycle 1: Week 1 and 2: Day 1 pre-dose.
  - Part A only - 2-on 5-off schedule only**: Week 1 Day 3 pre-dose
  - Part A only - 4-on 3-off schedule only**: Week 1 Day 5 pre-dose
- Cycles 2+: Week 1: Day 1 pre-dose.
- Discontinuation of AZD5363/placebo: at any time of the day.

- Discontinuation of paclitaxel: at any time of the day.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.4.8 WHO Performance status

**Previous text:**

Performance status will be assessed at the times indicated in the Study Plan (see Figure 6 and Figure 7) at the following timepoints (assessment may be conducted at any time of the day unless otherwise indicated):

Part A and Part B:

- Screening
- Cycle 1: Week 1: Day 1 pre-dose,

Part B only:

- Cycle 1: Week 1 Days 2 and 3; Weeks 2 and 3 Day 1; Week 4 Day 2.  
4-on 3-off schedule only: Week 1 Day 5
- Cycle 2: Weeks 1, 2, 3 and 4: Day 1.
- Cycles 3+: Week 1: Day 1.
- Discontinuation of AZD5363/placebo.
- Discontinuation of paclitaxel.

**Revised text:**

Performance status will be assessed at the times indicated in the Study Plans (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) at the following timepoints (assessment may be conducted at any time of the day unless otherwise indicated):

Part A and Part B:

- Screening
- Cycle 1: Week 1: Day 1 pre-dose,

Part B only:

- Cycle 1: Week 1 Days 2 ~~and 3~~; Weeks 2 and 3 Day 1; ~~Week 4 Day 2.~~  
4-on 3-off schedule only: Week 1 Day 5
- Cycle 2: Weeks 1, 2, ~~and 3~~ ~~and 4~~: Day 1.
- Cycles 3+: Week 1: Day 1.
- Discontinuation of AZD5363/placebo.
- Discontinuation of paclitaxel.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.4.9 Resting ECG

**Previous text:**

ECG measurements will be conducted at the study site or other local institution as applicable.

At each timepoint, at approximately the same time of day, a standard 12-lead ECG should be performed after the patient has been resting in a semi-supine position for at least 5 minutes. A paper speed of 25mm/second, covering at least 6 sequential beats, is recommended. Three ECGs per timepoint should be conducted within a 5-minute period.

ECG measurements should be conducted as indicated in the Study Plan (see Figure 6 and Figure 7) at the following timepoints:

- Screening.
- Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose, 1, 2, 6 and 24 hours post-dose; Week 2: Day 1 pre-dose.

4-on 3-off schedule only: Week1 Day 5 post-dose.



- Cycle 2: Week 1: Day 1 post-dose.
- Cycles 3+: Week 1: Day 1 at any time of the day.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.

**Revised text:**

ECG measurements will be conducted at the study site or other local institution as applicable.

At each timepoint, at approximately the same time of day, a standard 12-lead ECG should be performed after the patient has been resting in a semi-supine position for at least 5 minutes. A paper speed of 25mm/second, covering at least 6 sequential beats, is recommended. Three ECGs per timepoint should be conducted within a 5-minute period.

ECG measurements should be conducted as indicated in the Study Study Plans (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) at the following timepoints:

- Screening.
- Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose, 1, 2, and 6 and 24 hours post-dose; Week 2: Day 1 pre-dose.

**Part A only - Cycle 1: Week 1 Day 3 pre-dose; 4-on 3-off schedule only:  
Cycle 1: Week1 Day 5 post-dose.**

- Cycle 2: Week 1: Day 1 post-dose.
- Cycles 3+: Week 1: Day 1 at any time of the day.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.4.10 MUGA scan / Echocardiogram

**Previous text:**

A MUGA scan or echocardiogram to assess LVEF will be conducted at the times indicated in the Study Plans (see Figure 6, and Figure 7) at the following timepoints:

- Screening.  
Part A - 4-on 3-off schedule only: Cycle 2: Week 1: Day 1 ( $\pm 1$  week).
- Every 12 weeks from baseline thereafter: at any time of the day.
- Where clinically indicated.
- Discontinuation of AZD5363/placebo: at any time of the day.

**Revised text:**

A MUGA scan or echocardiogram to assess LVEF will be conducted at the times indicated in the Study Plans (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) at the following timepoints:

- Screening.  
Part A only - 4-on 3-off schedule only: Cycle 2: Week 1: Day 1 ( $\pm 1$  week).
- Every 12 weeks from baseline (Cycle 1, Week 1, day 1) thereafter: at any time of the day.
- Where clinically indicated.
- Discontinuation of AZD5363/placebo: at any time of the day.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.4.11      Vital signs: Pulse and blood pressure

**Previous text:**

Supine blood pressure and pulse rate will be measured after 10 minutes rest.

Assessments will be conducted at the times indicated in the Study Plan (see Figure 6 and Figure 7) at the following timepoints:

- Screening

- Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose; 1, 2, and 6 hours post-dose; Weeks 2 and 3 Day 1 pre-dose; Week 4 Day 2 pre-dose.

2-on 5-off schedule only: Week 1 Day 3 post-dose

4-on 3-off schedule only: Week 1 Day 5 post-dose

- Cycle 2: Week 1: Day 1 pre-dose; Weeks 2, 3 and 4: Day 1 post-dose.
- Cycles 3+: Week 1: Day 1 at any time of the day.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.

**Revised text:**

Supine blood pressure and pulse rate will be measured after 10 minutes rest.

Assessments will be conducted at the times indicated in the Study Plans (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) at the following timepoints:

- Screening
- Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose; 1, 2, and 6 hours post-dose; Weeks 2 and 3 Day 1 pre-dose; ~~Week 4 Day 2 pre-dose.~~

**Part A only - 2-on 5-off schedule only**: Week 1 Day 3 post-dose, **Week 4 Day 2 pre-dose.**

**Part A only - 4-on 3-off schedule only**: Week 1 Day 5 post-dose, **Week 4 Day 2 pre-dose.**

- Cycle 2: Week 1: Day 1 pre-dose; Weeks 2, ~~and 3 and 4~~: Day 1 post-dose.

**Part A only – both schedules: Week 4 Day 1 post-dose**

- Cycles 3+: Week 1: Day 1 at any time of the day.
- Discontinuation of AZD5363/placebo: at any time of the day.
- Discontinuation of paclitaxel: at any time of the day.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.4.12.1      Lipids

**Previous text:**

Blood samples for determination of triglycerides, HDL, LDL and cholesterol will be taken at the times indicated in the Study Plan (see Figure 6 and Figure 7) at the following timepoints:

- Screening.
- Every 12 weeks from baseline: at any time of the day. Up to cessation of AZD5363/placebo.
- Discontinuation of AZD5363/placebo: at any time of the day.

