Clinical Study Protocol

Drug Substance AZD8931

Study Code D0102C00010

Edition Number 3

[redacted]

A Phase I, Open-label, Multiple-dose, Dose-escalation Study To Assess the Safety and Tolerability of AZD8931 Monotherapy in Japanese Patients with Advanced Solid Malignancies and in Combination with Paclitaxel in Japanese Female Patients with Advanced Breast Cancer

Sponsor:

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

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
Administrative Change No.	**Date of Administrative Change**	**Local Administrative Change No.**	**Date of Local Administrative Change**

PROTOCOL SYNOPSIS

A Phase I, Open-label, Multiple-dose, Dose-escalation Study To Assess the Safety and Tolerability of AZD8931 Monotherapy in Japanese Patients with Advanced Solid Malignancies and in Combination with Paclitaxel in Japanese Female Patients with Advanced Breast Cancer

Investigator

Name and address of principal investigator are shown in

Study centre(s) and number of subjects planned

This study is a single-centre study in Japan. A minimum of 3 patients with advanced solid malignancies (Monotherapy part) or 3 female patients with advanced breast cancer (Combination therapy part) will be recruited at each dose level. Also, a maximum of 6 evaluable patients may be recruited at each dose level.

Phase of development

Phase I

Objectives

Primary objective

Monotherapy part

The primary objective is to explore the safety and tolerability of multiple ascending doses of AZD8931 in Japanese patients with advanced solid tumours.

Combination therapy part

The primary objective is to explore the safety and tolerability of combination with weekly Paclitaxel and AZD8931 in Japanese female patients with advanced breast cancer.

Secondary objectives

Monotherapy part

The secondary objectives are as follows:

- To identify the maximum tolerated dose (MTD) of AZD8931 following repeated twice-daily administration.

- To explore the Pharmacokinetics of single doses of AZD8931 in Japanese patients with advanced solid tumours

- To explore the Pharmacokinetics of multiple doses of AZD8931 in Japanese patients with advanced solid tumours

Combination therapy part

The secondary objective is as follows:

- To identify the maximum tolerated dose (MTD) of AZD8931 following repeated twice-daily administration when given in combination with weekly paclitaxel

- To explore the Pharmacokinetics of AZD8931 and paclitaxel when co-administered in Japanese female patients with advanced breast cancer

Exploratory Objectives

Monotherapy part

The exploratory objectives are as follows:

- To obtain preliminary assessments of the efficacy of AZD8931 according to RECIST in patients with measurable lesion.

- To measure exploratory biomarkers from blood and tumour tissue samples and examine the relationship of these biomarkers with clinical outcome (optional)

- To obtain a blood sample for DNA extraction for possible pharmacogenetic analysis (optional).

Combination therapy part

The exploratory objectives are as follows:

- To seek preliminary evidence of the anti-tumour activity of AZD8931 in Japanese female patients with advanced solid breast cancer as measured by tumour response and change in tumour size according to RECIST in patients with measurable lesions.

- To measure exploratory biomarkers from blood and tumour tissue samples and examine the relationship of these biomarkers with clinical outcome (optional).

- To obtain a blood sample for DNA extraction for possible pharmacogenetic analysis and other potential correlative markers of AZD8931 activity and drugs taken in addition to AZD8931 (optional).

Study design

Monotherapy part

This is an open-label, Multiple-dose, Dose-escalation Study.

Combination therapy part

This is an open-label, Multiple-dose, Dose-escalation Study in Combination with Paclitaxel.

Target subject population

Monotherapy part

Adult Japanese patients with advanced solid malignancies that is refractory to standard therapies, or for which no standard therapies exist will be eligible for enrolment into this study.

Combination therapy part

Adult Japanese female patients with advanced breast cancer who is eligible to Paclitaxel treatment will be eligible for enrolment into this study.

Investigational product, dosage and mode of administration

AZD8931 is available as plain, round, biconvex, white film coated tablets containing 40 mg or 100 mg of AZD8931 (expressed as free base). Tablets to be taken orally.

Monotherapy part

AZD8931 tablets will be taken orally twice daily (except for the single dose on D1), with the doses being taken approximately 12 hours apart. The AZD8931 tablets should be taken with a glass of water (approximately 150 mL) at approximately the same time each day. The effect of food on the absorption of AZD8931 has not been established. Therefore it is requested that AZD8931 be taken at least 2 hours after a meal and that no food is consumed until 2 hours after the tablets are taken. There is no restriction on the consumption of water.

Combination therapy part

Paclitaxel is commercially available and supplied locally, as per standard practice at the investigator site.

Each AZD8931 plus paclitaxel treatment cycle will be 28 days duration. Multiple (twice daily) dosing of AZD8931 will start on D2, and will be twice daily for 27 days (D2 to D28) including 12-hour interval. There will be no single dose administration of AZD8931. Paclitaxel will be administered as an intravenous drip infusion of 90 mg/m^2 (body surface

area) on D1, D8 and D15 of the 28 day treatment cycle. On days when both AZD8931 and paclitaxel are administered, AZD8931 should be administered immediately prior to paclitaxel administration.

Duration of treatment

Patients may continue treatment indefinitely assuming they do not meet a withdrawal criterion and sign on the informed consent form for treatment continuation in both therapies. Patients should each be followed up for a period of 30 days from time of last dose of study treatment in order to follow-up adverse events.

Outcome variable(s):

- Safety
  - Adverse events (AE)
  - Laboratory findings
  - Physical examination
  - Vital signs
  - Cardiac monitoring (including 12-lead electrocardiograms [ECGs] and echocardiography)
  - Respiratory examination (chest X-ray, high resolution CT scan thorax)
  - Arterial oxygen saturation (SpO_2)
  - Ophthalmological examinations (including visual acuity, Schirmer's test, slit-lamp examination, pupil dilation and intraocular pressure measurements [if considered appropriate by investigator]).
- Pharmacokinetics

Monotherapy part

- Single dose plasma PK: $AUC_{0\text{-}10}$, $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, AUC, C_{max}, t_{max}, $t_{1/2}$, CL/F, Vss/F
- Multiple dose plasma PK: $AUCss_{0\text{-}10}$, $AUCss_{0\text{-}12}$, Css_{max}, tss_{max}, Css_{min}, CLss/F, R_{AC} and linearity factor

Combination therapy part

- the AZD8931 and paclitaxel PK parameters to be calculated during the combination arm are: t_{max}, C_{max}, $AUC_{0\text{-}10}$

- Exploratory
  - Correlation of biomarkers with AZD8931 therapy (optional)
  - Optional pharmacogenetic sampling (blood sample) for DNA extraction and archiving (optional)
  - Objective Response Rate (based on RECIST)

Statistical methods

No formal statistical hypothesis testing will be performed. The analyses of safety and Pharmacokinetics will be summarised descriptively including tables, listings and graphs, as appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACE	Angiotensin-converting enzyme
AE	Adverse event (see definition in Section 17.3.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from zero to infinity
$AUC_{(0-10)}$	Area under the plasma concentration-time curve from zero to 10 hours
$AUC_{(0-12)}$	Area under the plasma concentration-time curve from zero to 12 hours
$AUCss_{(0-10)}$	Area under the plasma concentration-time curve from zero to 10 hours at steady state
$AUCss_{(0-12)}$	Area under the plasma concentration-time curve from zero to 12 hours at steady state
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from zero to 24 hours
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to the last quantifiable concentration
BP	Blood pressure
CL/F	Total apparent drug clearance
CLss/F	Total apparent drug clearance at steady state
C_{max}	Maximum plasma drug concentration
$Css,_{max}$	Maximum steady state drug concentration
C_{min}	Minimum plasma drug concentration
$Css,_{min}$	Minimum steady state drug concentration
CR	Complete response
CRF	Case Report Form (electronic/paper)
CSR	Clinical study report
CT	Computerised tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event

Abbreviation or special term	Explanation
CV	Coefficient of variation
CYP	Cytochrome P450
DAE	Discontinuation due to Adverse Event
DEC	Dose Escalation Committee
DLT	Dose-limiting toxicity
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
GCP	Good Clinical Practice
GCSF	Granulocyte-colony stimulating factor
HbA1c	Glycosylated haemoglobin
HB-EGF	Heparin-binding EGF
H&N	Head and neck
HER	Erbal or type 1 growth factor
HIV	Human immunodeficiency virus
HRG	Heregulin
HRCT	High resolution computed tomography
IB	Investigator brochure
IC_{50}	Concentration giving 50% of the drug-induced inhibitory effect
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
IT	Intolerable toxicity
λ_z.	Terminal elimination rate constant
LIMS	Laboratory Information Management System
LVEF	Left ventricular ejection fraction
MAD	Multiple ascending dose

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MTD	Maximum tolerated dose
MRI	Magnetic resonance imaging
NOAEL	No observed adverse effect level
NRG	Neuregulin
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 22.1.1
PA	Protection Grade of UVA
pCRF	Paper case report form
PD	Progression of disease
PET	Paraffin embedded tissue
PGx	Pharmacogenetics
PK	Pharmacokinetic(s)
PR	Partial response
Principal investigator	A person responsible for the conduct of a clinical study at a study site. Every study centre has a principal investigator.
QRS	QRS complex is a structure on the ECG that corresponds to the depolarisation of the ventricles
QT	Interval from the beginning of the QRS complex to the end of the T wave
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using the Fridericia correction
QWBA	Quantitative whole-body autoradiography
R_{AC}	Accumulation ratio
RECIST	Response Evaluation Criteria In Solid Tumours
SAD	Single ascending dose
SAE	Serious adverse event (see definition in Section 17.3.2).
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class

Abbreviation or special term	Explanation
SOP	Standard Operating Procedures
SPF	Sun protection factor
ss	Steady state
$t_{1/2}$	Half-life
TKI	Tyrosine Kinase Inhibitor
t_{max}	Time to reach maximum concentration following drug administration
tss_{max}	Time to reach maximum plasma concentration at steady state
TNM	Tumour, node, metastases
ULN	Upper limit of normal
Vss/F	Apparent volume of distribution at steady state
WHO	World Health Organization
Investigators	Principal investigator and sub-investigator

1. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

1.1 Medical emergencies and AstraZeneca contacts

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 17.3.4**

In the case of a medical emergency the investigator may contact the persons below.

Name	Role in the study	Address & telephone number

Name	Role in the study	Address & telephone number

1.2 Overdose

To date no patient has experienced an overdose with AZD8931. There is currently no known antidote to AZD8931. The treatment of AEs associated with overdose should be supportive for the underlying symptoms. A dose of AZD8931 in excess of that planned according to the protocol is to be considered an overdose. Should an overdose (accidental or deliberate) of AZD8931 occur, it must be reported in accordance with the following procedures, regardless of whether the overdose was associated with any symptom or not.

- An overdose with an associated adverse event should be recorded as the AE diagnosis/symptoms on the AE (and SAE, if appropriate) and Overdose the paper Case Report Forms (pCRF) modules.
- An overdose without associated symptoms should only be reported on the Overdose pCRF module.

1.3 Pregnancy

To date there is no experience of exposure to AZD8931 in pregnancy. Administration of AZD8931 to women who are pregnant or who intend to become pregnant should be avoided. Should a patient become pregnant, they should immediately be withdrawn from study treatment. All outcomes of pregnancy must be reported to AstraZeneca.

1.3.1 Maternal exposure

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

If any pregnancy occurs in the course of the study, then investigators or other site personnel discontinue the study immediately and inform appropriate AstraZeneca representatives

immediately but no later than the end of the next business day of when he or she becomes aware of it.

The Pregnancy Outcome Report, part 1, is used to report the pregnancy and the Pregnancy Outcome Report, part 2, is used to report the outcome of the pregnancy.

1.3.2 Paternal exposure

Male patients must refrain from fathering a child during the study and **three** months following the last dose of study treatment, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated

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

In case having information of pregnancy of the subject partners, investigators should report to the sponsor within one day from the day of their recognition.

2. INTRODUCTION

AZD8931 is an oral, equipotent inhibitor against Epidermal Growth Factor Receptor (EGFR), erbB2 and erbB3, in development for the treatment of solid tumours.

The broad clinical objectives of AZD8931 in early clinical development include determination of safety, tolerability and pharmacokinetics (PK) of AZD8931 administered as an oral formulation either as a single agent or in combination with paclitaxel, as well as identification of early signals of clinical activity. The assessment of safety will be based mainly on the frequency of AEs, cardiac monitoring, ophthalmology data, and on laboratory parameters.

2.1 Background

The ErbB family of receptors (also known as the Type 1 Growth Factor receptor family or HER family) has been identified as a promising target for anti-cancer therapy. The family includes four members; EGFR/ErbB1, ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4.

The ErbB family is bound by the epidermal growth factor (EGF) family of ligands which can be divided into three groups: the first includes EGF, transforming growth factor-α (TGFa) and amphiregulin (AR), which bind specifically to EGFR; and the second includes betacellulin (BTC), heparin-binding EGF (HB-EGF) and epiregulin (EPR), which show dual specificity, binding both EGFR and ErbB4. The third group is composed of the neuregulins or heregulins (NRG or HRG) and forms two subgroups based on their capacity to bind ErbB3 and ErbB4 (NRG1 and NRG2) or only ErbB4 (NRG3 and NRG4). EGFR is primarily activated via heterodimerisation, induced following ligand binding (Hynes and Lane 2005). ErbB2 is peculiar in that it lacks any ligand binding capacity, whereas ErbB3 is intrinsically kinase inactive and becomes activated only following heterodimerisation and cross-phosphorylation

by another ErbB receptor. In the case of ErbB2, activation may arise via a) overexpression (gene amplification) inducing homodimerisation and b) heterodimerisation with another family member, from which ErbB3 is considered to be the preferable and most oncogenic partner. ErbB2 receptor heterodimerisation is induced by ligands such as HRG, which specifically binds to ErbB3, exposing its heterodimerisation domain (arm), which then interacts with that of ErbB2. ErbB2 itself maintains a constantly extended heterodimerisation arm.

Ligand binding to the ErbB receptors induces receptor homo- and hetero dimerisation, leading to phosphorylation of critical sites in the tyrosine kinase domain, and subsequent activation of downstream pathways involved in cellular proliferation and survival (Olayioye et al 2000).

ErbB2 is the preferred dimerisation partner, as ErbB2 containing dimers exert the most potent mitogenic signal (Giuliani et al 2007, Graus Porta et al 1997). ErbB2 is expressed in a variety of epithelial cell types in the gastrointestinal tract, respiratory, reproductive and urinary tracts, skin and breast. In general, expression levels are higher in foetal tissues than in adult tissues (Press et al 1990). There is also evidence of a role for ErbB2 in cardiac development (Hudelist et al 2006, Hynes and Lane 2005, Lee et al 1995). In contrast EGFR is expressed in all epithelial and stromal cells as well as in some glial cells and smooth muscle cells, but it is not found in haematopoietic cells. Growth factor-induced EGFR signalling is important in many normal cellular processes in adult tissues, with effects including cell proliferation, cell migration and cell differentiation.

Aberrant EGFR and ErbB2 activity has been identified in a number of human malignancies and is notable for its association with a more aggressive disease course and poor clinical outcome (Sjogren et al 1998; Nicholson et al 2001). In human tumours, activation occurs through receptor over-expression, autocrine growth factor loops, or the presence of activating mutations in the kinase domain (Voldborg et al 1997).

EGFR activation is seen in tumour types such as non-small cell lung cancer (NSCLC), breast, colorectal, and head and neck (H&N) cancer. Over-expression of ErbB2 is seen in a proportion of breast, ovarian, bladder, and gastric malignancies.

Therapeutic approaches to EGFR/ErbB2 signalling pathways include the use of monoclonal antibodies targeting the extra cellular domain (eg, trastuzumab [Herceptin®, Chugai Pharmaceutical] and cetuximab [Erbitux®, Merck Serono]) and small molecule EGFR tyrosine kinase inhibitors (eg, gefitinib [Iressa™] and erlotinib (Tarceva®, Chugai Pharmaceutical). More recently, dual tyrosine kinase inhibitors, with the ability to inhibit the tyrosine kinase domain of both EGFR and ErbB2, have been generated. The reversible dual tyrosine kinase inhibitor, lapatinib (Tykerb, GlaxoSmithKline) has shown activity in pre treated patients (Arteaga 2007, El-Rehim et al 2004, Geyer et al 2006), and has been approved for use in combination with capecitabine (Xeloda™, Chugai Pharmaceutical) for inoperable or recurrent breast cancer that is ErbB2 overexpression.

The role of EGFR, ErbB2 and ErbB3 in cancer is well documented. The significance of ErbB4 in carcinogenesis is still very unclear. In breast cancer, expression of the individual

receptors has been shown to correlate with poor prognosis which worsens when more than one ErbB receptor is expressed (Slamon et al 1987; Slamon et al 1989; Thor et al 2000; El-Rehim et al 2004). In addition, pre-clinical and clinical evidence indicate that blocking all family members may be necessary in order to effectively block signalling via these receptors. Even if individual EGFR (eg, by Gefitinib) or ErbB2 (eg, by Trastuzumab) activation is inhibited, signalling and activation is rescued by the presence of another ErbB receptor or ligands (Olayioye et al 2000; Giuliani et al 2007; Smith et al 2004; Tovey et al 2006; Arteaga 2007; Hudelist et al 2006). None of the ErbB targeted agents currently undergoing clinical evaluation has conclusively demonstrated that they can effectively and simultaneously inhibit EGFR, ErbB2 and ErbB3 receptor activation in relevant clinical settings. Our pre-clinical work has demonstrated that AZD8931 is able to potently inhibit the activation of these receptors whether constitutively or ligand-induced.

Pre-clinical evidence indicates that in tumours the ErbB3 receptor is the ErbB family member coupled to the PI3K/Akt survival pathway, inhibition of which leads to apoptosis. The drug exposure required to induce apoptosis through this pathway in tumours has not been identified (Hsieh and Moasser 2007, Sergina et al 2007).

In vitro studies to clarify the pharmacology of AZD8931 and, more specifically, how the mechanism of action of this potent and balanced inhibitor of EGFR, HER2 and HER3 differs from that of agents that are selective inhibitors of either EGFR or ErbB2, have indicated that AZD8931 is much more potent in inhibiting activated ErbB2/ErbB3 heterodimers, formed in the presence of ligand, than any of the other agents. Effects on cellular proliferation mirrored the effects on phosphorylation by AZD8931, gefitinib and a selective ErbB2 inhibitor, with AZD8931 always being more potent.

AZD8931 is being developed with the expectation that, as an equipotent inhibitor of EGFR, ErbB2 and ErbB3 receptor kinases - specifically inhibiting the signals through both homo- and heterodimer configurations of these targets - it will provide superior efficacy compared to currently available inhibitors that are reported to target one or more of these receptors. Relevant preclinical data for AZD8931 are presented in the current investigator's brochure (IB).

2.1.1 Non-clinical studies

AZD8931 pre clinical information is summarised below and further information on pre clinical toxicology and pharmacology can be found in the current IB.

2.1.1.1 Pharmacology

AZD8931 inhibits the activity of ErbB2 and EGFR kinase in in-vitro isolated enzyme assays and in screening kinase panels, and inhibits auto-phosphorylation in cellular assays, with an activity in the nM range. AZD8931 demonstrated at least 100 fold selectivity towards ErbB2 and EGFR over other kinase enzymes in a screening panel of >200 protein kinases.

AZD8931 inhibits the growth of a wide range of tumour cell lines that depend on ErbB2 and EGFR signalling. Treatment of mice and rats bearing a variety of xenografted tumours,

including breast, lung, gastric and prostate carcinomas, with AZD8931 resulted in dose dependent inhibition of tumour growth at well tolerated doses, and produced regressions in some models. AZD8931 at 105 and 53 μmol/kg (50 and 25 mg/kg) produces dose dependent inhibition of EGFR (88% and 67%) and ErbB2 (90% and 59%) phosphorylation in BT474C tumour xenografts.

