Revised Clinical Study Protocol	
Drug Substance	AZD1775
Study Code	D6014C00006
Version	3.0
Date	15 May 2018

A Phase I Open-label Study to Evaluate the Effect of Multiple Doses of AZD1775 on the Pharmacokinetics of Substrates for CYP3A, CYP2C19, CYP1A2 and to Provide Data on the Effect of AZD1775 on QT Interval in Patients with Advanced Solid Tumours

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 3.0, 15 May 2018 Changes to the protocol are summarised below
Section 1.1: Updated information on safety data. **Section 3.2, Section 3.8, Sections 7.7.1 and 7.7.2, Appendix E and H:** Updated to include information on CYP1A2 and CYP2C19 inhibitors/inducers which could interfere with the primary objectives in Part A of the study. **Synopsis, Section 1.4, Section 4 and Section 7.2:** Text updated to indicate that the mandatory overnight stays required for Part B may be accommodated either at the study centre or a nearby hotel or residence. **Section 3.1, Section 3.2, Section 3.8, Section 7.7.2, Appendix H:** Addition that any patient taking an oral contraceptive must be discussed with the Medical Monitor to ensure that it is not a prohibited brand. **Section 3.2:** Updated for exclusion criterion #23 for added clarity.

Version 2.0, 1 February 2018 Changes to the protocol are summarised below
Cover page: Addition of the AstraZeneca logo. **Sections 1.1. and 1.2 and list of references**: Updated due to latest version of Investigator's Brochure **Section 3.8:** Restriction 1 updated to clarify the restrictions regarding water intake for both Periods. **Table 1:** Table column revision in Part A to clarify that Part A has 2 treatment periods (as per Figure 1). The viral serology assessment at the End of Treatment visit was removed. Footnotes were updated to reflect the following design changes or clarifications:

- Initially it was planned that patients could join the study directly into Part B, however, this was changed before protocol finalisation and footnote was mistakenly not removed at that stage.
- Updated the footnote regarding vital signs and ECG assessments to clarify which assessments should be prioritized.
- Remove all reference to paper based ECGs as all ECGs will be digital
- Optional use of dexamethasone as a second anti-emetic clarified
- Typographical error corrections

Synopsis - Study design, Synopsis – Investigational product, dosage and mode of administration, Section 1.4, Table 1, footnote p, Table 3, footnote c, Section 6.8.3, and **Section 7.2**: Updated to explain that in Part A dexamethasone cannot be used until after the last PK sample is drawn. In Part B dexamethasone use as a pre-medication is acceptable, if indicated. Updated to clarify procedures with respect to use of anti-emetics.

Synopsis, Target study population and Section 8.2: Updated as initially it was planned that patients could join the study directly into Part B, however, this was changed before protocol finalisation. Updated to clarify when additional patients may join the study.

Section 3.2 criteria no. 14: Exclusion criteria No 14 changed and split into 2 separate components as, reference point may be different for the various drugs.

Section 3.9: Has been amended to provide elaboration on the clinical and special investigations scenarios that will dictate that treatment with AZD1775 must be discontinued.

Section 4.1 and Table 1: Per Schedule of Events, demographics are to be assessed during screening, and this section is added to clarify what endpoints will be collected.

Section 4.3 and Table 1, footnote a: Updated to provide clarity around the End of Treatment (EoT) visit and the window allowed.

Section 5.2.5: Updated as per latest AstraZeneca safety standards.

Section 6.4 and Section 6.6: Updated to indicate that Sarah Cannon Research Institute will no longer be responsible for the safety database as of 1 March 2018, as the safety database will revert to AstraZeneca.

Section 6.8.1: Updated as per latest AstraZeneca safety standards.

Section 6.8.2: The word “mandatory” in the heading was removed as it is clear from the following text that pre-treatment with anti-emetics are mandatory.

Section7.7.2: Updated as the calcium channel blockers felodipine and nisoldipine was added as substrates of CYP3A4, and diltiazem and verapamil added as moderate inhibitors of CYP3A4. Indinavir, ritonavir and nelfinavir – HIV protease inhibitors were also correctly listed. **Appendix H, Table H1**: Updated to clearly indicate that rosuvastatin is prohibited.

Version 1.0, 25 April 2017
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

CLINICAL STUDY PROTOCOL SYNOPSIS

A Phase I Open-label Study to Evaluate the Effect of Multiple Doses of AZD1775 on the Pharmacokinetics of Substrates for CYP3A, CYP2C19, CYP1A2 and to Provide Data on the Effect of AZD1775 on QT Interval in Patients with Advanced Solid Tumours

Principal Investigator

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Study centre(s) and number of subjects planned

This study will be conducted at approximately 10 study centres in the United States of America (USA). Approximately 30 patients will be entered to ensure that at least 20 evaluable patients complete both parts of the study. Additional patients may be enrolled to ensure at least 20 evaluable patients complete both study parts.

Phase of development: Phase I (Clinical pharmacology)

Study design

Overall Study Design:

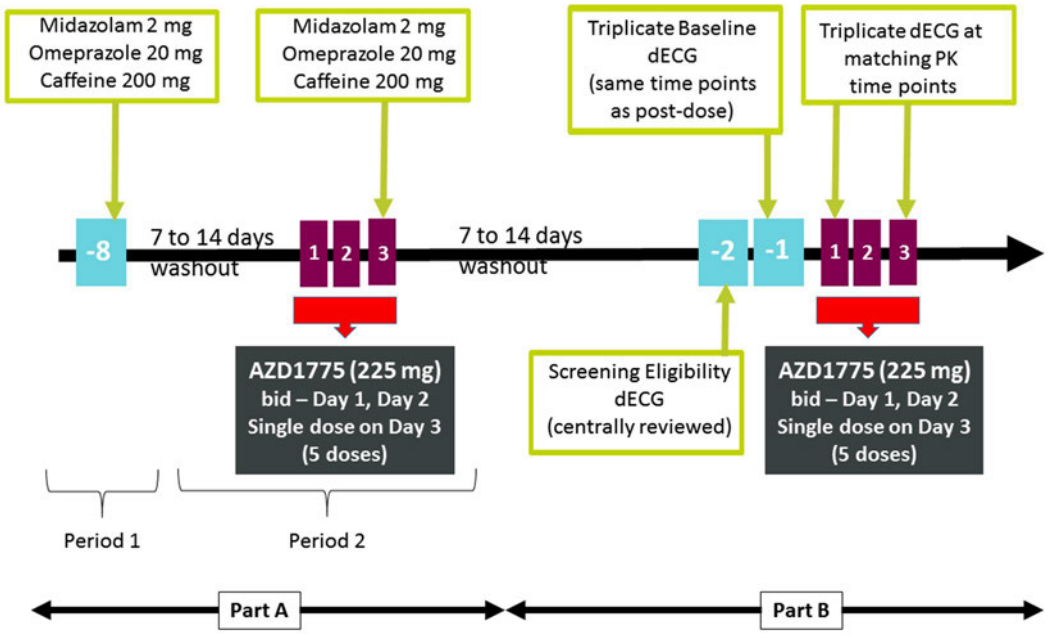
This is a Phase I, 2-part study (Part A and Part B) in patients with advanced solid tumours.

Part A

Part A of this study is an open-label, non-randomised, 2-period design. Patients will be screened 28 days relative to the first AZD1775 dose and within 14 to 21 days relative to the first cocktail administration. Patients should be admitted to the study centre on Day -9 for safety assessments and may remain resident overnight. The treatment starts with the administration of a cocktail of 3 medications (Day -8) followed by pharmacokinetic (PK) sampling for 24 hours (Period 1) and a washout period of at least 7, but no more than 14 days. In Period 2, AZD1775 will be administered twice daily (bid) until steady state for 2.5 days (total of 5 doses) with 240 mL of water and the final dose will be administered in combination with the cocktail in the morning of Day 3. Patients should be administered Kytril (granisetron) 1 mg orally 30 minutes prior to administration of the cocktail drugs on Day -8 and administration of each dose of AZD1775 capsules with a small amount of water.

All patients will receive a single dose of the cocktail containing caffeine (200 mg), omeprazole (20 mg capsule) and midazolam (1 mL of 2 mg/mL syrup formulation) alone (Period 1) and combined with the last dose of AZD1775 (225 mg, 3 x 75 mg capsules) at steady state (Day 3 Period 2). Patients are required to fast from 2 hours before until 2 hours after the cocktail administration alone, as well as each administration of AZD1775 alone, or in combination with the cocktail. Water intake is restricted from 1 hour before until 1 hour after cocktail, and cocktail and AZD1775 administrations (Day -8 and Day 3, respectively), excluding the 240 mL of water to be used for administration of AZD1775 and the cocktail. Patients must take all 3 cocktail drugs alone, or in combination with AZD1775, with the 240 mL water provided. Decadron (dexamethasone) cannot be used until after the last PK sample is drawn. Compazine (prochlorperazine), Phenergan (promethazine) and/or Ativan (lorazepam) can be used as occasion requires (prn) for nausea/vomiting.

Figure 1 Overall study plan



Period 1

A single administration of cocktail on Day -8 followed by PK sampling for 24 hours for assessment of cocktail analytes. Patients should be administered Kytril (granisetron) 1 mg orally 30 minutes prior to administration of the cocktail with a small amount of water. Patients should be admitted to the study centre on Day -9 for safety assessments and may remain resident overnight, but should remain in the study centre for the first 12 hours of PK sample collections following the cocktail administration on Day -8; the 24-hour sample may be collected on an outpatient basis, if desired by the patient.

Period 2

After a washout period of at least 7, but no more than 14 days, AZD1775 will be administered at a dose of 225 mg twice a day (bid) with an adequate amount of water (ideally 240 mL) for 2 days (Period 2, Days 1 and 2). Patients should be administered Kytril (granisetron) 1 mg orally 30 minutes prior to administration of the AZD1775 capsules with a small amount of water. In the morning of Day 3, the cocktail will be administered in combination with AZD1775 at steady state. Patients must take all 3 cocktail drugs in combination with AZD1775 with the 240 mL water provided. Patients are required to fast from 2 hours before until 2 hours after each AZD1775 administration alone and when administered in combination with the cocktail. Pharmacokinetic sampling will take place for 24 hours following dose administration on Day 3, for assessment of cocktail analytes as well as AZD1775.

Patients will self-administer their granisetron (with a small amount of water) 30 minutes before their AZD1775 doses under fasted conditions (AZD1775 doses -2 to 2 hours away from meals) the evening of Day 1 through the evening on Day 2 on an outpatient basis, with an adequate amount of water (ideally 240 mL). Patients will be admitted the morning of Day 3 and will remain in the study centre for the first 12 hours of PK sample collections; the 24-hour sample may be collected on an outpatient basis, if desired by the patient. Phenergan, Ativan and/or Compazine may be used prn for nausea/vomiting. Decadron, if needed, cannot be administered until after the last PK sample is drawn.

Part B

Part B is an open-label, non-randomised study in the same patients who participated in Part A. Upon completion of Part A, following a washout period of at least 7, but no more than 14 days between the last dose in Part A and Day -1 of Part B and provided the patient continues to meet all the study inclusion and none of the exclusion criteria, patients will check into the study centre on Day -2. Patients will be required to stay overnight, either at the study centre or a nearby hotel or residence, from Day -2 to Day 1 (2 nights) and from Day 2 to Day 3 (1 night) to ensure that conditions for the dECG assessments on Day 1 and Day 3 match those from Day -1. Patients may stay overnight on the other nights, but this is optional. However, patients experiencing nausea/vomiting or any other safety issues, should remain in the study centre**.**

Upon arrival on Day -2, patients will undergo a digital electrocardiogram (dECG) to determine eligibility by central review. On Day -1, baseline dECG assessments will be performed at clock times matched to planned/scheduled dECG assessment times on Days 1 and 3.

Starting the morning of Day 1, each patient will receive 3 x 75 mg AZD1775 capsules (225 mg) bid for 2.5 days with 240 mL water; administered under fasting conditions (from 2 hours pre-dose to 2 hours post-dose). Water is restricted from 1 hour before until 1 hour after AZD1775 administration in the morning of Day 1 and of Day 3 and time-matched on Day -1, excluding the 240 mL water required for the administration of the study treatment, as well as the water required to swallow the assigned pre-treatment anti-emetic(s). Treatment

with 1 mg Kytril (granisetron) orally 30 minutes prior to all AZD1775 administrations is mandated. Patients may also receive Decadron (dexamethasone) 4 mg orally/IV prior to each dose of AZD1775 along with granisetron if medically indicated as long as consistent pre-treatment conditions are maintained in the mornings prior to all serial ECG collections.

Since patients need anti-emetics prior to AZD1775 administration on Day 1, all patients will receive granisetron (and dexamethasone, if applicable) orally 30 minutes prior to dose administration on Day -1 time-matched to the clock time for granisetron (and dexamethasone, if applicable) administration on Day 1 (scheduled for 30 minutes prior to the time of AZD1775 administration). If patients are to receive dexamethasone along with granisetron in the morning of Day 1, they must also receive the same dexamethasone treatment in the morning of Day -1 and in the morning of Day 3. However, if patients are not scheduled to receive dexamethasone on the morning of Day 1, they should not have received dexamethasone on Day -1 and may not receive dexamethasone in the morning of Day 3. Ativan, Compazine and/or Phenergan can be used prn but not as part of the pre-treatment regimen.

