Revised Clinical Study Protocol

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A Phase Ib, Dose Finding Study Evaluating AZD1775 in Monotherapy, in Combination with Carboplatin and Paclitaxel, and in Combination with Only Carboplatin in Adult Asian Patients with Advanced Solid Tumours

Sponsor:

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

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1	04 Nov 2015		
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Principal Investigators

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For contact details of AstraZeneca personnel, see Section 7.2.

PROTOCOL SYNOPSIS

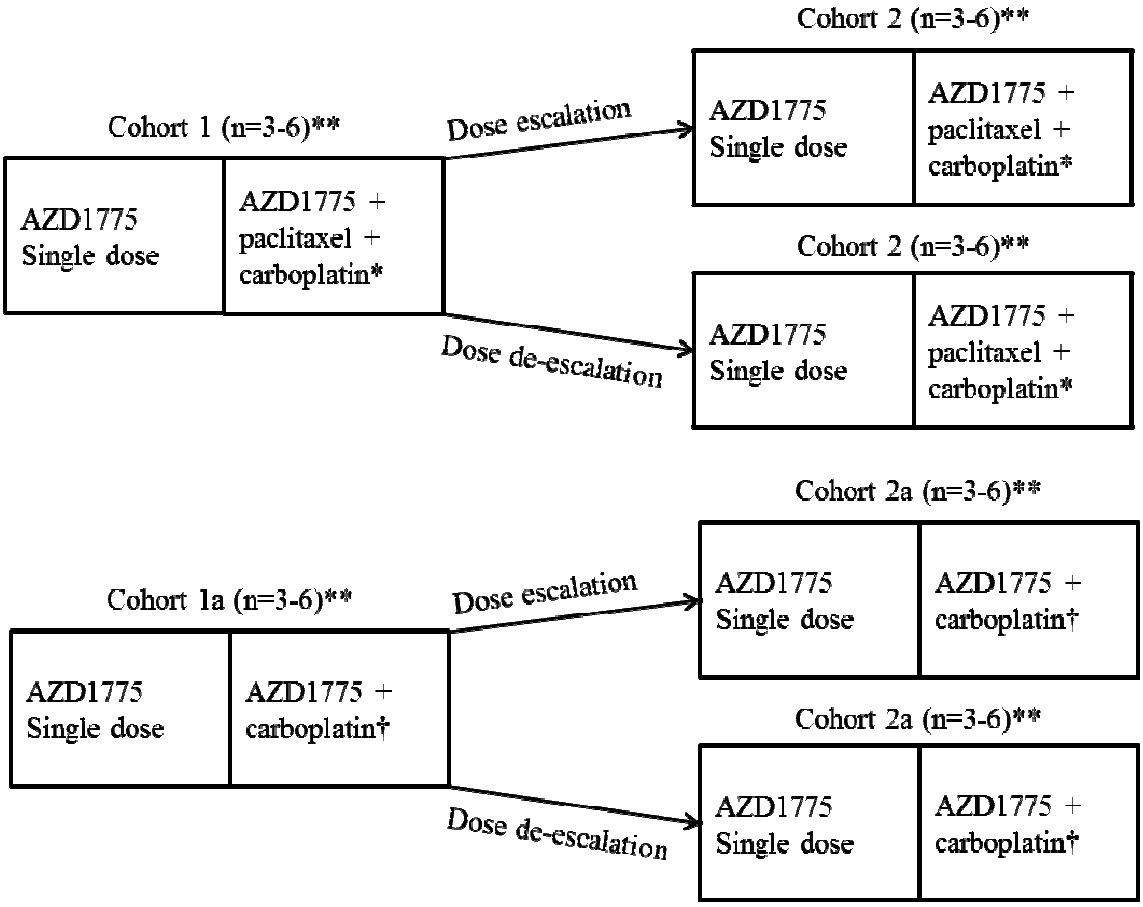
A Phase Ib, Dose Finding Study Evaluating AZD1775 in Monotherapy, in Combination with Carboplatin and Paclitaxel, and in Combination with Only Carboplatin in Adult Asian Patients with Advanced Solid Tumours

Study Design

AstraZeneca AZD1775 is a novel, highly selective, adenosine triphosphate (ATP)-competitive, small-molecule inhibitor of the Wee1 kinase that acts against cancer by sensitising tumour cells to cytotoxic agents. Clinical data demonstrate AZD1775 225 mg twice daily for 5 total doses in combination with carboplatin and paclitaxel in each 21-day cycle as tolerable and as the recommended phase II dose in Western patients.

This is a phase Ib, open-label, multicentre study of AZD1775 administered orally in monotherapy, in combination with carboplatin and paclitaxel, and in combination with only carboplatin to Asian patients with advanced solid tumours. The study has been designed to allow an investigation of the optimal combination dose and schedule whilst ensuring the safety of patients with intensive safety monitoring.

Study flow chart



* Following 6 cycles of combination treatment, at investigator's discretion and in the absence of discontinuation criteria, patients may continue on AZD1775 monotherapy

** Once the recommended dose for further clinical evaluation is established, an additional 3 to 6 patients may be enrolled to the cohort where the recommended dose has been defined to further characterise safety, tolerability, pharmacokinetics, and efficacy profiles.

† Combination therapy will be administered until disease progression or unacceptable toxicity.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
5-FU	5-fluorouracil
AE	Adverse event (see definition in Section 7.1.1)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{(0-8)}$	Area under the plasma concentration-time curve from zero to 8 hours
$AUC_{(0-10)}$	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
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to the time of the last measurable concentration
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from zero to infinity
BCRP	Breast cancer resistance protein
BID	Twice daily
C_{8hr}	Concentration at 8 hours
CDC2	Cell division cycle protein 2
CDK1	Cyclin-dependent kinase 1
CDK2	Cyclin-dependent kinase 2
C_{max}	Maximum plasma concentration
CR	Complete response
CrCl	Calculated creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation or special term	Explanation
FBR	Future biomedical research
FMO	Flavin-containing monooxygenase
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
IB	Investigator Brochure
INR	International normalised ratio
IV	Intravenous
λz	Terminal elimination rate constant
MATE	Multidrug and toxin extruder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
NTL	Non-target lesion
OAE	Other adverse event
PD	Progression of disease
PK	Pharmacokinetic(s)
PR	Partial response
PT	Prothrombin time
QD	Once daily
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RANKL	Receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious adverse event (see definition in Section 7.1.2)
SAP	Statistical analysis plan

Abbreviation or special term	**Explanation**
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SRC	Safety Review Committee
$t_{1/2\lambda z}$	Terminal half-life
TGI	Tumour growth inhibition
TL	Target lesion
t_{last}	Time to last detectable concentration
t_{max}	Time to maximum concentration in plasma
ULN	Upper limit of normal
WHO	World Health Organization

1. BACKGROUND

1.1 Investigational agent

AZD1775 (also known as MK-1775) is an inhibitor of Wee1, a protein tyrosine kinase. Wee1 phosphorylates and inhibits cyclin-dependent kinases 1 (CDK1) and 2 (CDK2), and is involved in regulation of the intra-S and G2 cell cycle checkpoints. Proper functioning of these checkpoints is essential for deoxyribonucleic acid (DNA) metabolism and the DNA damage response (Medema and Macurek 2012).

Cyclin-dependent kinase 1 (also called cell division cycle protein 2 or CDC2) activity drives a cell from the G2 phase of the cell cycle into mitosis. In response to DNA damage, Wee1 becomes activated and inhibits CDK1 to prevent the cell from dividing until the damaged DNA is repaired (G2 checkpoint arrest). Inhibition of Wee1 is expected to release a tumour cell from chemotherapeutically-induced arrest of cell replication. In vitro experiments demonstrate that AZD1775 has synergistic cytotoxic effects when administered in combination with various DNA damaging agents that have divergent mechanisms of action. Therefore, the primary objective of the clinical development of AZD1775 is its use as a chemosensitising drug in combination with a cytotoxic agent (or combination of agents) for treatment of advanced solid tumours.

CDK2 activity drives a cell into, and through, S-phase of the cell cycle where the genome is duplicated in preparation for cell division. Inhibition of Wee1 is expected to cause aberrantly high CDK2 activity in S-phase cells which, in turn, leads to unstable DNA replication structures and ultimately DNA damage. Therefore, it is anticipated that AZD1775 will have independent anti-tumour activity in the absence of added chemotherapy.

The tumour suppressor protein p53 regulates the G1 checkpoint. As the majority of human cancers harbour abnormalities in this pathway they become more dependent on S- and G2-phase checkpoints (Sherr 1996; Parker et al 1992; Kuerbitz et al 1992). Thus, S- and G2-phase checkpoint abrogation caused by inhibition of Wee1 may selectively sensitise p53-deficient cells to anti-cancer agents (Sherr 1996; Parker et al 1992; Kuerbitz et al 1992; Nigro et al 1989).

1.2 Non-clinical information and correlative studies

Preclinical evidence shows that AZD1775 selectively enhanced chemotherapy induced death of cells deficient in p53 signalling, both in vitro and in vivo. Tumour context-specific sensitisation to the DNA damaging agents, gemcitabine and platinums, was observed in TOV21G (ovarian carcinoma) cell lines matched for wild type and knock down of p53.

In studies with matched ovarian cell lines (p53 wild-type and short hairpin ribonucleic acid [RNA] p53 knockdown), AZD1775 enhanced cell death induction by gemcitabine in p53-deficient but not in p53-positive control cells. AZD1775 also demonstrated synergistic effects on cell death induction when used in combination with cisplatin and carboplatin in a p53-

dependent manner. Cervical cancer cells with human papillomavirus–induced inactivation of p53 demonstrated chemosensitisation to cisplatin and topotecan by AZD1775.

The ability of AZD1775 to affect tumour growth as monotherapy or to enhance the anti-tumour effects of gemcitabine, carboplatin, cisplatin, capecitabine, 5-fluorouracil (5-FU), and gamma irradiation was evaluated in immunocompromised host animals bearing human xenograft tumours.

The anti-tumour effect of AZD1775 dosed as monotherapy was investigated in the A427 non-small-cell lung cancer (NSCLC) nude mouse xenograft model. Daily treatment with AZD1775 led to 51% tumour regression (n = 10) and mean body weight loss did not exceed 5% over the course of the study. AZD1775 monotherapy also led to tumour growth inhibition (TGI) in additional xenograft models: 92% TGI (day 28) in SKMES1 model of NSCLC, 13% regression (day 11) in LoVo colorectal cancer model and 64% TGI (day 19) in NCI-H2122 NSCLC.

The anti-tumour effect of AZD1775 in combination with gemcitabine was investigated in the WiDr (human colorectal adenocarcinoma) nude rat xenograft model. Several schedules of gemcitabine + AZD1775 were explored. A 10-mg/kg dose of AZD1775 significantly enhanced the anti-tumour effect of gemcitabine in WiDr tumours with % treated/control (T/C) = -2%.

The anti-tumour effect of AZD1775 in combination with carboplatin was investigated in the HeLa-luc (human cervical adenocarcinoma) nude rat xenograft model. AZD1775 dose-dependently enhanced the anti-tumour effect of carboplatin tumours with %T/C = 85%, 39% and 28% at doses of 10, 20 and 30 mg/kg, respectively.

The anti-tumour effect of AZD1775 in combination with cisplatin was also investigated in the HeLa-luc nude rat xenograft model. These experiments showed dose-dependently enhanced the anti-tumour effect of cisplatin with %T/C = -5 and -16% at doses of 10 and 20 mg/kg respectively, compared with cisplatin alone.

AZD1775 enhanced the anti-tumour efficacy of 5-FU and capecitabine when used in combination with these agents, as well; experiments with nude mouse xenograft models of A549 (p53 wild-type) and Calu-6 (p53 null) NSCLC cell lines showed an enhanced anti-tumour growth effect of radiotherapy preferentially in p53 mutant xenograft tumours.

Refer to the AZD1775 Investigator Brochure (IB) for more detailed information regarding these studies and findings.

1.3 Clinical experience

AZD1775 has been administered to patients in 12 AstraZeneca-sponsored or Merck-sponsored clinical studies, 6 of which are ongoing.

Completed or terminated early:

- PN001 (NCT00648648): a first-time-in-patients, Phase I, dose-escalation study evaluating AZD1775 both as monotherapy and combination therapy with gemcitabine, cisplatin, or carboplatin in adult patients with advanced solid tumours.

- PN004 (NCT01357161): a Phase II study evaluating AZD1775 combined with carboplatin and paclitaxel in patients with platinum-sensitive p53-mutant ovarian cancer.

- PN005 (NCT01047007): a Phase I, dose-escalation study evaluating AZD1775 as monotherapy (Part 1), combination therapy with 5-FU (Part 2), and combination therapy with 5-FU plus cisplatin (Part 3) in adult Japanese patients with advanced solid tumours was terminated early due to portfolio prioritisation in oncology at Merck after 3 patients had been enrolled in Part 1 and 8 patients had been enrolled in Part 2. Part 3 was not initiated.

- PN008 (NCT01076400): a Phase I/IIa, dose-escalation study evaluating AZD1775 in combination with topotecan plus cisplatin in adult patients with cervical cancer was terminated early due to portfolio prioritisation in oncology at Merck after 7 patients had been enrolled in the dose-escalation part of the study. The Phase IIa part was not initiated.

- D6011C00001 (NCT02087176; SCRI LUN 262): a lead-in Phase II multicentre, randomised, double-blind study comparing AZD1775 plus docetaxel with placebo plus docetaxel in previously treated patients with non-small-cell lung cancer (NSCLC).

- D6011C00002 (NCT02087241; SCRI LUN 261): a Phase II study of AZD1775 plus pemetrexed and carboplatin followed by a randomised comparison of pemetrexed and carboplatin with or without AZD1775 in patients with previously untreated stage IV non-squamous NSCLC.

Ongoing:

- D6010C00004 (NCT02272790; SCRI GYN 49): a multicentre Phase II study of AZD1775 plus either paclitaxel, gemcitabine, carboplatin, or pegylated liposomal doxorubicin in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.

- D6010C00005 (NCT02511795; SCRI REFMAL 384): a Phase I study evaluating AZD1775 in combination with olaparib in refractory solid tumours.

- D6015C00001 (NCT02482311; SCRI REFMAL 383): a Phase I, dose escalation, safety and pharmacokinetic study of AZD1775 monotherapy (Schedule 1) in patients with advanced or metastatic solid tumours.

- D6015C00002 (NCT02617277; SCRI REFMAL 412): a Phase I study assessing the safety, tolerability, and pharmacokinetics of AZD1775 in combination with MEDI4736 in patients with advanced solid tumours.

- D6015C00003 (NCT02610075; SCRI REFMAL 398): a Phase Ib study to determine the maximum-tolerated dose (MTD) of AZD1775 monotherapy (Schedule 2) in patients with locally advanced or metastatic solid tumours.

In addition, Phase I and II studies are being conducted and sponsored by the National Cancer Institute's (NCI's) Cancer Therapy Evaluation Program, and by several other institutions as investigator-sponsored studies (see IB for details).

Safety

As of 11 November 2016, a total of approximately 551 patients have been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies. In addition, approximately 350 patients have received AZD1775 as part of externally sponsored scientific research. These patients have received single doses per cycle as high as 1300 mg of AZD1775 as monotherapy, 325 mg of AZD1775 as a single-dose in combination with chemotherapy, and 325 mg BID in a multiple-dose regimen in combination with chemotherapy.

Adverse drug reactions to AZD1775 in combination with cytotoxic chemotherapy include febrile neutropenia, leukopenia, stomatitis, asthenia, fatigue, mucosal inflammation and myalgia. Potential risks for AZD1775 in combination with cytotoxic chemotherapy are tachycardia and pancytopenia.

Adverse drug reactions to AZD1775 monotherapy include: anaemia, neutropenia, thrombocytopenia, QTc prolongation, gastrointestinal events such as dyspepsia, diarrhoea, nausea and vomiting (with or without dehydration or serum electrolyte decreases), as well as decreased appetite. Potential risks with AZD1775 monotherapy include asthenia/fatigue, febrile neutropenia, gastrointestinal haemorrhage, lymphopenia/lymphocytes count decreased, leukopenia/WBC count decreased, myalgia, stomatitis, sepsis and transaminases elevation.

The single-dose maximum tolerated dose (MTD) for both the gemcitabine and cisplatin combination therapies was 200 mg of AZD1775. Dose-limiting toxicities (DLTs) tended to be haematological in nature in the gemcitabine group and constitutional in the cisplatin group. The single-dose MTD for the combination with carboplatin was 325 mg of AZD1775. Dose-limiting toxicities in this group were related to serum chemistry.

Haematological DLTs were most commonly observed in the multiple-dose AZD1775 combination treatment groups with gemcitabine and cisplatin. An MTD of AZD1775 in combination with gemcitabine was established with an interim dose of 50 mg twice daily (BID) on Day 1, 25 mg BID on Day 2, and 25 mg on Day 3. An attenuated once daily (QD) dose given over 2 days in combination with gemcitabine is currently under investigation. Two DLTs (grade 3 febrile neutropenia, grade 3 aspartate aminotransferase [AST] and alanine

aminotransferase [ALT] increase) were observed at the 200 mg QD dose given for 2 days with the regimen in combination with gemcitabine. The dose was adjusted to 175 mg QD for 2 days, and 1 DLT has been reported to date. The MTD for combination with cisplatin was exceeded at the 250 mg dose level, and tolerability of the MTD at 200 mg BID has been confirmed. Dose-limiting toxicities observed in the multiple-dose carboplatin combination have been both haematological and constitutional in nature. The multiple-dose MTD in combination with carboplatin is AZD1775 225 mg BID.