The effects of AZD8931 in combination with paclitaxel when dosed concurrently have been assessed in non-clinical studies. Two breast cancer cell lines were tested based on their differing ErbB receptor levels. SKBR3 cells (driven by erbB2 homodimerisation) and BT474C cells (driven by ErbB2 homodimerisation and EGFR/ErbB2 heterodimerisation) were treated with AZD8931, paclitaxel or the combination of AZD8931 and paclitaxel for 96 hours and proliferation analysed by the MTS assay [viable cell number was determined using the MTS Colorimetric Assay reagent (#G1111, Promega) as per the manufacturer's instruction]. The combination index (CI) is used as a measure of benefit for each combination and is the ratio of the predicted number of cells affected divided by the actual number of cells affected. The predicted numbers of cells affected were based on the monotherapy results. Importantly, for both cellular systems no antagonism was seen (CI<2) for the combination of AZD8931 and paclitaxel in two cell lines driven by a range of ErbB hetero- and homo-dimers. Furthermore, the addition of AZD8931 was beneficial to the activity of paclitaxel

The combination of AZD8931 and paclitaxel was assessed using the BT474C xenograft model. AZD8931 was dosed once daily (po) and paclitaxel once weekly (ip) for a total of 14 days. The AZD8931 and paclitaxel combination therapy showed significantly enhanced tumour growth inhibition compared to either AZD8931 or paclitaxel monotherapy. No apparent antagonism was observed in these *in vivo* studies when both agents were combined.

AZD8931 demonstrates potent activity (IC_{50} ≤0.01 μM) when cell survival and proliferation is driven by any of the erbB ligands. Furthermore, the potency of AZD8931 against ErbB ligand driven p-EGFR, p-erbB2 or p-erbB3 inhibition demonstrates AZD8931 as a potent and balanced inhibitor for all of these receptors. In particular, AZD8931 inhibition of neuregulin driven p-erbB3 and HB-EGF, BTC, EGF, or TGFα driven p-EGFR demonstrates significant differentiation from other agents (eg, gefitinib or lapatinib) and are all clearly important components of the ErbB signalling axis in metastatic breast cancer where total erbB2 protein levels are low.

2.1.1.2 Pharmacokinetics

The absorption, distribution, metabolism and excretion (ADME) of AZD8931 has been studied in the species and strains used in the toxicology program except for the quantitative whole-body autoradiography (QWBA) which used a pigmented rat strain.

In the rat, oral bioavailability was found to be low to moderate, ranging from 21 to 41%, and volume of distribution and clearance were moderate with an oral t½ of approximately 2 hours. The protein binding of AZD8931 was in the range of 93.7 to 98.2% in all species. In a rat QWBA study, radioactivity was widely distributed to all tissues with the exception of the brain. The elimination of radioactivity was generally rapid; however, in pigmented tissues

(uveal tract, skin, meninges) radioactivity was only slowly eliminated; in the uveal tract concentrations decreased by less than 25% over the course of 14 days.

In hepatocytes from rat, dog and human, metabolism of AZD8931 was primarily to hydroxylated and dealkylated products with conjugation to a range of glucuronide and sulphate conjugates. *In vivo* in the rat, the main circulating components in addition to parent compound were a de-methylated metabolite and its corresponding glucuronide conjugate. All of the [14C]AZD8931 metabolites formed by human hepatocytes were also formed in at least one of the pre clinical species under study. The principal human P450 involved in metabolism was CYP3A4. In rats, almost all [14C]AZD8931 was recovered in the faeces (±96%) and urine (±2%) over a 7-day period and was principally recovered within the first 24 hours.

AZD8931 did not show a marked potential for clinically relevant inhibition or induction of any major CYP isoform. There was some evidence for time dependent inhibition of CYP3A4 but this was equivocal.

2.1.1.3 Toxicology

A battery of safety pharmacology and genetic toxicology studies, in addition to toxicology studies in rats and dogs, have been conducted with AZD8931.

AZD8931 was not genotoxic in either *in vitro* or *in vivo* assays.

On repeat administration of AZD8931 in rats, gastrointestinal toxicity was dose limiting. Epithelial degeneration and atrophy, consistent with the pharmacology of the compound, was evident on histopathological examination of a number of tissues including skin, gastrointestinal and genitourinary tract. There was evidence of reversibility following a 4-week recovery period. The no observed adverse effect level (NOAEL) in rats after 1 month's dosing was 4.74 mg/kg/day.

In dogs, repeat administration of AZD8931 was associated with epithelial degeneration and atrophy in the cornea, skin, gastrointestinal tract and genitourinary tract. These findings are consistent with the pharmacology of AZD8931 and there was evidence of reversibility of findings following a 4-week recovery period.

Dose limiting toxicity on repeat administration in the dog was corneal epithelial ulceration and in the one month study resulted in the termination of one high dose animal following 7 days of dosing due to a severe ulceration. In surviving animals recovery of less severe corneal ulceration was observed in life, despite continued dosing. In a single ascending dose (SAD) study in the dog, corneal translucency was observed in life but a mild corneal epithelial ulceration was seen on histopathology. Gastrointestinal toxicity was dose limiting in the SAD study. The NOAELs for corneal translucencies and ulceration in dogs was 1.42 mg/kg/day (group mean free $AUC_{(0-24)}$ 0.39 μmol.h/L) in the 1 month study and 7.1 mg/kg (free $AUC_{(0-48)}$ 1.20 μmol.h/L) in the single escalating oral dose study.

In-vitro assays indicate a potential for QT prolongation and arrhythmia with AZD8931. There was no evidence of QT prolongation in in-vivo cardiovascular studies. Intravenous

administration of AZD8931 in an anaesthetised dog model at a dose of 30 mg/kg resulted in hyperkalaemia with associated ECG waveform changes. Hyperkalaemia was not seen following oral dosing to conscious dogs. Reductions in arterial BP were also observed at this dose level in anaesthetised dogs. In a dog SAD study, at doses of 7.1 mg/kg and above, AZD8931 produced reversible reductions in arterial BP.

Dose related increases in plasma glucose, generally accompanied by increases in plasma cortisol have been observed in dogs following oral administration of AZD8931. Hyperglycaemia had reversed within 24 hours of dosing. The insulin response to hyperglycaemia appeared to be attenuated at high plasma levels of AZD8931.

A potential photo toxicity risk with AZD8931 has been identified based on the light absorption profile of the compound and a positive result in the fibroblast 3T3 cell assay.

2.1.2 Clinical studies

At the time of preparation of this document, the AZD8931 AstraZeneca clinical development programme comprises: one completed Phase I study in healthy male volunteers (D0102C00001), one ongoing Phase I multiple ascending dose (MAD) study in patients with advanced solid malignancies (D0102C00002), and one planned Phase I/II multiple ascending dose study of AZD8931 in combination with paclitaxel in patients with advanced solid malignancies/advanced breast cancer (D0102C00003).

2.1.2.1 Western Phase I Study in Healthy Volunteer Data

The tolerability and initial PK of AZD8931 monotherapy was investigated in a Phase I study (D0102C00001) in 40 healthy male volunteers recruited in the west. On the basis of all safety data, AZD8931 has shown a favourable safety profile, being tolerated at single oral doses ranging from 2.5 mg up to 200 mg in healthy volunteers. Rash/acne type events were reported for AZD8931, events consistent with the known safety profile of the EGFR tyrosine kinase inhibitor (TKI) class.

No volunteer experienced a clinically relevant change in safety parameters such as physical examinations (including ophthalmological assessments), BP, pulse, ECG parameters, urinalysis, clinical chemistry or haematological assessments. Asymptomatic corneal epithelial changes, detected by fluorescence staining, were noted in 1/5 healthy volunteers treated at 200 mg in this study. These findings were suggestive of superficial desquamation, and an external ophthalmology expert confirmed that normal environmental factors (eg, swimming in chlorinated water) could result in similar observations. These findings were seen on day 5 only and began resolving within a few hours of being noticed, complete resolution being documented 3 days later. The external ophthalmologist providing corneal evaluation expertise to the AZD8931 clinical studies has deemed these findings as highly unlikely to be drug-related. Based upon the comprehensive review of the safety data, PK data and statistical analyses of ECGs, it was concluded that no changes in QTc of any clinical concern were seen at the exposures reached in this study.

PK data indicate that at single oral doses of 2.5 mg to 200 mg AZD8931 was orally bioavailable, rapidly absorbed (median t_{max} of 1 to 2 hours) and had an average terminal elimination half-life of 11.7 hours. A slightly greater than proportional increase in exposure with increasing dose was observed. Renal clearance was low with no more than 4% of the dose excreted unchanged in the urine within the first 24 hours post-dose.

2.1.2.2 Western Phase I Study in Advanced Solid Malignacies Data

In the ongoing Phase I MAD study in the west, AZD8931 monotherapy at 40 mg, 80 mg, 160mg, 240 mg and 300 mg (twice daily) have already been tested in 5, 8, 6, 6 and 3 patients with advanced cancer, respectively, and found be to tolerated. The key safety findings from the ongoing Phase I MAD study in the west, based on preliminary, unvalidated information provided as of 26 May 2009, are as follows:

- AZD8931 has been declared tolerable at oral doses of 40 mg, 80 mg, 160 mg and 240 mg twice daily in patients with advanced cancer. But 300 mg twice daily has been declared a non-tolerated dose.
- One patient on 240 mg does cohort experienced a DLT of rash (CTCAE grade 3)
- Two patients on 300 mg dose cohort experienced DLTs : one had acute pre-renal failure, and the other had CTCAE grade 3 diarrhea.
- The death of one patient has been reported in this study. The cause of death was progression of left hip soft tissue sarcoma with abdominal metastases which occurred after the patient had discontinued treatment with AZD8931 160 mg twice daily. This death was not considered by the investigator to be related to study treatment.
- Adverse events consistent with rash have occurred in 27 of 28 patients receiving AZD8931 (7 of these events were CTCAE grade 3).
- Events of diarrhea have occurred in 21 of 28 patients. In the majority of these patients the maximum intensity of diarrhea was CTCAE grade 1 or 2; 7 patients experienced a CTCAE grade 3 event.

Preliminary PK data from the ongoing Phase I MAD study following single dose administration were reasonably similar to those obtained after the same single doses were administered to healthy volunteers, suggesting no difference in the PK between healthy volunteers and patients with advanced cancer. AZD8931 plasma concentrations after multiple dosing suggest steady state was reached by day 3, in agreement with the mean terminal half-life (11.7 hours) determined in study D0102C00001. The preliminary PK parameters were reasonably dose proportional across 40 to 160 mg dose range studied to date, however, data from higher doses are required to assess this further.

2.2 Research hypothesis (Not applicable)

2.3 Rationale for conducting this study

2.3.1 Rationale for safety and pharmacokinetics

AZD8931 is a new investigational medicinal product intended for the treatment of solid malignancies. Non-clinical studies have demonstrated the potential for AZD8931 to produce various toxicities in addition to its anti-cancer effect, possibly secondary to its pharmacological action. It is therefore imperative to determine the safety and tolerability of AZD8931 in the intended patient population before further studies of its potential efficacy can be done. Further, it is necessary to determine the PK profile of AZD8931 in this patient population to assess whether the intended dosing schedule will provide adequate exposure to the investigational product.

This study is therefore intended to assess the safety, tolerability, MTD and PK of AZD8931 in patients with advanced solid malignancies.

2.3.2 Rationale for planned biomarker research

As an exploratory objective, it is planned to investigate the correlation between biomarkers and AZD8931 therapy. This may provide preliminary evidence that AZD8931 induces apoptosis and tumour necrosis in EGFR- and ErbB-driven tumours.

2.3.3 Rationale for pharmacogenetic research

AstraZeneca intends to perform genetic research in the AZD8931 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD8931. Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD8931 but also susceptibility to disease for which AZD8931 may be evaluated. It is planned to take blood samples for future pharmacogenetic analysis, with the intention to determine any potential ability to identify individuals who may respond optimally to AZD8931 or a specific dose of AZD8931, or to identify factors that may affect the absorption, distribution, metabolism or excretion or tolerability of AZD8931.

Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

2.3.4 Rationale for efficacy assessments

As an exploratory objective, the anti-tumour activity of AZD8931 will be investigated. Results will be preliminary only, but will be used to aid design of future AZD8931studies.

2.4 Benefit/risk and ethical assessment

Modulation of the EGF and ErbB2 receptors has been shown to provide clinical benefit for other agents. AZD8931 is in development for the treatment of patients with solid malignancies and non-clinical testing has indicated that patients with ErbB family-driven solid tumours may benefit from treatment with AZD8931. However, at present there are no data

safety and tolerability available from exposure of Japanese patients to AZD8931 yet. Therefore this study is conducted to address the safety and tolerability of AZD8931 monotherapy in Japanese patients with advanced solid malignancies and in combination with Paclitaxel in Japanese female patients with advanced breast cancer. Clinical benefit of AZD8931 monotherapy and combination therapy with Paclitaxel is unclear currently, however target population in monotherapy part are patients with advanced solid malignacies which have no further response to standard therapies or which have no appropriate standard therapies, and in combination part advanced breast cancer patients being eligible to Paclitaxel will receive Paclitaxel treatment with standard dose and schedule. In this protocol clinical PD based on investigator's opinion is strictly defined one of criteria for discontinuation of investigational product to minimize the risk of patients. The study will provide information on the safety and tolerability profile of AZD8931, together with PK and pharmacodynamic data, which will support the future clinical development of AZD8931 for the treatment of cancer and potentially meeting the unmet medical need in future cancer patient populations. The study sponsor, principal investigators and Independent Data Monitoring Committee should review all grade 2 and over AEs and safety data, whether or not considered causally related to the investigational product.

Section 1 to 2 and Section 17 to 24 are common part. Section 3 to 9 are monotherapy part. Section 10 to 16 are combination therapy part.

Section 3 to 9 is specific procedure for **monotherapy part**

3. MONOTHERAPY, STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study is to explore the safety and tolerability of multiple ascending doses of AZD8931 in Japanese patients with advanced solid tumours.

3.2 Secondary objectives

The secondary objectives are as follows:

- To identify the maximum tolerated dose (MTD) of AZD8931 following repeated twice-daily administration.
- To explore the Pharmacokinetics of single doses of AZD8931 in Japanese patients with advanced solid tumours
- To explore the Pharmacokinetics of multiple doses of AZD8931 in Japanese patients with advanced solid tumours

3.3 Exploratory Objectives

The exploratory objectives are as follows:

- To obtain preliminary assessments of the efficacy of AZD8931 by using objective response rate and change of tumour size according to RECIST in patients with measurable lesion.
- To measure exploratory biomarkers from blood and tumour tissue samples and examine the relationship of these biomarkers with clinical outcome (optional)
- To obtain a blood sample for DNA extraction for possible pharmacogenetic analysis (optional).

4. MONOTHERAPY PART, STUDY PLAN AND PROCEDURES

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

4.1 Overall study design and flow chart

The Monotherapy part is an unblinded, multiple ascending dose study to assess the safety and tolerability of AZD8931 in Japanese patients with advanced solid malignancies.

This study will be conducted in Japanese patients with advanced solid tumours which have no further response to standard therapies or which have no appropriate standard therapies.

The starting dose is planned to be 80 mg. Patients will receive initial treatment with single dose of AZD8931 followed by a 6-day washout period, then a 21-day multiple dosing period of AZD8931. In each dose cohort a minimum of 3 and a maximum of 6 evaluable patients are enrolled. The starting dose will be AZD8931 80 mg, with escalation to a maximum of 300 mg.

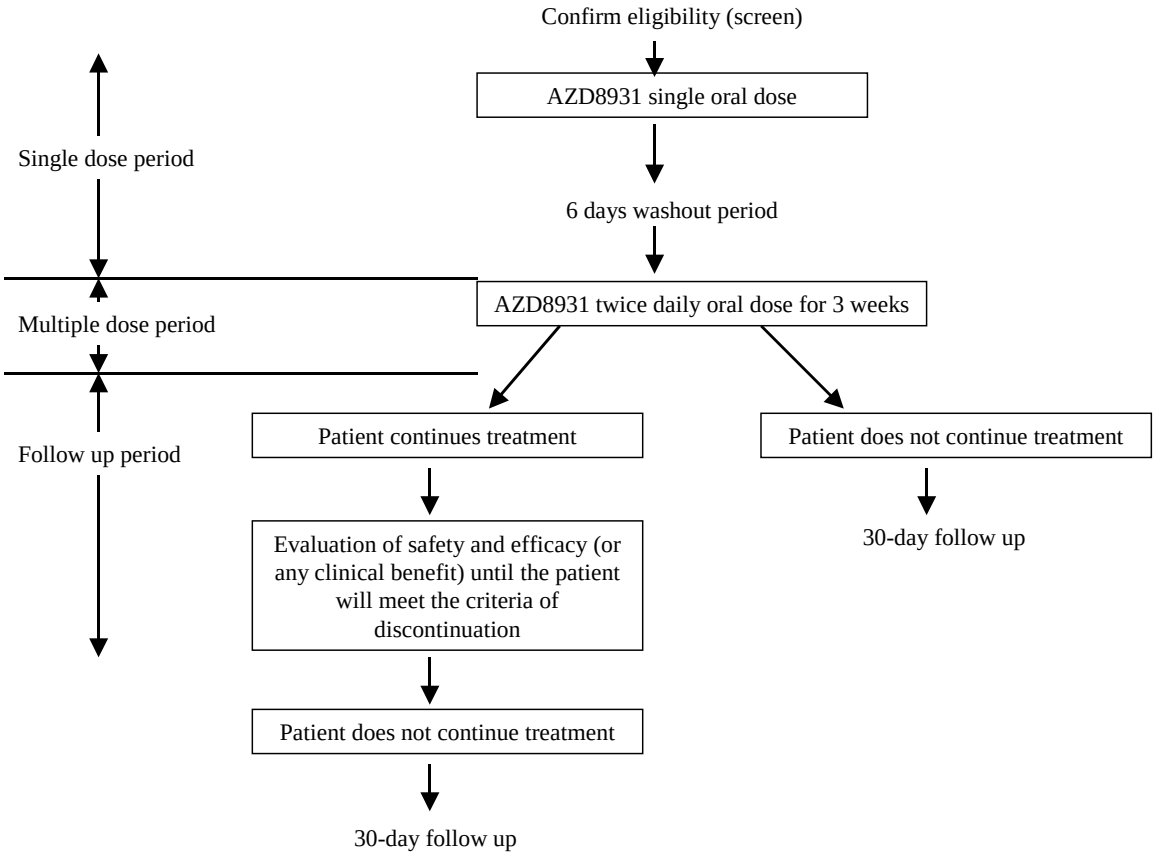
Dose	Single dose	Multiple dose
80 mg	80 mg/day	80 mg x2 (160 mg/day)
160 mg	160 mg/day	160 mg x2 (320 mg/day)
200 mg	200 mg/day	200 mg x2 (400 mg/day)
240 mg	240 mg/day	240 mg x2 (480 mg/day)
300 mg	300 mg/day	300 mg x2 (600 mg/day)

Patients may continue daily oral treatment indefinitely if they do not meet a withdrawal criterion and sign on the informed consent form for treatment continuation, are free from intolerable toxicity, and, in the investigators opinion, are receiving some benefit from the therapy.

The study flowchart for the monotherapy part of the study is presented in Figure 1.

Monotherapy part

Figure 1 Study Flow Chart for Monotherapy part



Monotherapy part

The study plan for Monotherapy is presented in Table 1.