**Revised text:**

Blood samples for determination of triglycerides, HDL, LDL and cholesterol will be taken at the times indicated in the Study Plans (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) at the following timepoints:

- Screening.
- Every 12 weeks from baseline (**Cycle 1, Week 1, Day 1**): at any time of the day. Up to cessation of AZD5363/placebo.
- Discontinuation of AZD5363/placebo: at any time of the day.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.4.12.3      Glucose, insulin and insulin c-peptide\*

**Previous text:**

Blood samples for determination of glucose insulin and insulin c-peptide will be taken at the times indicated in the Study Plan (see Figure 6 and Figure 7) at the following timepoints:

- Cycle 1: Week 1: Day 1 pre-dose; Day 2 pre-dose; 2, 4, 6 and 8 hours post-dose.  
Weeks 2, 3 and 4: Day 2 pre-dose.

2-on 5-off schedule only: Week 1 Day 3 pre-dose, 2, 4, 6 and 8 hours post-dose

4-on 3-off schedule only: Week 1 Day 5 pre-dose, 2, 4, 6 and 8 hours post-dose

- Cycles 2+: Week 1: Day 2 pre-dose and between 2 to 4 hours post-dose.
- Discontinuation of AZD5363/placebo: at any time of the day.

\* Note: Insulin c-peptide will be measured during study Part A only. During Part B glucose and insulin only will be determined.

#### **Revised text:**

Blood samples for determination of glucose insulin and insulin c-peptide will be taken at the times indicated in the Study Plans (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) at the following timepoints:

#### **Part A:**

- Cycle 1: Week 1: Day 1 pre-dose; ~~Day 2 pre-dose; 2, 4, 6 and 8 hours post-dose.~~  
Weeks 2, 3 and 4: Day 2 pre-dose.  
2-on 5-off schedule only: Week 1 Day 3 pre-dose, 2, 4, 6 and 8 hours post-dose  
4-on 3-off schedule only: Week 1 Days **2 and 5**; pre-dose, 2, 4, 6 and 8 hours post-dose.
- Cycles 2+: Week 1: Day 2 pre-dose and between 2 to 4 hours post-dose.
- Discontinuation of AZD5363/placebo: at any time of the day.

#### **Part B:**

- Cycle 1: Week 1: Day 1 pre-dose, Day 2 pre-dose; 2, 4 and 8 hours post-dose; Weeks 2 and 3: Day 2 pre-dose, 2 and 4 hours post-dose.
- Cycle 2: Week 1: Day 2 pre-dose and 2 and 4 hours post-dose.
- Cycles 3+: Week 1: Day 2 pre-dose and between 2 to 4 hours post-dose.
- Discontinuation of AZD5363/placebo: at any time of the day.

\* Note: Insulin c-peptide will be measured during study Part A only. During Part B glucose and insulin only will be determined.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.4.12.4 Patient meal information.

**Previous text:**

The times and types of meals (tickbox) received by patients will be recorded on the days that the patient attends the study site and receives AZD5363/placebo at the following timepoints:

- Cycle 1: Week 1: Day 2. Weeks 2, 3 and 4: Day 2.  
2-on 5-off schedule only: Week 1 Day 3  
4-on 3-off schedule only: Week 1 Day 5
- Cycles 2+: Week 1 Day 2.

**Revised text:**

The times and types of meals (tickbox) received by patients will be recorded on the days that the patient attends the study site and receives AZD5363/placebo at the following timepoints:

- Cycle 1: Week 1: Day 2. Weeks 2, ~~and 3 and~~ 4: Day 2.  
**Part A only - 2-on 5-off schedule only:** Week 1 Day 3, **Week 4 Day 2**  
**Part A only - 4-on 3-off schedule only:** Week 1 Day 5, **Week 4 Day 2**
- Cycles 2+: Week 1 Day 2.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.5.1 Quality of Life: EORTC QLQ C-30 and BR-23 questionnaires (Part B: Randomised expansion only). ( 4<sup>th</sup> Paragraph)

**Previous text:**

During the Randomised Expansion phase only; patients will be requested to complete both questionnaires at the times indicated in the Study Plan (see Figure 6 and Figure 7) at the following timepoints:

- Screening.
- Cycle 1: Week 1: Day 1: pre-dose.
- Every 12 weeks from baseline: at any time of the day and after cessation of study therapies up to disease progression or withdrawal of consent.
- Discontinuation of AZD5363/placebo: at any time of the day.

**Revised text:**

During the Randomised Expansion phase only; patients will be requested to complete both questionnaires at the times indicated in the Study Plan (see ~~Figure 6 and Figure 7~~ **Figure 6 and Figure 78**) at the following timepoints:

- Screening.
- Cycle 1: Week 1: Day 1: pre-dose.
- Every 12 weeks from baseline (**Cycle 1 Week 1 Day 1**): at any time of the day and after cessation of study therapies up to disease progression or withdrawal of consent.
- Discontinuation of AZD5363/placebo: at any time of the day.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.6.2 Pharmacokinetic sampling schedule

**Previous text:**

Code:

P = Samples for paclitaxel PK.

A = Samples for AZD5363 PK

Note: Timing of paclitaxel PK sampling on Day 1 is from start of the infusion; e.g if paclitaxel infusion commences at 9am, the 2, 4 and 8 hour samples should be taken at 11am, 1pm and 5pm respectively.

Table 2 PK sampling schedule: Safety Run-in Phase.

Time relative to first dose in cycle	Cycle 1						
	Week 1				Week 2	Week 3	Week 4
	Day 1	Day 2	Day 3	Day 5*	Day 2	Day 2	Day 2
Predose	P	P A	A	A*	P A	P A	A
2 hours	P	A					
4 hours	P	A					
8 hours	P	A					

\* 4-on 3-off dosing schedule only

Table 3 PK sampling schedule: Randomised Expansion Phase.

Time relative to first dose in cycle	Cycle 1						
	Week 1				Week 2	Week 3	Week 4
	Day 1	Day 2	Day 3	Day 5*	Day 2	Day 2	Day 2
Predose	P	P A	A	A*	A	A	A
2 hours	P	A					
4 hours	P	A					
8 hours	P	A					

\* 4-on 3-off dosing schedule only

**Revised text:**

Code:



P = Samples for paclitaxel PK.