The MTD for AZD1775 in combination with 5-FU has not been reached because of early study termination. Dose-limiting toxicities of encephalopathy and hyponatremia were observed in the AZD1775 20 mg BID in combination with 1000 mg/m^2 5-FU treatment group.

Triplet-based therapy was administered in the study PN004 [NCT01357161], consisting of AZD1775, carboplatin, and paclitaxel. The starting dose of 225 mg AZD1775 (BID for 5 total doses/21-day cycle) in Part 1 was generally well tolerated. One patient experienced a DLT in the first 6 patients treated and the dose remained at 225 mg BID for 2.5 days. A total of 15 patients were treated, with 3 DLTs being reported (grade 3 and 4 febrile neutropenia and grade 4 thrombocytopenia). Part B of the study has been completed with 119 patients dosed (59 in the AZD1775 and paclitaxel/carboplatin arm; 60 in the placebo and paclitaxel/carboplatin arm). The main toxicities observed in both arms were generally blood/lymphatic system disorders and gastrointestinal disorders. Although there was increased tolerability burden in the AZD1775 arm, treatment discontinuation rates between 2 arms were similar (20.3% and 21.7% for the AZD1775 arm and the placebo control arm, respectively).

For the combination of AZD1775 with topotecan plus cisplatin in study PN008 [NCT01076400], toxicities were generally haematological and gastrointestinal in nature. No unexpected toxicities were observed.

In study PN009 [NCT01164995] and the premarket formulation substudy to PN001 [NCT00648648] (both combining 2.5-day BID dosing of AZD1775 with carboplatin) there were no appreciable differences in toxicity from the ones observed in the carboplatin arm of study PN001. However, increased haematological toxicity was observed, which is considered to be a function of a drug-drug interaction with aprepitant (which was administered as anti-nausea medication in these studies). The MTD of AZD1775 in combination with carboplatin was 225 mg BID when taken for 2.5 days during Week 1 with carboplatin area under the concentration-time curve (AUC) 5 on Day 1 every 21 days in the PN001 study. At this dose, 7 of 26 evaluable patients experienced a DLT (diarrhoea [3 events], neutropenia [2 events], thrombocytopenia [2 events], febrile neutropenia [1 event], and agitation [1 event]). Of 46 patients, the most common grade 3/4/5 AEs were thrombocytopenia (43.5%), neutropenia (23.9%), and anaemia (19.6%). Drug-related serious AEs (SAEs) were reported in 15 patients (32.6%). The most frequently reported SAEs were diarrhoea (8.7%), febrile neutropenia (6.5%), and vomiting (6.5%). Similarly, in the PN009 study, of 23 patients with platinum-resistant ovarian cancer, the most common grade 3/4 AEs were thrombocytopenia (48%), neutropenia (39%), and anaemia (9%).

In the current study, as of 11 November 2016, in 6 patients treated at the starting dose of 225 mg AZD1775 in combination with carboplatin and paclitaxel in Cohort 2, there were 2 DLTs reported (one each of sepsis and interstitial pneumonia [fatal]), and this combination was deemed not tolerable in this study. Of 7 patients treated with 175 mg AZD1775 in combination with carboplatin and paclitaxel in Cohort 1, one patient experienced one DLT (platelet count decreased). In total, 937 AEs occurred in 19 patients dosed in Cohorts 1, 1A, and 2, of which 10 AEs were serious. Haematological events represented approximately 40% of the total AEs and accounted for all Grade 4 events (~7% of all AEs). Other common events included nausea (~10%), diarrhoea (~10%), and vomiting (~7%). The majority of AEs (~80%) were Grade 1 or 2.

Pharmacokinetics

The pharmacokinetic (PK) data after a single oral administration of AZD1775 showed a moderate rate of absorption with a time to maximum concentration in plasma (t_{max}) occurring at 3 to 4 hours. Post-peak plasma concentrations declined essentially in a mono-exponential manner with a half-life in the region of 10 hours. Exposure as measured by maximum plasma drug concentration observed (C_{max}) and $AUC_{(0-\infty)}$ increased in a dose-proportional manner over the dose range of 325 to 1300 mg. Following single (100 to 325 mg) and multiple dose administrations of AZD1775 (25 to 325 mg BID and 100 to 200 mg QD) with carboplatin, cisplatin, and gemcitabine, plasma exposure of AZD1775 was consistent with predictions based on the single-dose regimen. Preliminary investigation of drug-drug interactions in Study PN001 suggest a 60% increase in the exposure of AZD1775 in the presence of aprepitant (moderate CYP3A4 inhibitor), but no effect with the concomitant administration of steroids (moderate CYP3A4 inducers). Preliminary studies also suggested that the pre-marketed oral formulation of AZD1775 was similar to that of the fit-for-purpose formulation.

Efficacy

Six clinical studies with AZD1775 have been completed (Studies PN001 [NCT00648648] (Leijen S et al. 2016) and PN004 [NCT01357161]) or terminated early (Studies PN005 [NCT01047007], PN008 [NCT01076400], D6011C00001, and D6011C00002).

In Study PN001 (NCT00648648), of 176 evaluable patients who received AZD1775 (either single or multiple doses) as monotherapy or in combination with gemcitabine, cisplatin, or carboplatin, a PR (confirmed and unconfirmed) was observed in 17 (9.7%) patients, and SD was observed in 94 (53%) patients.

No complete responses (CRs) or partial responses (PRs) were observed in either of Studies PN005 (NCT01047007) or PN008 (NCT01076400) at the time that they were terminated.

For Study PN004 (NCT01357161), all patients were treated at the 225 mg AZD1775 BID 2.5 day dose level in combination with paclitaxel and carboplatin. Of the 14 evaluable patients by RECIST v1.1 in Part 1, there were 11 PRs (6 confirmed and 5 unconfirmed), and 3 SDs; 7 patients were evaluable by CA-125 with 3 CRs and 4 PRs.

In Study D6011C00001, all 32 patients were in the efficacy population. The 3 patients (9.4%) that achieved PR by RECIST v1.1 had TP53 mutations. Twenty-one patients (65.6%) had SD and 10 (47.6%) of these patients had TP53 mutations.

In Study D6011C00002, the initial response data was 27% of patients with PRs and 43% of patients with stable disease (SD).

1.4 Rationale

1.4.1 Rationale for conducting this study

AZD1775 is a highly selective, adenosine triphosphate (ATP)–competitive small-molecule inhibitor of the Wee1 kinase that sensitises tumour cells to cytotoxic agents and is being developed for the treatment of advanced solid tumours including p53 pathway-deficient malignancies. From a therapeutic standpoint, inhibition of checkpoint kinases that mediate cell-cycle arrest could force tumour cells to continue cell division before chemically induced DNA damage is repaired causing apoptosis or mitotic catastrophe (Medema and Macurek 2012). The combination of AZD1775 with carboplatin or carboplatin and paclitaxel has not been tested in Asian patients, therefore this is the first Asian patient study designed to evaluate the safety and tolerability of these combinations at various doses and/or schedules in patients with advanced solid tumours for whom no standard of care regimen currently exists. The study will also characterise the PK of AZD1775 with carboplatin or paclitaxel and carboplatin and explore potential anti-tumour activity and biomarkers. The results from this study will form the basis for decisions for future studies.

1.4.2 Rationale for study design

1.4.2.1 Study design

In this study, AZD1775 will be administered in monotherapy, in combination with carboplatin and paclitaxel, and in combination with only carboplatin to patients with advanced solid tumours at a starting dose of 175 mg. The dose finding part of the study will determine the dose for further clinical evaluation based upon assessment of the safety, tolerability and available PK data collected during the assessment period (the single dose period and the first 21-day cycle of AZD1775 in combination with carboplatin or in combination with carboplatin and paclitaxel).

The dose finding cohort size of at least 3 and up to 6 patients (Rolling 6 design) has been employed to improve the rate of accrual of patients to cohorts nearer the presumed combination therapeutic dose by reducing the need for late replacement of patients who become non-evaluable (NE) during the DLT evaluation period, whilst not compromising collection of safety data (Skolnik et al 2008). Once the recommended dose for further clinical evaluation is established, additional 3 to 6 patients may be enrolled to the cohort where the recommended dose has been defined to further characterise the safety, tolerability, PK and efficacy profiles of AZD1775 and in combination with carboplatin or in combination with paclitaxel and carboplatin.

There will be a minimum of 2 days between completion of Cycle 1, in the last required evaluable patient from 1 cohort and the start of dosing in the subsequent cohort in order for the Safety Review Committee (SRC) meeting to be called, and minutes of the dose decision to be distributed to all participating sites.

Stopping criteria for dose finding have been set in accordance with traditional oncology phase I study methodology. If 2 or more patients experience a DLT in a group of up to 6 patients, irrespective of the number of patients enrolled, the dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease.

Upon the completion of 6 cycles of AZD1775 in combination with paclitaxel and carboplatin, patients may continue on the same multiple dosing schedule of AZD1775 in monotherapy at the investigator's discretion and in the absence of discontinuation criteria.

For the AZD1775 and carboplatin cohort, study drug will be administered in 21-day cycles until PD or an unacceptable toxicity occurs.

1.4.2.2 Starting dose

The selected AZD1775 starting dose is 175 mg. The rationale of this starting dose is based upon the clinical data obtained from below studies.

In the first-in-man study PN001, patients were treated with a BID dosing regimen of AZD1775 simultaneously with chemotherapy for 2.5 days to provide continued G2-checkpoint coverage up to 60 hours. A combination of carboplatin AUC 5 and 5 doses of 225 mg AZD1775, for a total cumulative dose of 1125 mg every 21-day cycle have been generally well-tolerated.

In the study PN004, a 2-part, phase II study evaluating AZD1775 in combination with paclitaxel and carboplatin in adult subjects with platinum sensitive p53 mutant ovarian cancer, the starting dose of 225 mg AZD1775 (BID for 5 total doses/21-day cycle) in combination with paclitaxel and carboplatin in Part 1 was generally well-tolerated. A total of 15 patients were treated in Part 1, with 3 DLTs being reported (grade 3 and 4 febrile neutropenia and grade 4 thrombocytopenia). Part 2 of the study has been completed with 119 patients dosed (59 in AZD1775 and paclitaxel/carboplatin arm; 60 in placebo and paclitaxel/carboplatin arm). The main toxicities observed in both arms were generally blood/lymphatic system disorders and gastrointestinal disorders. There was increased tolerability burden in the AZD1775 arm; however, the treatment discontinuation rates between 2 arms were similar (20.3% and 21.7% for AZD1775 arm and the placebo control arm, respectively).

An interim PK analysis was conducted based on preliminary AZD1775 concentration data from patients in cohort 1 (175 mg) and cohort 2 (225 mg) using nominal blood sampling times. The similarity of PK parameters, $AUC_{(0-8)}$, $C_{max,}$ and concentration at 8 hours (C_{8hr}) between Japanese and non-Japanese subjects was assessed in comparison with the data obtained from multiple clinical studies (PN001, PN004, and PN011) and is presented in Table 1.

Table 1 **Summary of preliminary pharmacokinetic parameters of AZD1775 following single or multiple oral dose administration of AZD1775 twice daily as monotherapy or in combination with paclitaxel and carboplatin from cohort 1 and cohort 2: Comparison with pharmacokinetic parameters from Western patients.**

	Cohort 1 (Asian Population) (175 mg QD in Cycle 0, BID in Cycle 1) N=5	**Cohort 2 (Asian Population) (225 mg QD in Cycle 0, BID in Cycle 1) N=5**	**Western Population PN001[a] (225 mg BID + Carboplatin) N=9**	**Western Population PN004[a] (225 mg BID + Carboplatin + Paclitaxel) N=15**	**Western Population PN011[b] (225 mg BID) N=17**
Cycle 0 Day 1					
C_{max} (nM)	629.9 (51.68)	1073 (42.81)	--	--	740 (35.9)
t_{max}[a,e] (h)	2.00 (1.00-4.00)	4.00 (1.00-4.00)	--	--	3.53 (1.12)[d]
C_{8h} (nM)	323.5 (19.34)	564.1 (33.47)	--	--	422 (42.7)
AUC_{0-8} (nM*h)	3177 (40.42)	5373 (42.09)	--	--	3990 (35.1)
Cycle 1 Day 1					
C_{max} (nM)	588.7 (37.13)[c]	1094 (15.63)	987 (51%)	719 (37.2)	--
t_{max}[a,e] (h)	4.00 (4.00-8.00)[c]	4.00 (4.00-6.00)	2.03 (1.98-6.00)	4.03 (2.00-6.00)	--
C_{8h} (nM)	411.6 (18.88)[c]	739.5 (18.97)	535 (42.5)	500 (31.0)	--
AUC_{0-8} (nM*h)	3260 (45.75)[c]	5440 (21.28)	5120 (39.2)	4110 (38.8)	--
Cycle 1 Day 3					
C_{max} (nM)	1058 (11.62)[c]	2188 (31.93)	1850 (46.3%)	1300 (31.1)	1490 (46.2)
t_{max}[a,e] (h)	4.00 (4.00-4.00)[c]	4.00 (1.00-8.00)	4.00 (2.02-4.13)	2.54 (0.00-8.00)	3.65 (1.77)[d]
C_{8h} (nM)	841.5 (22.29)[c]	1615 (39.81)	1340 (45.7)	824 (26.2)	1030 (49.4)
AUC_{0-8} (nM*h)	6894 (11.61)[c]	14230 (34.86)	11800 (44.1)	7430 (29.3)	9630 (47.9)

Geometric mean and coefficient of variation (%) presented unless otherwise specified.
BID=twice daily, QD=once daily.

[a] Data provided in Investigator's Brochure.
[b] Data derived from Do et al 2015.
[c] N=4.
[d] Data presented as mean (standard deviation).
[e] Median (min, max) presented for t_{max} unless otherwise noted.

Based on the preliminary comparison of the results of AZD1775 PK parameters at the 225 mg dose, PK estimates in Asian patients were higher than in Western patients. After single dose administration on Cycle 0 Day 1 (monotherapy), C_{max} and AUC at 225 mg dose were 45% and

35% higher, respectively, in the Asian population as compared to the Western population (PN011 study). At steady state (Cycle 3 Day 1), a similar trend of higher exposure in Asian patients was observed. Since the exposure at the 175 mg dose in the Asian population is similar to or lower than the 225 mg dose in the Western population, a starting dose of 175 mg is considered appropriate for this Asian Phase Ib study.

1.4.2.3 Combination dose finding scheme

The proposed combination dose finding schemes (Table 2 and Table 3 below) are based on the dose levels previously evaluated as monotherapy/combination treatment and found to be tolerated (i.e., did not exceed the MTD) and were associated with biological and potential clinical activity. If the proposed Dose Level 1 is determined to be not tolerated, AZD1775 may be dose de-escalated first in the next cohort unless the SRC determines carboplatin/paclitaxel as the predominant contributor. Combination dose finding decisions will be based on review of all available data from this study and additional emerging data from other ongoing clinical studies. The dose of AZD1775 will not exceed the recommended phase II dose of 225 mg in combination with carboplatin and paclitaxel or carboplatin only in the PN004 study and the PN009 study.

If the sequential adjustments in doses of the initial regimen are unable to identify a well-tolerated combination dose then the SRC may decide to further adjust the treatment schedules of either AZD1775 or carboplatin/paclitaxel in subsequent cohorts to investigate alternative dosing schedules.

Table 2 Potential combination dose-finding options for AZD1775, paclitaxel, and carboplatin

Drug[a]	Dose level -1	Dose level 1	Dose level 2 (if dose level 1 tolerated)
AZD1775	125 mg	175 mg	225 mg
Paclitaxel	175 mg/m2	175 mg/m2	175 mg/m2
Carboplatin	AUC 5	AUC 5	AUC 5

[a] Final doses for subsequent cohorts will be determined by the Safety Review Committee (SRC).
AUC=area under the concentration-time curve.

For the AZD1775 + carboplatin cohorts, the proposed dose combinations are shown in Table 3 below. These doses are based on the preliminary data from the AZD1775 + paclitaxel/carboplatin cohorts in the current study, as well as the PN009 study. A preliminary comparison of PK parameters ($AUC_{[0-8]}$, C_{max}, and C_{8hr}), between Japanese and non-Japanese data obtained from multiple clinical studies (PN001, PN004 and PN011) at 225 mg AZD1775 BID either as monotherapy or in combination was conducted. Refer to Section 1.4.2.2 for exposure comparison between Asian and Western patient populations.

Table 3 Combination dose levels for AZD1775 and carboplatin

Drug[a]	Dose level -1	Dose level 1	Dose level 2 (if dose level 1 tolerated)
AZD1775	125 mg	175 mg	225 mg
Carboplatin	AUC 5	AUC 5	AUC 5

[a] Final doses for subsequent cohorts will be determined by the Safety Review Committee (SRC).
AUC=area under the concentration-time curve.

1.4.2.4 Exploratory research

The collection of samples to allow investigation of the presence and/or identity of metabolites of AZD1775 and, if appropriate, characterise their PK will generate data to allow AstraZeneca to fulfil regulatory requirements related to the testing of the safety of metabolites.

As part of the clinical drug development program for AZD1775, AstraZeneca plans to include investigations into exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from DNA, RNAs, proteins, and/or metabolites. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or non-responders, or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how it can be utilised to bring better drugs to the clinic. The ability to acquire appropriate consent to collect biological samples is of utmost importance in order to establish an archive and allow future meta-analysis of data derived from a number of studies with AZD1775.