On Day 1 patients will undergo dECG and PK assessments pre-dose (post anti-emetic administration) and for 12 hours post AZD1775 dose and may be discharged after completion of the Day 1 assessments as long as they are not experiencing nausea/vomiting or any other safety issues. Patients will continue to take AZD1775 every 12 hours under fasted conditions (AZD1775 doses -2 to 2 hours away from meals) with prescribed anti-emetic(s) given orally 30 minutes prior to each dose.

Patients will be admitted to the study centre on the evening of Day 2 and stay overnight at either the study centre or nearby hotel or residence. On Day 3, patients will receive their final AZD1775 dose (30 minutes after anti-emetic administration) and undergo dECG and PK assessments pre-dose (post anti-emetic administration) and for 12 hours post-dose. Patients may be discharged after completion of the Day 3 assessments, as long as they are not experiencing nausea/vomiting, or any other safety issues, and will be asked to return to the study centre in the morning of Day 4 for their final (24-hour) PK/dECG assessments relative to the AZD1775 dose administered on Day 3. The dECGs performed on Day 1 and Day 3 will be clock-time matched to the actual clock times that the Day -1 dECGs are performed. Similar, standard meals will be provided on Day -1 (time matched to those on Days 1 and 3) and at 2 hours post morning dose on Days 1, and 3.

When a meal, dECG and PK samples are scheduled at the same time, the dECG should be obtained first, followed by the PK sample and then the meal. Patients will be discharged from the study centre after completing their 24-hour PK/dECG assessments on Day 4 of Part B.

On completion of Part B (ie, collection of the 24-hour PK sample/dECG and safety assessments on Day 4) patients will enter a 4-day washout period relative to the last dose of AZD1775. Within 3 days after the washout period, patients will be required to attend an end of treatment (EoT) visit. Patients will be evaluated per current assessments for their eligibility and interest to enrol into the open-label continued access (CA) study (D6014C00007). All patients who do not enrol in the CA study will be asked to return to the study centre

30 (-7) days after the last dose of AZD1775 for a final follow-up visit (end of study [EoS] visit).

For patients interested in enrolling in the open-label CA study, the assessments taken at the EoT visit will serve as the screening for the CA study. However, this is providing their EoT safety assessments are in accordance with the CA study inclusion and exclusion criteria. Please refer to the CA study protocol for additional required screening assessments and other eligibility criteria.

Objectives

Primary Objectives:	**Outcome Measure:**
Pharmacokinetics To assess the effect of AZD1775 on the PK of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole), and CYP3A (midazolam)	**Pharmacokinetic Endpoints** **Part A** Plasma AUC, AUC_{0-t} and C_{max} for cocktail parent compounds (midazolam, omeprazole and caffeine)
Pharmacodynamics To assess the effect on QT interval corrected for heart rate (QTc) following multiple oral doses of AZD1775	**Pharmacodynamic Endpoints** **Part B** dECG intervals (QTcF) for absolute values and time-matched change from baseline

AUC: Area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}: area under the plasma concentration-time curve from time zero to the time "t" of the last quantifiable concentration; C_{max}: maximum plasma drug concentration; CYP: cytochrome P450; dECG: digital electrocardiogram; PK: pharmacokinetics; QT interval: ECG interval measured from the onset of the QRS complex to the end of the T wave; QTc: QT interval corrected for heart rate; QTcF: QT interval corrected for heart rate using Fridericia's formula.

Secondary Objectives:	**Outcome Measure:**
Pharmacokinetics	**Pharmacokinetic Endpoints**
To describe the PK of midazolam, omeprazole, and caffeine and their metabolites (1'-hydroxy-midazolam, 5 hydroxy-omeprazole, and paraxanthine) in the absence and presence of AZD1775	Plasma t_{max}, $t_{½}$, λ_z, CL/F and V_z/F for cocktail parent compounds (midazolam, omeprazole, and caffeine) Plasma AUC, AUC_{0-t}, t_{max}, C_{max}, $t_{½}$, and λ_z for cocktail metabolites (1'-hydroxy-midazolam, 5-hydroxy-omeprazole, and paraxanthine) and the AUC and C_{max} ratios in relation to parent compound
To describe the PK of AZD1775 following single and multiple dose administration	Plasma AZD1775 Day 1: Part B only: AUC_{0-12}, t_{max}, and C_{max} Plasma AZD1775 Day 3: Parts A & B: AUC_{0-12}, t_{max}, C_{max}, C_{min}, C_{avg}, CL_{ss}/F and FI; Part B only: $RAUC_{0-12}$ and RC_{max}

Pharmacodynamics	**Pharmacodynamic Endpoints**
To evaluate the effect of single and multiple doses of AZD1775 on cardiac (ECG) parameters	dECG intervals (heart rate, RR, PR, QRS, QTcB, QTcF and QT) for absolute values and time-matched change from baseline; changes in dECG morphology
Safety	**Safety Endpoints**
To assess the safety and tolerability of AZD1775 when dosed with or without the cocktail drug substrates	Assessment of AEs, graded by CTCAE (version 4.03), physical examination, vital signs (blood pressure, pulse rate and body temperature), digital 12-lead ECG (Part B only), evaluation of laboratory parameters (clinical chemistry and haematology)

λ_z: Elimination rate constant; AEs: adverse events; AUC: area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}: area under the plasma concentration-time curve from time zero to the time "t" of the last quantifiable concentration; AUC_{0-12}: area under the plasma concentration-time curve from time zero to 12 hours; C_{avg}: average concentration over a dosing interval; CL/F: apparent clearance; CL_{ss}/F: apparent clearance at steady state; C_{max}: maximum plasma drug concentration; C_{min}: minimum plasma drug concentration; CTCAE: Common Terminology Criteria for Adverse Events; dECG: digital electrocardiogram; FI: fluctuation index over a dosing interval; PK: pharmacokinetics; PR: ECG interval measured from the onset of the P wave to the onset of the QRS complex; QRS: ECG interval measured from the onset of the QRS complex to the J point; QT interval: ECG interval measured from the onset of the QRS complex to the end of the T wave; QTcB: QT interval corrected for heart rate according to Bazett's formula; QTcF: QT interval corrected for heart rate according to Fridericia's formula; $RAUC_{0-12}$: accumulation ratio for AUC_{0-12}; RC_{max}: accumulation ratio for C_{max}; RR: time between corresponding points on 2 consecutive R waves on ECG; t_{max}: time to reach maximum plasma concentration; $t_{½}$: terminal half-life; V_z/F: apparent volume of distribution.

Exploratory Objectives:	**Outcome Measure:**
Plasma DNA extraction to investigate the impact of polymorphisms of ADME-related genes on the absorption, distribution, metabolism, and excretion	Not applicable[a]
Collect urine samples for 1β-hydroxy deoxycholic acid as a CYP3A4 biomarker	Not applicable[a]
To provide data as part of pooled data across studies to allow further analysis such as population PK modelling, PK/PD modelling, etc	Not applicable[a]

a The results of any further analyses will be reported separately from the Clinical Study Report
ADME: Absorption, distribution, metabolism and excretion; CYP: cytochrome P450; DNA: deoxyribonucleic acid; PD: pharmacodynamics; PK: pharmacokinetics

Target subject population

The target population for this study is patients with advanced solid tumours. Approximately 30 patients will be enrolled to ensure that at least 20 evaluable patients complete both parts of the study.

Additional patients may be enrolled in Part A if necessary to ensure at least 20 evaluable patients complete both study parts.

Duration of treatment

Patients will be screened 28 days relative to the first AZD1775 dose and within 14 to 21 days relative to the first cocktail administration in Part A, Period 1. Patients should be admitted to the study centre on Day -9 for safety assessments. The treatment starts with the administration of a cocktail (Day -8) followed by PK sampling for 24 hours and a washout period of at least 7 but no more than 14 days. In Period 2, AZD1775 will be administered until steady state for 2.5 days (total of 5 doses) and administered together with the cocktail in the morning of Day 3.

Upon completion of Part A, providing the patient continues to meet the study inclusion and none of the exclusion criteria and following a washout period of at least 7, but no more than 14 days between the last dose in Part A and Day -1 of Part B, each patient will receive 3 x 75 mg AZD1775 capsules (225 mg) bid for 2.5 days. Patients will be required to stay overnight, either at the study centre or a nearby hotel or residence, from Day -2 to Day 1 (2 nights) and from Day 2 to Day 3 (1 night) of Part B, to ensure that conditions for the dECG assessments on Day 1 and Day 3 match those from Day -1. Patients may stay overnight on the other nights, but this is optional. Patients will self-administer granisetron 30 minutes before the AZD1775 doses under fasted conditions (-2 to 2 hours away from meals) the evening of Day 1 and the morning of Day 2 on an outpatient basis. Patients will be discharged from the study centre after completing their 24-hour PK/dECG assessments on Day 4, Part B.

The maximum total duration of the study for patients who cannot or do not wish to participate in the CA study will be approximately 8 to 12 weeks.

Investigational product, dosage and mode of administration

Investigational product	Dosage form and strength	Manufacturer
AZD1775 printed capsules	225 mg (3 x 75 mg capsules)	AstraZeneca

The AZD1775 dose administered to patients in Period 2 of Part A and in Part B will be 3 x 75 mg (225 mg) capsules bid. AZD1775 will be taken orally approximately 2 hours before or 2 hours after food in approximately 12-hour intervals for 2.5 days, with 240 mL water. Patients should be administered Kytril (granisetron) 1 mg orally 30 minutes prior to administration of the AZD1775 capsules with a small amount of water.

In Part A, a cocktail of substrates which are all mainly eliminated by cytochrome P450 (CYP) will be administered on 2 occasions. The cocktail will include: caffeine (200 mg), omeprazole (20 mg) and midazolam (1 mL of 2 mg/mL syrup). The cocktail will be administered as a single dose in the morning of Day -8 (Period 1) and again together with the last dose of AZD1775 on Day 3 in Period 2. Dexamethasone, if needed, should not be administered until after the last PK sample is drawn on Part A, Day 4.

In Part B, dexamethasone 4 mg orally/IV can be used bid prn and/or given prior to each dose of AZD1775 along with granisetron if needed as long as consistent pre-treatment conditions are maintained in the mornings prior to all serial ECG collections. If patients are scheduled to receive dexamethasone with granisetron in the morning of Day 1, they must also receive dexamethasone (same dose) time-matched on Day -1 and in the morning of Day 3. However, if they did not receive dexamethasone on Day 1, they may not receive it on Day 3.

In both study parts, Ativan, Compazine and Phenergan may be used prn but not as part of the pre-treatment regimen.

Statistical methods

Pharmacokinetic and safety results obtained in Part A (Periods 1 and 2) and Part B will be summarised, as appropriate.

Part A analyses:

Estimates of the mean difference between treatments (AZD1775 + cocktail substrate compared to cocktail substrate alone) and corresponding 90% confidence intervals (CIs) will be calculated using a linear mixed effects model with a fixed effect for treatment and a random effect for patient. The natural log transformed PK parameters (maximum plasma drug concentration [C_{max}], area under the plasma concentration-time curve from time zero to infinity [AUC] and the area under the plasma concentration-time curve from time zero to the time "t" of the last quantifiable concentration [AUC_{0-t}]) of cocktail parent compounds and metabolites will be used in the mixed effects models as the dependent variables. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs will be estimated and presented by treatment.

Part B analyses:

A plasma concentration to QT (C-QT) relationship analysis will be conducted using a linear mixed model in which the placebo-corrected (Day -1-corrected) change from baseline in QT interval corrected for heart rate using Fridericia's formula (QTcF) is the dependent variable and the AZD1775 plasma concentration obtained on Day 1 and Day 3 is the independent variable. Hysteresis and departures from a linear relationships will be examined. Additional C-QT relationships other than the linear relationship may be explored if supported by data. A detailed plan of this analysis will be presented as part of the statistical analysis plan (SAP). The results for the C-QT analysis and modelling will form part of the clinical study report (CSR) for this study.

Results for AUC_{0-12} and C_{max} obtained after AZD1775 administration on Day 3 in Part B will be compared with those obtained on Day 3 in Part A to probe for potential effects by the cocktail drugs and to obtain an estimate of intra-subject variability following multiple dose administration. All evaluable data for Part A and Part B will be included in the analysis. To assess the potential effects of the cocktail drugs on AZD1775 exposure, a linear mixed effects

model using the natural log transformed AUC_{0-12} or C_{max} as the response variable, study part as a fixed effect and subject as a random effect will be performed. Estimates of the mean difference between study parts (Part A, Day 3 compared to Part B, Day 3) and corresponding 90% CIs will be calculated. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs will be estimated and presented by study part. Furthermore, an estimate of intra-subject variability following multiple dose administration will be estimated and presented

The QTcF outliers are defined as QTcF values following dosing that are greater than 450 ms or show an increase from baseline greater than 30 ms. QTcF outliers will be highlighted in the data listings and summarised using the following categories: values that are 450 ms or less, greater than 450 ms to 480 ms; greater than 480 ms to 500 ms and greater than 500 ms; or show an increase from baseline of 30 ms or less, greater than 30 ms to 60 ms or less; and greater than 60 ms. The number and percentage of patients who meet the QTcF outlier criteria at any assessment after start of study treatment (inclusive of Day -1 of Part B, where appropriate) will be tabulated by time and maximum QTcF value for the given Study Day.