Table 1 Study Schedule for Monotherapy part

Assessments	**Screening**	**Treatment period**									**Contin-uation beyond R21**	**Discontinuation of treatment [c]**	**Safety follow up[g]**
		Single dose	**Wash-out**			**Multiple dose**							
Day (h = hours)	**D–21 to D0**	**D1**	**D2 (24 h)**	**D3 (48 h)**	**D4 (72 h) to D7**	**D8**					**Every 3 weeks**		
Repeat dosing (R) day (d=day)						**R1**	**R3**	**R7** ±1d	**R14** ±1d	**R21** ±1d	±3d		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Informed consent (main study, genetics [optional], exploratory biomarkers [optional])	x												
Another informed consent [a] ; main study (study continuation)		◄———	———	———	———	———	———	———	———	———►			
Inclusion/exclusion criteria	x												
Tumour TNM stage at diagnosis	x												
Tumour assessment (RECIST)	x[b]										x[d]	x	
Chest X-ray	x												
High Resolution CT Scan Thorax and arterial oxygen saturation [q]	x	◄———	———	———	———	———	———	———	———	———	———	———	———►

Assessments	**Screening**	**Treatment period**									**Contin-uation beyond R21**	**Discontinuation of treatment** [c]	**Safety follow up** [g]
		Single dose	**Wash-out**			**Multiple dose**							
Day (h = hours)	**D–21 to D0**	**D1**	**D2 (24 h)**	**D3 (48 h)**	**D4 (72 h) to D7**	**D8**					**Every 3 weeks**		
Repeat dosing (R) day (d=day)						**R1**	**R3**	**R7** ±1d	**R14** ±1d	**R21** ±1d	±3d		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Demographics	x												
Medical/surgical history	x												
Previous anticancer therapy, including surgery and radiotherapy	x												
Urine pregnancy test [s]	x											x	
Administer AZD8931		Single dose [e]				Twice daily for 21 days [e]					Twice daily [e]		
Physical examination	x											x	
WHO Performance Status	x												
Ophthalmological examinations [h]	x									x	x	x	
Echocardiography	x									x	x [i]	x	
12-lead Electrocardiogram [j]	x [p]	x	x	x	x	x	x	x	x	x	x	x	
Vital signs (pulse, blood pressure)	x [p]	x	x	x	x	x	x	x	x	x	x	x	

Assessments	**Screening**	**Treatment period**									**Contin-uation beyond R21**	**Discontinuation of treatment [c]**	**Safety follow up[g]**
		Single dose	**Wash-out**			**Multiple dose**							
Day (h = hours)	**D–21 to D0**	**D1**	**D2 (24 h)**	**D3 (48 h)**	**D4 (72 h) to D7**	**D8**					**Every 3 weeks**		
Repeat dosing (R) day (d=day)						**R1**	**R3**	**R7** ±1d	**R14** ±1d	**R21** ±1d	±3d		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Blood sample for PK analysis		x[k]	x	x	x		x[k]	x[k]	x[k]				
Blood sample for clinical chemistry, haematology, coagulation parameters (including HbA1c[r] at screening)	x[p,f]	x[l,m]	x	x	x	x[l]	x[l]	x[l]	x[l,m]	x[l]	x	x	
Blood samples for exploratory biomarkers (optional)	x[p]	x[l, n]						x[l]		x[l]	x[l]	x	
Tumour tissue sample for exploratory biomarkers (optional)		x[o]											
Blood sample for pharmacogenetics (optional)		x[o]											
Urine sample for urinalysis	x[p]	x[l]	x	x	x	x	x	x	x	x	x	x	
Concomitant medications	←											→	
Adverse events	←											→	

Monotherapy part

TNM = Tumour, Node, Metastases; RECIST = Response Evaluation Criteria In Solid Tumours; HbA1c = glycosylated haemoglobin; D=Day, R=Repeated dose day

Notes to study plan

a Treatrment may be extended beyond day R21, providing that informed consent is obtained before R22 or restart of the dosing with a reduced dose after dose interruption as a result of DLT that occurred during the period from D1 to R21. (see Section 6.4.2.1).

b Baseline radiological tumour assessments should be performed no more than 4 weeks before the start of study treatment, but should be as close as possible to the start of study treatment. The tumour assessment obtained before consent can be used if the examination took place within 28 days before the first dosing (D1). This is applicable only when the subject agrees on the use of data measured before informed consent.

c The assessments for discontinuation of treatment should be done as soon as possible after last dose of study treatment

d Every 6 weeks (±7 days), relative to day R1, until objective disease progression, study drug discontinuation, withdrawal of informed consent or death (whichever is soonest).

e No food is allowed from 2 hours before to 2 hours after study drug dosing.

f Fasting glucose at screening

g As a minimum telephone contact must be made with the patient at least 30 days after discontinuing treatment to collect and/or complete AE and concomitant medication information.

h Full ophthalmological assessment must be performed at screening and R21. Beyond R21 a full examination should only be performed in case of clinically relevant ophthalmological abnormalities, see Section 17.3.9.3.

i Every 9 weeks for 3 times after R21, then every 18 weeks.

j 12-lead electrocardiogram (ECG) after 10 minutes rest in the supine position. The patient should be examined using the same machine throughout the study. Digital ECGs for QTc interval analysis (days D1 and R14) must be in triplicate (one after another). Paper read-outs of all ECG time points are sufficient for on site safety assessments.

k At pre-dose and at 1, 2, 4, 6, 8 and 10 (prior to AZD8931 administration on R14) hours post-dose (days D1 and R14). Pre-dose (days R3 and R7).

l Pre-dose.

m Glucose and potassium only at 6 hours post-dose (days D1 and R14).

n At 8 hours post-dose.

o After confirmation of eligibility. If for any reason the blood sample is not drawn on D1, it may be taken at any visit until the last study visit.

p If there are screening data within 2 days prior to first dose, pre-dosing data on Visit 2 are not mandatory

q HRCT and arterial oxygen saturation (SpO_2) are mandatory and should be performed before first dose of AZD8931 at baseline(and within 28 days prior to enrolment). The algorithm described in Appendix D should be followed if any of the following occur or worsen while on the study: dyspnoea, fever, cough, new pulmonary radiological finding. For determination of SpO_2, the same equipment or type should be used. SpO_2 should be performed every 6 weeks at R22 and thereafter. (see Section 17.3.9.1)

r For HbA1c, screening, D1, Every 9 weeks after R21 and withdrawal visit

s Only for women of childbearing potential

4.1.1 Dose, DLT evaluation and Criteria to conduct dose escalation

Dose

The dose of first cohort is 80 mg. The doses of next cohort are planed to 160 mg, 200 mg, 240 mg and 300 mg. The dose escalation committee will make the decision of dose of next cohort based on results of study D0102C00002.

DLT evaluation period and Dose Evaluation Committee

The DLT evaluation period starts from the first administration of AZD8931 and continues until the completion of all assessments prior to R22 (within the 28 days of the first dose).

The Dose Evaluation Committee is composed with three members of principal investigator, study team physician and leader. The committee will make final judge for DLT and final decision of dose escalation or de-escalation, and documents the final judge and decision.

DLT evaluation process

The investigator will report in a designated form patient information, all CTCAE grade 2 (according to Version 3 Common Terminology Criteria for Adverse Events) and greater adverse events observed in DLT period of each enrolled patient and DLT evaluation to the Dose Escalation Committee (DEC). Prior to each dose escalation, the DEC will meet to review the safety, tolerability and PK data (If prompt PK analysis of samples will be obtained, the data will be reviewed in each dose-escalation decision, in addition to review of all the safety and tolerability data.), then DEC will make final judge of DLT.

Criteria to conduct dose escalation

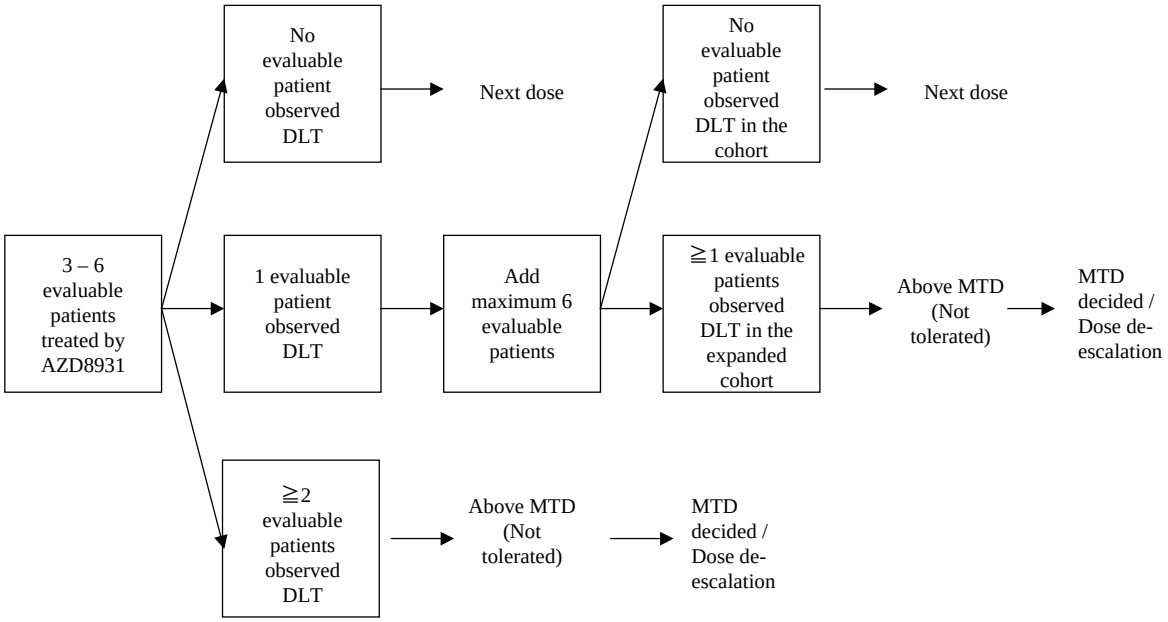
A minimum of 3 and a maximum of 6 evaluable patients are needed for dose escalation decision. Dose-escalation or de-escalation will be decided based on the safety data from a minimum of 3 evaluable patients obtained during DLT evaluation period of the previous cohort.

- No DLT permit to dose escalation, judging prior dose is tolerable.
- If one patient experiences a DLT, enrolment will be continued to accumulate total 6 evaluable patients. In case that only one patient out of 6 evaluable patients experience a DLT, dose escalation is permitted, judging prior dose is tolerable.
- If over two patients experiences a DLT, DEC will make decision of dose escalation stop or dose de-escalation which dose is decided by DEC, judging prior dose is non-tolerable.

DEC will be able to make the decision of dose escalation stop even before finding MTD based on the results of study D0102C00002.

Figure 2 summarises the rules to be applied.

Figure 2 Dose escalation decision tree



4.1.2 Definition of non tolerated dose

A dose will be considered non tolerated, and dose escalation will cease, if ≥2 DLTs occur within a dose group (see Section 4.1.1).

4.1.3 Definition of maximum tolerated dose

When a non-tolerated dose is defined, dose escalation will be stopped and the MTD will be confirmed at the previous dose level below the non-tolerated dose, or a dose between the non tolerated dose and last tolerated dose assessed may be investigated.

If a dose between the non-tolerated dose and the last tolerated dose assessed is selected for investigation, then the dose escalation criteria detailed in Section 4.1.1 apply

When a non-tolerated dose could not be defined, MTD is defined as a highest tolerable dose.

When MTD is defined and the data on the dose below is based on data from <6 patients, then additional patients will be recruited at this lower dose to confirm a MTD based upon data from 6 evaluable patients.

4.1.4 Definition of dose limiting toxicity

A dose-limiting toxicity (DLT) is defined as an intolerable toxicity (IT) of adverse events or laboratory abnormalities considered to be related to AZD8931, that commences within 28 days of the first dose and meets any of the following criteria:

- Ophthalmological toxicity

- Symptomatic ocular surface lesion (epitheliopathy or erosion) with the following clinically significant criteria: >1 mm in diameter, <1 mm in diameter and clustered in a group of 10 or more, appearance of filaments or multiple (>2) small (≤1 mm) areas or a large (>1 mm) area of negative fluorescein staining which cannot be attributed to another cause and which does not recover over a period of 3 days following detection of these findings.

- Haematological toxicity
  - Any Common Terminology Criteria for AEs (CTCAE) grade 4 haematological toxicity of any duration
  - Febrile neutropenia (CTCAE grade ≥ 3 with temperature ≥38.0°C which is unresponsive to antipyretics)
  - CTCAE grade ≥ 3 neutropenia requiring prolongation of hospitalisation due to complications associated with neutropenia
  - CTCAE grade ≥ 3 thrombocytopenia associated with non-traumatic bleeding (but not applicable to patients on therapeutic anticoagulation)
- Clinical chemistry toxicity
  - CTCAE ≥ grade 3 hyperkalemia (ie, >6.0 mEq/L; 6.0 mmol/L) which has been confirmed (by repeat sampling) and is considered to be drug related
  - CTCAE ≥ grade 3 hyperglycemia (ie, >250.2 mg/dL; 13.9 mmol/L), from fasting glucose, which has been confirmed (by repeat sampling) and is considered to be drug related
- Cardiovascular toxicity
  - QTcF (Fridericia's correction) interval > 500 msec or increase by >60 msec, compared to baseline on two ECGs at least 30 minutes apart, that cannot be attributed to another cause
  - Symptomatic congestive cardiac failure (New York Heart Association [NYHA] class III/IV) and a drop in left ventricular ejection fraction (LVEF) which cannot be attributed to another cause [1]
  - A decrease in LVEF of ≥20% to a level below the institution's lower limit of normal range

[1] Concomitant use of vasotonic drugs, adrenergic blockers, negative inotropic agents and anti hypertensives should be taken into consideration when assigning causality.

- CTCAE ≥ 3 hypotension which cannot be attributed to another cause

- Other toxicities
  - Clinically significant rash that despite optimal treatment remains CTCAE grade ≥3 for 5 days or longer and that cannot be attributed to another cause
  - CTCAE grade ≥ 3 renal/urinary toxicity which cannot be attributed to another cause
  - CTCAE grade ≥3 interstitial lung disease or pneumonitis which cannot be attributed to another cause
  - CTCAE grade ≥ 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 ≥ 3 toxicity which, in the opinion of the investigator, is clinically significant and related to the study drug

4.1.5 Definition of evaluable patient

An evaluable patient is defined as a patient that meets any of the following criteria:

- A patient completed 75% of planned daily dosed in the first 28 days and has enough information to be assessed for the dose escalation

- A patient who experienced a DLT within the initial 28 days

During this period, any patient required to have their daily dose of AZD8931 reduced will no longer be defined as evaluable in the study unless they have experienced a DLT.

4.2 Rationale for study design, doses, population

Patient population

This population has been chosen to obtain safety, tolerability and PK data in a patient population relevant to further studies and future use of this compound.

There are no data to indicate that the safety and tolerability of AZD8931 will differ significantly in patients with different types of tumour. An “all comers” population of patients with advanced solid malignancies are therefore eligible to enter this part of the study.

Doses

In the western Phase I study (D0102C00002), AZD8931 were tested at 40 mg, 80 mg, 160 mg 240 mg and 300 mg (twice daily). According to preliminary, unvalidated information provided as of 26 May 2009, the most frequently reported adverse events (AEs) in this study were rash and diarrhea. AZD8931 has been declared tolerable at oral doses of 40 mg, 80 mg,

160 mg and 240 mg twice daily in patients with advanced cancer. No dose limiting toxicities were reported on 160mg or lower dose cohorts. The starting dose in this study in Japanese patients is 80 mg twice daily, at which the possibility of severe adverse events occurrence may be low. The subsequent dose levels in this study are planed to be 160 mg, 200 mg, 240 mg and 300 mg twice daily with reference to the dose levels to be used in the D0102C00002. In addition, 240 mg is decided as MTD in D0102C00002.

Design

This is the first study of AZD8931 in Japanese cancer patients and as such follows a conventional sequential dose escalation design in Japan. The number of evaluable patients to be enrolled is based on the desire to gain adequate information whilst exposing as few patients as possible to the study medication and procedures.

A single dose followed by a washout will allow single dose PK in Japanese patients to be collected. No Japanese patient data currently exists but 21 days of twice daily dosing should allow AZD8931 to reach steady state.

5. MONOTHERAPY PART, SUBJECT SELECTION CRITERIA

Subject population should be selected without bias.

Investigator(s) must keep a record of subjects who entered pre-trial screening but were never enrolled eg, subject screening log. Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

5.1 Inclusion criteria

For inclusion in the study subjects must fulfil the following criteria.

For inclusion in this host genetic and biomarker research, subjects must fulfil all of the inclusion criteria described in the main body of the study protocol and: Provide informed consent for the genetic and biomarker sampling and analyses.

1. Provision of written informed consent

2. Japanese Male or female aged ≥20 years

3. Cancer that is refractory to standard therapies, or for which no standard therapies exist. Inclusion is irrespective of stage of disease or extent of prior therapy

4. Histologically or cytologically confirmed solid, malignant tumour

5. WHO performance status 0 to 2 (those with ps 2 must have been stable with no deterioration over the previous 2 weeks) (See Table 7)

6. Life expectancy of at least 12 weeks

7. Females must be of non-childbearing status defined as one of the following criteria at screening:

   - negative pregnancy test in women of childbearing potential
   - or women who are permanently or surgically sterilised (hysterectomy and/or bilateral oopherectomy and/or bilateral salpingectomy)
   - or postmenopausal (over 50 years old and amenorrheic for ≥12 months following cessation of all exogenous hormonal treatments, or over 57 years old).

8. The patient is able to be hospitalized at least within the first 28 days of dosing.

5.2 Exclusion criteria

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

1. Cardiac ejection fraction outside institutional range of normal as measured by echocardiogram (or MUGA scan if an echocardiogram cannot be performed or is inconclusive)

2. Any of the following is regarded as a criterion for exclusion from the study:

   - Inadequate bone marrow reserve as demonstrated by an absolute neutrophil count $<1.5 \times 10^9$/L or platelet count $<100 \times 10^9$/L.
   - Haemoglobin ≤9 g/dL (5.59 mmol/L).
   - Inadequate liver function as demonstrated by serum bilirubin ≥1.5 x ULN, or ALT or AST ≥ 2.5 x ULN, or ALP ≥2.5 x ULN in the absence of noted liver or bone metastases (ALP, AST or ALT ≥5.0 x ULN if judged by the investigator to be related to liver or bone metastases).
   - INR and APTT >1.2 x ULN.

3. Last dose of prior anticancer therapy received any of the following treatments within 4 weeks prior to study entry: chemotherapy (within 6 weeks for nitrosurea or mitomycin C), radiotherapy, hormone therapy (except for androgen-deprivation therapy for patients with prostate cancer), immunotherapy and any other anti-cancer therapies. 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 AstraZeneca and the investigator.

4. Unresolved toxicity greater than CTCAE grade 1 from previous anti-cancer therapy, except alopecia

5. Prior exposure to anthracyclines or mitoxantrone with cumulative exposure in excess of 360 mg/m^2 (body surface area) for doxorubicin, 720 mg/m^2 (body surface area) for epirubicin, or 72 mg/m^2 (body surface area) for mitoxantrone.

6. Resting ECG with measurable QTc interval of >450 msec at 2 or more time points within a 24 hour period

7. Known uncontrolled or symptomatic angina, arrhythmias or congestive heart failure; evidence of transmural infarction on ECG, poorly controlled hypertension (systolic >180 mmHg or diastolic >100 mmHg), significant valvular disease or history of high risk dysrhythmia (such as ventricular fibrillation or ventricular tachycardia [includes ventricular triplets]) or history of *Torsade de pointes*

8. Unable to discontinue medication with agents designated as Class I Arizona risk for QT prolongation (See Section 6.5)
Note: use of agents with Class II designation is allowed if patients have being receiving a stable dose for at least 5 half-lives of the drug.

9. Evidence of 'dry eye': persistent symptoms of ocular surface irritation, Schirmer's test without anaesthesia of less than 5 mm in 5 minutes and tear break-up time [TBUT] test of less than 10 seconds (if one of these is satisfactory, the patient may be included – both of these parameters should be normal if the patient is receiving anti-cholinergic medication. Eye conditions that are stable and of long standing, such as scars from trauma, pinguecula, atrophic pterygia etc, should not be considered as reasons to exclude the patient

10. Wearing contact lens (patients should discontinue wearing contact lens from at least 1 week prior to entering the study to 1 week following discontinuation of AZD8931)

11. Recent acute changes in patient's vision, or ongoing symptoms of ocular pain, discomfort or irritation

12. History of collagen vascular, chronic inflammatory or degenerative disease with eye involvement (eg, rheumatoid, Sjögren syndrome, systemic lupus erythematosus [SLE]) or of ocular surface disease (including Steven-Johnson syndrome, ocular cicatricial pemphigoid or chemical burns, herpes simplex or herpes zoster virus eye disease

13. History of corneal surgery, including laser refractive surgery, within the past 3 years

14. Medical diagnosis of acne rosacea, psoriasis, or severe atopic eczema (common acne vulgaris is acceptable for this study)

15. Brain metastases, unless surgically removed and/or irradiated at least 4 weeks before study entry and stable without anti-seizure or steroid treatment for >1 week. Brain metastasis with clinical signs and/or symptoms attributable to active intra-cerebral metastases and/or oedema or progressive growth demonstrated by brain imaging or use of concomitant anti-seizure medication or corticosteroids

16. No 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

17. No active or uncontrolled systemic disease which makes it undesirable for the patient to participate in the study or which would jeopardise compliance with the protocol

18. Fasting blood glucose at screening ≥126 mg/dL (7 mmol/L).

19. Elevated potassium levels at screening (>5.5 mEq/L [>5.5 mmol/L])

20. Inadequate renal function as demonstrated by serum creatinine >1.5 ULN, or creatinine clearance (estimated by Cockcroft-Gault equation or measured via 24 hr urine creatinine) <50 mL/min.