AstraZeneca intends to perform genetic research in the AZD1775 clinical development programme to explore how genetic alterations in the tissues from related patients may affect the clinical parameters associated with AZD1775. These studies may result in improvements in the design and interpretation of future clinical studies and potentially the development of treatment strategies based on the genetics of the tumour.

It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of, and tumour response to AZD1775 in patients with advanced solid tumours under study within the current protocol. No other research will be performed on the samples.

1.5 Benefit/risk and ethical assessment

1.5.1 Potential benefits

Cytotoxic agents that induce DNA damage activate cell cycle checkpoints in proliferating cells. These checkpoints cause transient arrest at the G1-, S-, and G2-phases of cycling cells, allowing time to repair the DNA damage or to initiate apoptosis if the DNA damage is too extensive. Human tumour cells are most sensitive to chemotherapy during the phase of DNA replication (S-Phase) which is variable in length and lasts up to ~60 hrs (Nigro et al 1989,

Medema and Macurek 2012) in human tumours in–situ. While DNA checkpoints can protect normal cells from DNA damage, they also reduce the effectiveness of chemotherapy on tumour cells by allowing tumour cells to repair DNA damage induced by the chemotherapy. Thus, selective inhibition of checkpoints in tumour cells is predicted to enhance the efficacy of DNA-damaging agents.

AZD1775 is a potent and selective small molecule of Wee1 inhibitor that inhibits G2 checkpoint activity.

In both in vitro studies and in vivo xenograft tumour models, AZD1775 showed single-agent anti-tumour activity, and when in combination with cytotoxic agents, caused significantly greater efficacy than chemotherapeutics alone.

Furthermore, AZD1775 combined with carboplatin or carboplatin and paclitaxel has demonstrated clinical efficacy in patients with ovarian cancer in the ongoing studies (PN004 and PN011).

The investigation of AZD1775 in this patient population appears acceptable based upon the non-clinical profile and emerging clinical data.

1.5.2 Potential risks

The types of toxicities observed in AZD1775 studies are not unexpected for therapies that include full-dose chemotherapy. Patients should therefore be closely monitored for signs of gastrointestinal AEs (including diarrhoea, nausea, and vomiting) and if necessary, they should be managed clinically with supportive treatment not limited to anti-emetics, intravenous (IV) hydration, and anti-diarrhoeals as needed. Weight should be carefully monitored with other vital signs and doses of AZD1775 and chemotherapeutics should be adjusted accordingly.

Haematological parameters should be carefully assessed after dosing of AZD1775 in combination with carboplatin and paclitaxel. Haematologic and laboratory toxicities should be managed clinically and supportive care measures (e.g., transfusion or/and growth factor support) should be taken for decreases that are clinically significant.

Overall the benefit/risk assessment supports the investigation of AZD1775 in combination with carboplatin and paclitaxel in this patient population for whom there is no alternative standard therapy.

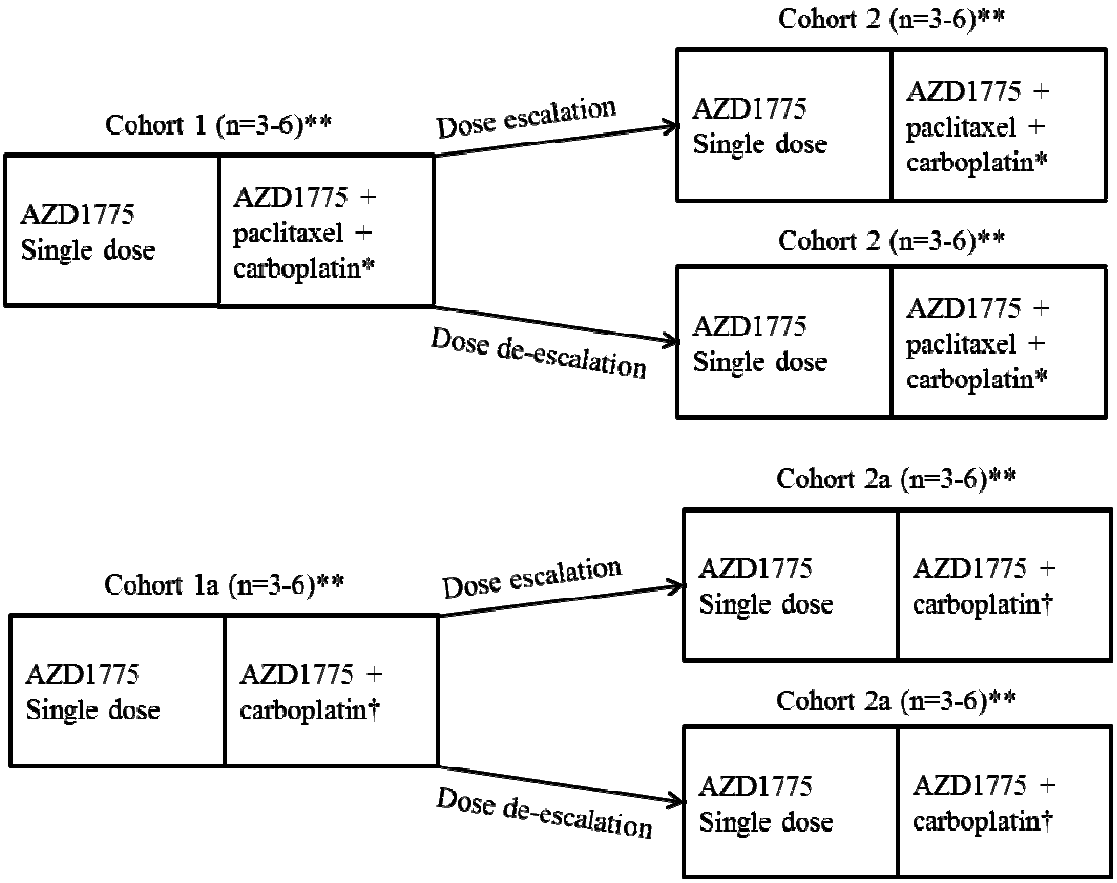
1.6 Overall study design and flow chart

This is a phase Ib, open-label, multicentre study of AZD1775 administered orally in monotherapy, in combination with carboplatin, and in combination with carboplatin and paclitaxel to Asian patients with advanced solid tumours. The study design allows escalation or de-escalation of AZD1775 in combination with carboplatin or in combination with carboplatin and paclitaxel with intensive safety monitoring to ensure the safety of the patients.

Figure 1 shows the study flow chart. Approximately 12 evaluable patients will be enrolled in the AZD1775 plus carboplatin and paclitaxel cohorts, and approximately 12 evaluable patients will be enrolled in the AZD1775 plus carboplatin only cohorts for the dose-finding portion of this study. The total number of patients will depend upon the number of combination dose level evaluations necessary to define the recommended dose for further clinical evaluation. The proposed combination doses are summarised in Table 2and Table 3 but all combination doses other than Combination Dose level 1 may be subject to change by the SRC in light of emerging data. At least 3 and up to 6 evaluable patients will be required for each dose finding cohort.

Once the recommended dose for further clinical evaluation is established, additional 3 to 6 patients may be enrolled to the cohort where the recommended dose has been defined to further characterise the safety, tolerability, PK, and efficacy profiles of AZD1775 in combination with carboplatin or in combination with paclitaxel and carboplatin. If this dose is subsequently found to be non-tolerated, alternative doses and/or schedules may be explored. This will be determined by the SRC.

Figure 1 Study flow chart



* Following 6 cycles of combination treatment, at investigator's discretion and in the absence of discontinuation criteria, patients may continue on AZD1775 monotherapy

** Once the recommended dose for further clinical evaluation is established, an additional 3 to 6 patients may be enrolled to the cohort where the recommended dose has been defined to further characterise safety, tolerability, pharmacokinetics, and efficacy profiles.

† Combination therapy will be administered until disease progression or unacceptable toxicity.

2. STUDY OBJECTIVES

2.1 Primary objective

- To investigate the safety and tolerability of AZD1775 when given orally to patients with advanced solid tumours in monotherapy, in combination with carboplatin, and in combination with carboplatin and paclitaxel, and define the recommended dose for further clinical evaluation

2.2 Secondary objectives

- To characterise the PK profile of AZD1775 after single dosing and at steady state after multiple dosing when given orally to patients with advanced solid tumours in combination with carboplatin or in combination with carboplatin and paclitaxel
- To characterise the PK profile of paclitaxel in combination with AZD1775 and carboplatin in patients with advanced solid tumours
- To characterise the PK profile of carboplatin in combination with AZD1775 alone and AZD1775 and paclitaxel in patients with advanced solid tumours
- To obtain a preliminary assessment of the anti-tumour activity of AZD1775 in combination with carboplatin and in combination with carboplatin and paclitaxel in patients with advanced solid tumours by evaluation of tumour response using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see Appendix B)

2.3 Exploratory objectives

- To perform correlative analysis of baseline biomarker blood samples (e.g., tumour-related mutations in the plasma).
- To perform correlative analysis of changes in biomarker blood samples observed at baseline and during treatment (changes in tumour-related mutations in the plasma).
- To perform correlative analysis of archived or fresh tumour tissue at baseline (e.g., status of TP53, CDKN2A, KRAS or BRAF).
- To provide PK data to allow a cross study analysis of PK using population PK approaches.

3. PATIENT SELECTION (PRE-STUDY) AND RESTRICTIONS (ON STUDY)

Investigators should keep a record (i.e., patient screening log) of patients who entered pre-study screening.

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

3.1 Inclusion criteria

For inclusion in the study, patients must fulfil all of the following criteria:

1. Provision of signed and dated, written informed consent before any study-specific procedures, sampling and analyses.

   If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the patient and he or she will not be excluded from other aspects of the study.

2. Aged ≥18 years; for patients enrolled in the study in Japan, patients must be ≥20 years of age.

3. Histological or cytological confirmation of a locally advanced or metastatic solid tumour, excluding lymphoma, that failed to respond to standard therapy, progressed despite standard therapy, or for which standard therapy does not exist.

4. At least 1 measureable lesion that can be accurately assessed at baseline by computed tomography or magnetic resonance imaging for solid tumours assessed using RECIST v1.1.

5. World Health Organisation performance status 0 to 1 with no deterioration over the previous 2 weeks and a minimum life expectancy of ≥12 weeks.

6. Females should agree to use adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test before the start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at Screening:

   – Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments

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

- Women under 50 years old would be considered postmenopausal if they have been amenorrhoeic for at least 12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone (FSH) and luteininzing hormone (LH) levels in the postmenopausal range for the institution.

7. Sexually active male patients should be willing to use barrier contraception (i.e., condoms).

8. **(Japanese Patients Only)** Patients should be willing to remain in hospital as appropriate during Cycle 0 and Cycle 1.

9. Baseline laboratory values as follows:

   - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
   - Haemoglobin ≥90 g/L
   - Platelets $\geq 100 \times 10^9$/L
   - ALT and AST ≤2.5 × upper limit of normal (ULN) or ≤5 × ULN if known hepatic metastases.
   - Total bilirubin ≤1.25 × ULN; or total bilirubin ≤3.0 × ULN with documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia)
   - International normalised ratio (INR) or prothrombin time (PT) ≤1.5 × ULN, activated partial thromboplastin time (aPTT) ≤1.5 × ULN
   - Serum creatinine ≤1.2 × ULN or a calculated creatinine clearance (CrCl) ≥60 mL/min by the Cockcroft-Gault method:

CrCl (glomerular filtration rate [GFR]) = (140 – age) × (weight [kg]) × (0.85 if female) / (72 × serum creatinine [mg/dL])

3.2 Exclusion criteria

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

1. Treatment with any of the following:

   - Any cytotoxic chemotherapy, investigational agents or other anticancer drugs from a previous treatment regimen or clinical study within 14 days (if investigational agent does not have well characterised PK profile) or 5 × half-lives of the first dose of study treatment

- Patient has had prescription or non-prescription drugs or other products (i.e., grapefruit juice) known to be sensitive to CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index, or to be moderate to strong inhibitors or inducers of CYP3A4, which cannot be discontinued 2 weeks before Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study drug. Co-administration of aprepitant during this study is prohibited (see Section 3.3.2)

- AZD1775 is an inhibitor of breast cancer resistance protein (BCRP). The use of statins including Atorvastatin which are substrates for BCRP are therefore prohibited and patients should be moved on to non-BCRP alternatives.

- Herbal preparations are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

- Prior dosing of AZD1775 in a previous study (i.e., dosing with AZD1775 previously initiated in another previous or current study).

- Major surgery (excluding placement of vascular access) or significant traumatic injury within ≤28 days of the first dose of study treatment, or have an anticipated need for major surgery during the study.

- Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study treatment.

2. Any unresolved toxicities from prior therapy, greater than Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade 1 at the time of starting study treatment with the exception of alopecia (any grade or duration).

3. Spinal cord compression or brain metastases unless asymptomatic and not requiring steroids for at least 4 weeks before start of study treatment.

4. As judged by the investigator, any evidence of severe or uncontrolled systemic diseases, including but not limited to: uncontrolled hypertension, renal transplant, active bleeding diatheses, or positive status for Hepatitis B surface antigen, Hepatitis C antibody, or human immunodeficiency virus (HIV). Screening for chronic conditions is not required.

5. Any of the following cardiac criteria:

- Mean resting corrected QT interval (QTc) >470 msec obtained from 3 electrocardiograms (ECGs)

- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block)

- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, any concomitant medication known to prolong the QT interval, family history of long QT syndrome, or unexplained sudden death under 40 years of age

6. Any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association (NYHA) ≥ Class 2 (see Appendix C)

   - Unstable angina pectoris

   - Congestive heart failure

   - Acute myocardial infarction

   - Conduction abnormality not controlled with a pacemaker or medication

   - Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)

7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD1775.

8. Any known hypersensitivity or contraindication to the components of study treatment (AZD1775, paclitaxel, or carboplatin).

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

3.3 Restrictions

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

1. Females of child-bearing potential should use reliable methods of contraception from the time of Screening until 1 month after discontinuing study treatment. Acceptable methods of contraception include abstinence, tubal ligation, tricycle

combined oral or transdermal contraceptives, copper-banded intra-uterine devices and vasectomised partner. All methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse.

2. Male patients should avoid unprotected sex with women of child-bearing potential during the trial and for a washout period of 3 months after the last dose of study drug. Patients should avoid procreation for 3 months after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until 3 months (6 months for patients undergoing study treatment in Japan) after discontinuing study treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples before the start of study treatment.

For restrictions relating to concomitant medications see next Section 3.3.1.

3.3.1 Concomitant treatments

Formal drug-drug interaction studies have not been performed with AZD1775. All concomitant medications received within 14 days before the first dose of study medication and 28 days (±7 days) after the last dose of study medication should be recorded with reasons for the treatment, in the Case Report Form (CRF).

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

Premedication with anti-emetics (excluding aprepitant [Emend]) is allowed according to standard practice guidelines. Aprepitant should not be used to manage nausea and vomiting as it is an inhibitor of CYP3A4.

Blood transfusions are allowed at any time during the study.

Patients already receiving erythropoietin at the time of Screening for the study may continue its use provided they have been receiving it for more than 1 month at the time study treatment is started. Prophylactic erythropoietin should not be started during Cycle 1 of the study but may be started during Cycle 2 and after (patients enrolled in Japan are exempt from this because it isn't used to meet the indication).

Granulocyte colony-stimulating factors (G-CSFs) may be used according to institutional guidelines. However, the prophylactic use of G-CSF in Cycle 1 is prohibited.

Medications may be administered for maintenance of existing conditions before study enrolment or for a new condition that develops while on study, including but not limited to the following:

- Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g., denosumab).

- Patients requiring therapeutic warfarin or Coumadin-derivative anticoagulants will be monitored with INR and PT as clinically indicated.

- Low molecular weight heparin (LMWH), rivaroxaban, or equivalent anticoagulant therapy is permitted where clinically indicated.

- Other medication, other than those described above, which is condsidered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the CRF.

3.3.2 Concomitant medications

The following treatments are prohibited while in this study (for a full list, see Appendix D):

- Drugs known to be moderate to strong inhibitors/inducers of CYP3A4 or sensitive CYP3A4 substrates or substrates of CYP3A4 with a narrow therapeutic window that cannot be discontinued 2 weeks before first dose of AZD1775 and withheld throughout the study until 2 weeks after the last dose of AZD1775 are prohibited. As grapefruit and Seville oranges are known to contain moderate inhibitors of CYP3A4, these fruits and their products (including marmalade, juice, etc.) should be avoided while taking AZD1775.

  – Strong Inhibitors of CYP3A4 include: azole antifungals (ketoconazole, fluconazole, voriconazole and itraconazole), macrolide antibiotics (clarithromycin and erythromycin), calcium channel blockers, HIV protease inhibitors (indinavir, nelfinavir, and ritonavir), and cimetidine, aprepitant, and nefazodone.

  – Inducers of CYP3A4: phenytoin, barbiturates, and rifampicin

  – Substrates of CYP3A4: statins (lovastatin, simvastatin), midazolam, terfenadine, astemizole, and cisapride

  Refer to Appendix D for a list of inhibitors, inducers and substrates of CYP3A4. Supportive care with a CYP3A4 inhibitor/inducer/substrate according to institutional guidelines in the context of standard of care chemotherapy will be exempt; however, concomitant treatment with aprepitant is not allowable per protocol. See AZD1775 IB for additional information.