For QTcF, figures will be generated for the mean time-matched change from baseline values on Day 1 and Day 3.

Figures for mean time-matched change from baseline QTcF values versus AZD1775 mean concentrations (time-matched with QTcF) on Day 1 and Day 3 will also be generated.

To assess the extent of accumulation of AZD1775 in Part B, a linear mixed effects model using the natural log transformed AUC_{0-12} or C_{max} as the response variable, day as a fixed effect and subject as a random effect will be performed. Estimates of the mean difference between days (Day 3 compared to Day 1) and corresponding 90% CIs will be calculated. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs will be estimated and presented by day.

Post-study analyses (exploratory):

Additionally, dECG data from this study may be pooled with data from another study(ies) and analysed by AstraZeneca using statistical methods and PK/pharmacodynamic (PD) modelling to evaluate the effect of AZD1775 concentration on QTc (mainly QTcF interval). The methodology for these analyses will be described separately from this protocol.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
λ_z	Elimination rate constant
%CV	Percentage coefficient of variation
%GCV	Geometric coefficient of variation
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the time "t" of the last quantifiable concentration
AUC_{0-12}	Area under the plasma concentration-time curve from time zero to 12 hours
bid	Twice a day
BRCA	Breast cancer susceptibility gene
CA	Continued access
C_{avg}	Average concentration over a dosing interval
CDC2	Cell division cycle protein 2
CDK1	Cyclin-dependent kinase 1
CDK2	Cyclin-dependent kinase 2
CI	Confidence interval
CL/F	Apparent clearance
CL_{ss}/F	Apparent clearance at steady-state
C_{max}	Maximum plasma drug concentration
C_{min}	Minimum plasma drug concentration
C-QT	Plasma concentration to QT
CrCl	Creatinine clearance
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report

Abbreviation or special term	Explanation
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
dECG	Digital electrocardiogram
DHEA	Dehydroepiandrosterone
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EoS	End of study
EoT	End of treatment
FI	Fluctuation index over a dosing interval
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Gx	Genetic research
HIV	Human immunodeficiency virus
IATA	International Airlines Transportation Association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International Normalised Ratio
IRB	Institutional Review Board
IV	Intravenous(ly)
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetics
PR	ECG interval measured from the onset of the P wave to the onset of the QRS complex

Abbreviation or special term	Explanation
prn	As occasion requires
PS	Performance status
PT	Preferred Term
RR	The time between corresponding points on 2 consecutive R waves on ECG
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT interval	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
$RAUC_{0-12}$	Accumulation ratio for AUC_{0-12}
RC_{max}:	Accumulation ratio for C_{max}
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System Organ Class
$t_{½}$	Terminal half-life
t_{max}	Time to reach maximum plasma concentration
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution
WBDC	Web Based Data Capture
WEE1	Protein tyrosine kinase
WNL	Within normal limits
WoCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

AZD1775 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 (Coleman and Dunphy 1994, Parker and Piwnica-Worms 1992).

CDK1 (also called cell division cycle 2 protein, or CDC2) activity drives a cell from the G2 phase of the cell cycle into mitosis. In response to DNA damage, WEE1 inhibits CDK1 to prevent the cell from dividing until the damaged DNA is repaired (G2 checkpoint arrest). CDK2 activity drives a cell into, and through, S-phase of the cell cycle in which the genome is duplicated in preparation for cell division. Inhibition of WEE1 is expected to cause aberrantly high CDK2 activity in S-phase cells that, in turn leads to unstable DNA replication structures and ultimately DNA damage.

Inhibition of WEE1 is expected to release a tumour cell from DNA damage-induced arrest at the G2/M boundary, so that unrepaired DNA damage may be taken into mitosis (M-phase). Since cancer cells exhibit higher levels of endogenous damage than normal cells, as well as exhibiting loss of 1 or more DNA damage response capabilities, this is expected to preferentially enhance cancer cell death through mitotic catastrophe compared to normal cells. In vitro experiments demonstrated that AZD1775 has synergistic cytotoxic effects when administered in combination with various DNA damaging agents that have divergent mechanisms of action. Therefore, the clinical development of AZD1775 includes its use as a chemosensitising drug in combination with a cytotoxic agent (or combination of agents) for treatment of advanced solid tumours.

Since the majority (if not all) of human cancers harbour abnormalities in their p53 G1/S checkpoint control, they become more dependent on S- and G2- phase checkpoints (Sherr 1996). Thus, S- and G2-checkpoint abrogation caused by AZD1775 may selectively sensitise p53-deficient cells to anti-cancer agents (Wang et al 2001) while single-agent activity may be seen in cancers with sufficiently high levels of replication stress and endogenous DNA damage.

It is anticipated that AZD1775 will have independent anti-tumour activity in the absence of added chemotherapy, particularly in cancer cells that already have significantly higher levels of replication stress. In preclinical cancer cell models associated with high levels of endogenous replication stress resulting from a combination of G1/S checkpoint deficiencies due to p53 mutations or CDKN2A deletions and the over-expression of oncogenic drivers such as MYC, mutant KRAS or the amplification of Cyclin E, AZD1775 demonstrated significant single-agent anti-tumour activity.

Efficacy with AZD1775 monotherapy has been observed in clinical studies. Six clinical studies with AZD1775 have been completed or terminated early. In Study PN001, of the

176 evaluable patients with advanced solid tumours who received AZD1775 (either single or multiple doses) as monotherapy or in combination with gemcitabine, cisplatin, or carboplatin, a partial response (confirmed and unconfirmed) was observed in 17 (9.7%) patients, and stable disease was observed in 94 (53.4%) patients (AZD1775 Investigator's Brochure). In Study PN011, which determined the maximum tolerated dose for AZD1775 monotherapy in patients with solid tumours (N=25), confirmed partial responses were observed in 2 patients carrying germline breast cancer susceptibility gene (BRCA1) mutations: 1 with head and neck cancer and 1 with ovarian cancer (Do et al 2015).

No complete or partial responses 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 twice daily (bid) 2.5 day dose level in combination with paclitaxel and carboplatin. Of the 14 evaluable patients in Part 1, there were 11 partial responses (6 confirmed and 5 unconfirmed), and 3 stable diseases.

In Study D6011C00001, a clinical study evaluating AZD1775 monotherapy in patients with advanced solid tumours, patients received either 200 mg or 175 mg bid for 3 days followed by 4 days off for 2 weeks out of a 3-week schedule. All 32 patients were included in the efficacy population. The 3 patients (9.4%) that achieved partial responses had TP53 mutations. Twenty-one patients (65.6%) had stable disease and 10 (47.6%) of these patients had TP53 mutations (Bauer et al 2016). In Study D6011C00002, the initial response data was 27% of patients having partial responses and 43% of patients with stable disease.

[redacted] a total of approximately 713 patients had been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies. In addition, approximately 559 patients have also received AZD1775 as part of externally-sponsored scientific research. These patients include those who have received single doses as high as 1300 mg of AZD1775 as monotherapy, 325 mg of AZD1775 in a single-dose in combination with chemotherapy, and 325 mg bid in a multiple-dose regimen in combination with chemotherapy.

Based on the safety data from the completed AZD1775 clinical studies and preliminary data from ongoing studies 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 where a causal relationship with AZD1775 monotherapy has not been established include asthenia/fatigue, febrile neutropenia, gastrointestinal haemorrhage, lymphopenia/lymphocyte count decreased, leukopenia/WBC count decreased, myalgia, stomatitis, sepsis and transaminases elevation.

Please refer to the latest version of the Investigator's Brochure (IB) for updated clinical information as it becomes available (AZD1775 Investigator's Brochure).

1.2 Rationale for study design, doses and control groups

AZD1775 has been and is being evaluated in several clinical studies as monotherapy and combination therapy, including both Phase I and Phase II studies in a variety of tumour settings. 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.

In Study PN011 (NCT01748825), which determined the maximum tolerated dose for AZD1775 monotherapy (225 mg bid on days 1 to 3 of weeks 1, 2 of each 21-day cycle) in patients with solid tumours (N=25), confirmed partial responses were observed in 2 patients carrying germline BRCA1 mutations: 1 with head and neck cancer and 1 with ovarian cancer (Do et al 2015). In an ongoing clinical study evaluating AZD1775 monotherapy in patients with advanced solid tumours (D6015C00001), 12 patients have received either 200 mg (7 patients) or 175 mg (5 patients) bid for 3 days followed by 4 days off for 2 weeks out of a 3-week schedule. Partial responses have been observed in 2 patients (17%) with small cell lung cancer with somatic mutations in both TP53 and RB1 (Bauer et al 2016).

In Study PN011 (NCT01748825), once daily doses of 200 mg to 400 mg have also been evaluated on a 5◦days on followed by 2 days off for 2◦weeks out of a 21-day schedule. Preliminary PK data from the once daily dosing shows that the exposure increases more than dose proportionally between 200 and 300 mg after both single and multiple doses. In comparison to the bid dosing data from Study REFMAL383, the area under the plasma concentration-time curve from time zero to 24 hours (AUC0-24) on Day 5 at 200 mg to 250 mg once daily dose is similar to that observed after bid dosing at 175 mg. At 300 mg once daily dose, the AUC_{0-24} (22498 nM*h) on Day 5 exceeds the exposure observed after bid dosing at 200 mg (19632 nM*h). (AstraZeneca data on file).

Study D6015C00003 (REFMAL 398) is a Phase Ib study designed to determine the maximum tolerated dose of AZD1775 monotherapy (on a 5 day regimen) in patients with locally advanced or metastatic solid tumours. This protocol was amended in 2016 to permit investigation of once a day dosing schedules on 5/2 and 5/9 schedule in addition to the existing bid dosing of AZD1775. As of the cut-off date for the current IB, a total of 61 patients have received AZD1775 monotherapy at either 125 mg bid or 150 mg bid

The recommended dosing schedule for monotherapy treatment of AZD1775 is currently still being explored. In combination with chemotherapy, the most common dosing schedule is 225 mg bid for 2.5 days over every 3 weeks. Further monotherapy/combination schedules are under evaluation. In this study AZD1775 (225 mg, orally bid) will be taken in approximate 12-hour intervals over 2.5 days (Days 1 to 3).

AZD1775 may decrease/increase exposure to compounds mainly eliminated by cytochrome P450 (CYP), thus this study will be conducted in order to quantify the effect of AZD1775 on the pharmacokinetics (PK) of probe substrates for CYP1A2, CYP2C19 and CYP3A. Part A of this study will assess the effect of AZD1775 on the PK of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole), and CYP3A (midazolam). The doses of drugs

(midazolam, 1 mL of 2 mg/mL syrup; omeprazole, 20 mg capsules and caffeine, 200 mg) included in the cocktail have been previously used for validation of this cocktail.

There are currently limited clinical data on the effect of AZD1775 on the QT interval prolongation. Therefore, Part B of the study will investigate the effect of AZD1775 on the QT interval after multiple dose administrations.

1.3 Benefit/risk and ethical assessment

This study is robustly designed to assess the primary objective while minimising the number of patients exposed to AZD1775. AstraZeneca considers that AZD1775 continues to demonstrate an overall acceptable benefit-risk balance to support its further clinical development.

Although patients may not initially gain any benefit from participation in this study due to the short dosing periods, some benefit may be gained in the open-label continued access (CA) study (D6014C00007). If the Investigator believes it is in the patient's interest, patients who complete this study may continue treatment with AZD1775 capsules in the open-label CA study until such time as their disease progresses, the Investigator believes they are no longer deriving clinical benefit, or they stop taking the AZD1775 capsules for any other reason. Patients who discontinue early from this study will be considered by the Sponsor and treating physician on a case-by-case basis for enrolment into the CA study.

The clinical profile for AZD1775 demonstrates tolerability in safety assessment studies. Based on the mechanism of action and on preclinical studies, AZD1775 as a single agent is expected to have anti-cancer activity when administered as monotherapy or in combination with chemotherapeutic agents.

The following have been identified during the clinical development programme as important and/or potential risks, to be closely monitored as the AZD1775 clinical development programme progresses:

- Based on the safety data from the completed AZD1775 clinical studies and preliminary data from ongoing studies, 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.

- Based on information emerging during the clinical development programme of AZD1775, potential risks with AZD1775 monotherapy include asthenia/fatigue, febrile neutropenia, gastrointestinal haemorrhage, lymphopenia/lymphocyte count decreased, leukopenia/white blood cell count decreased, myalgia, stomatitis, sepsis and transaminases elevation.