A = Samples for AZD5363 PK

Note: Timing of paclitaxel PK sampling on Day 1 is from start of the infusion; e.g if paclitaxel infusion commences at 9am, the 2, 4 and 8 hour samples should be taken at 11am, 1pm and 5pm respectively.

Table 2 PK sampling schedule: **Part A** Safety Run-in Phase.

Time relative to first dose in cycle	Cycle 1						
	Week 1				Week 2	Week 3	Week 4
	Day 1	Day 2	Day 3	Day 5*	Day 2	Day 2	Day 2
Predose	P	P A	A	A*	P A	P A	A
2 hours	P	A					
4 hours	P	A					
8 hours	P	A					

\* 4-on 3-off dosing schedule only

Table 3 PK sampling schedule: **Part B** Randomised Expansion Phase.

Time relative to first dose in cycle	Cycle 1						
	Week 1				Week 2	Week 3	<del>Week 4</del>
	Day 1	Day 2	<del>Day 3</del>	<del>Day 5*</del>	Day 2	Day 2	<del>Day 2</del>
Predose	P	P A	<del>A</del>	<del>A*</del>	A	A	<del>A</del>
2 hours	P	A					
4 hours	P	A					
8 hours	P	A					

~~\* 4 on 3 off dosing schedule only~~

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.7.1 Collection of pharmacodynamic markers (First paragraph)

**Previous text:**

Venous blood samples (8.1 mL) to provide platelet-rich plasma will be taken for assessment of pharmacodynamic (PD) markers at the times presented in the Study Plan (see Figure 6 and Figure 7) at the timepoints shown in Table 4.

**Revised text:**

Venous blood samples (8.1 mL) to provide platelet-rich plasma will be taken for assessment of pharmacodynamic (PD) markers at the times presented in the Study Plans (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) at the timepoints shown in Table 4 and **Table 5**.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.8.1.4 Collection of eyebrow hairs (optional) (*1st paragraph*)

**Previous text:**

Four eyebrow hairs will be taken at the times presented in the Study Plan (see Figure 6 and Figure 7) on each of the timepoints presented in Table 4 below.

**Revised text:**

Four eyebrow hairs will be taken at the times presented in the Study Plans (see Figure 6, ~~and~~ Figure 7 **and Figure 8**) at the timepoints shown in Table 4 and **Table 5**.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.8.1.5 Collection of exploratory blood-borne biomarkers (optional) (*1st paragraph*)

**Previous text:**

5mL venous blood will be taken at the times presented in the Study Plan (see Figure 6 and Figure 7) on each of the timepoints presented in Table 4 below.

**Revised text:**

5mL venous blood will be taken at the times presented in the Study Plans (see Figure 6, and Figure 7 and Figure 8) at the timepoints shown in Table 4 and Table 5.

**Reason for Amendment:**

Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 6.8.1.6 Pharmacodynamic and exploratory biomarker sampling schedule

**Previous text:**

The following samples will be taken on each of the timepoints presented below.

Code:

PD = venous blood for determination of pharmacodynamic parameters.

B = venous blood for analysis of exploratory biomarkers.

BH = 4 eyebrow hairs for analysis of exploratory biomarkers.

Table 4 PD and exploratory biomarker sampling schedule:

Time relative to first dose in cycle	Screen	Cycle 1							Cycle 2+	AZD5363 Disc
		Week 1				Week 2	Week 3	Week 4	Week 1	
		Day 1	Day 2	Day 3	Day 5*	Day 2	Day 2	Day 2	Day1	
Any time	B									B PD
Pre-dose		PD	B PD BH	PD BH <sup>†</sup>	PD* BH*	B PD	B PD	B PD	B PD	
2 hours			PD							
4 hours			PD BH							
8 hours			PD							

\* 4-on 3-off dosing schedule only

† 2-on 5-off dosing schedule only

**Revised text:**

The following samples will be taken on each of the timepoints presented below.

Code:

PD = venous blood for determination of pharmacodynamic parameters.

B = venous blood for analysis of exploratory biomarkers.

BH = 4 eyebrow hairs for analysis of exploratory biomarkers.

**Table 4 Part A Safety Run-in Phase: PD and exploratory biomarker sampling schedule:**

Time relative to first dose in cycle	Screen	Cycle 1							Cycle 2+	AZD5363 Disc
		Week 1				Week 2	Week 3	Week 4	Week 1	
		Day 1	Day 2	Day 3	Day 5*	Day 2	Day 2	Day 2	Day1	
Any time	B									B PD
Predose		PD	B PD BH	PD BH <sup>†</sup>	PD* BH*	B PD	B PD	B PD	B PD	
2 hours			PD							
4 hours			PD BH							
8 hours			PD							

\* 4-on 3-off dosing schedule only

† 2-on 5-off dosing schedule only

**Table 5 Part B Randomised Expansion Phase: PD and exploratory biomarker sampling schedule.**

Time relative to first dose in cycle	Screen	Cycle 1			Cycle 2+	AZD5363 Disc
		Week 1		Week 3	Week 1	
		Day 1	Day 2	Day 2	Day1	
Any time	B				B PD	B PD
Predose		PD	B PD BH	PD		
2 hours			PD			
4 hours			PD BH	PD		
8 hours			PD			

**Reason for Amendment:**

Separation of assessments to be conducted under study Parts A and B for clarity. Please refer to amendment rationale number 4.

**Section of protocol affected:**

Section 7.1 Volume of blood

**Previous text:**

The volume of blood that will be drawn from each patient will vary, dependent upon the dosing schedule and phase of the study:

- The volume of blood to be drawn from each patient during screening and Cycle 1 should not exceed 35 mL and 380 mL respectively
- The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 cycles of combination treatment and discontinuation visits should not exceed 750 mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

In both phases of the study, extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments or additional PK assessment.

The maximum volume of blood to be drawn from each patient in this study is as follows:

Table 5 Estimated Maximum volume of blood to be drawn per patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Haematology	5	17	85
	Clinical chemistry	10	17	170
	Additional Glucose	2	20	40
	Lipids and glycosylated haemoglobin	5	5	25
	Glucose, insulin and insulin c-peptide	5	25	125
CTCs		10	4	40

Table 5 Estimated Maximum volume of blood to be drawn per patient

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
<i>PIK3CA</i> mutation	10	1	10
Pharmacokinetic	4	16	64
Pharmacodynamic	8.1 (3 x 2.7)	16	129.6
Pharmacogenetics (optional)	5	1	5
Exploratory Biomarker (optional)	5	11	55
Total			748.6

Note: Maximum is taken to reflect Part A, 4-on 3-off dosing schedule: 6 Cycles plus discontinuation visits.