- In vitro data suggest that AZD1775 may also be a weak reversible inhibitor of CYP2C19. Caution should be exercised with concomitant administration of AZD1775 and agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range; refer to Appendix D for a list of sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range.

- In vitro studies have shown that AZD1775 may be a substrate and inhibitor for human P-glycoprotein. Caution should be exercised when inhibitors or substrates of P-glycoprotein are administered with AZD1775.

- Use of metformin is prohibited in this study as recent in vitro transporter data have shown AZD1775 is an inhibitor of multidrug and toxin extruder 1 (MATE1) and MATE2K. Caution should be used when administering drugs that are substrates of these transporters (e.g., cimetidine, acyclovir, fexofenadine) as the clinical relevance of AZD1775 inhibition of the MATE pathway is not known in these compounds.

- Aprepitant use is prohibited in this study. No formal clinical drug interaction studies have been performed with AZD1775. An exploratory assessment of the effect of aprepitant on AZD1775 exposure in oncology patients suggests that there is a drug interaction between AZD1775 and aprepitant, as exposure to AZD1775 increased by ~60% when aprepitant was co-administered with AZD1775. The observed increase in AZD1775 exposure is likely the result of CYP3A4 inhibition by aprepitant. This increase in exposure is statistically significant. At the selected MTDs, this increase may also be of clinical importance. Therefore, concomitant treatment with aprepitant is not allowable per protocol until further evaluation. See AZD1775 IB for more information.

- Recent in vitro transporter studies have shown AZD1775 to be an inhibitor of BCRP (IC_{50}=5.1 μM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins. Modelling has predicted a substantial increase in the exposure of rosuvastatin when co-administered with AZD1775 and the use of rosuvastatin is therefore prohibited in the current study. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug.

- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days before first dose of AZD1775.

- AZD1775 has been shown to be a weak inducer of CYP1A2 in vitro. Taking into account the anticipated plasma concentrations (C_{max}<1.5 μM) and the intermittent nature of the AZD1775 dosing schedule; however, the risk of induction in the clinic is considered low. No specific precautions are recommended at this time, except to be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range.

- Caution must be exercised with the concomitant use of aminoglycosides in keeping with the treatment guidelines for carboplatin.

- Paclitaxel is metabolised by CYP2C8 (mainly) and CYP3A4. Appendix D provides a list of CYP2C8 inhibitors that should be excluded as concomitant medications. This list is not all-inclusive, and for other concomitant medications, the Investigator and AstraZeneca will determine if they are known to significantly influence CYP2C8.

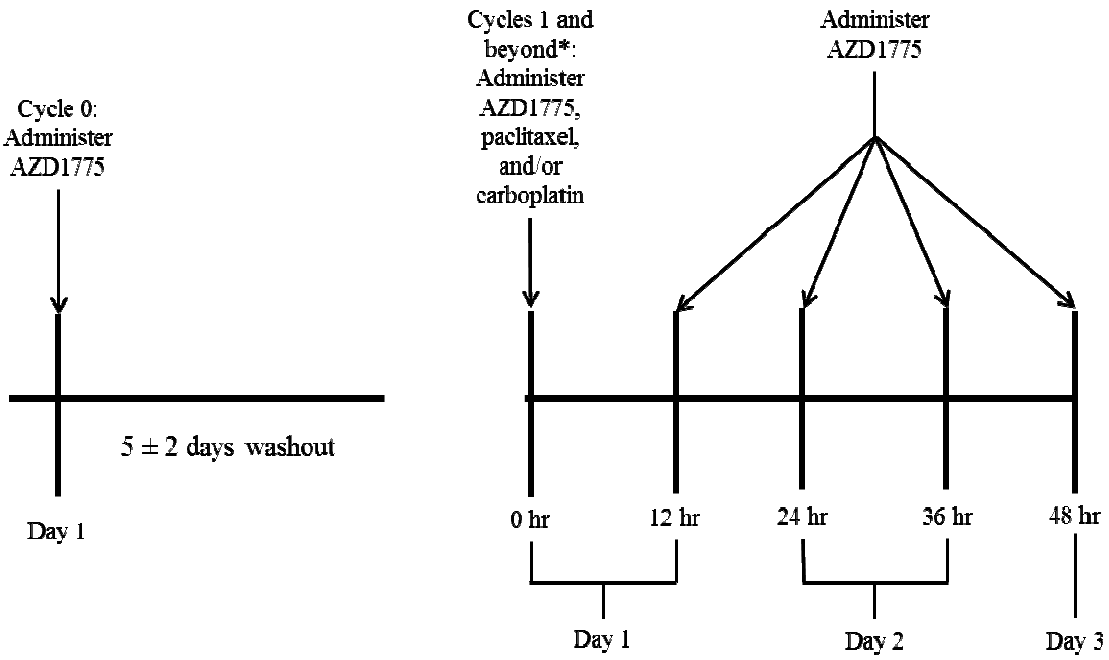
4. STUDY TREATMENT, CONDUCT, AND WITHDRAWAL

4.1 Treatment

4.1.1 Study drugs

Figure 2 shows the dosing scheme for AZD1775, paclitaxel, and carboplatin.

Figure 2 Dosing Schema



*In the AZD1775 plus carboplatin and paclitaxel cohorts, following 6 cycles of combination treatment, at investigator's discretion and in the absence of discontinuation criteria, patients may continue on AZD1775 monotherapy. In the AZD1775 and carboplatin only cohorts, combination therapy will be administered in 21-day cycles until disease progression or an unacceptable toxicity occurs.

4.1.1.1 AZD1775

AZD1775 will be administered orally as a single dose on Day 1 of Cycle 0. Following a 5±2 day washout period, AZD1775 (5 doses BID over 2.5 days) will be taken in combination with carboplatin or in combination with paclitaxel and carboplatin in each 21-day cycle.

In the AZD1775 plus carboplatin and paclitaxel treatment cohorts, patients will complete a maximum of 6 treatment cycles. Following 6 cycles of combination treatment, patients may continue on AZD1775 monotherapy (5 doses BID Day 1 to Day 2.5 in each 21-day cycle) at the investigator's discretion. Alternative schedules may be instigated in response to emerging safety, tolerability or PK data.

In the AZD1775 plus carboplatin cohort, therapy will be administered in 21-day cycles until PD or an unacceptable toxicity occurs.

Any patients still receiving investigational product at the time of primary data cut-off (as defined in Section 5.5) will visit the site to complete a 'Final Protocol Visit' following implementation of Revised Clinical Study Protocol Edition 2.0. This Final Protocol Visit should align with the next cycle scheduled visit.

Beyond the Final Protocol Visit, patients may continue to receive AZD1775 if they are deriving clinical benefit, in the opinion of the investigator, and not fulfilling any of the discontinuation criteria. For these patients, the following apply:

- Restrictions regarding concomitant medications (refer to Section 3.3) will be followed while the patient is receiving AZD1775. A change in AZD1775 dose/schedule should only occur for safety reasons, based on the Investigator's judgement, and generally follow the approach for dose reduction and discontinuation as described in the protocol. Combining AZD1775 with other chemotherapy (except carboplatin/paclitaxel in the case of the patient already receiving AZD1775 in combination with carboplatin or 'carboplatin plus paclitaxel' as per the study design) is not allowed. If a patient is no longer receiving benefit from AZD1775 in the opinion of the treating physician, then the drug should be stopped. The Investigator will inform the Sponsor when the patient discontinues the study drug.

- The patients will be treated in accordance with local practice and as deemed appropriate by the Investigator. It is recommended that these patients continue to be observed at the frequency employed prior to the Final Protocol Visit. However, the final decision rests with the investigator. If the investigator chooses to adopt a different approach, that approach will be documented locally. The patients will be monitored for safety while receiving investigational product. The Investigator should perform safety assessments (haematology, chemistry, and ECG) prior to the start of a treatment cycle, and the cycle should be initiated only if deemed safe for the patient.

- Patients will return used and unused medication at routine clinic visits, and drug accountability information must continue to be collected until the patient discontinues treatment. Patients must continue to be monitored for all serious adverse events (SAEs), pregnancies, and overdoses for 28±7 days after the last dose of the investigational product. In addition, provided the patient gives proper informed consent, a DNA blood sample for future biomedical research should be obtained at the time of AZD1775 discontinuation in patients who discontinue due to disease progression.

Since the effect of food on AZD1775 has not been determined, patients should take AZD1775 either 2 hours before or 2 hours after a meal.

If the patient misses a dose of AZD1775, the patient should take the dose as soon as possible, but not more than 6 hours after the missed scheduled dose. If greater than 6 hours, the missed dose should be skipped and the patient should take the next dose when scheduled.

If vomiting occurs after the patient takes the AZD1775, the patient should be instructed not to retake the dose, but to wait until the next scheduled dose of AZD1775. If vomiting persists, the patient should contact the Investigator.

AZD1775 will be supplied by AstraZeneca as capsules for oral use. The capsules will be supplied at 2 strengths, 100 and 25 mg, in high-density polyethylene bottles, which sufficiently protect the drug from light. The different capsule strengths should not be combined in the same bottle at any time. Additional information about the investigational product may be found in the IB.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

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

4.1.1.2 Paclitaxel

Commercially available paclitaxel will be administered at a dosage of 175 mg/m^2 as a 3-hour IV infusion on Cycle Day 1 of a 21-day cycle for 6 cycles. BSA should be recalculated if there is a change of +/- 10% in body weight between cycles.

Patients should be pre-medicated with corticosteroids, diphenhydramine and/or H2 antagonists according to institutional standards.

Refer to the paclitaxel package insert for additional information.

4.1.1.3 Carboplatin

Carboplatin will be administered at a dose of AUC 5 as an IV infusion on Cycle Day 1 of a 21-day cycle for 6 cycles for the AZD1775 in combination with carboplatin and paclitaxel cohort; carboplatin will be administered at a dose of AUC 5 as an IV infusion on Cycle Day 1 of a 21-day cycle until PD or unacceptable toxicity for the AZD1775 in combination with carboplatin cohort. If paclitaxel is also being administered, carboplatin should be administered after the paclitaxel infusion has completed. According to the Cancer Therapy Evaluation Program Information Letter Regarding the AUC Based Dosing of Carboplatin, the maximum carboplatin dose should not exceed the target AUC (mg*min/mL)*150 mL/min, but it may be less (Ivy et al 2010). For this study, the maximum dose of carboplatin cannot exceed a total dose of 750 mg. Alterations in renal function may require a recalculation of the carboplatin dose.

The carboplatin dose will be calculated using the Calvert Formula based on the patient's GFR which is estimated using CrCl:

$$Carboplatin\ dose\ (mg) = target\ AUC \times (GFR + 25)$$

Patients may receive prophylactic anti-emetic therapy for moderately emetogenic chemotherapy according to institutional standards, excluding aprepitant, (see Section 3.3.1).

Refer to the carboplatin package insert for additional information.

All patients are required to have an absolute neutrophil count $\geq 1.5 \times 10^9$/L and a platelet count $\geq 100 \times 10^9$/L on the day of retreatment (Day 1 of subsequent treatment cycle) or treatment is to be delayed until blood counts have returned to acceptable levels. Patients are evaluated for AEs, including tinnitus and hearing loss, at every visit. The Investigator and his/her staff are permitted (per-protocol) to perform any reasonable procedures they feel are warranted to insure the safety of the patient. This would include performing additional hearing tests, including audiometry, at the discretion of the Investigator.

4.1.2 Starting dose and combination dose finding scheme

The planned combination dose finding scheme has the flexibility to be amended in light of emerging data. A cycle of combination treatment will be defined as a 21-day cycle with 5 doses of AZD1775 administered BID on Day 1 to Day 2.5 in combination with either carboplatin or paclitaxel and carboplatin administered on Day 1. For the AZD1775 plus carboplatin and paclitaxel cohorts, a cycle of AZD1775 monotherapy after 6 cycles of combination treatment will also be defined as a 21-day cycle with 5 doses of AZD1775 administered BID on Day 1 to Day 2.5.

The potential combination dose options for investigation are presented in Table 2 and Table 3. All combination dose levels beyond Dose Level 1 may be adjusted by the SRC in response to emerging safety, tolerability and PK data. Similarly, the SRC may consider alternative dosing schedules in light of emerging data.

AZD1775 dosing will begin at 175 mg BID. One single oral dose AZD1775 will be administered on the morning of Day 1, followed by a washout of 5±2 days, and then multiple oral dosing of AZD1775 175 mg BID at intervals of approximately 12 hours for a total of 5 doses in combination with paclitaxel 175 mg/m2 administered as a 3-hour infusion (in the AZD1775 plus paclitaxel and carboplatin cohorts) followed with carboplatin AUC 5 on Day 1 per 21-day cycle for 6 cycles. The single dose monotherapy period will be defined as Cycle 0, which starts at a single dose on Day 1 until the day before the first dose of combination dosing. Cycle 1 will be a 21-day period from the first dose of AZD1775 multiple dosing in combination with carboplatin or paclitaxel and carboplatin. In AZD1775 plus paclitaxel and carboplatin cohorts, the maintenance treatment with AZD1775 as monotherapy may be allowed after 6 cycles of AZD1775 and carboplatin and paclitaxel combination treatment at the investigator's discretion. In AZD1775 plus carboplatin only cohorts, combination dosing will continue in 21-day cycles until disease progression or an unacceptable toxicity occurs. The DLT assessment period consists of Cycle 0 and Cycle 1.

After Cycle 1, patients will be treated until discontinuation criteria are met (Section 4.2).

Initially, 3 to 6 evaluable patients will be enrolled per cohort. Dose escalation and de-escalation will follow the scheme below, according to the following logic:

- If no DLT is observed (for definition of DLT see Section 4.1.3) in a cohort of 3 to 6 evaluable patients then dose escalation may occur. Dose increases will be permitted after review of data from a minimum of 3 evaluable patients has been performed.

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

- If 2 or more patients experience a DLT in a group of up to 6 patients, irrespective of the number of patients enrolled, the dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease. A lower intermediary dose (de-escalation) may be considered in order to better define the combination recommended dose for further clinical evaluation (for definition see Section 4.1.6).

See Table 2 and Table 3 for examples of the potential combination dose escalation or de-escalation schemes; however, the doses for subsequent cohorts or a decision to stop recruitment for combination dose finding will be agreed by the SRC after review of all the available safety and PK data from each cohort (see Section 4.1.6).

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

There will be no intra-patient dose escalations.

Once the recommended combination dose is defined, additional 3 to 6 patients may be recruited to the same cohort where the dose is defined for further evaluation of the safety, tolerability, and PK and/or pharmacodynamics of AZD1775.

4.1.3 Definition of dose-limiting toxicity

A DLT is defined as an AE or abnormal laboratory value that occurs from the first dose of study treatment up to the last day of Cycle 1, assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that, despite optimal therapeutic intervention meets any of the following criteria:

1. Haematological toxicity that is:
   - ≥ CTCAE v4.03 grade 4 for more than 7 days
   - Infection with febrile neutropenia
   - Grade 4 thrombocytopenia for more than 4 days, or for which platelet transfusion is required
2. Non-haematological toxicity ≥ CTCAE v4.03 Grade 3 with the specific exception of:
   - Nausea, vomiting, diarrhoea, or dehydration (all Grade 3) that in the opinion of the Investigator and Sponsor occurs in the setting of inadequate compliance with supportive care measures specified in Section 7.3.3 and lasts <48 hours
   - Inadequately treated hypersensitivity reactions
3. Any other toxicity that is clinically significant and/or unacceptable, does not respond to supportive care, results in a delay of >2 weeks in the scheduled administration of chemotherapy/AZD1775 due to drug-related toxicities, and/or is judged to be a DLT by the SRC

A DLT excludes:

1. Alopecia of any grade or duration
2. Isolated laboratory changes of any grade without clinical sequelae or clinical significance

However, the incidence and type of toxicity from Cycle 2 and beyond will be taken into account by the SRC in determining dose escalation or de-escalation steps.

4.1.4 Definition of maximum tolerated dose

A combination dose will be considered non-tolerated if more than one of 3 to 6 evaluable patients or ≥ 33% of 6 to 12 evaluable patients experience a DLT at the combination dose level. At least 6 evaluable patients are required to determine the combination recommended dose for further clinical evaluation.

4.1.5 Definition of an evaluable patient

An evaluable patient is defined as a patient that has received AZD1775, paclitaxel, and/or carboplatin, and either:

- has completed minimum safety evaluation requirements during the single-dose period and the first 21-day cycle (Cycle 0 to Cycle 1).

or

- has experienced a DLT during the single-dose period and the first 21-day cycle (Cycle 0 to Cycle 1).

4.1.6 Safety Review Committee

After each dose level during the dose escalation phase of the study, the SRC will evaluate the safety and tolerability and PK (where applicable) of AZD1775 in combination with carboplatin or in combination with carboplatin and paclitaxel to decide the next step.

The SRC will consist of:

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

In addition, one other physician from the following may be invited:

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

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

Further internal or external experts may be consulted by the SRC as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

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

The decision may be to:

1. Proceed with dose escalation – refer to Section 4.1.2

2. Expand the cohort to a maximum of 6 evaluable patients

3. De-escalate the dose either to a lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level

4. Stop the dose escalation

5. Evaluate alternative dosing frequencies or schedules

6. Enrol additional patients into the cohort of recommended combination dose level

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

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

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

4.1.7 Duration of therapy

For the AZD1775 plus carboplatin and paclitaxel treatment groups, after the AZD1775 single-dose monotherapy phase of Cycle 0, it is expected patients will receive 6 cycles of AZD1775 in combination with paclitaxel and carboplatin. After Cycle 6, at the investigator's discretion and in the absence of discontinuation criteria, patients may continue on AZD1775 monotherapy at the same dose level as the combination phase (5 doses BID on Day 1 to Day 2.5 in each 21-day cycle).