- AZD1775 is genotoxic and should be administered only to patients with cancer.

The identified risks (expected events) for AZD1775 are described in Section 5.4 (Emerging Safety Profile) of the IB. Section 6.4 (Risk Management) of the IB provides specific advice to the Investigator regarding standard safety practices to be followed when handling and administering AZD1775.

1.4 Study design

This is a Phase I, non-randomised, 2-part study (Part A and Part B) in patients with advanced solid tumours.

Part A

Part A of this study is an open-label, non-randomised, 2-period design. Patients will be screened 28 days relative to the first AZD1775 dose and within 14 to 21 days relative to the first cocktail administration. Patients should be admitted to the study centre on Day -9 for safety assessments and may remain resident overnight. The treatment starts with the administration of a cocktail of 3 medications (Day -8) followed by PK sampling for 24 hours (Period 1) and a washout period of at least 7, but no more than 14 days. In Period 2, AZD1775 will be administered twice daily until steady state for 2.5 days (total of 5 doses) with 240 mL of water and the final dose will be administered in combination with the cocktail in the morning of Day 3. Patients should be administered Kytril (granisetron) 1 mg orally with a small amount of water 30 minutes prior to administration of the cocktail drugs on Day -8 and prior to administration of each dose of AZD1775 capsules.

All patients will receive a single dose of the cocktail containing caffeine (200 mg), omeprazole (20 mg capsule) and midazolam (1 mL of 2 mg/mL syrup formulation) alone (Period 1) and combined with the last dose of AZD1775 (225 mg, 3 x 25 mg capsules) at steady state (Day 3 Period 2). Patients are required to fast from 2 hours before until 2 hours after the cocktail administration alone, as well as each administration of AZD1775 alone, or in combination with the cocktail. Water intake is restricted from 1 hour before until 1 hour after cocktail and AZD1775 and cocktail administrations (Day -8 and Day 3), excluding the 240 mL of water to be used for administration of AZD1775 and/or the cocktail. Patients must take all 3 cocktail drugs alone, or in combination with AZD1775 with the 240 mL water provided. Decadron (dexamethasone) cannot be used until after the last PK sample is drawn. Compazine (prochlorperazine), Phenergan (promethazine) and/or Ativan (lorazepam) can be used as occasion requires (prn) for nausea/vomiting – please see list of restricted medication in Appendix H.

Period 1

A single administration of the cocktail on Day -8 will be followed by PK sampling for 24 hours for assessment of cocktail analytes. Patients should be administered Kytril (granisetron) 1 mg orally 30 minutes prior to administration of the cocktail with a small amount of water. Patients should be admitted to the study centre on Day -9 for safety assessments and may remain resident overnight, but should remain in the study centre for the first 12 hours of PK sample collections following the cocktail administration on Day -8; the

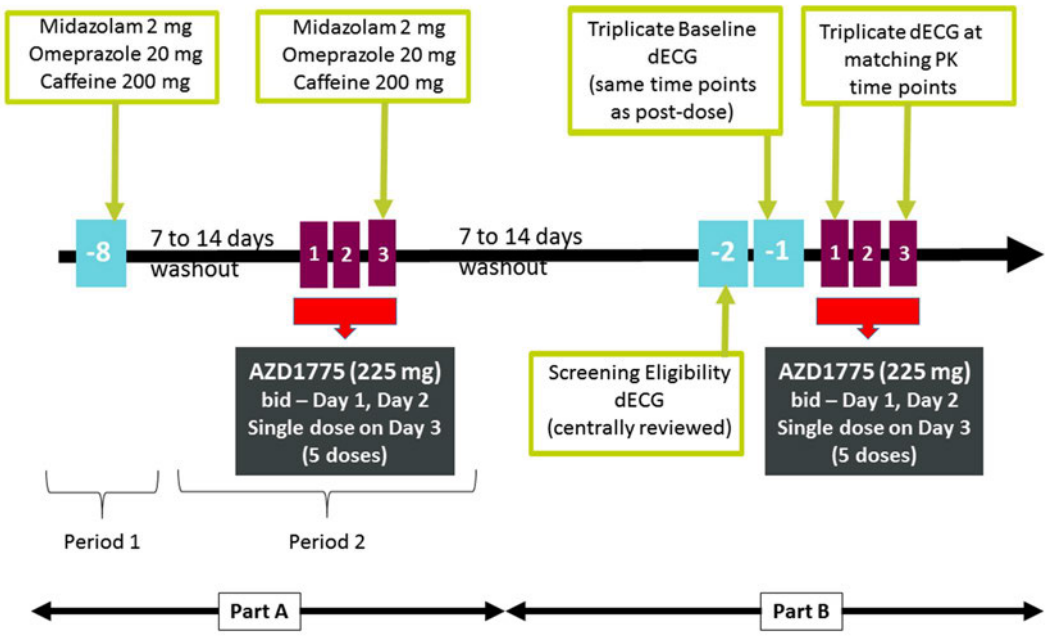
24-hour sample may be collected on an outpatient basis, if desired by the patient. The overall study plan is outlined in Figure 1.

Period 2

After a washout period of at least 7, but no more than 14 days, AZD1775 will be administered at a dose of 225 mg bid for 2 days (Period 2 Days 1 and 2) with an adequate amount of water (ideally 240 mL). Patients should be administered Kytril (granisetron) 1 mg orally 30 minutes prior to administration of the AZD1775 capsules with a small amount of water. Patients will self-administer their granisetron 30 minutes before their AZD1775 doses under fasted conditions (AZD1775 doses -2 to 2 hours away from meals) the evening of Day 1 and through the evening of Day 2 on an outpatient basis. In the morning of Day 3, the cocktail will be administered in combination with AZD1775 at steady state. Patients must take all 3 cocktail drugs in combination with AZD1775 with the 240 mL water provided. Patients are required to fast from 2 hours before until 2 hours after each AZD1775 administration alone and when administered in combination with the cocktail. Pharmacokinetic sampling will take place for 24 hours for assessment of cocktail analytes and AZD1775. Patients will be admitted the morning of Day 3 and will remain in the study centre for the first 12 hours of PK sample collections; the 24-hour sample may be collected on an outpatient basis, if desired by the patient.

Phenergan, Ativan and/or Compazine may be used prn for nausea/vomiting. Decadron, if needed, cannot be administered until after the last PK sample is drawn – please see list of restricted medication in Appendix H.

Figure 1 Overall study plan



Part B

Part B is an open-label, non-randomised study in the same patients who participated in Part A. Upon completion of Part A, following a washout period of at least 7, but no more than 14 days between the last dose in Part A and Day -1 of Part B and provided the patient continues to meet all the study inclusion and none of the exclusion criteria, patients will check into the study centre on Day -2. Patients will be required to stay overnight, either at the study centre or a nearby hotel or residence, from Day -2 to Day 1 (2 nights) and from Day 2 to Day 3 (1 night) to ensure that conditions for the dECG assessments on Day 1 and Day 3 match those from Day -1. Patients may stay overnight on the other nights, but this is optional. However, patients experiencing nausea/vomiting or any other safety issues, should remain in the study centre**.**

Upon arrival on Day -2, patients will undergo a digital electrocardiogram (dECG) to determine eligibility by central review. On Day -1, baseline dECG assessments will be performed at clock times matched to planned/scheduled dECG assessment times on Days 1 and 3.

Starting the morning of Day 1, each patient will receive 3 x 75 mg AZD1775 capsules (225 mg) bid for 2.5 days with 240 mL water; administered under fasting conditions (from 2 hours pre-dose to 2 hours post-dose). Water is restricted from 1 hour before until 1 hour after AZD1775 administration in the morning of Day 1 and of Day 3 and time-matched on Day -1, excluding the 240 mL water required for the administration of the study treatment, as well as the water required to swallow the assigned pre-treatment anti-emetic(s). Treatment with 1 mg Kytril (granisetron) orally 30 minutes prior to all AZD1775 administrations is mandated. Patients may also receive Decadron (dexamethasone) 4 mg orally/IV prior to each dose of AZD1775 along with granisetron if medically indicated as long as consistent pre-treatment conditions are maintained in the mornings prior to all serial dECG collections.

Since patients need anti-emetics prior to AZD1775 administration on Day 1, all patients will receive granisetron (and dexamethasone, if applicable) orally 30 minutes prior to dose administration on Day -1 time-matched to the clock time for granisetron (and dexamethasone, if applicable) administration on Day 1 (scheduled for 30 minutes prior to the time of AZD1775 administration). If patients are to receive dexamethasone along with granisetron in the morning of Day 1, they must also receive the same dexamethasone treatment in the morning of Day -1 and in the morning of Day 3. However, if patients are not scheduled to receive dexamethasone on the morning of Day 1, they should not have received dexamethasone on Day -1 and may not receive dexamethasone in the morning of Day 3. Ativan, Compazine and/or Phenergan can be used prn but not as part of the pre-treatment regimen – please see list of prohibited medications in Appendix H.

On Day 1, patients will undergo dECG and PK assessments pre-dose (post anti-emetic administration) and for 12 hours post AZD1775 dose and may be discharged after completion of the Day 1 assessments as long as they are not experiencing nausea/vomiting or any other

safety issues. Patients will continue to take AZD1775 every 12 hours under fasted conditions (AZD1775 doses 2 to 2 hours away from meals) with prescribed anti-emetic(s) given orally 30 minutes prior to each dose.

Patients will be admitted to the study centre on the evening of Day 2 and stay overnight either at the study centre, or nearby hotel or residence. On Day 3, patients will receive their final AZD1775 dose (30 minutes after anti-emetic administration) and undergo dECG and PK assessments pre-dose (post anti-emetic administration) and for 12-hours post-dose. Patients may be discharged after completion of the Day 3 assessments, as long as they are not experiencing nausea/vomiting, or any other safety issues, and will be asked to return to the study centre in the morning of Day 4 for their final (24-hour) PK/dECG assessments relative to the AZD1775 dose administered on Day 3. The dECGs performed on Day 1 and Day 3 will be clock-time matched to the actual clock times that the Day -1 dECGs are performed. Similar, standard meals will be provided on Day -1 (time matched to those on Days 1 and 3) and at 2 hours post morning dose on Days 1, and 3.

When a meal, dECG and PK samples are scheduled at the same time, the dECG should be obtained first, followed by the PK sample and then the meal. Patients will be discharged from the study centre after completing their 24 hour PK/dECG assessments on Day 4 of Part B.

On completion of Part B (ie, collection of the 24-hour PK sample/dECG and safety assessments on Day 4) patients will enter a 4-day washout period relative to the last dose of AZD1775. Within 3 days after the washout period, patients will be required to attend an end of treatment (EoT) visit. Patients will be evaluated per current assessments for their eligibility and interest to enrol into the open-label continued access (CA) study (D6014C00007). All patients who do not enrol in the CA study will be asked to return to the study centre 30 (-7) days after the last dose of AZD1775 for a final follow-up visit (end of study [EoS] visit).

For patients interested in enrolling in the open-label CA study, the assessments taken at the EoT visit will serve as the screening for the CA study. However, this is providing their EoT safety assessments are in accordance with the CA study inclusion and exclusion criteria. Please refer to the CA study protocol for additional required screening assessments and other eligibility criteria.

1.5 Study governance and oversight

No Data Monitoring Committee is planned, as this study is an open-label, non-randomised Phase I study. In addition the safety profile of AZD1775 from an ongoing Phase I study in a similar patient population is modest and predictable with no reported life-threatening adverse events (AEs). There is therefore no requirement for pre-planned specified expert independent safety reviews in this study.