21. Currently receiving inhibitors and inducers of CYP3A4 or CYP2D6, listed in Section 6.5. The patient should not have received the therapy within the stated washout periods.

22. Known hypersensitivity to AZD8931, its excipients, or drugs in its class (including oral tyrosine kinase inhibitors).

23. Current disease or condition known to interfere with absorption, distribution, metabolism or excretion of drugs

24. History or repeated unexplained episodes of syncope/dizziness

25. Breast-feeding women.

26. Female patients of child-bearing potential who are unwilling to use an acceptable highly effective method of contraception during the study and for 30 days after the last dose of study drug.

27. Male patients are unwilling to use an acceptable highly effective method of contraception during the study and for 3 months after the last dose of study drug.

28. History of use of an investigational agent within the 30 days prior to entry.

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

30. Clinical judgment by the investigator that the patient should not participate in the study

31. HBV, HCV or HIV infection. Screening of patients for these infection is not required, however, patients known to have such infection at screening should not be included

32. Known immunodeficiency syndrome

33. Unable to swallow and retain oral medication.

34. Prior history of eyelid or eyelash abnormalities, clinically significant ocular surface disease, eye injury, corneal surgery or prior orbital irradiation.

The following criterion will require exclusion from the optional **pharmacogenetic component** part of the study:

35. Receipt of a whole blood transfusion in the preceding 90 days, or a previous bone marrow transplant before genetic sample collection.

5.3 Procedures for handling incorrectly included subjects

Subjects that do not meet the inclusion/exclusion criteria for a study should not, under any circumstances, be enrolled into the study– there can be no exceptions to this rule.

Where subjects that do not meet the study criteria are enrolled in error, incorrectly randomised, or where subjects subsequently fail to meet the criteria for the study post enrolment, the procedures included in the protocol for the discontinuation of such subjects must be followed. These procedures must be included in the protocol and must take into consideration ethical and safety factors and how these subjects will be treated in the analyses. (See Section 5.4.2)

5.4 Withdrawal of subjects

5.4.1 Criteria for discontinuation from the study

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject are:

- Voluntary discontinuation or rejection to the informed consent for treatment continuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment

- Risk to subjects as judged by the investigator and /or AstraZeneca (including positive pregnancy test)

- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca

- Incorrectly enrolled subjects (ie, the patient does not meet the required inclusion/exclusion criteria for the study)

- Subject lost to follow-up

- Patient is considered to have clear evidence of clinically significant PD, which, in the investigator's opinion requires discontinuation of study treatment and initiation of an alternative anti-cancer treatment. (NOTE: discontinuation of study treatment for clinically insignificant and minimally progressive disease (PD) should not, of itself, be a reason for study treatment discontinuation)

Specific reasons for discontinuing a patient from the biomarker research component of the study are:

- Withdrawal of consent for biomarker research. A patient may withdraw from this component at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment

Specific reasons for discontinuing a patient from the genetic research component of the study are:

- Withdrawal of consent for genetic research. A patient may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment

5.4.2 Procedures for discontinuation of a subject from the study

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The principal investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (See Sections 17.3.3 and 17.3.4); and study drug should be returned by the subject.

Ongoing Serious Adverse Events (SAEs) and AEs should be followed up to resolution or stabilisation, unless the event is considered by the investigator to be unlikely to resolve due to the patient's underlying disease (in these cases, the investigator must record his/her opinion in the patient's medical records), or the patient is lost to follow-up.

5.4.3 Procedures for discontinuation from biomarker and genetic aspects of the study

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for the optional biomarker and genetic research. It must be established whether the patient:

Biomarker research

- Agrees to the blood and tumour tissue samples being kept for biomarker analyses.
- Withdraws consent for the sample to be kept for biomarker analysis and wishes the sample to be destroyed. Destruction of the sample will only be possible so long as the particular sample is traceable. In the event that biomarker research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

Genetic research

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic analyses in the future.
- Withdraws consent for the sample to be kept for genetic analysis in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

6. MONOTHERAPY PART, STUDY CONDUCT

6.1 Restrictions during the study

The following restrictions will apply:

1. Female patients of child-bearing potential must use an acceptable highly effective method of contraception plus condoms and spermicide during the study and for 30 days after the last dose of study drug. More than one contraceptive measures (e.g., condoms, intra-uterine contraceptive device, oral contraceptive, etc.) are recommended.

2. Male patients (including those that have undergone a successful vasectomy) must use condoms plus spermicide during sexual contact with a female of child-bearing potential (who is not using a highly effective method of contraception), for the duration of the study and for 3 months after the last dose of study drug.

3. Male patients should not donate sperm during the trial and for 3 months following their last dose of study treatment.

4. No food is allowed from 2 hours before to 2 hours after taking AZD8931

5. Patients must not receive any concomitant anti-cancer agents or any other investigational agents while receiving AZD8931.

6. Abstain from taking drugs with known significant CYP3A4 and CYP2D6 inducer/inhibitory effects (see Section 6.5)

7. Abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits, eg, grapefruit juice or marmalade) during the study. Amounts should not exceed more than a small glass of grapefruit juice (120 mL), or half a grapefruit, or 1-2 teaspoons (15 g) of Seville orange marmalade daily.

8. Refrain from driving for 4 hours following ophthalmic examination if pupillary dilatation performed.

9. Patients should refrain from wearing contact lenses from at least 1week prior to starting AZD8931 to 1 week after discontinuation of AZD8931.

10. Abstain from taking part in any other study whilst participating in this study.

11. Patients should use sunglasses and skin cream with UVA and UVB protection SPF >30 (PA++) if exposed to sunlight and avoid long-term daylight exposure or use of sun tanning booths during the study and for 3 months after the last dose of study treatment.

6.2 Subject enrolment

6.2.1 Method of assigning subjects to treatment groups

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

The investigator(s) will fill in the “Subject enrolment Form” after the written informed consent will be obtained, and send the form to the AZD8931 Centralised Registration Centre

by fax. The AZD8931 Centralised Registration Centre will record the E-code on the enrolment list and inform the enrolment to AstraZeneca K.K. by fax.

The E-code (EXXXXYYY) consists of a 4-digit centre number (XXXX) and a 3-digit serial number (YYY, starting with 001) issued by each study centre in order of informed consent taken. For centre number, see Supplement A "Investigators and Study Administrative Structure".

The investigator(s) will send the "Registration Notification" to the AZD8931 Centralised Registration Centre by fax (both eligible and ineligible) after the confirmation of subject's eligibility according to the results of screening tests. The AZD8931 Centralised Registration Centre will reconfirm the patient eligibility, and if eligible, the AZD8931 Centralised Registration Centre will register the subject and send by fax the "Registration Conformation Form" that includes the registration number to the investigator(s) and AstraZeneca K.K. If ineligible, the AZD8931 Centralised Registration Centre will send by fax the "Registration Conformation Form" that documented ineligible to the investigator(s) and AstraZeneca K.K.

The registration number is a 3-digit serial number, i.e., starting with number 001.

If a patient is not evaluable for the dose escalation, an additional patient should be entered in that dose level (see Section 4.1.1).

If a patient discontinues from the study the E-code will not be re-used and the patient will not be allowed to re-enter the study.

Interruption and restart

When the subject's treatment will be interrupted, the investigator(s) will fill in the "Treatment Interruption Form" and send the form to the AZD8931 Centralised Registration Centre by fax. The AZD8931 Centralised Registration Centre will inform the interruption to AstraZeneca K.K. by fax.

When the subject's treatment will be restarted, the investigator(s) will fill in the "Treatment Restart Form" and send the form to the AZD8931 Centralised Registration Centre by fax. The AZD8931 Centralised Registration Centre will inform the interruption to AstraZeneca K.K. by fax.

6.3 Blinding and procedures for unblinding the study (Not applicable)

6.4 Treatments

6.4.1 Identity of investigational product(s)

AstraZeneca will supply AZD8931 to the investigator as plain, white film coated, biconvex round tablets as follows:

Investigational product	Dosage form and strength	Manufacturer
AZD8931 40 mg tablet	40 mg film coated tablet	AstraZeneca
AZD8931 100 mg tablet	100 mg film coated tablet	AstraZeneca

6.4.2 Doses and treatment regimens

6.4.2.1 AZD8931 dosing

AZD8931 tablets will be taken orally twice daily (except for the single dose on D1), with the doses being taken approximately 12 hours apart. The AZD8931 tablets should be taken with a glass of water (approximately 150 mL) at approximately the same time each day. The effect of food on the absorption of AZD8931 has not been established. Therefore it is requested that AZD8931 be taken at least 2 hours after a meal and that no food is consumed until 2 hours after the tablets are taken. There is no restriction on the consumption of water.

Patients may continue daily oral treatment indefinitely if they do not meet a withdrawal criterion and sign on the informed consent form for treatment continuation, are free from intolerable toxicity, and, in the investigators opinion, are receiving some benefit from the therapy.

Patient may restart the dosing of AZD8931 with a reduced dose in accordance with the criteria for restart of the dosing shown in Section 6.4.2.2 after dose interruption as a result of DLT that occurred during the DLT evaluation period, if patients sign on another informed consent form for restart of the treatment beforehand.

6.4.2.2 Dose adjustment of AZD8931

Intra-patient dose adjustment of AZD8931 may be permitted according to the criteria detailed below and only after discussion and agreement of individual patient situations between the investigator, and AstraZeneca. During the study, the dose of AZD8931 may only be reduced by one dose level for an individual patient if required.

- For all patients who experience a DLT or an unacceptable toxicity, if the toxicity does not resolve to CTCAE ≤grade 1 or baseline (pre-study) after 21 days of onset, then the patients must be discontinued from the study

- If the toxicity resolves or reverts to CTCAE ≤grade 1 or baseline levels within 21 days of onset and the patient is showing clinical benefit, treatment with AZD8931 may be restarted at a preceding, lower dose level that has been defined as tolerated. Patient on 80 mg twice daily can have dose reduction to 40 mg twice daily (80 mg /day).

(a) Dose adjustments during the DLT evaluation period

If a patient experiences a DLT, AZD8931 treatment must be stopped and supportive therapy administered as required. The criteria for restarting is described above.

(b) Dose adjustment after completion of the DLT evaluation period

If a patient experiences tolerability issues with the study drug, the dose of AZD8931 may be reduced by one dose level only. Patient on 80 mg twice daily can have dose reduction to 40 mg twice daily (80 mg /day).

Even if a patient don't experience tolerability with the study drug, a patient will continue to take one level lower dose when the dose is confirmed as a non-tolerable dose.

6.4.3 Additional study drug

(Not applicable)

6.4.4 Labelling

All investigational product will be labelled with "for clinical study use only" and other information. Regarding the details of labelling, see the document 'Procedure of storage conditions for investigational product'.

6.4.5 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified on the document 'Procedure of storage conditions for investigational product'.

6.5 Concomitant and post-study treatment(s)

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator and should be recorded in the paper Case Report Forms (pCRF).

Patients are not eligible to enter the study if they have taken any of the following within the specified timeframe and concomitant use of these medications are not allowed during study treatment:

- Within 4 weeks prior to study entry: chemotherapy (within 6 weeks for nitrosurea or mitomycin C), radiotherapy, hormone therapy (except for androgen-deprivation therapy for patients with prostate cancer), immunotherapy and any other anti-cancer therapies

- Currently receiving, or taken within the stated washout period: inhibitors and inducers of CYP3A4 or CYP2D6 listed below;

  – Within 2 days prior to study entry:
  (CYP3A4 inhibitors) ketoconazole, ritonavir, indinavir, saquinovir, nelfinavir,

atazanavir, amprenavir, fosamprenavir, nefazodone, verapamil
(CYP2D6 inhibitors) duloxetine, terbinafine

– Within 7 days prior to study entry:
(CYP3A4 inhibitors) itraconazole, erythromycin, clarithromycin, telithromycin, fluconazole
(CYP2D6 inhibitors) quinidine

– Within 2 weeks prior to study entry:
(CYP3A4 inhibitor) diltiazem
(CYP3A4 inducer) barbiturates, phenytoin, rifampicin, rifabutin, carbamazepine and St. John's wort
(CYP2D6 inhibitor) paroxetine

– Within 5 weeks prior to study entry:
(CYP2D6 inhibitor) fuloxetine

- Currently receiving, or taken within 7 half-lives of the drug: drugs (eg, prescribed and non-prescription) with known significant CYP3A4 and CYP2D6 inhibitor and inducer effects. Where drug half-life information is not available, the patient should not have received the therapy within the last 4 weeks

- Currently receiving, or taken within 7 half-lives of the drug: drugs designated as Class I Arizona risk for QT prolongation. Agents designated as Class II Arizona risk for QT are allowed provided the patient has received these agents for at least 5 half-lives of the drug with no change in dose

- Ongoing treatment with anti-cholinergic medication, oral steroids, angiotensin converting enzyme (ACE) inhibitors, potassium-sparing diuretics or potassium supplements is allowed, provided the patient has been on therapy for at least 4 weeks with no changes in dose in that time.

If a patient requires elective surgery with anaesthesia during the study, it is recommended that study drug therapy should be discontinued for 3 days beforehand. If urgent anaesthesia/ muscle relaxants such as suxamethonium are required, the anaesthetist should be informed that hyperkalemia has been seen in dogs anaesthetised with propofol and alfentanil and who received high doses of AZD8931. The decision to restart study drug will be taken in consultation with the AstraZeneca physician.

6.6 Treatment compliance

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the Case Report Forms.

When patients are at the clinic, compliance will be assured by supervised administration of AZD8931 by the investigator or his/her delegate. When patients are not at the clinic, patients

will be asked to return all unused study drug at each visit (if treatment is continuing). Compliance will be assessed by means of tablet counts of returned unused study drug at each clinic visit. Compliance will be calculated at the end of the study.

6.6.1 Accountability

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

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused study drug to AstraZeneca. The principal investigator/investigator is responsible for ensuring that the subject has returned all unused study drug. For details, to refer AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage', which AstraZeneca K.K. will provide for medical center.

7. MONOTHERAPY PART, COLLECTION OF PHARMACOKINETIC VARIABLES

For timing of individual samples refer to the study plan (See Table 1).

7.1 Collection of biological samples

PK samples (2.7 mL of venous blood) will be collected at the following time points for determination of AZD8931 plasma concentrations:

D1 and R14: pre-dose, 1, 2, 4, 6, 8, 10 (prior to AZD8931 administration on R14), 24 (D1 only), 48 (D1 only) and 72 (D1 only) hours post dose. R3 and R7: pre-dose (see Table 1).

Depending on emerging data/information, the timings and number of PK samples may be altered, but the maximum blood volumes from scheduled samples given in Table 2 will not be exceeded. The actual sample time and date of all PK samples must be recorded in the pCRF.

All biological samples will be collected, processed, labelled and shipped to a laboratory for analysis in accordance with the Laboratory Manual. At appropriate time intervals, the samples will be transported on dry ice to the appropriate laboratory(ies) for analysis. Samples should be analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable

Samples will be disposed of after the Clinical Study Report has been finalised.

7.2 Determination of drug concentration in biological samples

Analysis of plasma samples for the determination of AZD8931 concentrations will be the responsibility of the Clinical Pharmacology & DMPK Department, Alderley Park,

AstraZeneca, UK. If warranted, the samples may also be used for investigation/analysis of circulating metabolites and/or exploratory biomarkers.

8. MONOTHERAPY PART, CALCULATION OR DERIVATION OF PHARMACOKINETIC VARIABLES

The PK analyses will be performed at AstraZeneca R&D. The actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods. Where the data allow, the following PK parameters will be determined:

- Single dose plasma PK
  - AUC_{0-10}, AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, AUC, C_{max}, t_{max}, $t_{1/2}$, CL/F, Vss/F
- Multiple dose plasma PK
  - $AUCss_{0-10}$, $AUCss_{0-12}$, Css_{max}, tss_{max}, Css_{min}, CLss/F, R_{AC} and linearity factor

The C_{min}, C_{max} and t_{max} (and Css_{min}, Css_{max} and tss_{max}) will be determined by visual inspection of the plasma concentration time profile. The AUC_{0-10}, AUC_{0-12}, AUC_{0-24} and AUC_{0-t} will be calculated using the linear trapezoidal rule (linear/log interpolation). The $t_{1/2}$ will be calculated from the equation $\ln(2)/ \lambda_z$ (where the rate constant of the slowest disposition phase [λ_z] will be calculated by log linear regression of the terminal portion of the concentration time profile where there are sufficient data [ie, the terminal phase is followed for at least 3 x $t_{1/2}$]). The AUC will be derived by using λ_z to extrapolate AUC_{0-t} to infinity. CL/F and Vss/F will be estimated by dividing the dose by the AUC and multiplying mean residence time by CL/F, respectively. Linearity factor will be determined by dividing $AUCss_{0-12}$ by AUC after the single dose and R_{AC} will be determined by dividing $AUCss_{0-12}$ by AUC_{0-12} after the single dose.

9. MONOTHERAPY PART, VOLUME OF BLOOD

The total volume of blood from screening test to Visit 10 that will be drawn from each subject in this study is give in Table 2. Volume of blood sampling is 13 mL (including optional samples) for clinical chemistry and haematology at withdrawal visit and Visit 11 and so on. And volume of additional blood sampling is 4.0 mL for HbA1c every 9 weeks and withdrawal visit.

Table 2 Volume of blood to be drawn from each subject for Monotherapy part

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
PK		2.7	19	51.3
Safety	Clinical chemistry	3.0	10	30.0
	Haematology	4.0	10	40.0
	Glucose, potassium (6 hours post-dose on days D1 and R14)	2.0	2	4.0
	Screening tests (HbA1c, INR etc.)	4.0	1	4.0
Pharmacogenetics a		9.0	1	9.0
Biomarkers a		6.0	4	24.0
Total (with optional samples)				**162.3**
Total (without optional samples)				**129.3**

INR = International Normalized Ratio
a Optional sample.

Section 10 to 16 is specific procedure for **combination therapy part**

10. COMBINATION PART, STUDY OBJECTIVES

10.1 Primary objective

The primary objective of this study is to explore the safety and tolerability of combination with weekly Paclitaxel and AZD8931 in Japanese female patients with advanced breast cancer.

10.2 Secondary objectives

The secondary objective is as follows:

- To identify the maximum tolerated dose (MTD) of AZD8931 following repeated twice-daily administration when given in combination with weekly paclitaxel
- To explore the Pharmacokinetics of AZD8931 and paclitaxel when co-administered in Japanese female patients with advanced breast cancer

10.3 Exploratory Objectives

The exploratory objectives are as follows:

- To seek preliminary evidence of the anti-tumour activity of AZD8931 in Japanese female patients with advanced breast cancer as measured by tumour response and change in tumour size according to RECIST in patients with measurable lesions.
- To measure exploratory biomarkers from blood and tumour tissue samples and examine the relationship of these biomarkers with clinical outcome (optional).
- To obtain a blood sample for DNA extraction for possible pharmacogenetic analysis and other potential correlative markers of AZD8931 activity and drugs taken in addition to AZD8931 (optional).