For the AZD1775 plus carboplatin only treatment groups, after the AZD1775 single-dose monotherapy phase of Cycle 0, patients will receive the combination treatment in 21-day cycles until PD or an unacceptable toxicity occurs.

4.1.8 Treatment compliance and accountability

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

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

The study personnel at the investigational site will account for all drugs dispensed and returned. Study site personnel or the Clinical Research Monitor will return all unused drugs to Central Drug Depot. Certificates of delivery and return should be signed.

4.2 Discontinuation of investigational product and withdrawal from study

Patients may withdraw from any aspects of the voluntary exploratory research at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Section 6.5.5:

Patients will be discontinued from study therapy in the following situations:

- Patient decision. The patient is at any time free to withdraw his/her participation in the study, without prejudice
- Adverse events
- Severe non-compliance to this protocol as judged by the investigator and/or AstraZeneca
- Confirmed disease progression
- Patients incorrectly initiated on investigational product (Section 4.2.1)
- Risk to patients as judged by the Investigator and/or Sponsor

Patients that are withdrawn from the study but are evaluable per the definition in Section 4.1.5 will not be replaced. Any patient that is withdrawn and is NE will be replaced to ensure a minimum number of evaluable patients.

4.2.1 Procedures for handling patients incorrectly initiated on investigational product

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

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform INC Safety immediately. The INC Safety personnel are to ensure all such contacts are appropriately documented.

4.2.2 Procedures for withdrawal from study

Patients are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen by an investigator and undergo the assessments and procedures scheduled for the investigational product (IP) Discontinuation Visit and 28-day Follow-up Visit (see Section 5.4). Adverse events should be followed up (see Section 5.4) and study drug should be returned by the patient.

For patients enrolled in Japan: A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. 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 patient. They will also immediately inform Sponsor of the withdrawal. Adverse events will be followed up (Section 5.4); diary cards, questionnaires (e.g., for patient reported outcomes), and study drug should be returned by the patient.

5. STUDY PLAN AND TIMING OF PROCEDURES

5.1 Study plan

Figure 3 Study Plan

		Cycle 0	Cycles 1 and beyond					Addition-al Cycles	IP Discon. Visit	28-day Follow-up Visit[2]	Tumour Assess. Follow-up Visit[3]	Final Proto-col Visit[2]
	Screening		Combination of AZD1775 plus Paclitaxel and Carboplatin or Combination of AZD1775 plus Carboplatin[1]					AZD1775 mono-therapy[1]				
Cycle Day	-28 to -1	Day 1	Day 1	Day 2	Day 3	Day 8	Day 15					
Phase	Pretreatment[4]	Monotherapy	Combination Therapy									
Visit Number (Cycles 0 and 1)	1	2	3	N/A	4	5	6					
Visit Numbers (Cycles 2-and beyond)			7, 10, 14, 17, 21		11, 18	8, 12, 15, 19, 22	9, 13, 16, 20, 23					
Study Assessment												
Informed Consent	X											
Demography and Baseline Characteristics	X											
Baseline Tumour Sample[5]	X											
Inclusion/Exclusion Criteria	X											
Medical/Surgical History	X											
Vital Signs	X	X[6]	X					X	X			X
Physical Examination	X	X	X					X	X			X
WHO Performance Status	X	X	X					X	X			
Prior Medication[7]	X											
Haematology and Coagulation[8]	X	X	X			X	X	X	X			X
Chemistry[9]	X	X	X				X (Cycle 1 only)	X	X			X
Urinalysis	X	X	X					X				X
Blood for Future Biomedical Research[10]		X	X (Cycles 2,4 and 6 only)						X			(X)[10]
Urine/Serum Pregnancy Test[11]	X								X			X

		Cycle 0	Cycles 1 and beyond					Addition-al Cycles	IP Discon. Visit	28-day Follow-up Visit[2]	Tumour Assess. Follow-up Visit[3]	Final Proto-col Visit[2]
	Screening		Combination of AZD1775 plus Paclitaxel and Carboplatin or Combination of AZD1775 plus Carboplatin [1]					AZD1775 mono-therapy[1]				
Cycle Day	-28 to -1	Day 1	Day 1	Day 2	Day 3	Day 8	Day 15					
Phase	Pretreatment[4]	Monotherapy	Combination Therapy									
Tumour evaluation (RECIST)[12]	X		X[12]					X			X	
Tumour Marker Evaluation (CA-125)[13]	X		X								X	
Administer AZD1775[14]		X	X	X	X (1 dose only)			X				X
Administer Paclitaxel[15]			X									X[19]
Administer Carboplatin[16]			X									X[19]
12-Lead Electrocardiogram (ECG)[17]	X	X	X (Cycle 1 only)		X (Cycle 1 only)							X
PK Measurement (AZD1775)[18]		X	X (Cycle 1 only)		X[18] (Odd cycles)							
PK Measurement (paclitaxel)[18]			X (Cycle 1 only)									
PK Measurement (carboplatin)[18]			X (Cycle 1 only)									
Concomitant Medication			X---------->									X
Adverse Events			X----------> X									X[20]

Abbreviations: Assess., assessment; Discon, Discontinuation; FBR, future biomedical research; IP, investigational product; WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumours; PK, pharmacokinetics.

1 Cycle length is 21 days with a window of ±72 hours. Cycle 1 will start after a 5±2 day washout after Cycle 0 of AZD1775 single dose monotherapy phase. In the AZD1775 + carboplatin + paclitaxel cohort, after 6 cycles of combination treatment, patients may receive multiple dosing of AZD1775 as monotherapy in each 21-day cycle at the investigator's discretion. In the AZD1775 + carboplatin cohorts, combination treatment will be dosed in 21-day cycles until disease progression or an unacceptable toxicity occurs.

2 The Final Protocol Visit is to be performed only for patients who discontinue IP after the implementation of Revised Clinical Study Protocol Edition 2.0. This Final Protocol Visit should be aligned with the patient's next cycle scheduled visit following implementation of Revised Clinical Study Protocol Edition 2.0.
The IP Discontinuation Visit is to be performed at the time of IP discontinuation for all patients who discontinue before the Final Protocol Visit.
The 28-day Follow-up; visit is to be performed 28±7 days following the last dose of study medication for patients who discontinue IP before implementation of Revised Clinical Study Protocol Edition 2.0.

3 Follow-up tumour assessment visit will be scheduled every 6 weeks (±7 days) from the last tumour assessment (for patients who discontinue study treatment for reasons other than disease progression) until the earliest of either objective documented disease progression or death (unless informed otherwise by the Sponsor).

4 If Screening procedures are obtained within 72 hours of dosing, predose procedures for haematology, coagulation and chemistry do not need to be repeated.
5 Optional informed consent for future biomedical research must be obtained before submission of the tissue sample. Sample can be archival or fresh tumour biopsy.
6 Vital signs will be collected predose.
7 Report all non-chemotherapeutic medications taken within 14 days of the Screening visit (Visit 1). Report all previous cancer therapy and previous radiotherapy.
8 Haematology laboratory evaluations will be performed at Screening, on Cycle 0 Day 1, and on Cycle Days 1, 8, and 15 predose of combination treatment for Cycles 1 and beyond. Coagulation studies will only be performed at Screening and Day 1 (pretreatment) of every cycle, including Cycle 0 and Cycles 1 and beyond. Haematology laboratory samples should be obtained within 24 hours of the indicated Study Day.
9 Chemistry laboratory evaluations will be performed at Screening, on Cycle 0 Day 1, and on Days 1 and 15 of Cycle 1, and on Day 1 of each additional Cycle, all at pretreatment. Chemistry laboratory samples should be obtained within 24 hours of the indicated Study Day.
10 Informed consent for future biomedical research (FBR) samples must be obtained before the first DNA blood sample. DNA sample for FBR analysis should be obtained predose, on Day 1 of Cycles 0, 2, 4 and 6, and at the IP Discontinuation Visit (unless informed otherwise by the Sponsor). In addition, a DNA sample for FBR analysis should be obtained at the time of IP discontinuation after the implementation of Revised Clinical Study Protocol Edition 2.0 if discontinuation is due to disease progression (provided the patient gives proper informed consent).
11 For patients of child bearing potential, a negative urine or serum pregnancy test is required before receiving the first dose of study medication. If the urine test is positive or borderline a serum pregnancy test will be required. Pregnancy testing is required at Screening and at discontinuation, and can be performed per the discretion of the Investigator at any time during the study.
12 Patients with solid tumours should be assessed by contrast enhanced CT or MRI of the chest, abdomen, and pelvis with other regions as indicated by symptoms at Screening (no more than 28 days before start of study treatment), every 6 weeks (±7 days) from the start date of combination treatment (Cycle 1 Day 1), regardless of Cycle Day. Patients who discontinue study treatment for reasons other than progressive disease should continue to be assessed for disease progression every 6 weeks (±7 days) until objective documentation of progression or death. In addition to the above, for Japanese sites only, an additional assessment is performed at Day 1 of Cycle 2 (±3 days).
13 For patients with ovarian cancer, CA-125 evaluation will be performed on Day 1 of each cycle (Cycle 1 onwards) until the discontinuation of study medication, if progression occurs (unless informed otherwise by the Sponsor); patients who discontinue study treatment for reasons other than progressive disease should continue CA-125 evaluation at each Tumour Assessment Follow-up Visit (unless informed otherwise by the Sponsor). If Screening procedures are obtained within 7 days of dosing, CA-125 does not need to be repeated on Cycle 1 Day 1. This sample will only be taken for patients with ovarian cancer.
14 In single dose monotherapy phase, AZD1775 will be administered as a single dose. In the combination therapy phase, AZD1775 will be administered BID every 12 hours for 2.5 days. On Day 1, the first dose of AZD1775 will be administered before the administration of paclitaxel, which is then followed by the administration of carboplatin. Since the effect of food on AZD1775 has not been determined, patients should take AZD1775 either 2 hours before or 2 hours after a meal.
15 Paclitaxel (175 mg/m^2) will be administered after the first dose of AZD1775 is administered.
16 Carboplatin (AUC 5) will be administered after the patient has received the paclitaxel infusion.
17 A 12-lead ECG will be performed at Screening. In addition, 12-lead ECGs will be recorded on Cycle 0 Day 1, Cycle 1 Day 1, and Cycle 1 Day 3 within 1 hour before the first dose of AZD1775, as well as 1.5 and 4 hours after the first dose of AZD1775. ECG monitoring at subsequent cycles can be performed at the discretion of the Investigator.
18 PK sampling is required during Cycle 0, Cycle 1, and every odd-numbered cycle of the study as follows:
- AZD1775 PK samples will be obtained on Cycle 0 Day 1, Cycle 1 Day 1, and Cycle 1 Day 3 before the first (morning) dose of AZD1775 predose, and at 1, 2, 4, 6, and 8 hours after this initial administration. Additional samples will be collected at Day 3 predose on every odd cycle (unless informed otherwise by the Sponsor).
- Paclitaxel PK samples will be obtained before the initial administration of paclitaxel (predose) and at 1.5, 3 (end of infusion), 4, 6, and 8 hours after this administration. Postdose time points are calculated from the start of the paclitaxel administration (i.e., 4 hour time point is 4 hours after the start, as opposed to the completion, of the paclitaxel administration).
- Samples for total platinum will be collected before carboplatin infusion (predose) and at 1, 2, 4, 6, and 8 hours after the start of the carboplatin infusion. For carboplatin, time zero is defined as the start of the infusion.

19 As applicable.
20 At the time of the Final Protocol Visit, information since the previous protocol visit will be collected on all adverse events. After the Final Protocol Visit, only serious adverse events, pregnancies, and overdoses will be collected until 28±7 days following the patient's last dose of AZD1775.

5.2 Enrolment and screening

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

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

Demographic data and other characteristics will be recorded and will include date of birth or age, gender, race and/or ethnicity, and smoking history according to local regulation.

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

Each patient will undergo screening (see Study Plan Figure 3) during the 28 days before admission to confirm eligibility (see Section 3.1 and Section 3.2). Tumour assessments and other clinical data obtained as standard of care before consent may be used for the study provided the assessments fall within the protocol specified period before the first dose of study treatment.

5.3 Treatment period

Descriptions of the procedures for this period are included in the Study Plan Figure 3 and are detailed in Section 4.

5.4 Follow-up period

A post-study assessment will be performed at the time study drug is permanently discontinued unless the patient withdraws consent.

Approximately 28 days (±7 days) after the last treatment, patients will return to the clinic for a follow-up assessment. The primary purpose of this visit is to follow-up any AEs ongoing at the time of discontinuation and to assess any new AEs that may have occurred since discontinuation. Any AE, SAE, or abnormal laboratory findings that are ongoing at the time of study treatment discontinuation or any new events within 28 days of last study treatment, must be followed up to resolution or until the event becomes stable (or returns to baseline) or is unlikely to resolve further in the opinion of the Investigator.

Patients who discontinue study treatment for reasons other than progressive disease (PD) should continue to be assessed for disease progression every 6 weeks (±7 days) from the last tumour assessment until objective documentation of progression unless consent is withdrawn (see Tumour Assessment Follow-up visit, Figure 3).

Information pertaining to the type and dates of administration of post-study therapy will be collected when available.

5.5 Study timetable and end of study

The study is expected to start in January 2015, to have a primary data cut-off for preparation of a Clinical Study Report (CSR), and to have a final data cut-off after the primary analysis and following Revised Clinical Study Protocol Edition 2.0 implementation.

The planned duration of the study is 30 months (estimated) to CSR completion.

The primary data cut-off is defined as 6 months after the last patient recruited starts AZD1775 in combination with carboplatin for the primary analysis. Data analysis will be performed and a CSR written based on this data set.

Any patients still receiving AZD1775 at the time of the primary data cut-off will complete a Final Protocol Visit, which should be aligned with the next cycle scheduled visit following implementation of the Revised Clinical Study Protocol Edition 2.0.

Beyond the Final Protocol Visit, patients may continue to receive AZD1775 if they are deriving clinical benefit, in the opinion of the investigator, and not fulfilling discontinuation criteria. Such patients are to be treated in accordance with local practice and as deemed appropriate by the Investigator to ensure continued safety monitoring of the patient while receiving investigational product. It is recommended to continue observing ongoing patients at the frequency employed within the study plan as described in Figure 3. Restrictions regarding concomitant medications (refer to Section 3.3) will be followed while the patient is receiving AZD1775. A change in AZD1775 dose/schedule should only occur for safety reasons, based on investigator's judgement, and generally follow the approach for dose reduction and discontinuation as described in this protocol. Combining AZD1775 with other chemotherapy (except carboplatin/paclitaxel in the case of the patient already receiving AZD1775 in combination with carboplatin or 'carboplatin plus paclitaxel' as per the study design) is not allowed.

If a patient is no longer receiving benefit from AZD1775 beyond the Final Protocol Visit in the opinion of the treating physician, then the drug should be stopped. The Investigator will inform the Sponsor when a patient discontinues the study drug. Patient will return used and unused medication at routine clinic visits, and drug accountability information must continue to be collected in patient source documents until the patient discontinues the treatment. In addition, provided the patient gives proper informed consent, a DNA blood sample for future biomedical research should be obtained at the time of AZD1775 discontinuation, if due to disease progression. Patients will continue to be monitored for all SAEs, pregnancies, and overdoses for 28±7 days after the last dose of investigational product.

Following the primary analysis data cut-off, no further statistical analysis of the data will be conducted. All safety data collected after the primary analysis and up to (and including) the last of the patient Final Protocol Visits will be listed and/or summarised as appropriate. A CSR addendum will be prepared to include such data.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The investigator will ensure that data are recorded on the CRFs as specified in the protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and for the provision of answers to data queries according to the Clinical Study Agreement or applicable information.

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

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

For studies conducted in Japan, the Principal Investigator/Sub-investigator will record data on the observations, tests, and assessments specified in the protocol on the electronic CRFs (eCRFs) provided by Sponsor. The CRF will be accompanied with 'Instructions for the investigator', which should be followed. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded.

6.2 Safety procedures

Before discharge from each in-patient and clinic visit, the Investigator or their deputy will be responsible for reviewing all available safety data, including vital signs and ECGs.

6.2.1 Physical examination

A complete physical examination will be performed at the visits indicated in the Study Plan (Figure 3).

Performance status will be assessed at Screening, pre-dose on Day 1 of Cycle 0, on Day 1 of each subsequent cycle, study treatment discontinuation, and additionally at the discretion of the investigator if clinically indicated, according to criteria as follows:

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

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

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

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

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

6.2.2 Vital signs

Vital signs including resting pulse, blood pressure, respiratory rate, body temperature, height (at Screening), and weight should be assessed at the visits detailed in the Study Plan (Figure 3). Measurements should be taken in the sitting position following at least 10 minutes of rest.

6.2.3 ECG

A 12-lead ECG will be performed at the visits indicated in the Study Plan (Figure 3).

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

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes before times indicated. All ECGs should be recorded with the patient in the same physical position. At Screening, 3 ECG recordings should be taken at about 5 minute intervals. For each on-study time point, a single ECG recording should be taken. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study, where feasible.

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

If an abnormal ECG finding at Screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, pulse rate, R-R, QRS and QT intervals, and an overall evaluation will be recorded.

All ECG data will also be collected digitally and may be transferred electronically for central analysis as described in the study specific ECG manual (if applicable). Heart rate, pulse rate, R-R, QRS and QT intervals may be determined and reviewed by an external cardiologist.