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol (CSP) and letters to Investigators.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objectives:	Outcome Measure:
Pharmacokinetics To assess the effect of AZD1775 on the PK of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole), and CYP3A (midazolam)	**Pharmacokinetic Endpoints** **Part A** Plasma AUC, AUC_{0-t} and C_{max} for cocktail parent compounds (midazolam, omeprazole and caffeine)
Pharmacodynamics To assess the effect on QT interval corrected for heart rate (QTc) following multiple oral doses of AZD1775	**Pharmacodynamic Endpoints** **Part B** dECG intervals (QTcF) for absolute values and time-matched change from baseline

AUC: Area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}: area under the plasma concentration-time curve from time zero to the time "t" of the last quantifiable concentration; C_{max}: maximum plasma drug concentration; CYP: cytochrome P450; dECG: digital electrocardiogram; PK: pharmacokinetics; QT interval: ECG interval measured from the onset of the QRS complex to the end of the T wave; QTc: QT interval corrected for heart rate; QTcF: QT interval corrected for heart rate using Fridericia's formula

2.2 Secondary objectives

Secondary Objectives:	Outcome Measure:
Pharmacokinetics	**Pharmacokinetic Endpoints**
To describe the PK of midazolam, omeprazole, and caffeine and their metabolites (1'-hydroxy-midazolam, 5-hydroxy-omeprazole, and paraxanthine) in the absence and presence of AZD1775	Plasma t_{max}, $t_{½}$, λ_z, CL/F and V_z/F for cocktail parent compounds (midazolam, omeprazole, and caffeine) Plasma AUC, AUC_{0-t}, t_{max}, C_{max}, $t_{½}$, and λ_z for cocktail metabolites (1'-hydroxy-midazolam, 5-hydroxy-omeprazole, and paraxanthine) and the AUC and C_{max} ratios in relation to parent compound
To describe the PK of AZD1775 following single and multiple dose administration	Plasma AZD1775 Day 1: Part B only: AUC_{0-12}, t_{max}, and C_{max} Plasma AZD1775 Day 3: Parts A & B: AUC_{0-12}, t_{max}, C_{max}, C_{min}, C_{avg}, CL_{ss}/F and FI; Part B only: $RAUC_{0-12}$ and RC_{max}
Pharmacodynamics	**Pharmacodynamic Endpoints**
To evaluate the effect of single and multiple doses of AZD1775 on cardiac (ECG) parameters	dECG intervals (heart rate, RR, PR, QRS, QTcB, QTcF and QT) for absolute values and time-matched change from baseline; changes in ECG morphology

λ_z: Elimination rate constant; AUC: area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}: area under the plasma concentration-time curve from time zero to the time "t" of the last quantifiable

concentration; AUC_{0-12}: area under the plasma concentration-time curve from time zero to 12 hours; C_{avg}: average concentration over a dosing interval; CL/F: apparent clearance; CL_{ss}/F: apparent clearance at steady state; C_{max}: maximum plasma drug concentration; C_{min}: minimum plasma drug concentration; dECG: digital electrocardiogram; FI: fluctuation index over a dosing interval; PK: pharmacokinetics; PR: ECG interval measured from the onset of the P wave to the onset of the QRS complex; QRS: ECG interval measured from the onset of the QRS complex to the J point; QT interval: ECG interval measured from the onset of the QRS complex to the end of the T wave; QTcB: QT interval corrected for heart rate according to Bazett's formula; QTcF: QT interval corrected for heart rate according to Fredericia' formula; $RAUC_{0-12}$: accumulation ratio for AUC_{0-12}; RC_{max}: accumulation ratio for C_{max}; RR: time between corresponding points on 2 consecutive R waves on ECG; t_{max}: time to reach maximum plasma concentration; $t_{½}$: terminal half-life; V_z/F: apparent volume of distribution

2.3 Safety objectives

Safety	**Safety Endpoints**:
To assess the safety and tolerability of AZD1775 when dosed with or without the cocktail drug substrates	Assessment of AEs, graded by CTCAE (version 4.03), physical examination, vital signs (blood pressure, pulse rate and body temperature), digital 12-lead ECG (Part B only), evaluation of laboratory parameters (clinical chemistry and haematology)

AEs: Adverse events; CTCAE: Common Terminology Criteria for Adverse Events; ECG: electrocardiogram

2.4 Exploratory objectives

Exploratory Objectives:	**Outcome Measure:**
Plasma DNA extraction to investigate the impact of polymorphisms of ADME-related genes on the absorption, distribution, metabolism, and excretion	Not applicable[a]
Collect urine samples for 1β-hydroxy deoxycholic acid as s CYP3A4 biomarker	Not applicable[a]
To provide data as part of pooled data across studies to allow further analysis such as population PK modelling, PK/PD modelling, etc	Not applicable[a]

a The results of any further analyses will be reported separately from the Clinical Study Report

ADME: Absorption, distribution, metabolism and excretion; CYP: cytochrome P450; DNA: deoxyribonucleic acid; PK: pharmacokinetics

3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

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

3.1 Inclusion criteria

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

1. Has read and understands the informed consent form (ICF) and has given written informed consent prior to any study procedures.

2. Histologically or cytologically documented, locally advanced or metastatic solid tumour, excluding lymphoma, for which standard therapy does not exist or has proven ineffective or intolerable.

3. Any prior palliative radiation must have been completed at least 7 days prior to the start of study treatment (first administration of cocktail [Part A Day -8]), and patients must have recovered from any acute adverse effects prior to the start of study treatment.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 to 1.

5. Baseline laboratory values within 7 days of study treatment initiation (first administration of cocktail [Part A Day -8]):

   - Absolute neutrophil count (ANC) ≥1500/μL.
   - Haemoglobin ≥9 g/dL.
   - Platelets ≥100,000/μL.
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN) or ≤5 x ULN if known hepatic metastases.
   - Serum bilirubin within normal limits (WNL) or ≤1.5 x ULN in patients with liver metastases; or total bilirubin ≤3.0 x ULN with direct bilirubin WNL in patients with well documented Gilbert's Syndrome.
   - Serum creatinine ≤1.5 x ULN, or measured creatinine clearance (CrCl) calculated by Cockcroft-Gault method ≥45 mL/min (confirmation of creatinine clearance is only required when creatinine is >1.5 x ULN).

     $$\text{CrCl (glomerular filtration rate)} = \frac{(140\text{-age}) \times (\text{weight/kg}) \times F^{a}}{(72 \times \text{serum creatinine mg/dL})}$$

     [a]where F = 0.85 for females and F = 1 for males

6. Female patients who are not of childbearing potential and fertile females of childbearing potential who agree to use adequate contraceptive measures that are in place during screening (or consent), for the duration of the study, and for 1 month

after treatment stops, and who are not breastfeeding, and who have a negative serum or urine pregnancy test prior to the start of study treatment (first administration of cocktail [Part A Day -8]) (see Appendix E). Any patient taking an oral contraceptive must be discussed with the Medical Monitor to ensure that there will be no interaction with the brand of oral contraceptive and cocktail of drugs prior to trial entry to confirm eligibility.

7. Male patients should be willing to use barrier contraception (ie, condoms) for the duration of the study and for 3 months after study treatment discontinuation (see Appendix E).

8. Female and/or male patients ≥18 years of age.

9. Willingness and ability to comply with the study and follow-up procedures.

For inclusion in the optional genetic component of the study for all the patients:

10. Provision of informed consent for genetic research. If a patient declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in the CSP, as long as all the eligibility criteria are met.

3.2 Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca personnel and/or personnel at the study centre).

2. Previous enrolment or randomisation and received study treatment in the present study. Patients can, however, be re-screened if the reason for the screen failure no longer exists.

3. Known malignant central nervous system (CNS) disease other than neurologically stable, treated brain metastases – defined as metastasis having no evidence of progression or haemorrhage for at least 2 weeks after treatment (including brain radiotherapy). Must be off any systemic corticosteroids for the treatment of brain metastases for at least 14 days prior to enrolment.

4. Use of any anti-cancer treatment drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of AZD1775. For drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the prior treatment and administration of AZD1775 treatment is required.

5. No other anticancer-therapy (chemotherapy, immunotherapy, hormonal anti-cancer therapy, radiotherapy [except for palliative local radiotherapy]), biological therapy or other novel agent is to be permitted while patient is receiving study treatment.

Patients on LHRH analogue treatment for more than 6 months are allowed entry into the study and may continue at the discretion of the Investigator.

6. Previous radiation therapy completed ≤7 days prior to the start of study treatment (ie, first administration of cocktail [Part A Day -8]).

7. Major surgical procedures ≤28 days of beginning study treatment (ie, first administration of cocktail [Part A Day -8]), or minor surgical procedures ≤7 days. No waiting period required following port-a-cath placement or other central venous access placement.

8. Grade >1 toxicities from previous cancer therapy, according to the Common Terminology Criteria for Adverse Events [CTCAE]), excluding alopecia or anorexia.

9. Patient has an inability to swallow oral medications. Note: Patient may not have a percutaneous endoscopic gastrostomy tube or be receiving total parenteral nutrition.

10. Patients suffering from conditions which are likely to adversely affect gastrointestinal motility and/or transit (for example, diarrhoea, vomiting or nausea, gastroparesis, irritable bowel syndrome and malabsorption), or patients with gastrointestinal resection (eg, partial or total gastrectomy) likely to interfere with absorption of study treatment).

11. Patients who are not non-smokers or light smokers (no more than 5 cigarettes per day) and who cannot abstain from smoking from 2 weeks prior to first dose of cocktail until after the last PK sample collection in Part B.

12. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the start of treatment (ie, first administration of cocktail [Part A Day -8]).

13. Excessive intake of caffeine (more than 6 cups of coffee or equivalent per day) and/or consumption of any caffeine containing drinks or food, eg, coffee, tea, chocolate, caffeine-containing energy drinks (eg, Red Bull), or cola within 36 hours of administration of the cocktail on Day -8.

14. Patient has had prescription or non-prescription drugs or other products known to be sensitive to CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index which cannot be discontinued 2 weeks prior to the first administration of AZD1775 (Part A Day 1), or to be moderate to strong inhibitors/inducers of CYP3A4 which cannot be discontinued 2 weeks prior to beginning study treatment (ie, first administration of cocktail [Part A Day -8]) and withheld throughout the study until 2 weeks after the last administration of AZD1775. Co-administration of aprepitant or fosaprepitant during this study is prohibited (see Appendix H). Any patient taking an oral contraceptive must be discussed with the Medical Monitor to

ensure that there will be no interaction with the brand of oral contraceptive and cocktail of drugs prior to trial entry to confirm eligibility.

15. Patient has had prescription or non-prescription drugs or other products known to be moderate to strong inhibitors/inducers of CYP1A2 or CYP2C19 which cannot be discontinued 2 weeks prior to beginning study treatment (ie, first administration of cocktail [Part A Day -8]) and withheld through Day 4 of Part A (Appendix H).

16. Patient has had adjustments to prescription or non-prescription drugs or other products known to be mild inhibitors and/or inducers of CYP3A4 within 1 week prior to the first dose of the cocktail (Part A Day -8).

17. Herbal preparations taken within 7 days beginning study treatment (ie, first administration of cocktail [Part A Day -8]). However, in the case of St John's wort, patients cannot have taken this herbal preparation 21 days prior to first dose of cocktail (Part A Day -8). In the case of Angelica root (Bhai Zhi), patients cannot have taken this herbal preparation 2 weeks prior to beginning study treatment (ie, first administration of cocktail [Part A Day -8]).

18. Patients taking any concomitant medications that might affect QT/QTc intervals (see Appendix H).

19. Patients who have taken any proton pump inhibitors (omeprazole, lansoprazole, esomeprazole, pantoprazole, etc) within 7 days of beginning study treatment (ie, first administration of cocktail [Part A Day -8]). See all restricted medications in Section 7.7.2.

20. Patients who cannot withhold antacids for 6 hours or H2-antagonists (cimetidine, ranitidine, famotidine, nizatidine) for up to 96 hours at a time (24 hours prior to and following cocktail administration and 24 hours prior to and following AZD1775 administration). See prohibited medications in Section 7.7.2.

21. Patients who have received midazolam and/or omeprazole (or esomeprazole) within 14 days of beginning study treatment (ie, first administration of cocktail [Part A Day -8]).

22. Any known hypersensitivity or contraindication to the cocktail drugs (caffeine, omeprazole and midazolam) or AZD1775, or to the components thereof.

23. Any of the following cardio-vascular conditions currently or within the last 6 months:

    – Unstable angina pectoris.

    – Congestive heart failure ≥ Class 2 as defined by the New York Heart Association (see Appendix F).

- Acute myocardial infarction.
- Significant conduction abnormalities, eg, atrioventricular block II and III, sick sinus syndrome even if controlled with medication, as well as complete left bundle branch block (complete LBBB).
- Ventricular or supraventricular arrhythmias.
- Insufficiently controlled hypertension, ie, >160/100 mm Hg.
- Cardiac devices (pacemaker, implantable cardioverter defibrillator, cardiac resynchronisation therapy device, etc) that can affect the ST-T wave morphology and has a subsequent negative impact on the accuracy of the QTc measurement

24. Patients with centrally reviewed QT interval (specifically QTc calculated using the Fridericia formula) >450 ms [QTcF]) obtained from 3 dECGs 2 to 5 minutes apart at study entry, or congenital long QT syndrome.

25. AZD1775 should not be given to patients who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected. AZD1775 has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

26. Pregnant or lactating female patients.

27. Serious, symptomatic active infection at the time of study entry, or another serious underlying medical condition that would impair the ability of the patient to receive study treatment.

28. Presence of other active invasive cancers.

29. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

30. Active infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).

Any of the following is regarded as a criterion for exclusion from the optional pharmacogenetic part of the study:

31. Previous bone marrow transplant.

32. Non-leukocyte depleted whole blood product within 120 days of the genetic sample collection.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Subject enrolment and randomisation

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

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Assign the potential patient a unique enrolment number, beginning with 'E#'.

3. Determine patient eligibility. See Section 3.

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

3.4 Procedures for handling incorrectly enrolled or randomised subjects

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study treatment. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician or representative must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

This is an open-label, non-randomised study, therefore no randomisation of patients will take place.

3.6 Methods for ensuring blinding

The study is open-label, non-randomised; therefore, blinding procedures are not applicable.

3.7 Methods for unblinding

Not applicable.