11. COMBINATION PART, STUDY PLAN AND PROCEDURES

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

11.1 Overall study design and flow chart

The combination therapy part is an unblinded, combination multiple ascending dose study to assess the safety and tolerability of AZD8931 in combination with Paclitaxel in Japanese

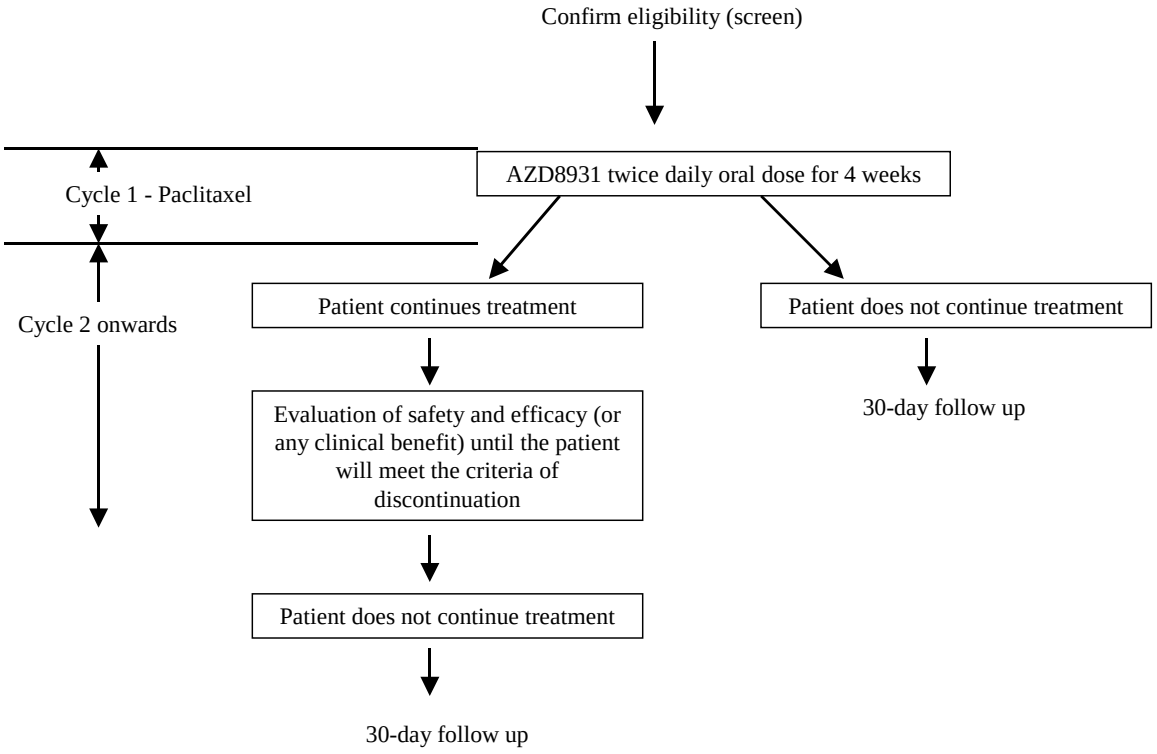
female patients with advanced breast cancer. The combination part will be soon started after confirmation of MTD in the monotherapy part.

The starting dose is decided based on the result of monotherapy part. In each dose cohort a minimum of 3 and a maximum of 6 evaluable patients are enrolled.

In this part AZD8931 is given in combination with weekly Paclitaxel that is three consecutive administration and one week rest in within 28 days. Patients may continue daily oral treatment indefinitely if they do not meet a withdrawal criterion and sign on the informed consent form for treatment continuation, are free from intolerable toxicity, and, in the investigators opinion, are receiving some benefit from the therapy.

The Study flow chart for the combination therapy part of the study is presented in Figure 3.

Figure 3 Study flow chart for Combination therapy part



Combination therapy part

The study plan for combination therapy is presented in Table 3.

Table 3 Study Schedule for Combination therapy part

Assessments	**Screening**	**Treatment period**									**Continuation beyond Cy1**	**Discontinuation of treatment [q]**	**Safety follow up [g]**
			Twice daily 8931										
		PTX					**PTX**	**PTX**					
Day (h = hours) (D=day)	**D–21 to D0**	**D1**	**D2 (24 h)**	**D3 (48 h)**	**D4**	**D5-D7**	**D8**	**D15**	**D22**	**D28**	**Every 4 weeks [c]**		
Repeat cycle day		**Cycle 1**					±1d	±1d	±1d	±1d	**Cycle 2 onwards ±3d**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Informed consent (main study, genetics [optional], exploratory biomarkers [optional])	x												
Another informed consent [a]; main study (study continuation)			◄———							———►			
Inclusion/exclusion criteria	x												
Tumour TNM stage at diagnosis	x												
Tumour assessment (RECIST)	x[b]										x[d]	x	
Chest X-ray	x												

Assessments	**Screening**	**Treatment period**									**Continuation beyond Cy1**	**Discontinuation of treatment [q]**	**Safety follow up [g]**
			Twice daily 8931										
		PTX					**PTX**	**PTX**					
Day (h = hours) (D=day)	**D–21 to D0**	**D1**	**D2 (24 h)**	**D3 (48 h)**	**D4**	**D5-D7**	**D8**	**D15**	**D22**	**D28**	**Every 4 weeks [c]**		
Repeat cycle day		**Cycle 1**					±1d	±1d	±1d	±1d	**Cycle 2 onwards ±3d**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
High Resolution CT Scan Thorax and arterial oxygen saturation [t]	x	←									→		
Demographics	x												
Medical/surgical history	x												
Previous anticancer therapy, including surgery and radiotherapy	x												
Urine pregnancy test [v]	x											x	
Administer AZD8931			x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]		
Administer paclitaxel		x					x	x			x [s]		
Physical examination	x											x	
WHO Performance Status	x												

Assessments	**Screening**	**Treatment period**									**Continuation beyond Cy1**	**Discontinuation of treatment [q]**	**Safety follow up [g]**
			Twice daily 8931										
		PTX					**PTX**	**PTX**					
Day (h = hours) (D=day)	**D–21 to D0**	**D1**	**D2 (24 h)**	**D3 (48 h)**	**D4**	**D5-D7**	**D8**	**D15**	**D22**	**D28**	**Every 4 weeks [c]**		
Repeat cycle day		**Cycle 1**					±1d	±1d	±1d	±1d	**Cycle 2 onwards ±3d**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Ophthalmological examinations[h]	x									x	x	x	
Echocardiography	x									x	x[i]	x	
12-lead Electrocardiogram [j]	x [n]	x	x	x	x			x			x	x	
Vital signs (pulse, blood pressure)	x [n]	x	x	x	x	x	x	x	x	x	x	x	
Blood sample for AZD8931 PK analysis						x[k]	x[k]						
Blood sample for paclitaxel PK analysis		x[r]	x[p]				x[r]						
Blood sample for clinical chemistry, haematology, coagulation parameters (including HbA1c [u] at screening)	x [n,f]	x[l]	x[m]	x	x[l]	x[l]	x[l]	x [m]	x[l]	x[l]	x	x	

Assessments	**Screening**	**Treatment period**									**Continuation beyond Cy1**	**Discontinuation of treatment [q]**	**Safety follow up [g]**
			Twice daily 8931										
		PTX					**PTX**	**PTX**					
Day (h = hours) (D=day)	**D–21 to D0**	**D1**	**D2 (24 h)**	**D3 (48 h)**	**D4**	**D5-D7**	**D8**	**D15**	**D22**	**D28**	**Every 4 weeks [c]**		
Repeat cycle day		**Cycle 1**					±1d	±1d	±1d	±1d	**Cycle 2 onwards ±3d**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Blood samples for exploratory biomarkers (optional)	x [n]	x[l,]								x[l]	x[l]	x	
Tumour tissue sample for exploratory biomarkers (optional)		x[o]											
Blood sample for pharmacogenetics (optional)		x[o]											
Urine sample for urinalysis	x [n]	x[l]	x	x	x	x	x	x	x	x	x	x	
Concomitant medications	←											→	
Adverse events	←											→	

TNM = Tumour, Node, Metastases; RECIST = Response Evaluation Criteria In Solid Tumours; HbA1c = glycosylated haemoglobin; D-Day

Notes to study plan

a Treatment may be extended beyond day Cy1, providing that informed consent is obtained before cycle 2 or restart of the dosing with a reduced dose after dose interruption as a result of DLT that occurred during Cycle 1. (see Section 13.4.2.1).

b Baseline radiological tumour assessments should be performed no more than 4 weeks before the start of study treatment, but should be as close as possible to the start of study treatment. The tumour assessment obtained before consent can be used if the examination took place within 28 days before the first dosing (D1). This is applicable only when the subject agrees on the use of data measured before informed consent.

c The assessments for paclitaxel dosing is scheduled separately (see Section 13.4.3.2).

d Every 8 weeks (±7 days) until objective disease progression, study drug discontinuation, withdrawal of informed consent or death (whichever is soonest).

e No food is allowed from 2 hours before to 2 hours after study drug dosing.

f Fasting glucose at screening

g As a minimum telephone contact must be made with the patient at least 30 days after discontinuing treatment to collect and/or complete AE and concomitant medication information.

h Full ophthalmological assessment must be performed at screening and Cycle 1 D28. Beyond Cycle 1 D28 a full examination should only be performed in case of clinically relevant ophthalmological abnormalities, see Section 17.3.9.3.

i Every 12 weeks for 3 times, then every 24 weeks.

j 12-lead electrocardiogram (ECG) after 10 minutes rest in the supine position. The patient should be examined using the same machine throughout the study. Digital ECGs for QTc interval analysis (days D1 and D15) must be in triplicate (one after another). Paper read-outs of all ECG time points are sufficient for on site safety assessments.

k At pre-dose (within 15 minutes prior to dosing, paclitaxel or AZD8931) and at 1, 2, 4, 6, 8 and 10 hours post-dose (days D7 and D8).

l Pre-dose.

m Glucose and potassium only at 6 hours post-dose (days D1 and D15).

n If there are screening data within 2 days prior to first dose, pre-dosing data on Visit 2 are not mandatory

o After confirmation of eligibility. If for any reason the blood sample is not drawn on D1, it may be taken at any visit until the last study visit.

p D2-Immediately prior to AZD8931 administration (ie 24 hours post start of paclitaxel infusion).

q The assessments for discontinuation of treatment should be done as soon as possible after last dose of study treatment.

r D1 and D8 - pre paclitaxel infusion , 0.5, 1 (end of infusion), 1.5, 2, 4, 6, 8 and 10 hours. Visit window will not be applied.

s Paclitaxel should be administered on D1, D8 and D15 of each cycle.

t HRCT and arterial oxygen saturation (SpO_2) are mandatory and should be performed before first dose of AZD8931 at baseline (and within 28 days prior to enrolment). The algorithm described in Appendix D should be followed if any of the following occur or worsen while on the study: dyspnoea, fever, cough, new pulmonary radiological finding. For determination of SpO_2, the same equipment or type should be used. SpO_2 should be performed every 4 weeks in cycle 2 and thereafter. (see Section 17.3.9.1)

u For HbA1c, screening, D1 of cycle 1, Every 8 weeks after cycle 1 and withdrawal visit

v Only for women of childbearing potential

11.1.1 Dose, DLT evaluation and Criteria to conduct dose escalation

Starting Dose and Width of dose escalation/de-escalation

The dose of first cohort is decided based on the result of monotherapy part. Once MTD on monotherapy part was confirmed, the starting dose for combination part is decided automatically a dose of one level lower from MTD of monotherapy part. The doses of next cohort are planed according to dose escalation plan of monotherapy part (See Section 4.1.1).

DLT evaluation period and Dose Evaluation Committee

The DLT evaluation period is first 28 days of cycle 1. The Dose Evaluation Committee is composed with three members of principal investigator, study team physician and leader. The committee will make final judge for DLT and final decision of dose escalation or de-escalation, and documents the final judge and decision.

DLT evaluation process

The investigator will report in a designated form patient information, all CTCAE grade 2 (according to Version 3 Common Terminology Criteria for Adverse Events) and greater adverse events observed in DLT period of each enrolled patient and DLT evaluation to the Dose Escalation Committee (DEC). Prior to each dose escalation, the DEC will meet to review the safety, tolerability and PK data (If prompt PK analysis of samples will be obtained, the data will be reviewed in each dose-escalation decision, in addition to review of all the safety and tolerability data.), then DEC will make final judge of DLT.

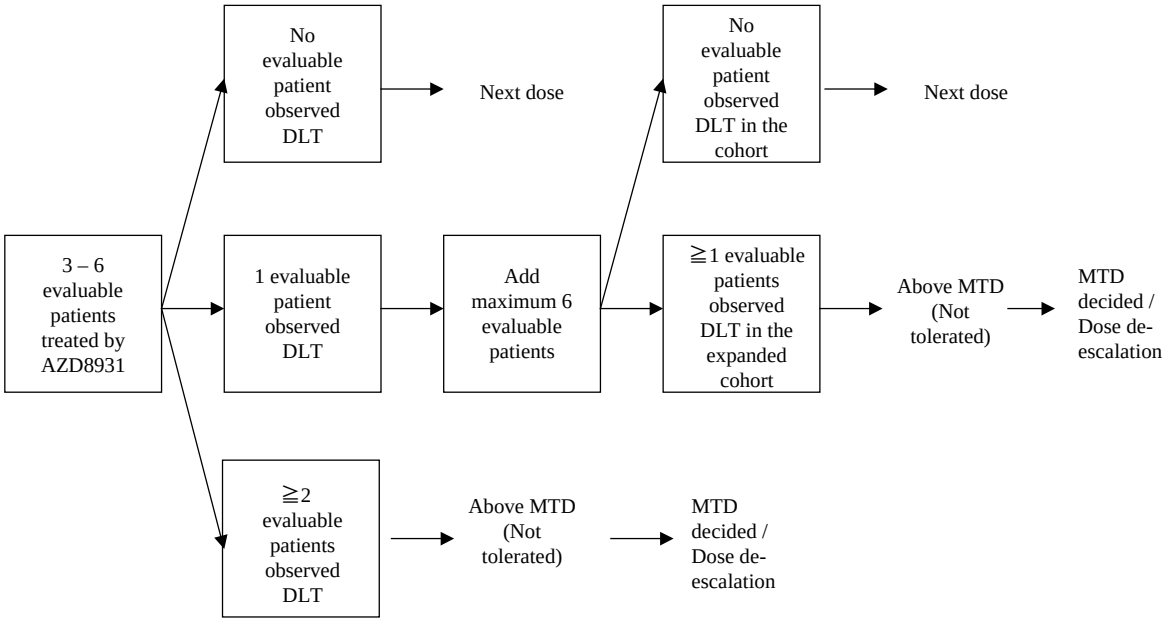
Criteria to conduct dose escalation

A minimum of 3 and a maximum of 6 evaluable patients are needed for dose escalation decision. Dose-escalation or de-escalation will be decided based on the safety data from a minimum of 3 evaluable patients obtained during DLT evaluation period of the previous cohort.

- No DLT permit to dose escalation, judging prior dose is tolerable.
- If one patient experiences a DLT, enrolment will be continued to accumulate total 6 evaluable patients. In case that only one patient out of 6 evaluable patients experience a DLT, dose escalation is permitted, judging prior dose is tolerable.
- If over two patients experiences a DLT, DEC will make decision of dose escalation stop or dose de-escalation which dose is decided by DEC, judging prior dose is non-tolerable.

DEC will be able to make the decision of dose escalation stop even before finding MTD based on the results of study D0102C00002. Figure 4 summarises the rules to be applied.

Figure 4 Dose escalation decision tree



11.1.2 Definition of non tolerated dose

A dose will be considered non tolerated, and dose escalation will cease, if ≥2 DLTs occur within a dose group (see Section 11.1.1).

11.1.3 Definition of maximum tolerated dose

When a non-tolerated dose is defined, dose escalation will be stopped and the MTD will be confirmed at the previous dose level below the non-tolerated dose, or a dose between the non tolerated dose and last tolerated dose assessed may be investigated.

If a dose between the non-tolerated dose and the last tolerated dose assessed is selected for investigation, then the dose escalation criteria detailed in Section 11.1.1 will apply

When a non-tolerated dose could not be defined, MTD is defined as a highest tolerable dose.

When MTD is defined and the data on the dose below is based on data from <6 patients, then additional patients will be recruited at this lower dose to confirm a MTD based upon data from 6 evaluable patients.

11.1.4 Definition of dose limiting toxicity

A DLT is defined as an IT of adverse events or laboratory abnormalities considered to be related to AZD8931, that commences within 28 days of the first dose and meets any of the following criteria:

- Ophthalmological toxicity

- Symptomatic ocular surface lesion (epitheliopathy or erosion) with the following clinically significant criteria: >1 mm in diameter, <1 mm in diameter and clustered in a group of 10 or more, appearance of filaments or multiple (>2) small (≤1 mm) areas or a large (>1 mm) area of negative fluorescein staining which cannot be attributed to another cause and which does not recover over a period of 3 days following detection of these findings.

- Haematological toxicity
  - Any Common Terminology Criteria for AEs (CTCAE) grade 4 neutropenia and thrombocytopenia of any duration
  - Febrile neutropenia (CTCAE grade ≥ 3 with temperature ≥38.0°C which is unresponsive to antipyretics)
  - CTCAE grade ≥ 3 neutropenia requiring prolongation of hospitalisation due to complications associated with neutropenia
  - CTCAE grade ≥ 3 thrombocytopenia associated with non-traumatic bleeding (but not applicable to patients on therapeutic anticoagulation)
- Clinical chemistry toxicity
  - CTCAE ≥ grade 3 hyperkalemia (ie, >6.0 mEq/L; 6.0 mmol/L) which has been confirmed (by repeat sampling) and is considered to be drug related
  - CTCAE ≥ grade 3 hyperglycemia (ie, >250.2 mg/dL; 13.9 mmol/L), from fasting glucose, which has been confirmed (by repeat sampling) and is considered to be drug related
- Cardiovascular toxicity
  - QTcF (Fridericia's correction) interval > 500 msec or increase by >60 msec, compared to baseline on two ECGs at least 30 minutes apart, that cannot be attributed to another cause
  - Symptomatic congestive cardiac failure (New York Heart Association [NYHA] class III/IV) and a drop in left ventricular ejection fraction (LVEF) which cannot be attributed to another cause[2]
  - A decrease in LVEF of ≥20% to a level below the institution's lower limit of normal range

[2] Concomitant use of vasotonic drugs, adrenergic blockers, negative inotropic agents and anti hypertensives should be taken into consideration when assigning causality.

- CTCAE ≥ 3 hypotension which cannot be attributed to another cause

- Other toxicities
  - Clinically significant rash that despite optimal treatment remains CTCAE grade ≥3 for 5 days or longer and that cannot be attributed to another cause
  - CTCAE grade ≥ 3 renal/urinary toxicity which cannot be attributed to another cause
  - CTCAE grade ≥3 interstitial lung disease or pneumonitis which cannot be attributed to another cause
  - CTCAE grade ≥ 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 ≥ 3 toxicity which, in the opinion of the investigator, is clinically significant and related to the study drug

- The following event should be defined as a DLT, even though it is an event out of DLT period.
  - Any delay to the administration of weekly paclitaxel chemotherapy on D1 of cycle 2 by ≥7 days as a consequence of AZD8931 induced toxicity

11.1.5 Definition of evaluable patient

An evaluable patient is defined as follows:

- A patient completed 75% of planned daily dosed in the first 28 days and planned weekly paclitaxel in the first 28 days and has enough information to be assessed for the dose escalation

- A patient experienced a DLT within the initial 28 days

During this period, any patient required to have their daily dose of AZD8931 reduced will no longer be defined as evaluable in the study unless they have experienced a DLT.

11.2 Rationale for study design, doses, population

Patient Population

Approximately 15% of patients with breast cancer have tumours that are suitable for treatment with currently approved HER2 directed therapies (trastuzumab and lapatinib) in combination with paclitaxel. There are currently no specific treatments for patients with locally recurrent or metastatic breast cancers that express low levels of HER2Based on the pharmacological profile from non-clinical testing, AZD8931 is in development for the treatment of breast

cancer including low levels of HER2 breast cancer. Weekly paclitaxel treatment with or without molecular target agents is a standard of care proven of safety and efficacy for patients who have locally recurrent or metastatic breast cancers. This population has been chosen to establish that AZD8931 in combination with Paclitaxel has an acceptable toxicity profile in patients at pharmacologically active doses.

Doses

The dose of first cohort is decided based on the result of monotherapy part. Considering patient safety the starting dose is decided to the one level lower dose from highest tolerable dose of monotherapt pert. Width of dose escalation is decided according to monotherapy dose plane.

Design

This part should use usual dose escalation manner for a first study of combination with AZD8931 and Paclitaxel in Japanese population. Dosing of investigational product and patient number of enrolment is planed to minimum to provide enough information for achieving study objectives. Dose and schedule of weekly Paclitaxel is widely accepted regimen in Japan.

12. COMBINATION PART, SUBJECT SELECTION CRITERIA

Subject population should be selected without bias.

Investigator(s) must keep a record of subjects who entered pre-trial screening but were never enrolled eg, subject screening log. Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

12.1 Inclusion criteria

For inclusion in the study subjects must fulfil the following criteria.

For inclusion in this host genetic and biomarker research, subjects must fulfil all of the inclusion criteria described in the main body of the study protocol and: Provide informed consent for the genetic and biomarker sampling and analyses.