6.2.4 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits as indicated in the Study Plan (pre-dose) (Figure 3). All blood and urine samples should be taken within 24 hours of Day 1 of any given cycle. Laboratory tests do not need to be repeated at baseline if the baseline visit is within 3 days of the Screening sample.

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

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

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

The following laboratory variables will be measured:

Table 4 Clinical Chemistry, Haematology, and Urinalysis Parameters

Clinical chemistry	**Haematology**
Serum (S)/Plasma (P)-Albumin	Blood (B)-Haemoglobin
S/P-ALT	B-Leukocyte
S/P-AST	B-Absolute leukocyte differential count:
S/P-Alkaline phosphatase	Neutrophils
S/P-Bilirubin, total	Lymphocytes
S/P-Calcium, total	Monocytes
S/P-Creatinine	Basophils
S/P-Glucose	Eosinophils
S/P-Magnesium	B-Platelet count
S/P-Phosphate	B-Haematocrit
S/P-Potassium	B-Reticulocytes
S/P-Sodium	B-Red blood cell (RBC)
S/P-Urea nitrogen	**Urinalysis**
Coagulation	Human chorionic gonadotrophin (hCG)
PT	Dipstick (pH, Glucose, Protein, Bilirubin, Ketones, Blood)
aPTT	Microscopic (only performed if dipstick abnormal) (WBC, RBC, Epithelial, bacteria, casts and crystals)
INR	

Additionally, a urine/serum sample will be collected from all females of child-bearing potential at Screening and at treatment discontinuation, and can be performed at the discretion of the Investigator at any time during the study.

Clinical chemistry, haematology, and urinalysis will be repeated as clinically indicated as part of the routine management of the patient on the occurrence of any relevant AEs.

In case a patient shows an AST or ALT ≥3 × ULN or total bilirubin ≥2 × ULN refer to Appendix G, ‘Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy’s Law’ for further instructions.

For blood volume see Section 6.5.1.

6.3 Pharmacokinetics

6.3.1 Collection of pharmacokinetic samples

Venous blood samples (4 mL each) for determination of concentrations of AZD1775 (and potential metabolites) in plasma will be collected in all treatment groups (see Table 5) on Cycle 0 Day 1, Cycle 1 Day 1, and Cycle 1 Day 3 before the first (morning) dose of AZD1775 (predose) and at 1, 2, 4, 6, and 8 hours postdose. Additionally, a sample will be collected predose on Day 3 of every odd-numbered cycle (unless informed otherwise by the Sponsor). All PK samples should be collected within 10% of nominal time (e.g., ±6 minutes for the 1-hour sample). The date and time of collection of each sample will be recorded. The PK samples will be divided: one for the primary analysis of AZD1775 (2 mL) and the remainder for backup and for future potential metabolite analysis.

Table 5 Pharmacokinetic sampling schedule for AZD1775

Sampling days	Timing of sample
Cycle 0 Day 1, Cycle 1 Day 1, and Cycle 1 Day 3	Predose
	1 hour postdose
	2 hours postdose
	4 hours postdose
	6 hours postdose
	8 hours postdose
Day 3 of Every Odd-Numbered Cycle (unless informed otherwise by the Sponsor)	Predose

Blood samples for PK should be taken before the first (morning) dose of AZD1775 (predose) for that day. All PK samples should be collected within 10% of nominal time (e.g., ±6 minutes for a 1-hour sample). The exact time and date of sampling should be recorded on the electronic Case Report Form, together with the exact time and date of dosing of AZD1775.

Venous blood samples (2 mL) for determination of concentrations of paclitaxel in plasma will also be collected in the AZD1775 plus carboplatin and paclitaxel treatment groups. These venous blood samples will be collected on Cycle 1 Day 1 before paclitaxel infusion (predose) and at 1.5, 3, 4, 6, and 8 hours after start of infusion, according to Table 6. All PK samples should be collected within 10% of nominal time (e.g., ±6 minutes for a 1-hour sample).

Table 6 Pharmacokinetic sampling schedule for paclitaxel

Sampling days	Timing of sample
Cycle 1 Day 1	Predose
	1.5 hours after start of the infusion
	3 hours after start of the infusion (end of infusion)
	4 hours after start of the infusion
	6 hours after start of the infusion
	8 hours after start of the infusion

Blood samples for PK should be taken relative to the start of paclitaxel infusion. All PK samples should be collected within 10% of nominal time (e.g., ±6 minutes for a 1-hour sample). The exact time and date of sampling should be recorded on the electronic Case Report Form, together with the exact time and date of infusion of paclitaxel.

Venous blood samples (2 mL) for determination of concentrations of total platinum in plasma will be collected in both combination treatment groups. These venous blood samples will be collected on Cycle 1 Day 1 before carboplatin infusion (predose) and at 1, 2, 4, 6, and 8 hours after start of infusion, according to Table 7. All PK samples should be collected within 10% of nominal time (e.g., ±6 minutes for a 1-hour sample).

Table 7 Pharmacokinetic sampling schedule for carboplatin

Sampling days	Timing of sample
Cycle 1 Day 1	Predose
	1 hours after start of the infusion
	2 hours after start of the infusion
	4 hours after start of the infusion
	6 hours after start of the infusion
	8 hours after start of the infusion

Blood samples for PK should be taken relative to the start of carboplatin infusion. All PK samples should be collected within 10% of nominal time (e.g., ±6 minutes for a 1-hour sample). The exact time and date of sampling should be recorded on the electronic Case Report Form, together with the exact time and date of infusion of carboplatin.

The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles. The total volume of blood taken from each patient during Cycle 0 and Cycle 1 will not exceed approximately 250 mL.

6.3.2 Determination of drug concentration in pharmacokinetic samples

Samples for determination of AZD1775 concentrations in plasma will be analysed by Covance on behalf of AstraZeneca, using an appropriate, validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analytes of interest (i.e., AZD1775) at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the backup AZD1775 PK samples may be subjected to further analyses in order to further investigate or quantify the presence, PK, and/or identity of drug metabolites. Any results from such analyses will be reported separately from the CSR.

Samples for the determination of carboplatin and paclitaxel in plasma will also be analysed on behalf of AstraZeneca at Covance using an appropriate validated bioanalytical method.

6.4 Exploratory research

6.4.1 Exploratory biomarker research

If a patient agrees to participate in the exploratory biomarker research component of the study biological samples (e.g., plasma, archived or study-obtained tumour) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, and clinical outcomes.

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

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

6.4.1.1 Collection of archival tumour samples

All patients will be asked to provide consent to supply a sample of their archival tumour blocks if a sample taken at the time of diagnosis is available. Tumour samples taken subsequent to diagnosis are also suitable for this study.

The tumour samples will preferably be in the form of a formalin-fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site). If this is not possible, 10 to 20 slides of freshly prepared unstained 5 micron sections from the archival tumour block may be provided.

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

6.4.1.2 Tumour or skin biopsies for future pharmacodynamic studies

Based on emerging data, the need for tumour or skin biopsies may arise in order to further define the pharmacodynamic properties of AZD1775 and combination therapies. The results of such studies will be reported separately and will not form part of the CSR for this study.

6.4.1.3 Collection of exploratory blood-borne biomarkers

Exploratory biomarker research samples

Blood samples (1 × 10 mL) will be taken per time-point. Timings are pre-treatment on Day 1 Cycle 0, as well as Day 1 (±2 days) of cycles 2, 4, and 6, and at discontinuation of therapy (unless informed otherwise by the Sponsor). For patients continuing on AZD1775 after the implementation of Revised Clinical Study Protocol Edition 2.0, provided the patient gives proper informed consent, a DNA blood sample for future biomedical research should be obtained at the time of AZD1775 discontinuation, if due to disease progression. The samples will be centrifuged on site to yield plasma for analysis of a range of oncology biomarkers which may correlate with drug response, including analysis of circulating free DNA for mutations in cancer-related genes such as TP53.

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

Details of exploratory biomarker research

The exploratory biomarker analyses planned for the optional tumour tissue includes analysis of the status of various cancer-related genes including TP53. The exploratory analysis may also include studies on the messenger RNA or protein expression of cancer-related genes in the tumour. Plasma samples will be obtained throughout the study, to follow the circulating tumour DNA that may be present in the plasma of cancer patients. Potential studies performed on the plasma include analysis of the presence and amount of DNA with TP53 mutations or other cancer-related genes.

6.5 Biological sampling procedures

6.5.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study during Cycle 0 and Cycle 1 is shown in Table 8. The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on AZD1775 become available. However, the total volume will not exceed 250 mL over a 1 month period.

Table 8 Volume of blood to be drawn from each patient during Cycle 0 and Cycle 1

		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical chemistry	5	3	15
	Haematology	5	4	20
	Coagulation	3	2	6
Pharmacokinetics	AZD1775	4	18	72
	Paclitaxel (AZD1775 + carboplatin + paclitaxel groups only	2	6	12
	Carboplatin	2	6	12
Exploratory biomarker research		10	1	10
TOTAL			40	147

6.5.2 Handling, storage and destruction of biological samples

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

Any PK sample remaining after analysis for AZD1775 and its metabolites may be used for biomarker analyses. These analyses are for AstraZeneca use only and will not be included in the CSR.

Biological samples for future research will be retained at AstraZeneca or at a contract research organisation on behalf of AstraZeneca for a maximum of 25 years following the last patient's last visit in the study. The results from future analysis will not be reported in the CSR but separately in a scientific report.

6.5.2.1 Pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported

separately from the CSR. Anonymised samples will be retained for no more than 5 years after the CSR is finalised.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate Bioanalytical Report.

6.5.2.2 Samples for exploratory research

Details of sample collection, processing, shipping, and storage will be described in the Laboratory Manual. The samples include blood samples to investigate tumour-derived mutations in the plasma and also archival tumour samples (optional).

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

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

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

6.5.3 Labelling and shipment of biohazard samples

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

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

All archival tumour samples should be shipped at ambient temperature according to the Laboratory Manual to the AstraZeneca designated central Contract Research Organisation.

6.5.4 Chain of custody of biological samples

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

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

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

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

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

6.5.5 Withdrawal of informed consent for donated biological samples

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

As collection of these biological samples is a voluntary part of the study, the patient may continue in the study after the samples are collected.

The Principal Investigator:

- Ensures Sponsor is notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site
- Ensures that the patient and Sponsor are informed about the sample disposal

Sponsor ensures the central laboratories holding the samples are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the document returned to the study site.

Sponsor ensures that biological samples are returned to the source at the end of a specified period as described in the informed consent.

6.6 Anti-tumour activity

6.6.1 Tumour assessments

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

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. The methods of assessment used at baseline should be used at each subsequent follow-up assessment. Follow-up assessments should be performed every 6 weeks (± 7 days) after the start of treatment until objective disease progression as defined by RECIST v1.1, death, or withdrawal of consent. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response: CR, PR, SD, and PD.

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

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

It is important to follow the assessment schedule as closely as possible. Refer to the study plan in Figure 3.

7. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

7.1 Adverse events

7.1.1 Definition of adverse events

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

For studies conducted in Japan, cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

Any deterioration related to the disease under study and associated symptoms or findings should not be regarded as an AE as far as the deterioration can be anticipated (see Section 7.1.3.7).

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

7.1.2 Definitions of serious adverse events

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix I of this Clinical Study Protocol.

For definition of other significant AEs (OAE) see Section 8.3.3.

7.1.3 Recording of adverse events

7.1.3.1 Time period for collection of adverse events

Adverse events will be collected throughout the study, from informed consent until the end of the follow-up period. The follow-up period is defined as 28 days (±7 days) after study treatment is discontinued or completed. Serious AEs occurring in the follow-up period should be reported to Sponsor in the usual manner (see Section 7.1.4).

7.1.3.2 Follow-up of unresolved adverse events

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

If an investigator learns of any SAEs, including death, at any time after a patient has completed the study and he or she considers there is a reasonable possibility that the event is related to AZD1775, the investigator should notify Sponsor.

7.1.3.3 Variables

The following variables will be collected for each AE:

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.1.2. 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 an 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 an SAE.

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

7.1.3.4 Causality collection

The investigator will assess causal relationship between investigational product and each AE, and answer ‘yes’ or ‘no’ to the question: ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

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

A guide to the interpretation of the causality question is found in Appendix I.

7.1.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferable (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 should be recorded separately.

7.1.3.6 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the CSR. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the criteria for an SAE, a DLT or are the reason for discontinuation of treatment with the investigational product unless clearly due to PD under study (see Section 7.1.3.7).

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

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

7.1.3.7 Disease progression

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

7.1.3.8 New cancers

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

7.1.3.9 Handling of deaths

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

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

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

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

7.1.4 Reporting of serious adverse events

All SAEs must be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF. For patients continuing after the Final Protocol Visit (see Section 5.5), SAEs should be determined per protocol and must continue to be reported via the standard pharmacovigilance process (in paper) as stated below. For medical emergencies, refer to Section 7.2 below.

If any SAE occurs in the course of the study, then investigators or other site personnel inform INC Safety immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated CRO/AstraZeneca representative works with the investigator to ensure that all the necessary information is recorded on the paper SAE form within **one calendar day** of initial receipt for all SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform INC Safety representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel identify a potential SAE, they should complete the INC SAE form and send it by email to INC. The SAE Reporting Form should be completed and emailed (preferable reporting method) directly to

.

INC will acknowledge the SAE report by email within one business day of receipt.

If the site does not receive confirmation of receipt from INC within **one business day**, the SAE report should be resent. The site should clearly indicate in the subject line that the report is being resent, as confirmation of receipt was not received.

The SAE report should be completed irrespective of the volume of information available about the event, though the investigator is expected to provide as much information as possible.

The reference document for definition of expectedness is Section 5.4 of the Investigator Brochure for AZD1775.

For studies conducted in Japan, all SAEs must be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded by INC Safety and reported to the regulatory authorities in Japan.

Investigators and other site personnel should inform (emergency report) appropriate INC Safety representatives of any SAE that occurs at his or her site immediately, or **no later than 24 hours** of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The Principal Investigator should provide detailed information to INC Safety in writing **within 1 calendar day** of the initial report. The Principal Investigator should immediately notify, in writing, the head of the study site about the SAEs.

Follow-up information on SAEs should also be reported to INC Safety by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to INC Safety immediately, or **no later than 24 hours** as described above.

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

The following detailed information should be sent to INC Safety 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 AE, 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, gender, other current illnesses, relevant medical history and, if applicable, date and course of death.

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

7.2 Medical emergencies and AstraZeneca contacts

The Principal Investigator(s) is/are responsible for ensuring that procedures and expertise are in place to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such (see Section 7.1.4).**

In the case of a medical emergency, the investigator may contact the Medical Monitor at . Additional contact persons for medical emergencies are listed below.

Name	Role in the study	Address & telephone number

7.3 Dose modifications and individual stopping criteria

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

- Any intolerable AE regardless of grade
- Any AEs ≥ CTCAE Grade 3 (despite optimal supportive care)
- A DLT

All dose delays, reductions and adjustments will be recorded in the appropriate electronic system (i.e., eCRF).

With the exception of Cycle 0 and Cycle 1, dose modification for toxicity will proceed according to guidelines detailed below, if needed. Dose modifications are not allowed during the DLT evaluation period of Cycle 0 and Cycle 1.

Any patient requiring a toxicity-related dose delay of more than 21 days from the intended day of the next scheduled dose must be discontinued from study treatment unless there is approval from the Sponsor Study Team Physician for the patient to continue.

7.3.1 Guidelines for dose modifications

If possible, the Investigator may attribute each toxicity event to either paclitaxel, carboplatin, or AZD1775 alone such that a stepwise dose reduction, upon resolution of the event to ≤Grade 1 or baseline, can be made according to Table 9, Table 10, Table 11, Table 12, Table 13, or Table 14. Reduction of 1 agent and not the 2 other agents is appropriate if in the opinion of the Investigator, the toxicity is clearly related to one of the study drugs. If, in the opinion of the Investigator, the toxicity is related to a combination of 2 agents, both drugs should be reduced according to the recommended dose modifications. If, in the opinion of the Investigator, the toxicity is related to the combination of all 3 agents, they should all be reduced according to the recommended dose modifications.

For individual patients experiencing a dose modification, treatment for each new cycle will be delayed if the scheduled off-drug periods are not adequate to allow for recovery to ≤ Grade 1 or the baseline status of the patient; with the exception of fatigue, anorexia, and transaminitis (asymptomatic ALT and AST elevation) that must have recovered to ≤ Grade 2 and be considered tolerable. Alopecia of any grade or duration will not lead to dose modification or treatment delay. Patients can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. Patients who require more than 2 dose modifications to any particular component will be discontinued from the study.

Patients who experience a hypersensitivity reaction ≥ Grade 3 should be discontinued from paclitaxel for the remainder of the study. Patients who discontinue paclitaxel may continue on

the study receiving only treatment with AZD1775 plus carboplatin pending consultation between the Sponsor and the Investigator. Patients with unresolved toxicities lasting 3 weeks or longer from the date of the next scheduled treatment will not be permitted to continue on the study.

Modifications may be made to any/all of the study therapies as outlined in Table 9, Table 10, and Table 11.