3.8 Restrictions

1. Patients are required to fast from 2 hours before until 2 hours after the cocktail administration alone as well as each administration of AZD1775 alone or in combination with the cocktail. If patients have signs or symptoms of

hypoglycaemia, they may have glucose (sugar tablets and/or juice [except for grapefruit juices or juices containing grapefruit or Seville oranges]). The time and nature of any such glucose (sugar tablet/juice) consumed in Part A must be recorded in the electronic caser report form (eCRF). In Part A. water is restricted from 1 hour before until 1 hour after cocktail substrates administration, excluding the 240 mL water required to take the cocktail substrates and study treatment, as well as the water required to swallow the Kytril (granisetron). In Part B, water is restricted from 1 hour before until 1 hour after AZD1775 administration in the morning of Day 1 and of Day 3 and time-matched on Day -1, excluding the 240 mL water required to study treatment, as well as the water required to swallow the pre-treatment anti-emetic(s).

2. On days (in Part B) when dECG measurements are being taken, patients should be restricted to a low level of physical activity and should refrain from any activities likely to stimulate or excite them (eg, video games, stimulating movies or television shows, etc). Additionally, they should refrain from using hand-held electronic or electrical devices (eg, cell phones, hair dryers, etc) as these have a potential to interfere with dECG signals.

3. Patients are to abstain from taking caffeine-containing drinks or foods (eg, coffee, tea, cocoa, chocolate, caffeine-containing energy drinks and cola) during the study. During the wash out periods, patients are to avoid excessive intake of caffeine-containing drinks or food, eg, coffee, tea, chocolate, caffeine-containing energy drinks (eg, Red Bull), and cola (more than 3 cups of coffee or equivalent, per day).

   – Patients may not consume caffeine-containing drinks or foods as follows:

      - Part A (both treatment periods): from 36 hours prior to the day of administration of the cocktail through the last PK sample of each treatment period.

      - Part B: from Day -2 through the final serial dECG assessments in the morning of Day 4.

4. Patients are to refrain from intake of alcohol within the 48 hours prior to and during each treatment period and the EoS or EoT visit.

5. Patients are to refrain from smoking or the use of any other nicotine containing products from 2 weeks prior to the first dose of the cocktail until after the last PK sample collection in Part A and during each in-patient period in Part B.

6. Women of childbearing potential (WoCBP) may be included only if acceptable contraception is in place from the time of screening (or consent), for the duration of the study and for 1 month after the last dose of AZD1775. Any patient taking an oral contraceptive must be discussed with the Medical Monitor to ensure that there

will be no interaction with the brand of oral contraceptive and cocktail of drugs prior to trial entry to confirm eligibility.

- WoCBP defined as: Women between menarche and menopause who have not been permanently or surgically sterilised and are capable of procreation. Refer to Appendix E for more information.

7. All WoCBP must have a negative pregnancy test during screening and prior to starting each treatment period.

8. Males patients must agree to avoid procreative and unprotected sex (ie, use acceptable forms of contraception as described in Appendix E) and must not donate sperm during the study and for 3 months after the last administration of study treatment. Where the female partner is pregnant or not using effective birth control, men should avoid procreation while in the study and for 3 months after the last administration of AZD1775. Female partners, who are of childbearing potential, of men participating in clinical studies of AZD1775 will also be required to use acceptable contraceptive measures (detailed in Appendix E) while their partner is on AZD1775 and for 3 months thereafter.

9. Male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children.

10. Herbal preparations are not allowed throughout the study. These herbal preparations include but are not limited to: St. John's wort, kava, ephedra (ma hung), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto and ginseng, as well as any food and beverages that may contain them. Angelica root (Bhai Zhi) is not allowed through Part A, Day 4.

11. All patients must avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known inducer/inhibitory effects on CYP3A4. Any permitted medication known to be weak inducers/inhibitors of CYP3A4 should not be changed (adjusted or discontinued) within 1 week of commencement of treatment in Part A through collection of the last planned PK sample in Part B (Day 3, 24 hours) unless medically necessary. Exceptions are the H2-antagonists and antacids (see below). Any addition of medication known to be weak inducers or inhibitors of CYP3A4 should be avoided during the treatment period where possible.

12. H2-antagonists (cimetidine, ranitidine, famotidine, nizatidine, etc) must be withheld for up to 96 hours at a time (24 hours prior to and following cocktail administration and 24 hours prior to the first, through 24 hours following the last AZD1775 administration in each study part) and antacids must be withheld for at least 3 hours prior to and 3 hours after AZD1775 administration.

13. All patients must avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known inducer/inhibitory effects on CYP1A2 or CYP2C19. Any permitted medication known to be weak inducers/inhibitors of CYP1A2 or CYP2C19 should not be changed (adjusted or discontinued) within 2 weeks of commencement of treatment (Day -8, cocktail administration) in Part A through collection of the last planned PK sample in Part A (Day 4, 24 hours) unless medically necessary. Any addition of medication known to be weak inducers or inhibitors of CYP1A2 or CYP2C19 should be avoided during the treatment period where possible.

14. Midazolam and/or omeprazole (or esomeprazole) must be withheld from within 14 days of beginning study treatment (ie, first administration of cocktail [Part A Day 8]) through the last PK sample collected in Part A.

15. Patients are not to consume grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges from 7 days prior to AZD1775 administration until completion of sample collections in Part B.

For information on permitted and prohibited concomitant medication, see Section 7.7.

3.9 Discontinuation of investigational product

Study treatment must be discontinued in any of the following situations:

- Patient decision. The patient is at any time free to discontinue treatment.
- Any of the following AEs occur:
  - Diarrhoea (CTCAE grade ≥3): hospitalisation required for the inability to take liquids by mouth, and inability to control diarrhoea within 24 hours of using loperamide or other prescribed anti-diarrhoeal medications
  - Vomiting (CTCAE grade ≥3): hospitalisation required for the inability to take fluids orally and inability to control vomiting on an out-patient basis despite optimally prescribed anti-emetics
  - QT interval (following correction for heart rate) prolongation: >501 ms or a shift from baseline of 60 ms, following a single dose of AZD1775
  - Febrile neutropenia: absolute neutrophil count <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour
  - CTCAE grade 4 infection with an associated CTCAE grade 4 neutropenia

  - Thrombocytopenic haemorrhage (gross bleeding) with an associated CTCAE grade ≥3 (<50,000/μL) platelet count
  - Any CTCAE grade 3 non-haematologic toxicity that persists at a grade 3 for >7 days
  - Any CTCAE grade 4 non-haematologic toxicity that is not expected to be manageable/reversible with dose reduction

- Severe non-compliance with the study protocol.
- Worsened condition.

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, patients are free to discontinue study treatment or withdraw from the study (ie, study treatment and assessments – see Section 3.10). A patient who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by the Investigator. Adverse events will be followed up (see Section 6).

If a patient is withdrawn from the study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be initiated on treatment. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not patients initiated on treatment).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (study treatment and assessments). Patients may withdraw from any aspects of the optional genetic research (see Sections 3.1 and 5.6) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by the Investigator. Adverse events will be followed up (see Section 6.3.2).

3.11 Withdrawal from the study

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

Patients may be withdrawn from the study for the following reasons:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study.
- Risk to patients as judged by the Investigator and/or AstraZeneca or its representative.
- Non-compliance to protocol as judged by the Investigator and/or AstraZeneca or its representative.
- Incorrectly enrolled patients, ie, the patient does not meet the required inclusion/exclusion criteria for the study.
- The patient becomes pregnant.
- Patient lost to follow-up.

If a patient wishes to withdraw their consent to further participation in the study entirely, this should be clearly documented in the patient notes, eCRF and in the clinical study database

3.12 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant.
- Are assessed as causally related to study treatment.
- Are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan detailing the procedures

		PART A								PART B						End of Study	
		Treatment Period 1			Treatment Period 2					Treatment Period						EoT[a, c]	EoS[b, c]
Assessments	**Screening (D-28 to D-9)**	**D-9**	**D-8**	**D-7**	**D1**	**D2**	**D3**	**D4**		**D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D11 (-3)**	**30 (-7) Days post last dose of AZD1775**
In-house stay of approximately 14 hours/optional overnight stay[d]		X	X				X			X	X	X	X	X			
Washout period (7 to 14 days)				X					X								
Informed consent	X																
Demography	X																
Viral serology screen[e]	X																
Medical/surgical history	X	X								X							
Inclusion/exclusion[f, g]	X	X			X					X							
Physical examination[g]	X	X			X					X						X	X
ECOG performance status[g]	X	X			X					X						X	X
Vital signs[g, h]	X	X			X		X			X		X		X		X	X
Weight and height[i]	X	X								X							
Haematology[g, jk]	X	X			X					X						X	X

		PART A								PART B						End of Study	
		Treatment Period 1			Treatment Period 2					Treatment Period						EoT[a, c]	EoS[b, c]
Assessments	**Screening (D-28 to D-9)**	**D-9**	**D-8**	**D-7**	**D1**	**D2**	**D3**	**D4**		**D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D11 (-3)**	**30 (-7) Days post last dose of AZD1775**
Clinical chemistry[g, j]	X	X			X					X						X	X
Coagulation (PT or INR with PTT)[j]	X																
Pregnancy test (urine or serum)[k]	X	X			X					X						X	X
dECG for eligibility by central review	X									X						X	
Digital 12-Lead ECG[l]					X		X				X	X		X	X		
PK sample collection[m]			X	X			X	X				X		X	X		
Urine sample for 1β-hydroxy deoxycholic[n]			X				X					X		X			
Blood sample for Gx			X														
Cocktail substrates administration			X				X										
AZD1775 administration					X	X	X					X	X	X			
Anti-emetic premedication[o]			X		X	X	X				X	X	X	X			
Concomitant medication	←														→		X

		PART A								PART B						End of Study	
		Treatment Period 1			Treatment Period 2					Treatment Period						EoT[a, c]	EoS[b, c]
Assessments	**Screening (D-28 to D-9)**	**D-9**	**D-8**	**D-7**	**D1**	**D2**	**D3**	**D4**		**D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D11 (-3)**	**30 (-7) Days post last dose of AZD1775**
AEs	←														→		X
Involvement in CA study																X	
Non-involvement in CA study																	X

a EoT: End of Treatment visit: To occur within 3 days after a 4-day wash-out period relative to the last dose of AZD1775 in Part B. All patients are required to have an EoT visit. If the patient is interested in continuing into the CA study, the patient may be consented for the CA study at this time to allow for evaluation of eligibility to the CA study. If the patient meets the entry criteria for the CA study, then the EoT assessment can also be used as a screening visit for the CA study.

b EoS: End of Study visit: Only required for patients who are not interested in, or are deemed screen failures for the CA study. To take place within 30 days (-7 days) from the last dose of AZD1775.

c Patients who consent to participation in the CA study should have all EoT procedures per this study (including the following assessments: vital signs, physical examination, ECOG assessment, follow-up on open AEs/SAEs, follow-up on changes in concomitant medication and laboratory safety assessments), as well as the screening procedures per the CA study protocol. Please refer to the CA study protocol for additional requirements. Please note: patients not enrolling in the CA study are required to visit the study centre within 30 days of the last dose of AZD1775 for an EoS visit, where the above listed assessments will be done.

d Part A: Day -9 is an outpatient visit. On Days -8 and -3, patients will check in to the study centre in the morning to allow for administration of study medication and subsequent PK sampling for 12 hours. Patients may stay overnight on other nights preceding scheduled procedures on the morning of the following day.
Part B: patients will be required to stay overnight, either at the study centre or a nearby hotel or residence, the evenings of Day -2, Day -1 and Day 2, to ensure that conditions for the dECG assessments on Day 1 and Day 3 match those from Day -1. Patients may stay overnight on the other nights, but this is optional. However, if patients experience nausea or vomiting, or any other safety issues they are required to stay at the study centre.

e Hepatitis B DNA and Hepatitis C RNA if required to confirm active disease.

f On Day -9 and Day 1 of Part A and on Day -2 of Part B only inclusion/exclusion criteria relating to restrictions, as well as ECG and laboratory safety assessments, will be investigated.

g Must be completed prior to the first dose on Day -9 and Day 1 (of each part, ie anywhere between check-in on Day -1 to pre-dose of Day 1).

h Vital signs need to be performed at pre-dose and at 2 hours and 4 hours post-dose on Day 1 and Day 3.

i Weight and height will be collected at baseline on the following days: height will be assessed on Day -9 of Part A only. Weight will be assessed at Screening, at Day -9 of Part A (if screening values were obtained >7 days from Day -9) and on Day-2, Part B. Indoor clothing may be worn but shoes should be removed. For weight assessment, the same weighing scales should be used for each visit.

j Screening laboratory values must be obtained within 7 days of administration of the first cocktail substrates. If screening clinical laboratory assessments were performed within 7 days of dosing, it is not necessary to repeat them prior to the first dose of cocktail substrates. However, coagulation is only performed at screening (see Section 5.2.1) therefore there is no repeat on Day -9. Chemistry and haematology should be repeated on Day-1 if Screening laboratory values were obtained >7 days from first dose of the cocktail substrates.

k Negative pregnancy test results needs to be available prior to AZD1775 dose administration (this can be done anytime between check-in on Day -1 and dose administration on Day 1, both in Part A and Part B).

l Screening dECGs for Part A and all dECGs in Part B need to reviewed centrally. At simultaneously scheduled time points, the dECG assessment should be performed prior to the vital sign assessment. At times simultaneously scheduled with PK sample or other blood collections, dECG and vital assessments should be performed prior to the blood collection. In Part A, dECGs (and Vital signs) need to be performed at pre-dose and at 2 hours and 4 hours post-dose on Day 1 and Day 3. These dECGs will be digital and will be centrally reviewed. Part B: dECGs on Day -1 must be clock time matched to the dECGs collected on Day 1 and Day 3 and pre-dose dECGs must be collected after granisetron administration

m Please refer to Table 2 and Table 3 for a complete schedule of PK assessments.

n Part A urine samples to be taken pre-dose both on Day -8 and Day 3. Part B urine samples taken pre-dose Day 1 and Day 3.

o All patients must receive (Kytril) granisetron 1 mg orally 30 minutes prior to each dose of AZD1775. On Day -8 of Part A (30 minutes prior to cocktail drug administration) and Day -1 of Part B (time-matched to Day 1 of Part B) granisetron 1 mg orally will also be administered. In Part B of the study only, patients may receive Decadron (dexamethasone) along with granisetron if needed as long as consistent pre-treatment conditions are maintained (See Section 6.8.3).