**Revised text:**

The volume of blood that will be drawn from each patient will vary, dependent upon the dosing schedule and phase of the study:

- The volume of blood to be drawn from each patient during screening and Cycle 1 should not exceed ~~35~~ **55** mL and 380 mL respectively **in Part A and 55mL and 240mL respectively in Part B.**
- The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 cycles of combination treatment and discontinuation visits should not exceed 750 mL **in Part A and 615ml in Part B.**

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

In both phases of the study, extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments or additional PK assessment.

The maximum volume of blood to be drawn from each patient in this study is as follows:

Table 56 **Part A Safety Run-in Phase:** Estimated Maximum volume of blood to be drawn per patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Haematology	5	17	85
	Clinical chemistry	10	17	170
	Additional Glucose	2	20	40

**Table 56 Part A Safety Run-in Phase: Estimated Maximum volume of blood to be drawn per patient**

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Lipids and glycosylated haemoglobin	5	5	25
Glucose, insulin and insulin c-peptide	5	25	125
CTCs	10	4	40
<i>PIK3CA</i> mutation	10	1	10
<b>PIK3CA analytical development</b>	<b>20</b>	<b>1</b>	<b>20</b>
Pharmacokinetic	4	<del>16</del> <b>13</b>	<del>64</del> <b>52</b>
Pharmacodynamic	8.1 (3 x 2.7)	16	129.6
Pharmacogenetics (optional)	5	1	5
Exploratory Biomarker (optional)	5	11	55
<b>Total</b>			<del>748</del> <b>6756.6</b>

Note: Maximum is taken to reflect Part A, 4-on 3-off dosing schedule: 6 Cycles plus discontinuation visits.

**Table 7 Part B Randomised Phase: Estimated Maximum volume of blood to be drawn per patient**

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
<b>Safety</b>			
<b>Haematology</b>	<b>5</b>	<b>14</b>	<b>70</b>
<b>Clinical chemistry</b>	<b>10</b>	<b>14</b>	<b>140</b>
<b>Lipids and glycosylated haemoglobin</b>	<b>5</b>	<b>4</b>	<b>20</b>
<b>Glucose and insulin</b>	<b>5</b>	<b>24</b>	<b>120</b>
CTCs	10	4	40
<i>PIK3CA</i> mutation	10	1	10
<b>PIK3CA analytical development</b>	<b>20</b>	<b>1</b>	<b>20</b>
Pharmacokinetic	4	<b>10</b>	<b>40</b>
Pharmacodynamic	8.1 (3 x 2.7)	<b>13</b>	<b>105.3</b>
Pharmacogenetics (optional)	5	1	5
Exploratory Biomarker (optional)	5	8	40
<b>Total</b>			<b>610.3</b>

**Note: Maximum is taken to reflect 6 Cycles plus discontinuation visits.**

**Reason for Amendment:**

Revised first paragraph reflects addition of an optional 20ml sample for evaluation of *PIK3CA* analytical platforms (see below) and differentiation of blood sample volumes to be collected during study parts A and B. Please refer to amendment rationale number 4.

Revised Table 6 reflects addition of an optional 20ml sample for evaluation of *PIK3CA* analytical platforms (see below) and correction of a calculation error in revised protocol edition 2.

Additional Table 7 reflects amended and reduced volumes of blood to be collected following revisions to the patient assessment schedule. Please refer to amendment rationale number 4.

Addition of an optional 20ml sample for evaluation of *PIK3CA* analytical platforms reflects collection of a voluntary blood sample at screening to be used assess new analytical technologies that may enable more rapid and/or more accurate measurement of *PIK3CA* tumour mutations.

**Section of protocol affected:**

Section 11.1.1 Progression-free Survival (PFS) (*1<sup>st</sup> and 2<sup>nd</sup> paragraph*)

**Previous text:**

The primary outcome variable for Part B of the study is PFS. 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.

**Revised text:**

The primary outcome variable for Part B of the study is PFS. PFS is defined as the time from ~~start of treatment~~ **date of randomisation** until objective disease progression as defined by RECIST 1.1 or death (by any cause in the absence of progression).

Patients who have not progressed or died at the time of the statistical analysis will be censored at the time of their last evaluable RECIST assessment. [REDACTED]

[REDACTED] 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.

**Reason for Amendment:**

Paragraph 1: Revision from ‘start of treatment’ to ‘date of randomisation’ – for consistency with other analytical timepoints within this protocol.

Paragraph 2: Additional text – to clarify criteria for PFS analytical evaluability for patients that progress or die having not attended for two or more prior RECIST assessments.

**Section of protocol affected:**

Section 11.1.5 Duration of response (DoR)

**Previous text:**

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).

**Revised text:**

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).

**If a subject does not progress following a response, then their duration of response will use the PFS censoring time.**

**Reason for Amendment:**

Clarification of criteria for determining DoR in the event that a patient that has responded does not subsequently progress prior to study closure.

**Section of protocol affected:**

New Section 11.1.6 Durable Response Rate

**Additional text:**

**Durable Response Rate (DRR) is defined as the percentage of patients who have a complete or partial response lasting continuously for at least 24 weeks.**

**Reason for Amendment:**

Please refer to amendment rationale number 3.

*Please note – subsequent section numbering revised upwards, following addition of this new section.*

**Section of protocol affected:**

Section 12.1.1 Efficacy analysis set (*1<sup>st</sup> paragraph*)

**Previous text:**

All efficacy data in Part B of the study (PFS, change in tumour size at 12 weeks, ORR, **DRR** DoR **and** percentage of patients without progression at 12 weeks and OS) will be analysed on an intention-to-treat basis (ITT). This will include all randomised patients, wherever possible, and compare treatment groups on the basis of randomised treatment, regardless of the treatment they actually received.

**Revised text:**

All efficacy data in Part B of the study (PFS, change in tumour size at 12 weeks, ORR, DoR percentage of patients without progression at 12 weeks and OS) will be analysed on an intention-to-treat basis (ITT). This will include all randomised patients, wherever possible, and compare treatment groups on the basis of randomised treatment, regardless of the treatment they actually received.

**Reason for Amendment:**

Please refer to amendment rationale number 3.

**Section of protocol affected:**

New Section 12.2.5 Durable Response Rate

**Additional text:**

**Durable Response rate will be tabulated by randomised treatment (AZD5363 + paclitaxel or placebo + paclitaxel)**

**Durable Response rate will be analysed for the overall population and for the subgroup of *PIK3CA* mutation-positive patients using separate logistic regression models allowing for the effect of treatment and including a term for *PIK3CA* mutation status in the overall analysis.**

**Reason for Amendment:**

Please refer to amendment rationale number 3.