1. Provision of written informed consent

2. Japanese female with locally advanced or metastatic breast cancer aged ≥20 years

3. Histologically or cytologically confirmed breast cancer

4. WHO performance status 0 to 2 (those with ps 2 must have been stable with no deterioration over the previous 2 weeks) (See Table 7)

5. Life expectancy of at least 12 weeks

6. Females must be of non-childbearing status defined as one of the following criteria at screening:

   - negative pregnancy test in women of childbearing potential
   - or women who are permanently or surgically sterilised (hysterectomy and/or bilateral oopherectomy and/or bilateral salpingectomy)
   - or postmenopausal (over 50 years old and amenorrheic for ≥12 months following cessation of all exogenous hormonal treatments, or over 57 years old).

7. The patient is able to be hospitalized at least during Cycle1

8. Patients are intended to treat with weekly Paclitaxel by investigators, who are not candidates for hormonal and antracycline therapy.

12.2 Exclusion criteria

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

1. Cardiac ejection fraction outside institutional range of normal as measured by echocardiogram (or MUGA scan if an echocardiogram cannot be performed or is inconclusive)

2. Any of the following is regarded as a criterion for exclusion from the study:

   - Inadequate bone marrow reserve as demonstrated by an absolute neutrophil count $<1.5 \times 10^9$/L or platelet count $<100 \times 10^9$/L.
   - Haemoglobin ≤9 g/dL (5.59 mmol/L).
   - Inadequate liver function as demonstrated by serum bilirubin ≥1.5 x ULN, or ALT or AST ≥ 2.5 x ULN, or ALP ≥2.5 x ULN in the absence of noted liver or bone metastases (ALP, AST or ALT ≥5.0 x ULN if judged by the investigator to be related to liver or bone metastases).
   - INR and APTT >1.2 x ULN.

3. Last dose of prior anticancer therapy received any of the following treatments within 4 weeks prior to study entry: chemotherapy (within 6 weeks for nitrosurea or mitomycin C), radiotherapy, hormonetherapy, immunotherapy and any other anti-cancer therapies. 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 AstraZeneca and the investigator.

4. Unresolved toxicity greater than CTCAE grade 1 from previous anti-cancer therapy, except alopecia

5. Prior exposure to anthracyclines or mitoxantrone with cumulative exposure in excess of 360 mg/m^2 (body surface area) for doxorubicin, 720 mg/m^2 (body surface area) for epirubicin, or 72 mg/m^2 (body surface area) for mitoxantrone.

6. Resting ECG with measurable QTc interval of >450 msec at 2 or more time points within a 24 hour period

7. Known uncontrolled or symptomatic angina, arrhythmias or congestive heart failure; evidence of transmural infarction on ECG, poorly controlled hypertension (systolic >180 mmHg or diastolic >100 mmHg), significant valvular disease or history of high risk dysrrhythmia (such as ventricular fibrillation or ventricular tachycardia [includes ventricular triplets]) or history of *Torsade de pointes*

8. Unable to discontinue medication with agents designated as Class I Arizona risk for QT prolongation (See Section 13.5)
Note: use of agents with Class II designation is allowed if patients have being receiving a stable dose for at least 5 half-lives of the drug.

9. Evidence of 'dry eye': persistent symptoms of ocular surface irritation, Schirmer's test without anaesthesia of less than 5 mm in 5 minutes and tear break-up time [TBUT] test of less than 10 seconds (if one of these is satisfactory, the patient may be included – both of these parameters should be normal if the patient is receiving anti-cholinergic medication. Eye conditions that are stable and of long standing, such as scars from trauma, pinguecula, atrophic pterygia etc, should not be considered as reasons to exclude the patient

10. Wearing contact lens (patients should discontinue wearing contact lens from at least 1 week prior to entering the study to 1 week following discontinuation of AZD8931)

11. Recent acute changes in patient's vision, or ongoing symptoms of ocular pain, discomfort or irritation

12. History of collagen vascular, chronic inflammatory or degenerative disease with eye involvement (eg, rheumatoid, Sjögren syndrome, systemic lupus erythematosus [SLE]) or of ocular surface disease (including Steven-Johnson syndrome, ocular cicatricial pemphigoid or chemical burns, herpes simplex or herpes zoster virus eye disease

13. History of corneal surgery, including laser refractive surgery, within the past 3 years

14. Medical diagnosis of acne rosacea, psoriasis, or severe atopic eczema (common acne vulgaris is acceptable for this study)

15. Brain metastases, unless surgically removed and/or irradiated at least 4 weeks before study entry and stable without anti-seizure or steroid treatment for >1 week. Brain metastasis with clinical signs and/or symptoms attributable to active intra-cerebral metastases and/or oedema or progressive growth demonstrated by brain imaging or use of concomitant anti-seizure medication or corticosteroids

16. No 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

17. No active or uncontrolled systemic disease which makes it undesirable for the patient to participate in the study or which would jeopardise compliance with the protocol

18. Patients with concurrent infection which is expected to become to worse due to myelosuppresion

19. Fasting blood glucose at screening ≥126 mg/dL (7 mmol/L).

20. Elevated potassium levels at screening (>5.5 mEq/L [>5.5 mmol/L])

21. Inadequate renal function as demonstrated by serum creatinine >1.5 ULN, or creatinine clearance (estimated by Cockcroft-Gault equation or measured via 24 hr urine creatinine) <50 mL/min.

22. Currently receiving inhibitors and inducers of CYP3A4 or CYP2D6, listed in Section 13.5. The patient should not have received the therapy within the stated washout periods.

23. Known hypersensitivity to AZD8931, its excipients, or drugs in its class (including oral tyrosine kinase inhibitors).

24. Known hypersensitivity to Paclitaxel or polyoxyethylene caster oil.

25. Current disease or condition known to interfere with absorption, distribution, metabolism or excretion of drugs

26. History or repeated unexplained episodes of syncope/dizziness

27. Breast-feeding women.

28. Female patients of child-bearing potential who are unwilling to use an acceptable highly effective method of contraception during the study and for 30 days after the last dose of study drug.

29. History of use of an investigational agent within the 30 days prior to entry.

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

31. Clinical judgment by the investigator that the patient should not participate in the study

32. HBV, HCV or HIV infection. Screening of patients for these infection is not required, however, patients known to have such infection at screening should not be included

33. Known immunodeficiency syndrome

34. Unable to swallow and retain oral medication.

35. Prior history of eyelid or eyelash abnormalities, clinically significant ocular surface disease, eye injury, corneal surgery or prior orbital irradiation.

36. Second primary malignancy (except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin or squamous cell carcinoma of the skin with no relapse in the past 5 years).

37. Progression of disease during previous taxane chemotherapy treatment or within 6 months of completing taxane treatment.

The following criterion will require exclusion from the optional **pharmacogenetic component** part of the study:

38. Receipt of a whole blood transfusion in the preceding 90 days, or a previous bone marrow transplant before genetic sample collection

12.3 Procedures for handling incorrectly included subjects

Subjects that do not meet the inclusion/exclusion criteria for a study should not, under any circumstances, be enrolled into the study– there can be no exceptions to this rule.

Where subjects that do not meet the study criteria are enrolled in error, incorrectly randomised, or where subjects subsequently fail to meet the criteria for the study post enrolment, the procedures included in the protocol for the discontinuation of such subjects must be followed. These procedures must be included in the protocol and must take into consideration ethical and safety factors and how these subjects will be treated in the analyses. (See Section 12.4.2)

12.4 Withdrawal of subjects

12.4.1 Criteria for discontinuation from the study

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject are:

- Voluntary discontinuation or rejection to the informed consent for treatment continuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment

- Risk to subjects as judged by the investigator and /or AstraZeneca (including positive pregnancy test)

- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca

- Incorrectly enrolled subjects (ie, the patient does not meet the required inclusion/exclusion criteria for the study)

- Subject lost to follow-up

- Patient is considered to have clear evidence of clinically significant PD, which, in the investigator's opinion requires discontinuation of study treatment and initiation of an alternative anti-cancer treatment. (NOTE: discontinuation of study treatment for clinically insignificant and minimally progressive disease (PD) should not, of itself, be a reason for study treatment discontinuation)

Specific reasons for discontinuing a patient from the biomarker research component of the study are:

- Withdrawal of consent for biomarker research. A patient may withdraw from this component at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment

Specific reasons for discontinuing a patient from the genetic research component of the study are:

- Withdrawal of consent for genetic research. A patient may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment

12.4.2 Procedures for discontinuation of a subject from the study

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The principal investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (See Sections 17.3.3 and 17.3.4); and study drug should be returned by the subject.

Ongoing Serious Adverse Events (SAEs) and AEs should be followed up to resolution or stabilisation, unless the event is considered by the investigator to be unlikely to resolve due to the patient's underlying disease (in these cases, the investigator must record his/her opinion in the patient's medical records), or the patient is lost to follow-up.

12.4.3 Procedures for discontinuation from biomarker and genetic aspects of the study

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for the optional biomarker and genetic research. It must be established whether the patient:

Biomarker research

- Agrees to the blood and tumour tissue samples being kept for biomarker analyses.
- Withdraws consent for the sample to be kept for biomarker analysis and wishes the sample to be destroyed. Destruction of the sample will only be possible so long as the particular sample is traceable. In the event that biomarker research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

Genetic research

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic analyses in the future.
- Withdraws consent for the sample to be kept for genetic analysis in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

13. COMBINATION PART, STUDY CONDUCT

13.1 Restrictions during the study

The following restrictions will apply:

1. Female patients of child-bearing potential must use an acceptable highly effective method of contraception plus condoms and spermicide during the study and for 30 days after the last dose of study drug. More than one contraceptive measures (e.g., condoms, intra-uterine contraceptive device, oral contraceptive, etc.) are recommended.

2. No food is allowed from 2 hours before to 2 hours after taking AZD8931

3. Patients must not receive any concomitant anti-cancer agents (except for Paclitaxel) or any other investigational agents while receiving AZD8931.

4. Abstain from taking drugs with known significant CYP3A4 and CYP2D6 inducer/inhibitory effects (see Section 13.5)

5. Abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits, eg, grapefruit juice or marmalade) during the study. Amounts should not exceed more than a small glass of grapefruit juice (120 mL), or half a grapefruit, or 1-2 teaspoons (15 g) of Seville orange marmalade daily.

6. Refrain from driving for 4 hours following ophthalmic examination if pupillary dilatation performed.

7. Patients should refrain from wearing contact lenses from at least 1week prior to starting AZD8931 to 1 week after discontinuation of AZD8931.

8. Abstain from taking part in any other study whilst participating in this study.

9. Patients should use sunglasses and skin cream with UVA and UVB protection SPF >30 (PA++) if exposed to sunlight and avoid long-term daylight exposure or use of sun tanning booths during the study and for 3 months after the last dose of study treatment.

13.2 Subject enrolment

13.2.1 Method of assigning subjects to treatment groups

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

The patient will be enrolled and registered in the same manner of the monotherapy part except for assignment of enrolment code. The E-code (EXXXXYYY) consists of a 4-digit centre number (XXXX) and a 3-digit serial number (YYY, starting with 101) issued by each study centre in order of informed consent taken. For centre number, see Supplement A "Investigators and Study Administrative Structure".

The registration numbers should be started with number 101.

If a patient is not evaluable for the dose escalation, an additional patient should be entered in that dose level (see Section 11.1.1).

If a patient discontinues from the study the E-code will not be re-used and the patient will not be allowed to re-enter the study.

Interruption and restart

When the subject's treatment will be interrupted, the investigator(s) will fill in the "Treatment Interruption Form" and send the form to the AZD8931 Centralised Registration Centre by fax. The AZD8931 Centralised Registration Centre will inform the interruption to AstraZeneca K.K. by fax.

When the subject's treatment will be restarted, the investigator(s) will fill in the "Treatment Restart Form" and send the form to the AZD8931 Centralised Registration Centre by fax. The AZD8931 Centralised Registration Centre will inform the interruption to AstraZeneca K.K. by fax.

13.3 Blinding and procedures for unblinding the study (Not applicable)

13.4 Treatments

13.4.1 Identity of investigational product(s)

AstraZeneca will supply AZD8931 to the investigator as plain, white film coated, biconvex round tablets as follows:

Investigational product	Dosage form and strength	Manufacturer
AZD8931 40 mg tablet	40 mg film coated tablet	AstraZeneca
AZD8931 100 mg tablet	100 mg film coated tablet	AstraZeneca

13.4.2 Doses and treatment regimens

13.4.2.1 AZD8931 dosing

AZD8931 tablets will be taken orally twice daily (except for the single dose on cycle 1 D1 when AZD8931 is not administered), with the doses being taken approximately 12 hours apart. The AZD8931 tablets should be taken with a glass of water (approximately 150 mL) at approximately the same time each day. The effect of food on the absorption of AZD8931 has not been established. Therefore it is requested that AZD8931 should be taken at least 2 hours after a meal and that no food is consumed until 2 hours after the tablets are taken. There is no restriction on the consumption of water.

Patients may continue daily oral treatment indefinitely if they do not meet a withdrawal criterion and sign on the informed consent form for treatment continuation, are free from

intolerable toxicity, and, in the investigators opinion, are receiving some benefit from the therapy.

Patients may restart the dosing of AZD8931 with a reduced dose in accordance with the criteria for restart of the dosing shown in Section 13.4.2.3 after dose interruption as a result of DLT that occurred during the DLT evaluation period, if patients sign on another informed consent form for restart of the treatment beforehand.

13.4.2.2 Paclitaxel dosing

In the combination part of the study, patients will receive an intravenous drip infusion of paclitaxel 90 mg/m^2 (body surface area) given over 1 hour on D1, D8 and D15 of each 28 day treatment cycle. Patients will receive 3 consecutive once weekly paclitaxel infusions followed by 1 week of rest to complete each 28 day treatment cycle. On D1 (except for cycle 1), D8 and D15, paclitaxel and AZD8931 are administered at the same time point. On days when both AZD8931 and paclitaxel are administered, AZD8931 should be administered immediately (within 5 minutes) prior to paclitaxel administration.

Patients may continue daily oral treatment indefinitely if they do not meet a withdrawal criterion and sign on the informed consent form for treatment continuation, are free from intolerable toxicity, and, in the investigators opinion, are receiving some benefit from the combination therapy with AZD8931.

Patients may restart the dosing of AZD8931 with a reduced dose in accordance with the criteria for restart of the dosing shown in Section 13.4.2.3 after dose interruption as a result of DLT that occurred during the DLT evaluation period, if patients sign on another informed consent form for restart of the treatment beforehand.

Guidelines for paclitaxel administration

Paclitaxel should be diluted in 5% dextrose (or normal saline) to a final concentration of 0.3 to 1.2 mg/mL and given by iv administration. iv tubing should not consist of DEHP (di-(2-ethylthxyl)phthalate). The calculated dose of paclitaxel should be intravenous drip infusion as a 1-hour infusion.

Pre-medication for paclitaxel

Due to known toxicity of paclitaxel and/or of the Cremophor EL vehicle, the following pre-medications (or suitable alternatives according to local practice at the investigator site) may be given approximately 30 minutes prior to paclitaxel administration to minimize the chances of hypersensitivity reaction.

Table 4 Pre-medications for paclitaxel

Agent	Dose
Dexamethasone	**First week: 8 mg iv** **Subsequent weeks: 4 mg iv**

Table 4 Pre-medications for paclitaxel

Agent	Dose
Diphenhydramine hydrochloride	**50 mg oral administration**
Ranitidine	**50 mg iv**
Famotidine	**20 mg iv**

Resuscitation equipment and relevant expertise should be readily available during the intravenous drip infusion for emergency treatment of hypersensitivity reactions.

Pre-medications and food timings should be consistent across PK days within a patient to minimize variability. All pre-medications must be recorded in the pCRF.

13.4.2.3 Dose adjustment of AZD8931

Intra-patient dose adjustment of AZD8931 may be permitted according to the criteria detailed below and only after discussion and agreement of individual patient situations between the investigator, and AstraZeneca K.K. During the study, the dose of AZD8931 may only be reduced by one dose level for an individual patient if required.

- For all patients who experience a DLT or an unacceptable toxicity (not DLT), if the toxicity does not resolve to CTCAE ≤grade 1 or baseline (pre-study) after 28 days of onset, then the patients must be discontinued from the study

- If the toxicity resolves or reverts to CTCAE ≤grade 1 or baseline levels within 28 days of onset and the patient is showing clinical benefit, treatment with AZD8931 may be restarted at a preceding, lower dose level that has been defined as tolerated. Patient on 80 mg twice daily can have dose reduction to 40 mg twice daily (80 mg /day).

(a) Dose adjustments during the DLT evaluation period

If a patient experiences a DLT, AZD8931 treatment must be stopped and supportive therapy administered as required. The criteria for restarting is described above.

(b) Dose adjustment after completion of the DLT evaluation period

If a patient experiences tolerability issues with the study drug, the dose of AZD8931 may be reduced by one dose level only. Patient on 80 mg twice daily can have dose reduction to 40 mg twice daily (80 mg /day).

Even if a patient don't experience tolerability with the study drug, a patient will continue to take one level lower dose when the dose is confirmed as a non-tolerable dose.

Dose reductions of AZD8931 should precede that of cytotoxic chemotherapy if the investigator considers the toxicity related to AZD8931 dosing. If tolerability does not improve after reduced or omitted doses of AZD8931, consideration should be given to delay or reducing dose of the chemotherapy according to the guidelines detailed within Section 13.4.3.

If in the investigator's opinion cytotoxic chemotherapy dosing should be stopped for tolerability reasons and it is felt that the patient may gain benefit from continuing on AZD8931 monotherapy, this course of action may be permitted following discussion and agreement by the investigator and AstraZeneca.

13.4.3 Management of paclitaxel related toxicity

13.4.3.1 During the DLT evaluation period

During the DLT evaluation period individual patient dose adjustments of paclitaxel are not permitted. Paclitaxel dosing may be delayed for up to 7 days within the DLT evaluation period as a consequence of toxicity. If Paclitaxel dosing is delay for over 7 days and is needed to skip injection at least one time due to toxicities, Paclitaxel dosing should be stopped.

13.4.3.2 After the DLT evaluation period

Dose delay of paclitaxel

These are applicable to patients who continue after the DLT evaluation. In the event of toxicity thought to be related to paclitaxel, treatment may be delayed for up to 28 days. If Paclitaxel dosing is delay for over 28 days due to toxicities, Paclitaxel dosing should be stopped. Paclitaxel treatment may be restarted immediately after recovery from toxicity; that is neutrophils $\geq 1.5 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L, and recovery to baseline or CTCAE grade 1 or less non-haematological toxicity.

Dose adjustments of paclitaxel as a consequence of toxicities

Dose should be permanently reduced to 65 mg/m^2 (body surface area) in case of the following haematological toxicities:

- Febrile neutropenia (temperature ≥38.0°C, ANC $<1.0 \times 10^9$/L, requiring hospitalisation and IV antibiotics)
- ANC $<1.0 \times 10^9$/L for more than 3 days
- Clinically significant bleeding and/or non-traumatic bleeding associated with platelet count of $\leq 40 \times 10^9$/L occurs and when the platelet count is $\leq 20 \times 10^9$/L

Dose should be transiently reduced (ie, may return to full dose in subsequent cycles) for the following haematological and non-haematological toxicities:

- ANC $\geq 1 \times 10^9$/L and $<1.5 \times 10^9$/L

- Platelets ≥75 x 10^9/L and <100 x 10^9/L
- AST >5 x ULN and ≤10 x ULN
- Bilirubin >2 x ULN and ≤3 x ULN

In the case of more than CTCAE grade 3 neuropathy, paclitaxel should be withheld and then resumed at 65 mg/m^2 (body surface area) on resolution to CTCAE grade 1 or less.