Table 9 Dose Reduction Table for Carboplatin

Carboplatin Dose	Carboplatin Dose Modification #1	Carboplatin Dose Modification #2
AUC 5	AUC 4	AUC 3

Table 10 Dose Reduction Table for Paclitaxel

Paclitaxel Dose	Paclitaxel Dose Modification #1	Paclitaxel Dose Modification #2
175 mg/m^2	135 mg/m^2	90 mg/m^2

Table 11 Dose Reduction Table for AZD1775

AZD1775 Dose	AZD1775 Dose Modification #1	AZD1775 Dose Modification #2
225 mg BID	175 mg BID	125 mg BID
175 mg BID	125 mg BID	100 mg BID
125mg BID	100 mg BID	75 mg BID

7.3.1.1 Recommended dose adjustments for paclitaxel for non-DLT hepatic toxicity

Table 12 displays the protocol-recommended dose adjustments for paclitaxel therapy dependent upon non-DLT bilirubin and transaminase values for the patient. These values should be determined from the pre-chemotherapy chemistry labs drawn on Day 1 of each cycle.

Table 12 Paclitaxel Hepatic Dose Modification Table (Non-DLT)*

Degree of Hepatic Impairment			
Transaminase Levels		**Bilirubin Levels**	**Adjusted Dose (From Prior Course)†**
<10 × ULN	and	≤1.25 × ULN	No Adjustment
<10 × ULN	and	1.26 – 2.0 × ULN	Reduce by 1 DL
<10 × ULN	and	2.01 – 5.0 × ULN	Reduce by 2 DLs
≥10 × ULN	Or	➢ ≤5.0 × ULN	Discontinue Paclitaxel

ULN, upper limits of normal; DL, dose level
* The hepatic values should be determined from the pre-chemotherapy labs drawn on Day 1 of each cycle.
† Should the adjusted dose fall below 90 mg/m^2, as detailed in Table 10, paclitaxel should be discontinued.

7.3.1.2 Dose modification for neurotoxicity

In the event of a neurologic DLT, treatment should be held pending resolution of the toxicity.

If the observation of a neurologic toxicity is considered by the Investigator to be related to study therapy, this will result in stepwise modifications as outlined in Table 13.

Table 13 Dose Modifications for Neurologic Toxicity*

Neurotoxicity Starting Dose	**Paclitaxel Dose** 175 mg/m^2	**AZD1775 Dose Level (DL)** Current DL	**Carboplatin Dose** AUC 5
1st occurrence	135 mg/m^2	Stay	AUC 5
2nd occurrence	135 mg/m^2	Reduce by 1 DL	AUC 5
3rd occurrence	135 mg/m^2	Reduce by 1 DL	AUC 5
4th occurrence	**Off-study**	**Off-study**	**Off-study**

* If the dosing schedule was modified due to a prior toxicity event, the next appropriate dose modification step should be used

7.3.1.3 Dose modification for all other toxicities

In the event of a DLT, treatment should be held pending resolution of the toxicity.

If the observation of a toxicity is considered by the Investigator to be related to study therapy, this will result in stepwise modifications as outlined in Table 14.

Table 14 Dose Modifications for Toxicity*

Toxicity** Starting Dose	**AZD1775 Dose Level (DL)** Current DL	**Carboplatin Dose** AUC 5	**Paclitaxel Dose** 175 mg/m^2
1st occurrence	Reduce by 1 DL	AUC 5	175 mg/m^2
2nd occurrence	Stay	AUC 4	175 mg/m^2
3rd occurrence	Stay	AUC 4	135 mg/m^2
4th occurrence	Reduce by 1 DL	AUC 4	135 mg/m^2
5th occurrence	**Off-study**	**Off-study**	**Off-study**

* If the dosing schedule was modified due to a prior toxicity event, the next appropriate dose modification step should be used.
** Granulocyte colony-stimulating factor (G-CSF) can be administered in subsequent cycles for febrile neutropenia in lieu of the initial dose reduction. If the febrile neutropenia occurs despite the dose reductions suggested in this table, the patient may receive G-CSF following local institutional guidelines.

Dose interruptions or visit delays (±7 days) beyond Cycle 1 for reasons not related to study therapy are permitted. The reason for interruption should be documented in the eCRF.

7.3.2 Dose modifications for infusion reactions

Infusion reactions (e.g., rash, urticaria, erythema, pruritus, bronchospasm, hypotension) can occur with the agents used in this study. There is increased risk of a reaction with carboplatin and paclitaxel. Carboplatin must be discontinued in patients experiencing a Grade 3 or 4 infusion reaction during treatment.

To identify the grade of a reaction, refer to the list below adapted for the General Disorders and Administration Site Conditions section of the NCI CTCAE v4.03:

Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated.

Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.

Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic mediation and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for other clinical sequelae. Note: any infusion that is interrupted and not resumed within the visit will be considered a Grade 3 reaction.

Grade 4: Life-threatening consequences; urgent intervention indicated

7.3.3 Supportive care guidelines

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- Diarrhoea: Due to frequent reports of diarrhoea with AZD1775 administration, vigorous anti-diarrhoeal treatment loperamide (Imodium) is required at the first onset of diarrhoea according to American Society of Clinical Oncology (ASCO) guidelines. Oral loperamide 4 mg should be administered at the first onset of diarrhoea and then 2 mg every 2 hours until diarrhoea-free for at least 12 hours. The first dose of loperamide could be lowered to 2 mg if the diarrhoea is recurrent and if, in the opinion of the treating physician, the diarrhoea is not severe. Patients should be instructed to notify the Investigator or research staff of the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhoea within 24 hours of using loperamide or other prescribed anti-diarrhoeal medications. If diarrhoea is severe (ie, requiring intravenous [IV] rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhoea or any diarrhoea associated with severe nausea or vomiting should be hospitalised for IV hydration and correction of electrolyte imbalances.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Table 15 depicts examples of anti-emetic treatment schedules which, at the discretion of the investigator, can be modified for use in this study. Patients should be strongly encouraged to maintain liberal oral fluid intake.

Table 15 Examples of anti-emetic pre-medication schedules

Drug	Day 1	Day 2	Day 3	Day 4	Day 5
Granisetron (Kytril®)	2 x 1 mg IV**	2 x 1 mg PO	2 x 1 mg PO	--	--
Dexamethasone	1 x 10 mg IV	2 x 3 mg PO	2 x 3 mg PO	2 x 1.5 mg PO	2 x 1.5 mg PO
Magnesium oxide*	Max 3 x 500 mg	Max 3 x 500 mg	Max 3 x 500 mg	Max 3 x 500 mg	Max 3 x 500 mg
Metoclopramide (Primperan®)	--	--	--	4 x 10 mg PO or 3 x 20 mg as suppository on indication	4 x 10 mg PO or 3 x 20 mg as suppository on indication
Lorazepam (temesta®)	Max 3 x 1 mg PO on indication	Max 3 x 1 mg PO on indication	Max 3 x 1 mg PO on indication	--	--

Abbreviations: IV=intravenous, Max=maximum, PO=by mouth.
* Because AZD1775 can induce diarrhoea, it is recommended that caution be taken with the administration of magnesium oxide.
** Second dose may be given PO.

Note that aprepitant (Emend®) is a substrate, moderate inhibitor and inducer of CYP3A4 and also an inducer of CYP2C9. Therefore, the use of aprepitant is NOT allowed in this study for the treatment of nausea and vomiting induced by the study drugs. In general, drugs that interfere with CYP3A4 are not allowed in this study. For further information about CYP3A4, CYP2C9, or prohibited/allowed medications in this study, see Appendix D (Disallowed Medications and Medications to be Administered with Caution) and Section 3.3.2.

- Anaemia: Transfusions and/or erythropoietin may be utilised as clinically indicated for the treatment of anaemia, but should be clearly noted as concurrent medications.
- Neutropenia: Colony-stimulating factors including G-CSF, pegylated G-CSF, or granulocyte/macrophage colony stimulating factor according to institutional standards after the first cycle of combination therapy.
- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated.
- Hypersensitivity: Patients who experience a hypersensitivity reaction to carboplatin should be treated according to institutional practice. Alternatively, hypersensitivity to carboplatin can be managed according to the National Comprehensive Cancer Network Guidelines Version 1.2013 for Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer.

7.3.4 Interruptions in study variable collection

Discussion will be required with the Sponsor as to any effect on the PK sample schedule if the interruption occurs within 3 days of PK sampling. All other assessments, including laboratory safety assessments, vital signs, and RECIST should continue to be performed as per study plan, relative to the baseline assessment.

7.4 Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

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

If an overdose occurs during the course of the study, then investigators or other site personnel should inform appropriate INC Safety and Sarah Cannon Research Institute (SCRI) Safety representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it to the SCRI SAE mailbox at

.

The designated INC representative will work with the investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site.

For overdoses associated with an SAE, standard reporting timelines apply, see Section 7.1.4. For other overdoses, reporting should be done within 28 days.

7.5 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be reported to INC Safety and SCRI Safety using the appropriate forms to the INC SAE mailbox at

.

7.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, AZD1775 should be discontinued immediately and the patient should be removed from the study.

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

If a pregnancy occurs during exposure to investigational product, or in the 28 days after discontinuing investigational product, then investigators or other site personnel should inform INC Safety immediately, or **no later than 24 hours** of when he or she becomes aware of it, to the INC SAE mailbox at .

The same timelines apply when outcome information is available.

7.5.2 Paternal exposure

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

Any conception occurring from the date of dosing until 3 months (6 months for patients enrolled in Japan) after dosing should be reported to Sponsor and followed up for its outcome.

8. EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

8.1 Definition of study endpoints

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

- Safety and tolerability (Primary)
- Pharmacokinetics of AZD1775, paclitaxel, and carboplatin (Secondary)
- Tumour response (Secondary)
- Exploratory biomarkers (Exploratory)
- Cross-study PK analysis (Exploratory)

Derivations, calculations and analysis plans for each of these endpoints are presented below.

8.2 Determination of sample size

The primary objective of this study is to investigate the safety and tolerability and thereby identify the recommended dose of AZD1775 in combination with carboplatin and in combination with carboplatin and paclitaxel in Asian patients with advanced solid tumours.

Hence the number of patients has been based on the desire to obtain adequate safety, tolerability, PK, data while exposing as few patients as possible to the investigational product and procedures.

For the combination tolerability phase of the study, cohorts of 6 evaluable patients will be required. The total number of patients will depend upon the number of dose finding cohorts necessary. Once MTD/recommended dose is established, 3 to 6 additional patients may be enrolled in the same cohort where the recommended dose has been established to further evaluate safety and tolerability of AZD1775 in combination with carboplatin and in combination with paclitaxel and carboplatin.

The expected sample size will be approximately 18 patients.

8.3 Calculation or derivation of safety variables

A comprehensive description of the statistical analyses and related activities for this study will be documented in a statistical analysis plan (SAP) which will be finalised before database lock.

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, ECG changes, and physical examination. These will be collected for all patients. Appropriate summaries of these data will be presented.

8.3.1 ECG changes

Immediate clinical management of patients will occur according to local assessment of the QT interval. For the CSR, QTc will be calculated using Fridericia's Formula:

$$QTcF = QT / (\sqrt[3]{RR})$$

8.3.2 Creatinine clearance

Estimated creatinine clearance will be calculated using the Cockcroft-Gault Formula:

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

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

8.3.3 Other significant adverse events

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

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

8.4 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma concentration data will be performed by Covance on behalf of AstraZeneca. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where possible the following PK parameters will be determined for AZD1775 for Day 1 C_{max}

- C_{8hr} (AZD1775 only)
- Time to C_{max} (t_{max})
- Time to last detectable concentration (t_{last})
- Terminal half-life ($t_{½\lambda z}$)
- Area under the plasma concentration-time curve from zero to 8 hours ($AUC_{(0-8)}$) (AZD1775 only), from zero to the time of the last measurable concentration ($AUC_{(0-t)}$), from zero to infinity ($AUC_{(0-\infty)}$), and from zero to 12 h ($AUC_{(0-12)}$)

Following the multiple dose part of the study (Day 3) the following additional parameters will be calculated

- Accumulation on day 3 compared to day 1 for C_{max} and $AUC_{(0-8)}$

The $AUC_{(0-\infty)}$, will not be calculated after multiple dosing on Day 3.

Where possible the appropriate PK parameters will also be determined for the metabolites of AZD1775, if measured.

For paclitaxel and total platinum the following parameters will be calculated on day 1:

- C_{max}
- Concentration at end of infusion (C_o)
- t_{max}
- t_{last}
- $AUC_{(0-t)}$

The C_{max} and t_{max} parameters will be determined by inspection of the concentration time profiles. Where possible the terminal elimination rate constant (λz) will be calculated by log linear regression of the terminal portion of the concentration-time profiles when there are sufficient data and the $t_{½\lambda z}$ will be calculated as 1n2/λz. The area under the concentration-time curve up to the last quantifiable sample ($AUC_{[0\text{-}t]}$) and the $AUC_{(0\text{-}10)}$ will be calculated using the linear up, log down trapezoidal rule. Where appropriate, the $AUC_{(0\text{-}t)}$ will be extrapolated to infinity using λz to obtain AUC. The apparent oral steady state clearance (CL_{ss}/F) following multiple dosing will be determined from the ratio of dose/$AUC_{(0\text{-}12)}$. The apparent volume of distribution (V_z/F) will be determined from the apparent total clearance of the drug from plasma (CL/F) divided by λz, as appropriate.

8.5 Calculation or derivation of tumour response variables

A comprehensive description of the statistical analyses and related activities for this study will be documented in a SAP.

At each visit, patients will be programmatically assigned a RECIST visit response depending on the status of their disease compared with baseline and previous visit assessments.

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

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

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

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

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

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

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10mm to be considered nonpathological) and no new lesions have developed since baseline. A visit response of PR is

defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.

In the case of SD, measurements should meet the SD criteria at least once after the study start.

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

The following tumour response variables will then be derived:

- Best objective response/Objective response rate
- Clinical benefit rate
- Duration of response
- Best and Week 12 percentage change in tumour size

8.5.1 Objective response rate

Objective response rate is defined as the percentage of patients who have at least one confirmed response of CR or PR before any evidence of progression (as defined by RECIST v1.1). Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of objective response rate.

8.5.2 Clinical benefit rate

Clinical benefit rate is defined as the proportion of patients with a best overall response of confirmed CR, confirmed PR, or SD. In the case of SD, measurements should have met the SD criteria for at least one visit after the study start.

8.5.3 Duration of response

Duration of response will be defined as the time from the date of first documented response (that is, subsequently confirmed as defined in Section 8.5) until date of documented progression or death in the absence of disease progression; the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If the response is not confirmed, it will not be included. If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

8.5.4 Change in tumour size

Tumour size is defined as the sum of the lengths of the longest diameters of the RECIST v1.1 TLs. Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs compared to baseline. The best change in tumour size (defined as the maximum reduction from baseline or the minimum increase from baseline, in the absence of a reduction) will include all assessments up to and including progression. Missing TL data at visits may be imputed using appropriate imputation rules.

Patients who progress before their scheduled assessment (week 6 or week 12) should have had a tumour assessment performed at the time of progression prior to treatment discontinuation. The tumour size from their latest progression assessment will be used instead of the scheduled (week 6 or week 12) assessment for these patients.

For further details, see Appendix B.

8.6 Calculation or derivation of exploratory research variables

Results from the exploratory pharmacogenetic and pharmacodynamic research will be reported separately from the CSR for the main study.

8.7 Description of analysis sets

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

Analysis sets are presented in Table 16.

Table 16 Analysis sets

Analysis Set	Definition
All Patients	All patients who are enrolled in the study or are screening failures
Safety	All patients who received at least 1 dose of AZD1775, paclitaxel, or carboplatin
Evaluable-for-Response	Dosed patients who have measurable disease at baseline
Pharmacokinetics	Dosed patients for whom an adequate PK profile has been obtained.

8.8 Methods of statistical analysis

The statistical analyses will be performed by INC Research, LLC, under the direction of the Biostatistics Group, AstraZeneca.

The study will have a primary data cut-off for the primary analysis (see Section 5.5). Following the primary analysis data cut-off, no further statistical analysis of the data will be conducted. All safety data collected after the primary analysis and up to (and including) the last of the Final Protocol Visits will be listed and/or summarised as appropriate. A CSR addendum will be prepared to include such data.

8.8.1 Demographic data

Demographic data will be summarised using the safety analysis set.

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

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

8.8.2 Exposure

Exposure data will be summarised using the safety analysis set.

Exposure to investigational product (i.e., total amount of study drug received) will be listed for all patients.

Total exposure and total time on study (date of last dose minus date of first dose) will be summarised by the following: mean, standard deviation, minimum, maximum, median, and number of observations. In addition, the number and percentage of patients with at least one dose interruption/dose delay and at least one dose reduction will be presented separately for the initial period of evaluability defined as Cycle 0 and Cycle 1 and for any time following this initial period of the study.

8.8.3 Safety

Safety data will be summarised in the safety analysis set.

Safety data will not be formally analysed. All patients who receive at least one dose of AZD1775 will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles of initial treatment will be combined in the presentation of safety data. Adverse events will be listed individually by patient and dose group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term

and CTCAE grade. The number and percentage of patients with AEs in different categories (e.g., causally related, CTCAE grade ≥3) will be summarised by dose group, and events in each category will be further summarised by MedDRA system organ class and preferred term, by dose group. Serious AEs will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of investigational product (i.e., before Cycle 0 Day 1) will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring within the defined 28 day follow-up period after discontinuation of investigational product will be included in the AE summaries. Any AEs in this period that occur after a patient has received further therapy for cancer (following discontinuation of investigational product) will be flagged in the data listings. AEs occurring after the 28 day follow-up period after discontinuation of investigational product will be listed separately, but not included in the summaries.

Haematology, clinical chemistry, vital signs, ECG data, physical examination demographic data, medical histories and concomitant medications will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used.