*Please note – subsequent section numbering revised upwards following addition of this new section.*

**Section of protocol affected:**

Section 12.2.6 (Revised to 12.2.7) Safety (*1<sup>st</sup> paragraph*)

**Previous text:**

Safety data will not be analysed formally. All patients who receive at least 1 dose of study treatment will be included in the assessment of the safety profile (safety analysis set). Safety and tolerability data will be presented by treatment received for patients in Part B and by dose and schedule for patients in Part A. For Part B, the main set of safety tables will consist of the overall population in the randomised expansion, but a reduced set of key safety outputs will also be repeated on patients with *PIK3CA* mutation positive tumours (as according to stratification levels determined at randomisation) to assess if the safety profile remains consistent within these patients.

**Revised text:**

Safety data will not be analysed formally. All patients who receive at least 1 dose of study treatment will be included in the assessment of the safety profile (safety analysis set). Safety and tolerability data will be presented by treatment received for patients in Part B and by dose and schedule for patients in Part A. For Part B, the main set of safety tables will consist of the overall population in the randomised expansion, but a reduced set of key safety outputs will also be repeated on patients with *PIK3CA* mutation positive tumours (as according to ~~stratification levels determined at randomisation~~ **confirmed *PIK3CA* tumour mutation status**) to assess if the safety profile remains consistent within these patients.

**Reason for Amendment:**

Correction to state that population of the patient Safety analysis set for patients with *PIK3CA* mutation-positive tumours will be determined by confirmed mutation status – i.e. following full central laboratory analyses. Please refer to amendment rationale number 2.

**Section of protocol affected:**

Section 12.2.7 (Revised to 12.2.8) Pharmacokinetics

**Previous text:**

Part A Safety Run-in AZD5363 and paclitaxel pharmacokinetics

Plasma concentrations of AZD5363 and paclitaxel will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by dose level and schedule. Plasma concentrations at each time point will be summarised according to dose and schedule by the following summary statistics:

- The geometric mean (gmean, calculated as  $\exp[\mu]$ , where  $\mu$  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  $\pm$  standard deviation (calculated as  $\exp[\mu \pm s]$ )
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

In the calculation of plasma concentration summary statistics, plasma concentrations below the lower limit of quantification (LLOQ) will be set to zero at pre-dose. Summary statistics will be presented according to the following rules:

- If, at a given time point, 50% or less of the plasma concentrations are non-quantifiable (NQ), the geometric mean (gmean), CV, gmean  $\pm$  standard deviation (SD), arithmetic mean, SD and median will be calculated by substituting the LLOQ for values which are NQ. The minimum at that time point will be reported as NQ.
- If more than 50%, but not all, of the concentrations are NQ, the gmean, CV, gmean  $\pm$  SD, arithmetic mean and SD will be reported as not calculable (NC). The minimum and median at that time point will be reported as NQ.
- If all the concentrations are NQ, the gmean, arithmetic mean, median, minimum and maximum will be reported as NQ and the CV, gmean  $\pm$  SD and SD as NC.
- If the calculation of the gmean - SD results in a value less than the LLOQ, NQ will be displayed.

#### Part B Randomised expansion

The plasma concentrations determined using the sparse PK sampling scheme, at sampling timepoints, will be listed but not summarised.

#### **Revised text:**

~~Part A Safety Run in AZD5363 and paclitaxel pharmacokinetics~~

~~Plasma concentrations of AZD5363 and paclitaxel will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by dose level and schedule. Plasma concentrations at each time point will be summarised according to dose and schedule by the following summary statistics:~~

- ~~• The geometric mean (gmean, calculated as  $\exp[\mu]$ , where  $\mu$  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  $\pm$  standard deviation (calculated as  $\exp[\mu \pm s]$ )~~
- ~~• Arithmetic mean calculated using untransformed data~~
- ~~• Standard Deviation calculated using untransformed data~~
- ~~• Minimum~~
- ~~• Maximum~~
- ~~• Number of observations~~

~~In the calculation of plasma concentration summary statistics, plasma concentrations below the lower limit of quantification (LLOQ) will be set to zero at pre-dose. Summary statistics will be presented according to the following rules:~~

- ~~• If, at a given time point, 50% or less of the plasma concentrations are non-quantifiable (NQ), the geometric mean (gmean), CV, gmean  $\pm$  standard deviation (SD), arithmetic mean, SD and median will be calculated by substituting the LLOQ for values which are NQ. The minimum at that time point will be reported as NQ.~~
- ~~• If more than 50%, but not all, of the concentrations are NQ, the gmean, CV, gmean  $\pm$  SD, arithmetic mean and SD will be reported as not calculable (NC). The minimum and median at that time point will be reported as NQ.~~
- ~~• If all the concentrations are NQ, the gmean, arithmetic mean, median, minimum and maximum will be reported as NQ and the CV, gmean  $\pm$  SD and SD as NC.~~
- ~~• If the calculation of the gmean  $\pm$  SD results in a value less than the LLOQ, NQ will be displayed.~~

#### Part B Randomised expansion

~~The plasma concentrations determined using the sparse PK sampling scheme, at sampling timepoints, will be listed but not summarised.~~

**The plasma concentrations, determined using the sparse PK sampling scheme data will be analyzed using population non-linear mixed effects approach (Beal and Sheiner 1988-1998). If data from the current study proves limited and is identified as insufficient to define the pharmacokinetics (large standard errors, non-identifiable PK profile), additional data will be included from previous clinical studies. Parameters will include AUCss, Cmaxss, CL/F and other PK parameters will be determined where appropriate and possible.**

**Once the population PK model is defined, covariates (age, weight, renal function etc) relationship and it's clinical relevant to the model will be explored.**

**The population PK analysis of data from this study will form part of the overall population analysis for the AZD5363 programme and is described in a population PK analysis plan associated with this programme.**

**Reason for Amendment:**

Clarification and simplification of parameters for analysis of pharmacokinetic data.

Inclusion of an option to combine data with outputs from other AZD5363 clinical studies in the event that PK outputs from D3610C00002 prove to be insufficient to enable a sufficiently robust evaluation.

**Section of protocol affected:**

Section 12.2.8 (Revised to 12.2.9) Pharmacodynamics and PK/PD relationships

**Previous text:**

Biomarker levels at various time points in addition to changes from baseline will be plotted and summarized appropriately; by treatment group for Part B, and by dose and schedule for Part A.

The relationship between biomarkers, PK parameters and clinical efficacy endpoints may be explored by graphical presentations and modelling techniques, the details of which will be documented in a separate analysis plan.