Paclitaxel should be permanently discontinued for the following non-haematological toxicities:

- Severe hypersensitivity reactions
- CTCAE grade 3 or 4 neuropathy lasting more than 4 weeks
- CTCAE grade 3 or 4 neuropathy recurring after dose reduction
- AST and/or ALT >5 x ULN (>20 x ULN or above in case of liver metastases)
- Bilirubin >3 x ULN

Dose reductions of paclitaxel as a consequence of non-haematological toxicities:

For non-haematological toxicities other than those mentioned above and excluding nausea, vomiting and asthenia:

- If CTCAE grade 3, patients should have a permanent dose reduction to 65 mg/m^2 (body surface area)

Patients who experience CTCAE grade 4 non-haematological toxicity may have their dose held for up to 4 weeks (1 cycle) to permit recovery to CTCAE grade 3 or below followed by a permanent dose reduction to 65 mg/m^2 (body surface area)

Table 5 Dose reductions for paclitaxel

Reductions	Dose Level (body surface area)
Initial dose level	90 mg/m^2 on D1, 8 and 15 of a 28 day cycle
Transient dose reduction[a]	65 mg/m^2 on D1, 8 and 15 of a 28 day cycle
1st dose reduction	65 mg/m^2 on D1, 8 and 15 of a 28 day cycle
2nd dose reduction	No additional reduction allowed – stop paclitaxel

a Dose may be re-escalated to full dose once toxicities have resolved

Hypersensitivity reactions:

Discontinue paclitaxel infusion for significant hypersensitivity reactions defined as:

- Hypotension requiring pressor therapy
- Angiodema
- Respiratory distress requiring bronchodilator therapy
- Generalised urticaria

For other hypersensitivity reactions, paclitaxel may be discontinued at the discretion of the investigator.

Any significant hypersensitivity reaction and any hypersensitivity reaction requiring treatment discontinuation should be reported as an AE or SAE.

The following management of hypersensitivity reactions is recommended or local standard practice:

- Administer cholorpheniramine 10 mg iv, or equivalent
- Administer adrenaline (or its equivalent) sub-cutaneous every 15 to 20 minutes until the reaction subsides or a total of 6 doses given
- If hypotension is present that does not respond to adrenaline, administer iv fluids
- If wheezing is present that is not responsive to adrenaline, administration of nebulized salbutamol solution (or equivalent) is recommended.

Although corticosteroids have no effect on the initial reaction, they have been shown to block "late" allergic reactions to a variety of substances. Thus, methylprednisolone 125 mg iv (or its equivalent) may be administered to prevent recurrent or ongoing allergy manifestations.

Patients should not be re-challenged with paclitaxel in case of a severe hypersensitivity reaction. These patients should be discontinued from treatment with paclitaxel.

13.4.4 Additional study drug

Cytotoxic chemotherapy medications (paclitaxel) is commercially available and supplied locally, as per standard practice at the investigator site.

Descriptive information for paclitaxel can be found in the package inserts for those products. Study treatment with paclitaxel should be administered according to institutional standards at each site.

13.4.5 Labelling

All investigational product will be labelled with "for clinical study use only" and other information. Regarding the details of labelling, see the document 'Procedure of storage conditions for investigational product'.

13.4.6 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified on the document 'Procedure of storage conditions for investigational product'.

13.5 Concomitant and post-study treatment(s)

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator and should be recorded in pCRF.

Patients are not eligible to enter the study if they have taken any of the following within the specified timeframe and concomitant use of these medications are not allowed during study treatment:

- Within 4 weeks prior to study entry: chemotherapy (within 6 weeks for nitrosurea or mitomycin C), radiotherapy, hormone therapy, immunotherapy and any other anti-cancer therapies

- Currently receiving, or taken within the stated washout period: inhibitors and inducers of CYP3A4 or CYP2D6 listed below;

  - Within 2 days prior to study entry:
    (CYP3A4 inhibitors) ketoconazole, ritonavir, indinavir, saquinovir, nelfinavir, atazanavir, amprenavir, fosamprenavir, nefazodone, verapamil
    (CYP2D6 inhibitors) duloxetine, terbinafine

  - Within 7 days prior to study entry:
    (CYP3A4 inhibitors) itraconazole, erythromycin, clarithromycin, telithromycin, fluconazole
    (CYP2D6 inhibitors) quinidine

  - Within 2 weeks prior to study entry:
    (CYP3A4 inhibitor) diltiazem
    (CYP3A4 inducer) barbiturates, phenytoin, rifampicin, rifabutin, carbamazepine and St. John's wort
    (CYP2D6 inhibitor) paroxetine

  - Within 5 weeks prior to study entry:
    (CYP2D6 inhibitor) fuloxetine

- Currently receiving, or taken within 7 half-lives of the drug: drugs (eg, prescribed and non-prescription) with known significant CYP3A4 and CYP2D6 inhibitor and inducer effects. Where drug half-life information is not available, the patient should not have received the therapy within the last 4 weeks

- Currently receiving, or taken within 7 half-lives of the drug: drugs designated as Class I Arizona risk for QT prolongation. Agents designated as Class II Arizona risk for QT are allowed provided the patient has received these agents for at least 5 half-lives of the drug with no change in dose

- Ongoing treatment with anti-cholinergic medication, oral steroids, ACE inhibitors, potassium-sparing diuretics or potassium supplements is allowed, provided the patient has been on therapy for at least 4 weeks with no changes in dose in that time.

If a patient requires elective surgery with anaesthesia during the study, it is recommended that study drug therapy should be discontinued for 3 days beforehand. If urgent anaesthesia/ muscle relaxants such as suxamethonium are required, the anaesthetist should be informed that hyperkalemia has been seen in dogs anaesthetised with propofol and alfentanil and who received high doses of AZD8931. The decision to restart study drug will be taken in consultation with the AstraZeneca physician.

13.6 Treatment compliance

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the Case Report Forms.

When patients are at the clinic, compliance will be assured by supervised administration of AZD8931 by the investigator or his/her delegate. When patients are not at the clinic, patients will be asked to return all unused study drug at each visit (if treatment is continuing).

13.6.1 Accountability

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

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused study drug to AstraZeneca. The principal investigator/investigator is responsible for ensuring that the subject has returned all unused study drug. For details, to refer AstraZeneca will provide the study documents ‘Procedures for drug accountability’ and ‘Procedures for drug storage’, which AstraZeneca K.K. will provide for medical center.

14. COMBINATION PART, CALCULATION OF PHARMACOKINETIC VARIABLES

For timing of individual samples refer to the study plan (Table 3).

14.1 Collection of biological samples

PK samples (2.7 mL of venous blood) will be collected at the following time points for determination of AZD8931 plasma concentrations: Cycle 1, D7 and D8: pre-dose (within 15 minutes prior to dosing), 1, 2, 4, 6, 8 and 10 hours post dose (see Table 3).

PK samples (4 mL of venous blood) will be collected at the following time points for determination of paclitaxel plasma concentrations: Cycle 1, D1 and D8: pre-infusion, 0.5, 1 (end of infusion), 1.5, 2, 4, 6, 8, 10 (prior to AZD8931 administration on D8) and 24 hours (post -dose D1 only, immediately prior to AZD8931 administration on D2) post start of infusion (see Table 3).

Depending on emerging data/information, the timings and number of PK samples may be altered, but the maximum blood volumes from scheduled samples given in Table 6 will not be exceeded. The actual sample time and date of all PK samples must be recorded in the pCRF.

All biological samples will be collected, processed, labelled and shipped to a laboratory for analysis in accordance with the Laboratory Manual. At appropriate time intervals, the samples will be transported on dry ice to the appropriate laboratory(ies) for analysis. Samples should be analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable

Samples will be disposed of after the Clinical Study Report has been finalised.

14.2 Determination of drug concentration in biological samples

Analysis of plasma samples for the determination of AZD8931 and paclitaxel concentrations will be the responsibility of the Clinical Pharmacology & DMPK Department, Alderley Park, AstraZeneca, UK. If warranted, the samples may also be used for investigation/analysis of circulating metabolites and/or exploratory biomarkers.

15. COMBINATION PART, CALCULATION OR DERIVATION OF PHARMACOKINETIC VARIABLES

The PK analyses will be performed at AstraZeneca R&D. The actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods. Where the data allow, the following PK parameters will be determined:

- the AZD8931 and paclitaxel PK parameters to be calculated during the combination arm are:

  – t_{max}, C_{max}, AUC_{0-10}

Other PK parameters may be determined if deemed appropriate.

The C_{max} and t_{max} will be determined by visual inspection of the plasma concentration time profile. The AUC_{0-10} will be calculated using the linear trapezoidal rule (linear/log interpolation).

16. COMBINATION PART, VOLUME OF BLOOD

The total volume of blood from screening test to Visit 10 that will be drawn from each subject in this study is give in Table 6. Volume of blood sampling is 13 mL (including optional samples) for clinical chemistry and haematology at withdrawal visit and Visit 11 and so on. And volume of additional blood sampling is 4.0mL for HbA1c every 8 weeks and withdrawal visit.

Table 6 Volume of blood to be drawn from each subject for Combination therapy part

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
PK	AZD8931	2.7	14	37.8
	Paclitaxel	4.0	19	76.0
Safety	Clinical chemistry	3.0	10	30.0
	Haematology	4.0	10	40.0
	Glucose, potassium (6 hours post-dose on days D1 and R14)	2.0	2	4.0
	Screening tests (HbA1c, INR etc.)	4.0	1	4.0
Pharmacogenetics [a]		9.0	1	9.0
Biomarkers [a]		6.0	3	18.0
Total (with optional samples)				**218.8**
Total (without optional samples)				**191.8**

INR = International Normalized Ratio
a Optional sample.

17. COLLECTION OF STUDY VARIABLES

17.1 Recording of data

The principal investigator/sub-investigator will record data (from informed consent to finish follow up period) on the observations, tests and assessments specified in the protocol on the paper pCRFs provided by AstraZeneca. The pCRF will be accompanied with 'Instructions for the Investigator', which should be followed to record study data in the pCRF and to change data incorrectly recorded.

The investigator will ensure that all data collected in the study are provided to AstraZeneca. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the paper Case Report Form or electronic Case Report Form and according to any instructions provided.

The Principal Investigator will provide AstraZeneca with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to AstraZeneca in pCRF and in all required reports.

17.2 Screening and demography procedures

17.2.1 MEASUREMENT OF STUDY VARIABLES

The following study measurements will be obtained. The timing of these measurements is detailed in the study plan (See Table 1 and Table 3).

- AEs
- Echocardiography
- 12-lead ECG
- Vital sign (Pulse and BP)
- Safety blood sampling
- PK sampling (planned for the exact time of assessment)
- High resolution CT scan thorax
- Arterial oxygen saturation (SpO_2)
- Ophthalmological examination
- Urine sampling.

- Assessment of tumour
- Blood sampling of biomarker

17.2.2 Enrolment medical examination and demographic measurements

The following screening and demographic data will be collected in the pCRF within the 21 days prior to the first treatment visit (see Table 1 and Table 3. for the timing of these assessments).

- Provision of written informed consent
- Date of birth, sex, height, weight, race, and ethnic group
- Relevant medical and surgical history, including concurrent illness and recent and current medications
- Urine pregnancy test
- Previous anti-cancer therapy, including surgery and radiotherapy
- Echocardiography and 12-lead ECG
- Chest X-ray
- Physical examination
- Safety blood sampling and urine sampling
- WHO performance status
- HRCT scan of the thorax
- Arterial oxygen saturation (SpO_2)
- Ophthalmological examination
- Vital signs (resting BP and pulse)
- Type of tumour, TNM (tumour, node, metastases) stage at diagnosis
- Tumour assessment according to RECIST criteria

17.2.3 Treatment period medical examinations

Refer to Table 1 and Table 3 for details of examinations to be performed during the treatment period. Ophthalmological is detailed in Section 17.3.9.3.

17.2.4 Medical examinations after completion of the DLT evaluation period

Patients who continue treatment with AZD8931 after the DLT evaluation period should have their safety parameters monitored and clinically assessed at least once during each cycle in accordance to the protocol schedule. From the second cycle onwards, periodic clinic visits are according to Table 1 and Table 3. Where appropriate a visit window of ±3 days (±7 days for tumour assessment) is permitted for the scheduled study procedures to be combined.

17.2.5 Post-study medical examination

A post study medical examination will be conducted as specified in Table 1 and Table 3. As a minimum telephone contact must be made with the patient at least 30 days after discontinuing treatment to collect and/or complete AE and concomitant medication information.

17.3 Safety

It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

17.3.1 Definition of adverse events

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

Any deterioration of the disease targeted in the study and associated symptoms should not be regarded as an adverse event as far as the deterioration can be anticipated.

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

17.3.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening

- Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to adverse events), except hospitalisation that has been planned before enrolment
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and is reported in an expedited manner. Any organism, virus or infectious particle (for example prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

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

17.3.3 Recording of adverse events

Adverse Events will be collected from time of signed informed consent throughout the treatment period and including the 30-day safety follow-up period after the last dose of study treatment.

Variables

The following variables will be recorded in the pCRF for each AE; description of the AE, the date and time when the AE started and stopped, CTC grade, whether the AE is serious or not, causality rating (yes or no), causality for paclitaxel, action taken with regard to investigational product, AE caused subject to discontinue study and outcome.

The degree of severity will be recorded by means of the National Cancer Institute CTCAE Version 3.0 for Cancer Clinical Trials 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. AEs will be coded according to the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

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 17.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE

The Investigator will assess causal relationship between Investigational Product and Adverse Events, 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.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.

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

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

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *"Have you had any health problems since the previous visit?"*, or revealed by observation will be collected and recorded in the pCRF. 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

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. 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.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AE(s).

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease or and increases in the symptoms of the disease. Expected progression of the disease under study and/or expected progression of signs and symptoms of the disease under study, unless more severe in intensity or more frequent than expected for the patient's condition, should not be reported as an AE. The development of new, or progression of

existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression must not be reported as an AE.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the pCRF. 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.

17.3.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the pCRF. SAEs will be recorded from the time of informed consent.

The investigator is responsible for informing the Head of study site and of the Sponsor. The Sponsor is responsible for informing Heads of other study sites, Investigators and the Regulatory Authority of the SAE as per local requirements. The Head of study site is responsible for informing the Ethical Committee.

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

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

The following information is required in the initial SAE report to AstraZeneca KK from the investigator(s); study code, site number, Enrolment code, adverse event, seriousness, start date. The following detailed information must be sent to AstraZeneca KK as soon as it becomes available;

Severity, outcome (including stop date, if available), causality (investigational product and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of adverse event, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

For all SAEs, the AstraZeneca representative will inform the AstraZeneca Patient Safety Department of it by day 1 and will work with the investigator(s) to compile all the necessary information and ensure that the Patient Safety Department receives a report within 4 calendar days.

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

Deaths

All deaths that occur during the treatment period and including the 30-day safety follow-up period after the last dose of study treatment, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the pCRF but should not be reported as a SAE.

- Where death is not due (or not clearly due) to progression of disease under study, the AE causing the 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.

Deaths with an unknown cause should always be reported as a SAE (event term ‘Death’). A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca, Patient Safety within the usual timeframes.

17.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times given in the study plan (see Table 1 and Table 3). Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date and time of blood and urine sample collection will be recorded on the appropriate pCRF.

Blood samples should be collected for all clinical chemistry and haematology parameters. Fasting samples are not required for this study except for blood glucose at screening (except if random blood glucose is >250.2 mg/dL (13.9 mmol/L) then a fasting blood glucose [minimum 8 hours fast without sugar-containing drinks is recommended] should be measured to confirm hyperglycemia).

The laboratory assessments will be performed locally at each centre's laboratory by means of their established methods.

Glucose and potassium monitoring: A blood sample should be taken according to the study plan (see Table 1 and Table 3). for measurement of potassium and glucose levels only. Additional monitoring of potassium should be undertaken if the patient receives drugs that may cause hyperkalemia. Hyperkalemia should be managed according to local standards. Hyperglycemia should be managed according to local standards.

The evaluation of post-prandial glucose as an assessment of a patient's glycemic state in this study population may be confounded by disease burden, concomitant medications (steroids and iv paclitaxel administration), study conditions (food restrictions, disturbed circadian activity, mobility etc). The clinical picture of day-to-day glycemic state obtained from random pre- and post-dose glucose samples may not reflect the true glycemic state. Although not validated in this study population, periodic assessment of HbA1c will be used for preliminary corroboration of long term glycemic state on AZD8931 (as monotherapy and in combination).

Females of child bearing potential must give a sample of the first urine passed during the day (see Table 1 and Table 3) for a pregnancy test to be performed.

All laboratory safety analyses will be performed by a local laboratory.

The following laboratory variables will be measured:

Clinical chemistry

S – Urea nitrogen

S – Creatinine

P – Glucose (random)

P – Glucose (fasting)

S – Sodium

S – Potassium

S – Calcium (total)

S – Albumin

S – Total bilirubin

S – Alkaline phosphatase

S – AST

S – ALT

S – Gamma glutamyltransferase

S – Lactate dehydrogenase

S – Unconjugated bilirubin (if total bilirubin elevated)

S – Creatine kinase (CK)

B – HbA1c

Haematology

B – Haemoglobin

B – Erythrocyte count

B – Haematocrit

B – Platelet count

B – Total leukocyte count

B – Mean cell haemoglobin concentration

B – Mean cell volume

B – Mean cell haemoglobin

B – Monocytes (absolute)

B – Eosinophils (absolute)

B – Basophils (absolute)

B – Neutrophils (absolute)

B – Lymphocyte (absolute)

B – Fibrinogen

Additional analyses at screening only

B – Activated partial thromboplastin time

B – International normalisation ratio

Urinalysis

U – Glucose

U – Protein [a]

U – Blood [a]

U – Urine sediment microscopy (Crystals, Casts, Epithelial Cells, Leucocytes and Erythrocytes)

U – Specific gravity

U – pH

U – ketones

U – bilirubin

[a] If blood or protein are present at ≥ +, urine sediment microscopy will be performed on the sample.

B – Blood, P – Plasma, U – Urine, S – Serum

For blood volume see Section 9 and 16.

17.3.6 Physical examination

Physical examination, includes but not limited to the following body systems: general appearance, skin, head and neck, lymph node, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen, and neurological.

17.3.6.1 WHO performance status

The performance status is assessed at screening (See Table 7):

Table 7 WORLD HEALTH ORGANIZATION PERFORMANCE STATUS

	Score
Fully active, able to carry out all usual activities without restrictions and without the aid of analgesia.	0
Restricted in strenuous activity, but ambulatory and able to carry out light work or pursue a sedentary occupation. This group also contains subjects who are fully active, as in grade 0, but only with the aid of analgesics	1
Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	3
Completely disabled, unable to carry out any self-care and confined totally to bed or chair	4

* Miller AB, Hoostraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207-214

17.3.7 ECG and Echocardiography

For timing of individual measurements, refer to the study plan (See Table 1 and Table 3).

17.3.7.1 Resting 12-lead ECG

ECG measurements should be done at the times specified in Table 1 and Table 3. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study. 12-lead ECGs will be recorded at 25 mm/sec after the patient has been resting in a supine position for 10 minutes in each case.

Digital 12-lead ECGs (in triplicate) are required for analysis of QTc interval, and should be repeated 3 times (one after another) at each sampling time. Paper read-outs of all ECG time points are sufficient for on site safety assessments.

The QTc interval should be the mean of the 3 digital 12-lead ECG recordings, taken from the lead in which the T-wave is highest.

The investigator or designated physician will review the paper copies of each of the ECGs. Decisions on dose escalation will be based on the local reading of the ECGs. Also, ECGs with evidence of increased QTc intervals should be collected. If any clinically significant finding is observed on the ECG, the investigator will record this as an AE. If present, the clinical signs and symptoms associated with the abnormal finding should be reported as the AE, with the ECG abnormality given as explanatory information.

17.3.7.2 Echocardiography

Echocardiography and Doppler measurements should be done at the times specified in Table 1 and Table 3. Echocardiography will also be carried out if a patient develops signs and/or symptoms suggestive of a deterioration in left ventricular function.

Echocardiography should include assessment of LVEF. It is strongly encouraged that the same laboratory and operator perform the procedure for each individual patient.

Other alternative methods of cardiac assessment may be used instead of echocardiography if they are a part of the local standard of care e.g. MUGA, or if the investigator considers them necessary for the therapeutic management of the patient.

Important cardiac symptoms should be reported as AEs. If necessary to safeguard the patient's safety, the patient should be withdrawn from the study.

Congestive cardiac failure should be treated and followed according to standard medical practice.

17.3.8 Vital signs

17.3.8.1 Pulse and blood pressure

For timing of individual measurements, refer to the study plan (See Table 1 and Table 3).

BP and pulse will be measured (single measurement) using a semi automatic BP recording device with an appropriate cuff size after the patient has been resting supine for a minimum of 5 minutes.