AEs: Adverse events; CA study: continued access study (D6014C00007); dECG: digital electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoS: End of Study; EoT: End of Treatment; Gx: Pharmacogenetic research; INR: International normalised ratio; PK: pharmacokinetic; PT: prothrombin time; PTT: partial thromboplastin time; SAE: serious adverse event

Table 2 Part A: Schedule of PK assessments

Time relative to oral dose[a]	Day -8 (Period 1)	Day 3 (Period 2)	
	Cocktail drugs[b]	Cocktail drugs[b]	AZD1775
Pre-dose	X	X	X[c]
15 minutes	X	X	X
30 minutes	X	X	X
45 minutes	X	X	X
1 hour	X	X	X
2 hours	X	X	X
3 hours	X	X	X
4 hours	X	X	X
6 hours	X	X	X
8 hours	X	X	X
10 hours	X	X	X
12 hours	X	X	X
24 hours	X	X	X

a A -30-minute window will be allowed for samples taken pre-dose, a ±5-minute window will be allowed for samples taken up to and including 1 hour post-dose, a ±15-minute window for samples taken 2 to 12 hours (inclusive) post-dose and a ±1-hour window for samples taken at 24 hours post-dose.
b Midazolam, omeprazole and caffeine and metabolites (1'-hydroxy midazolam, 5-hydroxy omeprazole and paraxanthine).
c The pre-dose AZD1775 sample on Day 3 should be taken within 15 minutes of administration.
PK: Pharmacokinetics

Table 3 Part B: Schedule of PK and dECG assessments

Time relative to oral dose[a]	Day -2	Day -1	Day 1		Day 3	
	dECG	dECG[b]	PK	dECG[d]	PK	dECG[d]
Screening for eligibility	X					
Pre-dose		X[c]	X	X[c]	X	X[c]
15 minutes			X		X	
30 minutes		X	X	X	X	X
45 minutes			X		X	
1 hour		X	X	X	X	X
2 hours		X	X	X	X	X
3 hours		X	X	X	X	X
4 hours		X	X	X	X	X
6 hours		X	X	X	X	X
8 hours		X	X	X	X	X
10 hours			X		X	
12 hours		X	X	X	X	X
24 hours[e]		X		X	X	X

a A -30-minute window will be allowed for samples taken pre-dose on Day 1, a -15 minute window will be allowed for samples taken pre-dose on Day 3, a ±5-minute window will be allowed for samples taken up to and including 1 hour post-dose, a ±15-minute window for samples taken 2 to 12 hours (inclusive) post-dose and a ±1-hour window for samples taken at 24 hours post-dose.

b dECGs on Day -1 must be clock time matched to the dECGs collected on Day 1 and Day 3.

c Granisetron 1 mg should be given orally 30 minutes prior to administration of AZD1775 on Day 1 and Day 3, and time matched on Day -1. Patients may receive dexamethasone along with granisetron if needed as long as consistent pre-treatment conditions are maintained (see Section 6.8.3). dECGs on Day -1 must be clock time matched to the dECGs collected on Day 1 and Day 3 and pre-dose dECGs must be collected after granisetron administration.

d dECG assessments will be performed **prior** to the PK sample collection and should be collected as close to the scheduled times as possible. For dECG assessments scheduled for up to and including 6 hours, the Investigator should make an effort to schedule the dECG assessments within 10 minutes prior to the PK sample collection; for subsequent dECG assessment, a window of 30 minutes prior to PK collection (or less) is desired.

e If the 24-hour time point For Day -1 is the same as pre-dose Day 1, only one dECG assessment should be recorded and used as both the 24-hour and pre-dose time point.

dECG: Digital electrocardiogram; PK: pharmacokinetics

4.1 Screening/enrolment period

Written informed consent must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. All patients will be requested to provide consent for entry into this study.

Procedures will be performed according to the Study Plan (Table 1). At screening, consenting patients will be assessed to ensure that they meet eligibility criteria (Section 3.1 and 3.2). Patients who do not meet these criteria will not be enrolled in the study.

The study procedures carried out during this period include: physical examination, vital signs (blood pressure, pulse rate, body temperature), triplicate dECG, weight, height, demographics, prior and concomitant medication, medical/surgical history, blood samples for haematology, clinical chemistry and coagulation, virology screen, pregnancy test and ECOG performance status.

4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plan (Table 1) with exceptions of the PK and dECG specific requirements for the treatment periods listed in Table 2 and Table 3.

If a patient vomits or experience intense nausea within 3 hours post-dose in Part A, subsequent PK samples will not be taken. However, if this should happen in Part B, the PK samples along with dECGs will still be taken, even if the patient did not receive the full dose. Both PK and dECGs are still relevant and can potentially be used for modelling purposes. It is recommended to record vomiting or intense nausea in the patient eCRF, as these might impact the ECGs results.

4.3 Follow-up period

On completion of the study (ie, collection of 24-hour PK sample/dECG from Part B of study) patients will enter a 4-day washout period relative to the last dose of AZD1775. Within 3 days after the washout period, patients will be required to attend an EoT visit. Patients who complete this study will be asked about their interest to enrol into the open-label CA study (D6014C00007). .

- All patients are required to have an EoT visit. If the patient is interested in continuing into the CA study, the patient may be consented for the CA study at this time to allow for evaluation of eligibility for the CA study. If the patient meets entry criteria for the CA study, then EoT assessment can also be used for the Screening visit of the CA study. Please see the CA study protocol for required screening assessments and the time limit for the screening period.

- The EoS visit is only required for patients who are not interested in, or are deemed a screen failure for the CA study. The EoS visit is to take place within 30 days (-7 days) of the last administration of study treatment. Patients who enrol in the CA study are not required to complete the EoS visit.

Descriptions of the procedures for this period are included in the Study Plan (Table 1).

5. STUDY ASSESSMENTS

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

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

5.1 Efficacy assessments (Not applicable)

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood samples for determination of clinical chemistry, haematology, coagulation (only at baseline) and PK will be taken at the times indicated in the Study Plan (Table 1) and the schedule of PK and dECG assessments (Table 2 and Table 3).

The laboratory variables (listed in Table 4) will be measured.

Additional safety samples may be collected if clinically indicated and at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry and haematology analysis will be performed at an accredited laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the study centre.

Pre-menopausal WoCBP must have a negative urine or serum pregnancy test during screening, and a confirmatory test prior to each treatment period in Part A and on Day -2 of Part B. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately. Laboratory tests will be performed by an accredited laboratory. If results are positive, the patient is ineligible and must be discontinued from the study.

Table 4 Laboratory Safety Variables

Haematology (±3 mL whole blood sample)	Clinical chemistry (±3 mL serum or plasma sample)
B-Haemoglobin	S/P-Albumin
B-Leukocyte	S/P-Alanine transaminase
B-Haematocrit	S/P-Aspartate transaminase
B-Red blood cell count	S/P-Alkaline phosphatase
B-Absolute or percentage leukocyte counts	S/P-Bilirubin, total
Neutrophils	S/P-Calcium, total
Lymphocytes	S/P-Creatinine
Monocytes	S/P-Glucose
Basophils	S/P-Total protein
Eosinophils	S/P-Chloride
B-Platelet count	S/P-Magnesium
Coagulation (±2 mL sample)[a]	S/P-Potassium
B-PT or INR with PTT	S/P-Sodium
Pregnancy test	S/P-Urea nitrogen or blood urea nitrogen
Blood or urine	
Viral serology screen (±2 mL sample)	
Hepatitis B and C[b]	

a Coagulation performed at screening only (PT or INR with PTT). Patients requiring therapeutic warfarin or coumarin derivative anticoagulant will be monitored as per institutional guidelines
b Hepatitis B DNA and Hepatitis C RNA if required to confirm active disease
B: Blood; INR: international normalised ratio; P: plasma; PT: prothrombin time; PTT: partial thromboplastin time; S: serum

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

Please note. In case a patient shows an AST **or** ALT ≥3 x ULN (upper limit of normal) **and** total bilirubin ≥2 x ULN please refer to Appendix D 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

5.2.2 Physical examination

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

If new or aggravated physical findings imply deterioration compared with baseline, the finding should be reported as an AE (Section 6.3.6). Performance status will be assessed using the ECOG Performance Status criteria (see Appendix G).

5.2.3 Vital signs

Vital signs will be measured at the times specified in the Study Plan (Table 1) and recorded in the eCRF. However, the Investigator reserves the right to add additional assessments if there are any abnormal findings or for any other reason the Investigator feels meets this requirement.

Deterioration as compared with baseline in protocol-mandated vital signs should only be reported as AEs if they fulfil any of the serious adverse event (SAE) criteria or are the reason for discontinuation of treatment with the study treatment, or the Investigator insists the abnormality should be reported as an AE (see Section 6.3.6).

5.2.3.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size after the patient has been at rest for 10 minutes.

5.2.3.2 Body temperature

Body temperature will be measured using a semi-automatic body temperature recording device in accordance with local practice at the times specified in the Study Plan (Table 1).

5.2.4 Weight and height

Weight and height will be collected at baseline on the following days: height will be assessed on Day -9 of Part A only. Weight will be assessed at Screening, at Day -9 of Part A (if screening values were obtained >7 days from Day -9) and on Day -2, Part B. Indoor clothing may be worn but shoes should be removed. For weight assessment, the same weighing scales should be used for each visit.

5.2.5 Digital ECG

Digital ECGs will be collected to determine eligibility to participate in Part A and Part B of the study at screening and on Day -2 of Part B, respectively, as specified in the Study Plan (Table 1). The dECGs will be recorded using ECG equipment provided to the study centres by the central ECG laboratory and sent to the central ECG laboratory for review and interpretation. dECG assessments will be performed prior to the PK sample collection and should be collected as close to the scheduled times as possible. For dECG assessments

scheduled for up to and including 6 hours, the Investigator should make an effort to schedule the dECG assessments within 10 minutes prior to the PK sample collection; for subsequent dECG assessment, a window of 30 minutes prior to PK collection (or less) is desired.

At the time points indicated in the Study Plan (Table 1) and Table 3, triplicate dECG recordings should be taken within an approximate 5-minute period. The patients will rest for at least 10 minutes before the start of each dECG recording time point and they must be in the same supine body position (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) at each recording time point during all visits. Additional safety dECGs may be taken at any other time the Principal Investigator deems necessary for safety during the administration period.

In Part A, dECGs need to be performed at pre-dose and at 2 hours and 4 hours post-dose on Day 1 and Day 3. These ECGs will be digital and will be centrally reviewed.

All dECG recordings should be transferred to the central ECG laboratory for analysis and interpretation according to the standard procedures of the central ECG laboratory (see Section 5.5). Two ECGs will be printed for each time point, one for the Investigator evaluation and one as back-up for the central ECG laboratory, if the digital transfer fails.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. The paper copy of each dECG reading will be retained with the patient's completed source documents. Only overall evaluation (normal/abnormal) will be recorded in the eCRF. If there is a clinically significant abnormal unscheduled dECG finding during the treatment period, this should be recorded on the AE eCRF, according to standard AE collection and reporting processes (see Section 6.3.6).

Attention should be paid to any detected increases in QTc interval (see Section 6.8.1 for details).

5.3 Other assessments (Not applicable)

5.4 Pharmacokinetics

5.4.1 Collection of samples

Part A:

Venous blood samples (5 mL to 7 mL per time point), for determination of concentrations of AZD1775, cocktail drugs (midazolam, omeprazole, and caffeine), and cocktail metabolites (1'-hydroxy-midazolam, 5-hydroxy-omeprazole, and paraxanthine) in plasma, will be taken at the time points presented in the Study Plan (Table 1) and schedule of PK assessments (Table 2). It is essential that the actual time and date of collection of each blood sample (whether collected as per protocol or not) will be recorded in the eCRF. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

A -30-minute window will be allowed for all cocktail drug samples taken pre-dose on Day -8, and Day 3 (Part A). AZD1775 samples scheduled at pre-dose on Day 3 should be taken within 15 minutes prior to scheduled dose. A ±5-minute window will be allowed for samples taken up to and including 1 hour post-dose, a ±15-minute window will be allowed for samples taken 2 to 12 hours (inclusive) post-dose and a ±1-hour window will be allowed for samples taken at 24 hours post-dose.