**Revised text:**

Biomarker levels at various time points in addition to changes from baseline will be plotted and summarized appropriately; by treatment group for Part B, and by dose and schedule for Part A.

The relationship between biomarkers, PK parameters and clinical efficacy endpoints may be explored by graphical presentations and **population** modelling techniques, the details of which will be documented in a separate **population PK/PD** analysis plan.

**Reason for Amendment:**

Further clarification of parameters for PK/PD analytical populations.

**Section of protocol affected:**

Section 12.5 Data monitoring committee

**Previous text:**

Not applicable

**Revised text:**

Not applicable

**In addition to the ISRC (see section 5.11.2) Part B of the study will utilise an AstraZeneca internal Data Monitoring Committee (AZDMC), that is independent of the AZD5363 project team, to evaluate unblinded data outputs following the 1st and 2nd interim analyses (see section 12.3). The AZDMC will provide the project team with recommendations for action with respect to study conduct and the management of patients treated under the auspices of the study protocol. The AZDMC may recommend that the study should continue as planned, be terminated or modified in some way. It is then the responsibility of AZ to act as appropriate upon AZDMC recommendations concerning safety and study conduct.**

**The AZDMC is constituted of:**

- **Head of Early Clinical Development, or delegate, who serves as the chairperson of the AZDMC**
- **Head of Biometrics in Early Clinical Development**
- **Head of Innovative Medicines and Early Development**
- **Head of Regulatory in Global Medicines Development**
- **Head of Patient Safety in Global Medicines Development**

**The AZDMC charter for this study will define the remit of the committee.**

**Reason for Amendment:**

Please refer to amendment rationale number 5.

**Section of protocol affected:**

Section 13.1 Medical emergencies and AstraZeneca contacts (*table of contacts*)

**Previous text:**

Name	Role in the study	Address & telephone number
[REDACTED]	Study Delivery Team Leader responsible for the protocol at central R&D site	AstraZeneca, [REDACTED]
[REDACTED]	Study Delivery Team Physician responsible for the protocol at central R&D site	AstraZeneca, [REDACTED]
[REDACTED]	Patient Safety Physician responsible for the protocol at central R&D site	AstraZeneca, [REDACTED]

**Revised text:**

Name	Role in the study	Address & telephone number
[REDACTED]	Study Delivery Team Leader responsible for the protocol at central R&D site	AstraZeneca, [REDACTED]
[REDACTED]	<del>Study Delivery Team Physician</del> <b>Medical Science Director</b> responsible for the protocol at central R&D site	AstraZeneca, [REDACTED]
[REDACTED]	Patient Safety Physician responsible for the protocol at central R&D site	AstraZeneca, [REDACTED]



**Reason for Amendment:**

To reflect changes in the AstraZeneca project team personnel.

**Section of protocol affected:**

Section 14 List of references

**Additional text:**

**ADA 2014**

**American Diabetes Association; Clinical Practice Recommendations 2014. Diabetes care January 2014 Volume 37, Supplement 1. Retrieved from <http://www.diabetes.org/>.**

**Beal and Sheiner 1988-1998**

**Beal, SL, and Sheiner, LB (1988-1998). NONMEM Users Guides. Part I-VIII. NONMEM Project Group C255, University of California at San Francisco.**

**Reason for Amendment:**

Additional literature references in support of revisions incorporated in protocol Edition 3; refer to Sections 4.2 and 12.2.8.

**Section of protocol affected:**

Appendix G Guidance Regarding Cautions and Restrictions for Prior and Concomitant Medications

**Previous text:**

*Separate document provided*

**Revised text:**

*Separate document provided*

**Reason for Amendment:**

Following a thorough review of allowance/exclusion of concomitant medications for AZD5363 clinical studies, and based upon emerging information and with reference to the revised Washington School of Pharmacy Drug Interaction Database, several revisions and additions were made to Appendix G. Due to the number of these updates, a track-changed version of the Appendix is made separately available for ease of reference.

**Section of protocol affected:**

Appendix H Instructions for Study Drug Dose Modification

Section 1 Dose Adjustments for Toxicity (*6<sup>th</sup> paragraph*)

**Previous text:**

However, of particular note, it is highly recommended that where there is suspected myelosuppression attributed to receipt of study drug:

- Paclitaxel should be withheld where neutrophils fall  $<1 \times 10^9/L$  or platelets  $<75 \times 10^9/L$ . If toxicity resolves to neutrophils  $\geq 1.5 \times 10^9/L$  and platelets  $\geq 75 \times 10^9/L$ . Paclitaxel should be reintroduced and the dose should be reduced for the remainder of the cycle and subsequent cycles.

- AZD5363 –

█ [REDACTED]

█ [REDACTED]

**Revised text:**

However, of particular note, it is highly recommended that where there is suspected myelosuppression attributed to receipt of study drug:

- Paclitaxel should be withheld where neutrophils fall  $<1 \times 10^9/L$  or platelets  $<75 \times 10^9/L$ . If toxicity resolves to neutrophils  $\geq 1.5 \times 10^9/L$  and platelets  $\geq 75 \times 10^9/L$ . Paclitaxel should be reintroduced and the dose should be reduced for the remainder of the cycle and subsequent cycles.
- AZD5363 ~~Under the intermittent dosing schedule AZD5363 would~~ **should be** suspended while the paclitaxel is withheld. **Where paclitaxel has ceased -** ~~Under the continuous schedule~~ AZD5363 should be withheld where neutrophils  $<0.5 \times 10^9/L$  and platelets  $<25 \times 10^9/L$ , or non-traumatic bleeding with platelets: 25 to  $<50 \times 10^9/L$ .

**Reason for Amendment:**

Clarification of criteria for withholding of study treatments - under AZD5363 intermittent dosing schedules only – in the event of suspected treatment-related myelosuppression. A continuous dosing schedule is no longer under evaluation.

Clinical Study Protocol Amendment 3  
Drug Substance AZD5363  
Study Code D3610C00002  
Date 09 May 2014

**Section of protocol affected:**

Appendix H Instructions for Study Drug Dose Modification (*general*)

**Previous text:**

*References to:* ‘Guidance for the Management of Adverse Events in Studies of AZD5363’

**Revised text:**

*References to:* ‘Investigators’ Guide for the Management of Toxicities and Adverse Events’

**Reason for Amendment:**

This change reflects that an original project-level guide for management of adverse events was replaced by a study-specific investigator aide to management of adverse events and toxicities.