17.3.9 Other safety assessments

17.3.9.1 Respiratory Examination, Arterial oxygen saturation (SpO_2)

For timing of individual measurements, refer to the study plan (See Table 1 and Table 3).

HRCT and arterial oxygen saturation (SpO_2) are mandatory and should be performed before first dose of AZD8931 at baseline. The algorithm described in Appendix D should be followed if any of the following occur or worsen while on the study: dyspnoea, fever, cough, new pulmonary radiological finding. For determination of SpO2, the equipment that has been used in the study site should be used, and if the measurement is repeated, the same equipment or type should be used.

Patients will be instructed to visit, call or use other ways to contact the investigator(s) if symptoms such as dyspnoea, fever and cough occur or worsen.

17.3.9.2 Papulopustular reactions

If a new or aggravated papulopustular reaction implies a deterioration compared with baseline, the findings should be reported as an AE (graded by CTCAE) and followed up at study visits as appropriate. Any papulopustular reaction should also be graded according to a criteria based on Lynch et al, recording grade and grade changes on the pCRF (Lynch et al 2007).

17.3.9.3 Ophthalmic assessments

Ophthalmic assessment will be performed on each occasion by the same ophthalmic expert where possible. For timing of individual assessments, refer to the study plan (See Table 1 and Table 3). A full examination should be performed at screening, R21 and D28. 2) and 4) measurement will be performed at pre-study examination only but may be repeated at the ophthalmologist's discretion. Fundoscopy should be done after all other examinations. In case of clinically relevant ophthalmological abnormalities, a full examination (as detailed below) must be performed. Important symptoms should be reported as AEs (or DLT, if appropriate).

The following assessments will be performed in the order stated:

- 1) Visual acuity (best corrected) using both distance and near vision charts and Amsler grid test
- 2) Schirmer's test without anaesthesia
  - Read after 5 minutes (this test should be done before instillation of stains or dilatory agents)
- 3) Slit lamp examination:
  - Evert lid and assess for presence of tarsal, fornicial, bulbar and circumcorneal hyperaemia. Before staining, photograph any abnormalities to be captured
  - Apply 1 drop of 2% fluorescein followed by 1 drop of normal saline
  - Photograph any abnormalities
- 4) Intraocular pressure measurement and Fundoscopy following pupil dilatation

Any corneal changes must be monitored frequently, with therapeutic intervention as appropriate until resolution.

Clinical photographs with the slit-lamp camera should be taken, with and without fluorescein (please note images without fluorescein should be obtained first where possible). The patient

should be managed under the care of a competent ophthalmologist with appropriate medication and followed up until the condition has resolved

17.4 Efficacy

17.4.1 Tumour assessment for patients with measurable disease

17.4.1.1 Methods of assessment

Tumour assessment will be performed using RECIST criteria for patients with measurable disease. The definition for measurable, non-measurable, target and non-target lesions, and the objective tumour response criteria (complete response [CR], partial response [PR], stable disease [SD] or progression disease [PD]) are presented in the RECIST guidelines (Version 1.1). The RECIST criteria will be used to programmatically determine Best Overall Response.

Baseline radiological tumour assessments should be performed no more than 4 weeks before the start of study treatment, but should be as close as possible to the start of study treatment. The tumour assessment obtained before consent can be used if the examination took place within 4 weeks before the first dosing (D1). This is applicable only when the subject agrees on the use of data measured before informed consent. After the start of repeat dosing, efficacy for all patients with measurable disease will be assessed by objective tumour response at the times specified in Table 1 and Table 3. Assessments may be performed ±7 days relative to the specified visit date.

Baseline CT/MRI examination will be performed on anatomical coverage to adequately define all areas of disease. Post-baseline imaging should follow and evaluate all previous identified lesions.

All measurable lesions confirmed and assessed by radiological methods (CT or MRI scans) up to a maximum of 2 lesions per organ and 4 lesions in total, representative of all involved organs, should be identified as target lesions, recorded and measured at baseline, and at the time points specified above.

Measurable lesions that are in previous irradiation field will not be selected as target lesion.

Non-target lesions will also be monitored throughout the study, and an assessment of non target lesions will be made and recorded as “present”, “present with progression” or “absent”.

Details of any new lesions will also be collected.

It is important to follow the assessment schedule as closely as possible. If an unscheduled radiological and clinical tumour assessment is performed, and the patient has not progressed, the next scheduled tumour assessment should still be performed at the planned time (as detailed in the study plan, Table 1 and Table 3).

Tumour assessment will be performed in accordance with the protocol schedule until evidence of one of the following:

- Progression of disease
- Death without evidence of progression
- Withdrawal of consent
- Withdrawal from treatment

A patient will be determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions.

Death will be regarded as a progression event in those patients who die before disease progression. Unequivocal malignant disease not identified prior to starting study treatment on additional anatomical imaging (eg, CT, MRI or plain X-ray), prompted by symptoms is considered disease progression and should be recorded as new lesions. If progression is uncertain, patients may continue on treatment until the next scheduled assessment or may have an unscheduled assessment earlier than this if considered appropriate by the investigator.

Lesions must be assessed using the same method and technique on each occasion. Lesions will be recorded on the pCRF page in the same order as they were recorded at screening.

If a patient has received palliative radiotherapy to a lesion that lesion during study assessment period should not be included in assessment of response, but should be assessed for progression.

AstraZeneca will determine overall best response using the lesion assessments recorded on the pCRF.

17.4.1.2 Tumour assessment by imaging techniques for patients with non-measurable disease only at baseline

For patients with non-measurable disease only at baseline, the tumour assessments are done according to RECIST 1.1.

17.4.1.3 Derivation or calculation of outcome variable

Categorisation of overall visit response will be based on RECIST criteria using the following response categories: CR, PR, SD, and PD for patients with measurable disease at base-line. Patients with a best objective RECIST response of either CR or PR will be classified as responders. Response will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

In the case of SD, measurements must have met the SD criteria at least once after start of study treatment for a minimum interval of 6 weeks.

To be assigned a status of PR or CR, confirmation assessment is not necessary. Progression will be calculated in comparison to when the tumour burden was at a minimum.

17.4.2 Change in Tumour Size

17.4.2.1 Methods of assessment

Tumour size will be measured by the sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) of the RECIST target lesions.

17.4.2.2 Derivation or calculation of outcome variable

The % change from baseline in the sum of the RECIST target lesions will be calculated at each post baseline RECIST assessment.

17.4.3 Patient reported outcomes (PRO) (Not applicable)

17.5 Pharmacodynamics

17.5.1 Collection of biological samples

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

For blood volume see Section 9 and 16.

17.5.2 Exploratory biomarker research

Possible future analysis is likely to be performed retrospectively and only the appropriate subset of samples taken forward to formal analysis. The selection of this subset of samples will be wholly dependant on the outcome data of this study. Any data generated will not be reported as a part of the clinical study report for this study. The results may be pooled with biomarker data from other studies on AZD8931 to generate and or validate emerging hypotheses.

A record of the date of the patient consent to the exploratory (optional) biomarker research and the date of the blood sample collection will be recorded in the appropriate section of pCRF.

17.5.3 Plasma and serum sample

Blood will be collected for processing to plasma and serum storage for exploratory biomarker research. Blood samples 6 mL/visit(Plasma 3 mL, Serum 3 mL) will be collected at the investigator site, at the times referenced in the study plan (Table 1 and Table 3).

For blood volume see Section 9 and 16.

17.5.4 Archival diagnostic tumour sample

A historical tumour sample should be provided, if available, by the investigational site. This sample may either be in the form of a paraffin embedded tissue (PET) block or as a number of pre-cut slides. This tissue sample or slides will be stored for potential retrospective analysis of biomarkers.

17.6 Pharmacogenetics

17.6.1 Collection of samples

This section refers to the pre-dose blood sample collected for retrospective genotyping only, which is optional for the patient and involves a separate consent procedure.

The blood sample for genetic research will be obtained from the patients after randomization. Samples will be collected, labelled stored and shipped as detailed in Laboratory Manual.

An optional single venous blood sample of 9 mL will be collected prior to receiving the first dose of AZD8931.

Exclusion from the optional genetic research component of the study (blood sampling for DNA extraction and pharmacogenetics may be for any of the exclusion criteria specified

A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of pCRF.

The results of this genetic research will not form part of the CSR for this study. The results may be pooled with genetics data from other studies of AZD8931 and drugs taken in addition to AZD8931 to generate hypotheses to be tested in future studies.

For blood volume see Section 9 and 16.

17.7 Health economics (Not applicable)

18. BIOLOGICAL SAMPLING PROCEDURES

18.1 Handling, storage and destruction of biological samples

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

18.1.1 Pharmacokinetic and/or pharmacodynamic samples

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

Key samples for validation in incurred samples will be performed during the study. All PK samples will be disposed of soon after the CSR has been finalised. The results from the validation will not be reported in the CSR but separately in the bioanalytical report.

18.1.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality.

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 AstraZeneca employee working with the DNA.

The blood samples and data for genetic analysis in this study will be coded. The link between the subject enrolment/randomization 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.

18.2 Labelling and shipment of biohazard samples

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

Any samples identified as Infectious Category A materials are not shipped and further samples taken from the patient.

18.3 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 tractability of collected biological samples from the subjects while in storage at the centre until shipment.

The sample receiver keeps full tractability of the samples while in storage and during use until used or disposed.

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 is registered in AstraZeneca bio bank system during the entire life cycle.

18.4 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of biological samples donated the samples will be disposed/destroyed, if not already analysed and documented.

If collection of the biological samples is an integral part of the study then the subject is withdrawn from further study participation.

If collection of the biological samples is a voluntary part of the study then the subject may continue in the study.

The principal investigator:

- Ensures subjects withdrawal of informed consent is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed/destructed and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

AstraZeneca ensures the central laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

In the event that analysis/research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

19. ETHICAL AND REGULATORY REQUIREMENTS

19.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, ‘Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications and the AstraZeneca policy on Bioethics and Human Biological Samples.

19.2 Subject data protection

The Master Informed Consent Form will explain that:

- Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation.
- Subject data will be maintaining confidentiality in accordance with national data legislation.

- For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

- All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code).

(**PGx)** AstraZeneca will not provide individual genotype results to subjects, 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 subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate

19.3 Ethics and regulatory review

An Ethics Committee must approve the final study protocol, including the final version of the Informed Consent Form and any other written information to be provided to the subjects and pCRF. The investigator add Study site will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee must be given in writing. The head of the study site must submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee must approve all advertising used to recruit subjects for the study.

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

The protocol must be re-approved by the IRB annually. The principal investigator must submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.A valid contract between the medical institution and AstraZeneca Japan must be signed before the investigator can enrol any subjects into the study

The distribution of any of these documents to the national regulatory authorities will be handled by AstraZeneca.

19.4 Informed consent

The principal investigator(s) at each centre will:

- Ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.

- Ensure that the subjects are notified that they are free to discontinue from the study at any time.

- Ensure that the subject are given the opportunity to ask questions and allowed time to consider the information provided.

- Obtain and document the subject's signed and dated informed consent before conducting any procedure specifically for the study.

- Ensure the original, signed Informed Consent Form is stored in the Investigator's Study File.

- Ensure a copy of the signed Informed Consent Form is given to the subject.

- If any new information on the study medication becomes available which may influence the decision of the subject to continue the study, the investigator(s) must inform the subject of such information immediately, record this in a written form, and confirm with the subject if he or she wishes to continue the participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they must revise it immediately (Refer to Section 19.5). The investigator(s) must re-explain the subjects using updated Informed Consent Form even if although the subjects have already been informed of the new information verbally. Written informed consent to continue participation in the study must be provided separately.

19.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Co-ordinating Investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment must be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used.

If an administrative change is required, such a change must be notified to or approved by each IRB according to local requirements

19.6 Audits and inspections

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

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

20. STUDY MANAGEMENT BY ASTRAZENECA

20.1 Pre-study activities

Before the first subject 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
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator
- Discuss the specific requirements of the phamacodynamics and genetic research with the investigator(s) (and other personnel involved with the study)

20.2 Training of study site personnel

Before the first subject 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.

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).

20.3 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 pCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification (a comparison of the data in the pCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) incl. verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed/destructed accordingly, and the action is documented, and reported to the subject.

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.

20.3.1 Source data

Refer to Clinical Study Agreement for location of source data.

20.3.2 Direct access to source data in Japan

The Head of the institution and the principal investigator/sub-investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the pCRFs against source data before collecting the pCRFs to ensure accuracy and completeness of documentation, and assure that the principal investigator/sub-investigator has submitted the pCRFs to AstraZeneca. If the investigator wishes to amend the collected pCRFs, the monitor will ensure that the principal investigator/sub-investigator has documented the amendment in writing (signed and dated) and provided this to AstraZeneca.

20.4 Study agreements

The principal investigator at each/the centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency

between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

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

20.4.1 Deviation from the clinical study protocol in Japan

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval based on its deliberations.

The investigator(s) will record all deviations from the protocol.

The principal investigator should submit a report to AstraZeneca K.K. and the head of the study site (and the IRB via the head of the study site), to notify any change which may give a significant impact on the conduct of the study or increase a risk to the patient.

The investigator(s) may deviate from or make a change to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval, only in the event of a medical emergency, e.g. it is only way to avoid an emergency risk to the patient. In such case, the principal investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca K.K. and the head of the study site (and IRB via the head of the study site) as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca K.K. should be obtained via the head of the study site.

20.5 Study timetable and end of study

The end of the entire study is defined as ”the last visit of the last subject undergoing the trial”.

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 AZD8931.

Planned duration of the study

20.5.1 Discontinuation or suspension of the whole study programme

If AstraZeneca decides to prematurely terminate or suspend the study, the principal investigator, sub investigator, the head of the institution, and regulatory authorities must receive written notification of the reasons for the premature termination or suspension.The principal investigator/sub-investigator will immediately notify the decision to the subjects,

give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

20.5.2 Completion of the study

Upon terminating the study, the principal investigator/sub-investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the institution's rules. The head of the study site who is informed of the termination by the investigator will provide a written notification of the results to the IRB and AstraZeneca.

20.5.3 Archiving of study documentation

(i) Study files

AstraZeneca K.K. will provide the principal investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca K.K.) should be retained in this file by the principal investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca K.K.'s auditor, regulatory authorities, or IRB.

(ii) Period of record retention

The study site (and the principal investigator) will retain the essential documents specified in the ICH GCP (e.g., source document such as medical records, contract, signed consent form).Essential documents must be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca K.K.

However this is not always applied to those that are not preservable such as blood samples.

In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca K.K., and the specific period and method of retention will be separately discussed between the study site and AstraZeneca K.K. AstraZeneca K.K. should notify the head of the study site in writing when the study related records are no longer needed.

The records should be managed by a responsible person appointed by the head of the study site.

21. DATA MANAGEMENT BY ASTRAZENECA

The pCRF and the clinical database is created in accordance with Cognizant standard operating procedures using existing global and project standards. pCRF instructions are provided to sites for recording data. The data are entered, verified and cleaned and data sets

prepared according to Cognizant procedures. The data management staff is responsible for conducting and/or overseeing the following information.

Data Management Plan (DMP)

The study DMP will describe the methods used to collect, check and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process.

21.1 Dictionary coding

Medical coding is done using the most current version of MedDRA and AstraZeneca Drug Dictionary.

21.2 Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool will be tested/validated as needed. External data reconciliation will be done with the clinical database as applicable.

21.3 Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with Patient Safety database.

21.4 Quality Control Process

Data Management performs the quality control of the data in accordance with the Cognizant SOPs. Clean file occurs when all QC process have been completed.

21.5 Genotype Data

Genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system, separate from the database used for the main study.

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. The results from this genetic research will be reported separately from the clinical study report for the main study.

22. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

22.1 Calculation or derivation of safety variable(s)

22.1.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report.

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.

22.2 Calculation or derivation of efficacy variable(s)

Best overall response will be calculated as the best response recorded from date of start of study drug (taking as reference for PD the smallest measurements recorded since the treatment started) for each patient, and will be used for the summaries of objective response. Best overall response will be determined programmatically based on the RECIST criteria.

22.3 Calculation or derivation of pharmacodynamic variable(s)

22.3.1 Population analysis of pharmacokinetic/pharmacodynamic variables

PK and safety data from this study and other future studies may be subjected to exploratory population PK-pharmacodynamic analyses. If appropriate, a statistical analysis plan (SAP) will be produced prior to any such investigations and will be reported separately. The output of these analyses may be used to influence the design of future studies.

22.4 Calculation or derivation of pharmacogenetic variables

The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. SAP will be prepared where appropriate.

22.5 Calculation or derivation of health economics variables (Not applicable)

23. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

23.1 Description of analysis sets

23.1.1 Analysis of Safety population

All subjects who received at least 1 dose of AZD8931 and for whom post-dose data are available will be included in the safety population.

23.1.2 PK analysis set

The analysis of the PK variables will be performed for subjects with informative data for the analysis of a specific variable. The evaluability of the data will be determined and documented before database lock.

23.2 Methods of statistical analyses

Data cut-off

The data will be cut off at appropriate timing, after all subjects will completed Visit 10 assessment or 30 days follow-up after withdrawal of the study treatment before Visit 10 (any reason) . This first cut-off data will be applied to the evaluation (analysis) of study objectives. Therefore the clinical study report will be documented based on this data.

23.2.1 Patients demographic data

Continuous variables will be summarised using descriptive statistics (n, mean, standard deviation, min, median, max) by dose level. Categorical variables will be summarised in frequency tables (frequency and proportion) by dose level.

23.2.2 Safety and tolerability

Continuous variables will be summarised using the descriptive statistics by dose level. Categorical variables will be summarised in the frequency tables by dose level. Graphical presentations will be used as appropriate.

Adverse events will be summarised by PT (Preferred term) and SOC (System organ class) using MedDRA vocabulary. Furthermore, listings of serious adverse events and adverse events that led to withdrawal will be made and the number of patients who had any adverse events, serious adverse events, adverse events that led to withdrawal, and the drug-related adverse events will be summarised.

ECG parameters will be summarised for the absolute value at each scheduled assessment, together with the corresponding changes from the pre-dose value. The QT correction factor

will be based on the Fridericia's formula. Further categorical summaries of heart rate normalised QTcF values (> 450 ms, > 480 ms, > 500 ms) and change from pre-dose values in heart rate normalised QTcF values (> 30 ms, > 60 ms) may also be produced.

23.2.3 MTD

The number of patients who developed DLT will be summarized for each dose level.

23.2.4 Pharmacokinetics

PK variables will be summarised using appropriate descriptive statistics (e.g. n, geometric mean, coefficient of variance (CV), mean, min, median, max) by dose. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The CV is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where *s* is the standard deviation of the data on a log scale. Graphical presentations of PK variables will be used as appropriate.

23.2.5 Tumour response

All tumour response data will be listed for all patients. Best overall response assessed according to the RECIST criteria will be summarized by dose level.

All tumor size and its percentage change from baseline in sum of the lengths of the longest diameters of target lesions achieved at the time of the best overall response will be listed for all patients. In addition, the percentage change at an appropriate time point will also be listed. A plot for the percentage change will be made by dose level.

23.3 Determination of sample size

A minimum of 3 and maximum of 6 evaluable patients will be included in each dose level.

Since this study is a typical dose escalation study as a Phase I study of anti-tumour drug, the number of patients is determined in accordance with the "Guideline for Clinical Evaluation of Anti-Malignant Tumor Agents (PFSB/ELD Notification No. 1101001 dated 1 November 2005)" that is applied to Phase I studies of anticancer drugs in Japan and there is no statistical rationale based on a calculation of power.

(**PGx)** The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

23.4 Interim analyses

No formal statistical interim analysis will be undertaken, though to aid in the efficient future development of AZD8931 earlier summaries of the data may be provided.

23.5 Data monitoring committee

The Data and Safety Monitoring Committee (DSMC) shall be managed according to "The Bylaw for the DSMC" produced by AstraZeneca and the committee.

The DSMC is established at the request by the study sponsor, but the DSMC is independent of the study sponsor, investigator(s) or any personnel directly involved in the study.

The role of the DSMC is to evaluate the progress and safety data of the study at adequate intervals and to recommend continuation, amendment, suspension or discontinuation of the study to the study sponsor after consideration of the reported safety information etc. The DSMC also has a role to give advice at the request by the study sponsor when the DSMC does not reach agreement on judgment about dose escalation.

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