Details of any deaths will be listed for all patients.

8.8.4 Pharmacokinetics

Pharmacokinetics will be summarised in the PK analysis set.

All plasma concentration data of all analytes and derived PK parameters will be summarised and presented according to AstraZeneca standards as described in the SAP.

8.8.5 Tumour response

Tumour response data will be listed and summarised by dose, if appropriate, using the following response categories: CR, PR, SD, PD, and NE.

Objective response rate and clinical benefit rate will be calculated for dosed patients with measurable disease at baseline.

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

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

The duration of overall response is measured from the time measurement criteria are first met for CR/PR until the first date that recurrent or progressive disease is objectively documented.

Waterfall plots (bar charts) indicating the percentage change and best percentage change from baseline in sum of the diameters of TLs will be produced.

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AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	AZD1775
Study Code	D6011C00003
Appendix Edition Number	1
Appendix Date	22 October 2014

Appendix B
Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

TABLE OF CONTENTS PAGE

1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D6011C00003 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

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

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

Measurable:

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

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions**
- Skin lesions assessed by clinical examination***
- Brain metastasis***

* Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

Special Cases:

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

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

Target lesions:

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

Non-Target lesions:

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

3. METHODS OF ASSESSMENT

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

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

Table 1 : Summary of Methods of Assessment

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

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D6011C00003 study it is recommended that CT examinations of the chest, abdomen, and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (IV) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

3.2 Clinical examination

In the D6011C00003 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3 X-ray

3.3.1 Chest X-ray

In the D6011C00003 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 Plain X-ray

In the D6011C00003 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In the D6011C00003 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the D6011C00003 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

3.6 Tumour markers

In the D6011C00003 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

In this study CA-125 will be collected for patients with ovarian cancer for separate analysis However, the results will not contribute to tumour response based on RECIST 1.1 assessment.

3.7 Cytology and histology

In the D6011C00003 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D6011C00003 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

In the D6011C00003 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based

on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. Follow-up assessments will be performed every 6 weeks (± 1 week) until objective disease progression as defined by RECIST 1.1 or withdrawal of consent. In addition to the above, for Japanese sites only, an additional assessment is performed at Day 1 of Cycle 2 (± 3 days). Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

4.2 Target lesions (TL)

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table 2 : Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

4.3 Non-Target lesions (NTL)

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 3 : Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

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

4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 4 : Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no NTL*s* at baseline).

5. CONFIRMATION OF RESPONSE

In the D6011C00003 study, imaging for confirmation of response (CR or PR) should be performed at next scheduled visit (certainly no less than 4 weeks) following the date the criteria for response were first met.

6. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

6.1 CT Scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

(a) **Anatomic coverage:** Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

(b) **IV contrast administration:** Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without i.v. contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

(c) **Slice thickness and reconstruction interval:** It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

6.2 MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

6.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

6.3.1 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

7. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45 (2009) 228-247

AstraZeneca

Clinical Study Protocol Appendix C	
Drug Substance	AZD1775
Study Code	D6011C00003
Edition Number	1
Date	22 October 2014

Appendix C
Stages of Heart Failure – New York Heart Association Classification

The Stages of Heart Failure – New York Heart Association Classification

Class I (Mild)

No Limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).

Class II (Mild)

Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.

Class III (Moderate)

Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, or dyspnoea.

Class IV (Severe)

Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, physical discomfort is increased.

Reference

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston (MA): Little, Brown & Co; 1994:253-256.

Clinical Study Protocol Appendix D	
Drug Substance	AZD1775
Study Code	D6011C00003
Edition Number	2
Date	27 March 2017

Appendix D
Disallowed Medications and Medications to be Administered with Caution

DISALLOWED MEDICATIONS AND MEDICATIONS TO BE ADMINISTERED WITH CAUTION

Formal drug-drug interaction studies have not yet been performed with AZD1775, therefore, the potential for drug-drug interaction described in this protocol are based on findings from in vitro studies and clinical experience.

In vitro data has shown that AZD1775 is metabolised predominantly by CYP3A4, with an FMO3 and/or FMO5 component. As a result, there is potential for the exposure of AZD1775 to be affected by drugs that inhibit or induce the metabolism of CYP3A4. In the clinic, co-administration of AZD1775 with the moderate CYP3A4 inhibitor, aprepitant, resulted in a 40% increase in the plasma levels of AZD1775. Drugs known to be moderate to strong inhibitors/inducers of CYP3A4 are therefore prohibited for use in the current study, including aprepitant.

In vitro data suggests that AZD1775 may be a weak reversible inhibitor of CYP2C19 (IC_{50} 12 µM). Caution should therefore be exercised when AZD1775 is co-administered with agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with a narrow therapeutic range.

Based on in vitro studies, AZD1775 has been shown to be a weak reversible inhibitor (IC_{50} 14 µM) and a time-dependent inhibitor of CYP3A4 (K_{inact} 0.061/min, K_i 6.04 µM). The full impact of the time dependent inhibition is currently unknown, however, modelling data has predicted an 8-10 fold increase in the exposure of sensitive CYP3A4 substrates when administered with AZD1775 (250 mg BID for 5 doses). To date, no significant DDI effects have been reported in the clinic that may be related to the TDI finding. However, sensitive CYP3A4 substrates or substrates of CYP3A4 with a narrow therapeutic window are prohibited.

AZD1775 has been shown to be a weak inducer of CYP1A2 in vitro (39% increase in activity of positive control). Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low. No specific precautions are recommended at this time, except to be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range.

Transporter studies (in vitro) have shown that AZD1775 is both a substrate and inhibitor (IC_{50} 20 µM) of P-gp. Maximum impact of these finding is likely to occur for drugs administered orally at the same time as AZD1775. Caution should therefore be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with AZD1775.

Recent in vitro transporter studies have shown AZD1775 to be an inhibitor of BCRP (IC_{50} 5.1 µM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins, such as rosuvastatin. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug.

Use of metformin should be used with caution in this study as recent in vitro transporter data have shown AZD1775 is an inhibitor of Multidrug and Toxin Extruder 1 (MATE1) and MATE2K. Caution should be used

when administering drugs that are substrates of these transporters (e.g. cimetidine, acyclovir, fexofenadine) as the clinical relevance of AZD1775 inhibition of the MATE pathway is not known in these compounds.

Herbal preparations/medications can be substrates, inhibitors, and inducers, similar to any registered medication. Herbal preparations are therefore not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

In addition, any other drugs should be avoided at the Investigator's discretion if, in their opinion, the co-administration with AZD1775 may increase the risk of a clinically significant drug interaction.

A list of the main CYP3A4 substrates, inhibitors (strong and moderate) and inducers, CYP2C19 substrates, P-gp substrates and inhibitors and BCRP substrates are shown below. This is not an exhaustive list and further details can be found at Expert Opin. Drug Metab. Toxicol. (2013) 9(6):737-751.

CYP3A4 Inhibitors

Strong

Boceprevir
Clarithromycin
Cobicistat (GS-9350)
Conivaptan
Danoprevir
Elvitegravir
Fosamprenavir
Grapefruit juice
Idelalisib
Indinavir
Itraconazole
Ketoconazole
LCL161
Lopinavir
Mibefradil
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Tipranavir
Troleandomycin
Voriconazole

Moderate

ACT-178882
Amprenavir
Aprepitant
Atazanavir
Casopitant
Ciprofloxacin
Crizotinib
Darunavir
Diltiazem
Dronedarone
Erythromycin
FK1706
Fluconazole
Fosamprenavir
Grapefruit
Imatinib
Ledipasvir
Lomitapide
Netupitant
Schisandra sphenanthera
Seville oranges
Tofisopam
Verapamil

Weak

Almorexant
Alprazolam
AMD070
Amiodarone
Amlodipine
Atorvastatin
Azithromycin
Berberine
Bicalutamide
Blueberry juice
Chlorzoxazone
Cilostazol
Cimetidine
Clotrimazole
Cranberry juice
Cyclosporine
Daclatasvir
Delavirdine
Everolimus
Faldaprevir
Fluvoxamine
Fosaprepitant (IV)
Ginkgo
Goldenseal
GSK1292263
GSK2248761
Isoniazid
Ivacaftor
Lacidipine
l Linagliptin
Lomitapide
M100240
Nilotinib
Oral contraceptives
Pazopanib
Peppermint oil
Propiverine
Ranitidine
Ranolazine
Resveratrol
Roxithromycin
Seville orange juice
Simeprevir
Sitaxentan
Suvorexant
Tabimorelin
Tacrolimus
Teriflunomide
Ticagrelor
Tipranavir/ritonavir
Tolvaptan
Zileuton

CYP3A4 Inducers (Strong and Moderate)

Avasimibe
Bosentan
Carbamazepine
Efavirenz
Enzalutamide
Etravirine
Genistein
Lersivirine
Lopinavir
Mitotane
Modafinil
Nafcillin
Phenobarbital
Phenytoin
Rifabutin
Rifampin
Ritonavir
Semagacestat
St John's Wort
Thioridazine
Tipranavir

CYP3A4 Inducers (Weak)

Amprenavir
Aprepitant
Armodafinil
AZD 7325
Bexarotene
Boceprevir
Brivaracetam
Clobazam
Danshen
Dexamethasone
Echinacea
Eslicarbazepine
Garlic
Gingko
Ginseng
Glycyrrhizin
LCL161
Methylprednisolone
Nevirapine
Oritavancin
Oxcarbazepine
PA-824
Pleconaril
Prednisone
Quercetin
Raltegravir
Ritonavir
Rufinamide
Sorafenib
Stribild
Telaprevir
Terbinafine
Ticagrelor
Ticlopidine
Topiramate
Troglitazone
Vemurafenib
Vicriviroc and ritonavir
Vinblastine

CYP3A and CYP3A4 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

ABT-384
Alfentanil
Alfuzosin
Almorexant
Alpha-dihydroergocryptine
Amiodarone
Aplaviroc
Aprepitant
Aprepitant
Astemizole
Atazanavir
Atorvastatin
Avanafil
Bexarotine
BIRL 355
Bortezomib
Bosutinib
Brecanavir
Brotizolam
Budesonide
Buspirone
Capravirine
Carbamazepine
Casopitant
Cisapride
Conivaptan
Cyclophosphamide
Cyclosporine
Danoprevir
Darifenacin
Darunavir
Dasatinib
Dihydroergotamine
Disopyramide
Docetaxel
Dofetilide
Doxorubicin
Dronedarone
Ebastine
Eletriptan
Elvitegravir
Eplerenone
Ergotamine
Erlotinib
Etoposide
Everolimus
Felodipine
Fentanyl
Fluticasone
Gefitinib
Halofantrine
Ibrutinib
Ifosfamide
Imatinib
Indinavir
Ironotecan
Ivacaftor
Ixabepilone
L-771,688
Lapatinib
Levomethadyl (LAAm)
Lomitapide
Lopinavir
Lovastatin
Lurasidone
Maraviroc
Midazolam
Midostaurin
Mosapride
Neratinib
Nilotinib
Nisoldipine
Paclitaxel
Pazopanib
Perospirone
Pimozide
Propafenone
Propofol
Quetiapine
Quinidine
Ranolazine
Ridaforolimus
Romidepsin
Saquinavir
Sildenafil
Simeprevir
Simvastatin
Sirolimus
Tacrolimus
Temsirolimus
Terfenadine
Theoophylline
Thioridazine
Thiotepa
Ticagrelor
Tilidine
Tipranavir
Tolvaptan
Tretinoin
Triazolam
Ulipristal
Vardenafil
Vicriviroc
Voclosporin

CYP2C19 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Diazepam
Gliclazide
Lansoprazole
(R)-Lansoprazole
(S)-Lansoprazole
(S)-Mephenytoin
(R)-Mephobarbital
Omeprazole
(R)-Omeprazole
Pantoprazole
(+)-Pantoprazole
Rabeprazole
Tilidine

CYP1A2 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Alosetron
Caffeine
Duloxetine
Melatonin
Ramelteon
Tacrine
Theophylline
Tizanidine

P-gp Substrates

Colchicine
Digoxin
Fexofenadine
Indinavir
Paclitaxel
Topotecan
Vincristine

- If a patient requires initiation of digoxin during the study, or is already receiving treatment with digoxin, monitoring of digoxin levels is recommended according to local practice (as the levels of digoxin may increase). Monitoring of digoxin levels is also recommended when the patient has completed dosing with study treatment (as the levels of digoxin may then decrease).

P-gp Inhibitors (Strong)

Cyclosporine
Elacridar
Erythromycin
Itraconazole
Ketoconazole
LY335979
Quinidine
Ritonavir
Valspodar
Verapamil

BCRP Substrates

Daunorubicin
Doxorubicin
Rosuvastatin
Sulfasalazine
Topotecan

Clinical Study Protocol Appendix E	
Drug Substance	AZD1775
Study Code	D6011C00003
Edition Number	1
Date	22 October 2014

Appendix E
Ethical and Regulatory Requirements

1. ETHICAL AND REGULATORY REQUIREMENTS

1.1 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 the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications.

1.2 Ethics and regulatory review

An Ethics Committee should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. This will include approval of the exploratory biomarker and pharmacogenetic research and associated consent(s) forms. The investigator or Head of the study site for Japanese sites will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. If applicable this approval should clearly state that the exploratory biomarker and pharmacogenetic research is approved

For Japanese sites, the Head of the study site should submit a notification of direction/determination as well as a copy of the Institutional Review Board (IRB) written approval to AstraZeneca. A valid contract between the study site and AstraZeneca Japan should be signed before the investigator can enrol any patient into the study

The Ethics Committee should approve all advertising used to recruit patients for the study.

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

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

For Japanese sites, the protocol should be re-approved by the IRB annually. The Principal Investigator should submit progress reports to the IRB via the Head of the study site at the time of the protocol re-approval.

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

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

Each Principal Investigator is responsible for providing the Ethics Committees/Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

1.3 Informed consent

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

The Principal Investigator at each centre will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and the optional exploratory biomarker and genetic research component(s)
- Ensure that each patient is notified that they are free to withdraw from the study or the research components at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure each original, signed Informed Consent Form is stored in the Investigator's Study File
- Ensure a copy of each signed Informed Consent Form is given to the patient

The exploratory biomarker and genetic research component(s) of this study are voluntary and the patient may participate in the main study without participating in the exploratory biomarker and genetic research part(s) of the study. To participate in the exploratory biomarker and genetic component of the study the patient should sign and date the consent

form for the main study and as applicable separate consent forms for the exploratory biomarker and the genetic components of the study.

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

1.4 Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

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

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for Revised Protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator. For distribution to Ethics Committee see Section 1.2.

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

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

For Japan, study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should 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 should 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 should be notified to or approved by each IRB according to local requirements.

1.5 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.

In Japan, all study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

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Clinical Study Protocol Appendix F	
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Appendix F
Data and Study Management

1. DATA AND STUDY MANAGEMENT

1.1 Patient data protection

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

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. Confidentiality of patient data will be maintained in accordance with national data legislation. For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Institutional Review Board (IRB) 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).

Due to the exploratory nature of the biomarker research, there will be no routine communication of these results to patients. AstraZeneca will not provide individual results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

1.2 Pre-study activities

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

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

1.3 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative or delegate will visit the study site to review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also to train them in any study specific procedures including collection of samples and the Electronic Data Capture (EDC) system. The additional requirements for the collection of the patients' samples for the exploratory biomarker research will also be clarified.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of the 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 staff members involved in the study (medical, nursing and other staff).

1.4 Source data

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

1.4.1 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 case report forms (CRFs) against source data before collecting the CRFs to ensure accuracy and completeness of documentation, and assure that the Principal Investigator/Sub-Investigator has submitted the CRFs to AstraZeneca. If the investigator wishes to amend the collected CRFs, the monitor will ensure that the Principal Investigator/Sub-Investigator has documented the amendment in writing (signed and dated) and provided this to AstraZeneca.

Source data are any data generated as a result of the patient's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records.

1.5 Monitoring of the study

During the study, an AstraZeneca representative or delegate will have regular contacts with the study sites, 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 including the specific requirements of the biomarker research, that data are being accurately and timely recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to

the study) including verification of the Informed Consent Form(s) of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

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

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

1.6 Data management

Data management will be performed by INC Research.

1.6.1 Electronic Data Capture (EDC)

Data entered in the EDC system will be immediately saved to the applicable database and changes tracked to provide an audit trail. The data collected through third party sources will be obtained and reconciled against study data.

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

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

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

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

SAE Reconciliation will be performed by INC Research as defined in the SAE Reconciliation Plan.

1.7 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the

Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, the terms of the Clinical study Agreement shall prevail.

Specific reference to requirements relating to this optional biomarker research will be included in the study agreement(s).

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

1.7.1 Archiving of study documents

The investigator follows the principles outlined in the Clinical Study Agreement.

1.8 End of study

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

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (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 AZD1775.

1.8.1 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 should receive written notification of the reasons for the premature termination or suspension.

The Principal Investigator/Sub-Investigator will immediately notify the decision to the patients, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

1.8.2 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 Institutional Review Board and AstraZeneca.

Clinical Study Protocol Appendix G	
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Appendix G
Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 6)
- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.

- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]

  – If there is no significant change no action is required

  – If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described is Section 4.2of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease?

If No: follow the process described in Section 4.2 of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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Clinical Study Protocol Appendix H	
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Appendix H
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories**.** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg. Ebola, Lassa fever virus

- are to be packed and shipped in accordance with IATA Instruction 602

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg. Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol Appendix I

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Appendix I
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

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

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