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**Clinical Study Protocol Amendment**

Amendment Number	4
Drug Substance	AZD5363
Study Code	D3610C00002
Date	29 April 2015
Protocol Dated	13 May 2014

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**A Phase I/II, Multicentre, Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by *PIK3CA* Mutation Status (BEECH).**

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This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

**Sponsor:**

AstraZeneca AB, 151 85 Södertälje, Sweden.

**Centres affected by the Amendment:**

This amendment affects all centres in the study.

**Primary reason for amendment:**

To allow the use of the tablet formulation of AZD5363 in Part A patients.

In response to feedback from Investigators and emerging clinical data, other substantial changes have also been made to the protocol. These changes will simplify procedures, aid participation and adherence to the protocol, without compromising patient care.

**Persons who initiated the Amendment:**

AstraZeneca clinical study team.

For details of all revised text in each section of the protocol, refer to the revised protocol (and tracked change version of the revised protocol) submitted with this amendment.

Where deleted, additional or amended protocol text is included in this amendment document it has been presented in italic script to aid ease of identification.

**Primary protocol change in this amendment:**

1. **5.5.3 Doses and treatment regimens:** Changes have been made to the text to permit the use of dose-equivalent tablets in Part A of the study, as current wording specifies capsules only. This is supported by data generated from study D3610C00007 and is presented in Edition 6 of the Investigator's Brochure. The data show the comparability of PK exposure and safety between the original capsule (of the kind that has been dosed to patients in Part A of the study) and the new tablet formulation of AZD5363.

**Other substantial protocol changes in this amendment:**

1. **Part B Patient Assessments:** Changes to and an overall reduction in the number of patient assessments and the number of days on which patients are required to attend clinic for evaluation. This change was made in response to Investigators' observations that the schedule of assessments as documented in Revised Protocol Edition 3 presented a substantial burden to both patients and site staff.

After thorough consideration, AstraZeneca has concluded that it is appropriate to remove some and re-assign other Part B patient assessments associated with PK/PD, biomarker and safety assessments. The removal and reassignment of the former were based on the review of the objectives of Part B and the essential data required to address these objectives. The change of safety assessments was based on the judgement that sufficient safety data has been collected during Part A and the early stages of Part B of the study along with associated studies in the clinical development programme for AZD5363. The available data are considered to support a reduction in assessments without compromising patient care.

These changes are reflected in the following aspects of the protocol:

- a) Updates to the 3.1.4 Schedule of Assessments Part B (Figure 8) and Sections 6.4 to 6.9 to reflect all changes in this amendment.
- b) Consent to provide a plasma blood sample for biomarker analysis will no longer be optional; instead, the consent will be mandatory and included in the main study consent form. This sample has also been renamed ctDNA blood sample to clarify the intention and use of the sample.
- c) Removal of the obligation for patients to use urine dipsticks at home during cycle 1 in Part B of the study to monitor for presence of glycosuria. Emerging data have shown that glucose levels as a result of study treatment tend to peak at 2 to 4 hrs after ingestion of AZD5363 and are not associated with clinical sequelae. Patients will be monitored for hyperglycemia whilst in the clinic in the 2-4 hours after dosing of the study treatment during the first cycle of study

treatment. Monitoring will be achieved via the assessment of serum glucose levels. Additional monitoring in subsequent cycles may be instigated at the discretion of the investigator based on findings from the glucose sampling conducted during the first cycle of treatment.

- d) Updates to language related to analytical procedures (PK samples) and length of storage (CTC sample).
- e) Reductions to the volume of blood to be drawn, given the overall reduction in the number of assessments.
- f) Clarification concerning the acceptable time window around clinic visits.

2. **4.2 Exclusion Criteria: Change and clarification of Exclusion Criterion 4.**

Exclusion criterion 4 has been revised to:

*Receipt of any investigational drug within 30 days or 5 half-lives, whichever is shorter, of the first dose of AZD5363 or matching placebo. [Note: that this criterion does not apply where the investigational drug was an established or marketed breast cancer medication administered previously as part of a clinical trial, e.g., as a comparator in a randomised study.]*

This change has been made as patients requiring first-line chemotherapy for advanced or metastatic breast cancer often have rapidly progressive disease or disease impairing organ function and for which therapy without delay is warranted. This is at odds with the previously mandated 30 day washout period for the prior therapy and this stipulation has been removed. The 5 half-life washout has been retained to ensure patient safety in relation to potential drug interactions and to reduce the risk of confounding interpretation of safety and efficacy data collected in Part B of the study. Where the safety and efficacy profile of an established breast cancer therapy is well established and the drug has a long half-life (e.g. fulvestrant) the 5 half-life stipulation is also removed to reflect real-world clinical practice and patient need.

3. **4.2 Exclusion Criteria: Removal of Exclusion Criterion 11.**

This criterion has been removed as it applied to patients with primary tumour types other than breast cancer (which was in error as only patients with breast cancer may be entered into the study) and incorrectly differentiated between early disease and advanced or metastatic disease. The target population will commonly include women recurring with aggressive disease during or after adjuvant therapy for early disease. This criterion is also subsumed within the revised exclusion criterion 4 above and therefore redundant.

4. **5.2.1.1 Determination of *PIK3CA* mutation status and 5.2.2 Procedures for allocation and randomisation:** New text added to these sections.

*5.2.1.1: Alternatively, based on data from the interim analysis(es), it may be decided to permit unselected accrual to continue with the result that the number of patients in the two strata will be imbalanced (see section 5.2.2). In this instance, prospective screening will not be required however it will remain necessary to determine mutation status for all patients to enable sub-group analyses.*

*5.2.2: When one stratum is complete (i.e. the minimum of 50 patients corrected for any post-screening revised mutation status have been randomised to a stratum), based on results from one or more of the interim analyses or results of other studies of AZD5363 or agents that act on the *PIK3CA* pathway, AstraZeneca may elect to permit accrual to the completed stratum to continue or re-open. This may result in imbalanced accrual between the two strata as a result of competitive accrual. The total sample size of approximately 100 patients will not be affected.*

This text has been added to the protocol as the field of research relating to the *PIK3CA* pathway is rapidly evolving and it is anticipated that, during the recruitment period of this study, data may emerge to indicate that exploring the hypothesis of enhanced sensitivity to AZD5363 arising from *PIK3CA* mutation is no longer a valid exercise. If this becomes the case, forcing the enrichment of the study population with patients whose tumour bears the mutation may no longer be necessary.

**Other protocol changes in this amendment:**

1. **Section 1.1.3 Clinical Information:** Data presented were no longer the most up to date information. The reader is now referred to the Investigator's Brochure which details the emerging data thus far.
2. **Section 1.4.4 and 1.4.5 Patient risks:** Text has been included regarding the risk of hypersensitivity reactions due to AZD5363. This change has been made as a result of emerging information as documented in Investigator's Brochure Edition 6.
3. **Section 2.2. Part A and B Secondary Objectives:** Addition of the secondary objective to assess the toxicity burden associated with diarrhoea. This change has been made to reflect the intention and use of the current data collection. This data collection is also further documented in section 6.4.3.
4. **Section 2.3 Exploratory Objectives:** Clarification that the CTC assessment may also include characterisation of these samples.
5. **Section 3.1.1 Asian Patient evaluation:** Change of Japanese population to 'Asian' to allow sub-analyses and evaluation of emerging data from this population as centres in other Asian countries may be included in the study.

6. **4.1 Inclusion Criteria:** Part B Criterion 1. Patients with histological or cytologic diagnosis of ER+ve and HER2-ve breast cancer with evidence of ~~relapsed~~ advanced or metastatic disease. Lesions should not be amenable to surgery or radiation of curative intent and must be considered unlikely to be rendered eligible for surgery by treatment with paclitaxel in this study. Clarification and simplification of this criterion.
7. **4.2 Exclusion Criteria:** Removal of text within Exclusion Criterion 20. Aspartate aminotransferase (AST) >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases. ~~Elevated Alkaline phosphatase (ALP) is not exclusionary if due to the presence of bone metastasis and liver function is otherwise considered adequate in the investigator's judgement.~~ This latter part of the criterion has been removed as this current wording is confusing and does not describe an exclusion criterion.
8. **5.1 Restrictions during the study:** Restriction 4 is no longer applicable to Part B of the study and is therefore amended accordingly.
9. **5.2 Patient enrolment process:** Clarification that for Part B a separate patient allocation process document is not available, sufficient detail is given within section 5.2. Correction to the description of the allocation of randomisation identification codes.
10. **5.5 Treatments. Table 1:** Dosage form and strength of the investigational product updated to reflect Administrative Change Number 1, dated 8th December 2014.
11. **5.5.3 Dose and Treatment Regimens:** Removal of text relating to re-dosing study drug if vomiting occurs after ingestion. This deletion has been made to reduce the possibility of overdose.
12. **5.5.3 Dose and Treatment Regimens and 3.1.2 Treatment Schedules:** Clarification to the text relating to the dosing schedule of AZD5363 study treatment once paclitaxel has been permanently discontinued.
13. **5.5.4 Dose modifications:** Clarification to the text regarding the suspension of study treatment before permanent discontinuation. Appendix H has also been updated respectively.
14. **5.5.4 Dose modifications:** Permissible dose modifications during Part B have been updated to reflect the available formulation strengths of the new tablet formulation of the investigational product.
15. Update to the statistical section of the protocol to ensure consistency with all the changes in this protocol amendment.



Clinical Study Protocol Amendment 4  
Drug Substance AZD5363  
Study Code D3610C00002  
Date 29 April 2015

16. Minor clarifications to format or language that support the protocol (but do not change meaning).
17. Other minor updates relating to study personnel, contact details and timelines.
18. Changes to the number of participating centres and countries.
19. Update to Appendix B to provide further information on Adverse Event reporting.

It is the judgement of the AstraZeneca Project Team that none of the protocol changes detailed in this document present any additional risk or hazard to the welfare or safety of participating patients. The changes made to this protocol do not affect the overall risk-benefit profile to the patient.



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**Clinical Study Protocol Amendment**

Amendment Number	5
Drug Substance	AZD5363
Study Code	D3610C00002
Date	30 May 2017
Protocol Dated	29 April 2015

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**A Phase I/II, Multicentre, Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by *PIK3CA* Mutation Status (BEECH).**

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This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

**Sponsor:**

AstraZeneca AB, 151 85 Södertälje, Sweden.

**Centres affected by the Amendment:**

This amendment affects all centres in the study.

**Reason for Amendment:**

To clarify the steps that should be followed if an early clinical database closure is warranted based on data generated by the study. To clarify the information that should be recorded for patients who continue to take study medication after the formal closure of the database has been triggered by the primary analysis, if required. To clarify the procedure for long-term collection of survival data. To update the estimated date of the last patient completed.

**Persons who initiated the Amendment:**

AstraZeneca Clinical Project Team

**Section of protocol affected:**

**Protocol Synopsis**

**Previous text:**

Estimated date of last patient completed Q1 2017

**Revised text:**

Estimated date of last patient completed Q4 2017

**Additional Section**

**Section 3.1.5 Early Closure of the Database.**

In the event of an early closure of the database, patients are permitted to continue to receive study treatment if, in the opinion of the investigator, they are continuing to receive benefit from study treatment. For patients who do continue to receive treatment, investigators will continue to follow them for safety assessments as per the study plan (Figure 8) and in accordance with Section 6.4.3 Recording of Adverse Events. All SAEs must continue to be reported to AZ Patient Safety within the usual timelines until 28 days after study treatment is discontinued. All non-safety assessments will stop once the decision to close the clinical database has been communicated.

Any patients who are still receiving study medication, will be switched from IVRS/IWRS supply to a manual supply and the IVRS/IWRS will be closed, in line with the database closure.

Patients will not be considered formally withdrawn from the study until they stop taking study medication.

Survival status will not continue to be collected if the database is closed early. If this occurs, the overall survival analysis and safety update may be conducted using all available data the time of the database closure.

**Section 5.5.1 Identity of investigational product(s)**

**Additional text:**

Any patients who are still receiving study medication, will be switched from IVRS/IWRS supply to a manual supply and the IVRS/IWRS will be closed, in line with the database closure.

**Section 5.9 Withdrawal from the Study**

**Additional text:**

Patients will not be considered formally withdrawn from the study until they stop taking study medication.

**Section 6.2.3.4 Survival follow-up**

**Previous text:**

Survival status will continue to be collected until 50% of randomized patients have died. Optionally, continuation until 75% of randomized patients have died may be considered.

**Revised text:**

Survival status will continue to be collected until 50% of randomized patients have died (or the database is closed, if this occurs earlier). Optionally, continuation until 75% of randomized patients have died may be considered.

**Section 12.2 Methods of statistical analyses Table 12 Footnote**

**Previous text:**

PFS analysis and safety update will be combined if last patient has discontinued by the time the PFS events are reached

**Revised text:**

PFS analysis and safety update will be combined if last patient has discontinued by the time the PFS events are reached. The overall survival analysis and safety update may be conducted using all available data at the time of database closure if earlier.