Urine samples (approximately 10 mL) for determination of concentrations of 1β-hydroxy deoxycholic acid in urine will be taken from the total urine sample provided at the scheduled collection times, as presented in the Study Plan (Table 1). The collection time for each urine spot sample will be recorded. The date and time of collection of each sample will be recorded in the eCRF. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Part B:

Venous blood samples (1 mL) for determination of concentrations of AZD1775 in plasma will be taken at the time points presented in the Study Plan (Table 1) and schedule of PK and dECG assessments (Table 3). The actual time and date of collection of each blood sample (whether collected as per protocol or not) is recorded in the eCRF. Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual.

Pharmacokinetic samples will be collected after the time-matched dECG samples, with the PK samples to be collected on time. The conventions for sampling described for Part A will apply.

A -30 minute window will be allowed for samples taken pre-dose on Day 1, a ±15-minute window will be allowed for samples taken pre-dose on Day 3, a ±5-minute window will be allowed for samples taken up to and including 1 hour post-dose, a ±15-minute window for samples taken 2 to 12 hours (inclusive) post dose and a ±1-hour window for samples taken at 24 hours post-dose.

Urine samples (approximately 10 mL) for determination of concentrations of 1β-hydroxy deoxycholic acid in urine will be taken from the total urine sample provided at the scheduled collection times, as presented in the Study Plan (Table 1). The collection time for each urine spot sample will be recorded. The date and time of collection of each sample will be recorded in the eCRF. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual

5.4.2 Determination of drug concentration

Samples for determination of AZD1775, cocktail drugs (midazolam, omeprazole, and caffeine), and cocktail metabolites (1'-hydroxy-midazolam, 5-hydroxy-omeprazole, and paraxanthine) in plasma will be analysed by a third party on behalf of AstraZeneca R&D, using appropriate bioanalytical methods. Full details of the bioanalytical methods used will

be described in a separate Bioanalytical Report. All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analysed.

Samples for determination of 1β-hydroxy-deoxycholic acid in urine will be stored in the AstraZeneca BioBank for future analysis. Results of this analysis will not be reported in the CSR.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic plasma 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 plasma 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.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will be reported in a Bioanalytical Report.

Any residual back-up PK samples will be disposed of at the end of the study once the CSR is finalised (see details in the Laboratory Manual).

5.5 Pharmacodynamics

5.5.1 Collection of dECG endpoints

Digital ECGs will be collected in Part B on Day -2 (for eligibility by central review), Day -1, Day 1, and Day 3 (for PD evaluations) at the time points indicated in the Schedule of PK and dECG assessments (Part B) (Table 3).

The dECGs will be recorded and sent to the central ECG laboratory for review and interpretation, using the central ECG laboratory's standard operating procedures. The methodology used is the Manual Adjudication: 3 Beat on Lead II.

The following dECG intervals will be reported: heart rate, RR, PR, QRS, QTcF, QTcB, QTcF and QT.

5.5.2 Digital 12-lead ECG (dECG)

A central ECG laboratory will provide support in conducting the dECG collection, analysis and interpretation in the study, by providing digital 12-lead ECG equipment to the study centres to collect 12-lead dECG data.

At the time points indicated in the schedule of PK and dECG assessments (Table 3), digital 12-lead dECGs will be recorded and sent to the central ECG laboratory, according to the central ECG laboratory's standard procedures for settings, recording, and transmission of

dECGs. The dECG assessments must be performed **prior** to the PK sample collection and should occur as close to the scheduled times as possible. For the dECG assessments scheduled for up to and including 6 hours, the Principal Investigator should make an effort to schedule the dECG assessments within 10 minutes prior to the PK sample collection; for subsequent dECG assessment, a window of 30 minutes prior to PK collection (or less) is desired.

Digital ECGs on Day -1 should be clock time matched to the dECGs collected on Day 1 and Day 3.

5.6 Genetics

Additional written consent is mandatory for those patients who agree to participate in the pharmacogenetic (Gx) research components of the study. The results of this Gx research will be reported separately and will not form part of the CSR for this study.

5.6.1 Collection of genetic samples

The blood sample (9 to 10 mL) for Gx research will be obtained from the patients at any time during the study, but preferably prior to AZD1775 administration. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at screening it may be taken at any visit until the last study visit. Samples collected after the start of treatment should reflect the differences as a potential source of bias if AZD1775 has any potential effect on patient DNA. Only one sample should be collected per patient for genetics during the study.

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

5.6.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported separately in a scientific report or publication.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory personnel working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access within the relevant sample tracking system. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

5.7 Biomarker analysis (Not applicable)

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

6.2 Definitions of serious adverse event

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

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is 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 A of the CSP.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from time of signature of informed consent, throughout the treatment period. For patients who do not enrol into the open-label CA study, AEs will be followed and recorded up to and including the follow-up period (EoS visit). For patients who enrol in the open-label CA study, AEs will be collected up through the EoT visit, ie, up to commencement of AZD1775 dosing in the open-label CA study.

Serious adverse events will be recorded from the time of informed consent through the same period as above.

6.3.2 Follow-up of unresolved adverse events

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

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

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim).
- The date and time when the AE started and stopped.
- CTCAE grade and changes in grade during the course of the AE.
- Whether the AE is serious or not.
- Investigator causality rating against the study treatment (yes or no).
- Action taken with regard to study treatment.
- AE caused patient's withdrawal from study (yes or no).
- Outcome.

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

- Date AE met criteria for serious AE.
- Date Investigator became aware of serious AE.
- AE is serious due to [reason].
- Date of hospitalisation.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment in relation to other medication.
- Causality assessment in relation to module-specific combination treatments.
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. 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 unless it meets the criteria shown in Section 6.2. 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 when it satisfies the criteria shown in Section 6.2.

The grading scales found in the current National Cancer Institute CTCAE version 4.03 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).

6.3.4 Causality collection

The Investigator will assess causal relationship between the study treatment 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 study treatment?’

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

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

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately, these do not include metastases of the original cancer.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and dECG should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of the study treatment unless clearly due to the progression of disease under study (see Section 6.3.8).

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

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

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

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.

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study treatment is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE.

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.3.9 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least 1 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.

6.3.10 Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of study treatment, must 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 eCRF 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 by entering into the WBDC system as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.

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

6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then the Investigators or other study centre personnel will inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

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

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

6.5 Overdose

A dose of AZD1775 in excess of that specified according to the protocol will constitute an overdose. There is currently no known antidote to AZD1775, and the treatment of overdose should be supportive for the underlying symptoms. To date, there has been one patient who has experienced an overdose with AZD1775 which was associated with adverse events.

Overdoses with non-AZ products used in combination or comparative studies should be managed according to the product label.

Such overdoses should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study treatment occurs in the course of the study, then the Investigator or other study centre personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of any pregnancy should be reported to the appropriate AstraZeneca representative.

6.6.1 Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then the Investigator or other study centre personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

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 if possible be followed up and documented. To capture information about a pregnancy from the partner of a male patient, the male patient's partner's consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. The outcome of any conception occurring should be followed up and documented.

6.7 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study centre personnel or patient.

Medication error includes situations where an error:

- Occurred.
- Was identified and intercepted before the patient received the drug.
- Did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient.
- Drug not administered as indicated, for example, wrong route or wrong site of administration.
- Drug not taken as indicated eg, capsule dissolved in water when it should be taken as a solid capsule.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong patient received the medication (excluding Interactive Voice Response System [IVRS]/ Interactive Web Response System [IWRS] errors).
- Wrong drug administered to patient (excluding IVRS/IWRS errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error.
- Patient accidentally missed drug dose(s) eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Patient failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product.

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If an medication error occurs in the course of the study, then the Investigator or other study centre personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.8 Management of study treatment related toxicities

6.8.1 ECG abnormalities

If a patient has a centrally read or confirmed by cardiologist value (based on the average of the triplicate dECG) with a prolonged QTc interval ≥500 ms (absolute value) or ≥60 ms and over 480 ms from baseline, discontinue AZD1775 therapy and seek cardiologist advice. If the QTc interval is above ≥480 ms and below <500 ms, increase monitoring to confirm the QTc interval prolongation until recovery.

If the patient is taking part in Part A (DDI) of the study, this will result in monitoring the patient with cardiac telemetry/bedside cardiac monitoring for at least 24-hours, and collection of triplicate dECGs every 2 to 3 hours, keeping the potassium level >4 mmol, and avoiding any medication with potential QT prolonging impact.

If the patient is taking part in Part B (ECG), the patient needs to be monitored with telemetry/bedside cardiac monitoring and the dECGs are to be monitored on Day 2, in addition to the planned Days 1 and 3 as per Section 5.2.5. If the patient's QTc interval has recovered to Grade 1 (below 480 ms) by the time of the next dose, the patient can be re-dosed and continue with study participation. If the patient's QTc interval has not recovered to Grade 1, the patient should discontinue AZD1775 therapy.

6.8.2 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 (Imodium) 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. The maximum dose should not exceed 16 mg in any 24-hour period.

Patients should be instructed to notify the Investigator or study centre personnel 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 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.

6.8.3 Nausea and vomiting (anti-emetic prophylaxis)

All patients must receive (Kytril) granisetron 1 mg orally 30 minutes prior to each dose of AZD1775. Doses of the anti-emetics can be repeated orally q 8 hours prn. In addition, in Part B of the study only, dexamethasone 4 mg orally/IV may be given with each AZD1775 dose (ie, along with granisetron 30 minutes prior to each dose), unless contraindicated or not well-tolerated. Dexamethasone may also be used bid prn and/or given prior to each AZD1775 along with granisetron, if needed, potentially at a lower dose. However, if dexamethasone 4 mg orally/IV is given along with granisetron as pre-treatment anti-emetic medication it is critical that consistent pre-treatment conditions are maintained in the mornings prior to all serial dECG collections, ie, in the morning of Day -1, Day 1, and Day 3. Specifically, if patients are scheduled to receive dexamethasone along with granisetron in the morning of Day 1, they must also receive dexamethasone time-matched at the same dose in the morning of Day -1 and in the morning of Day 3. However, if a patient is not scheduled to receive dexamethasone in the morning of Day 1, the patient should not have received dexamethasone on Day -1 and may not receive dexamethasone as pre-treatment in the morning of Day 3.

Ativan (lorazepam), Phenergan (promethazine), Compazine (prochlorperazine), and benzodiazepine may be used as additional adjunctive treatments during AZD1775 therapy – please see list of restricted medication in Appendix H.

Patients should be strongly encouraged to maintain liberal oral fluid intake.

Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known drug-drug interactions.

6.8.4 Febrile neutropenia

Patients experiencing febrile neutropenia with significant symptoms should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Patients with febrile neutropenia without symptoms should be managed according to standard guidelines.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply AZD1775, midazolam, and omeprazole to study centres. Caffeine will be locally sourced. The same product (ie, same manufacturer, and, if possible lot number) will be used in both treatment periods for a given patient.

Investigational product	Dosage form and strength	Manufacturer
AZD1775 printed capsules	225 mg (3 x 75 mg capsules)	AstraZeneca

7.2 Dose and treatment regimens

Part A:

On Day -9 patients will be admitted to the study centre and may remain resident overnight. On the morning of Day -8, patients should be administered Kytril (granisetron) 1 mg orally 30 minutes prior to administration of the cocktail with a small amount of water. The date and time of granisetron administration will be documented in the eCRF. The cocktail (caffeine [1 x 200 mg tablet], omeprazole [1 x 20 mg capsule] and midazolam [1 mL of 2 mg/mL syrup formulation]) will be administered with 240 mL of water. The interval in which all 3 drugs are administered and ingested should be within 5 minutes. The midazolam syrup should not be held in the mouth but swallowed directly. The date and time of administration for each of the 3 drugs will be recorded in the eCRF. Granisetron administrations on Days 1 and 2 will be reported under concomitant medications, as appropriate.

On Day 1, sufficient supplies of AZD1775 will be dispensed to allow for 2 days of administration. The first dose in the morning of Day 1 and the final dose in the morning of Day 3 will be administered in the study centre. All other doses of AZD1775 and granisetron may be self-administered on an outpatient basis. The exact date and time of each dose administration will be recorded in the eCRF. Each patient will self-administer 225 mg (3 x 75 mg capsules) AZD1775 orally bid in approximately 12-hour intervals on Days 1 and 2 (the Day 1 morning dose may be taken in the study centre) over 2 days (Days 1 to 2). Patients should be administered Kytril (granisetron) 1 mg orally 30 minutes prior to administration each dose of AZD1775. Each AZD1775 dose should be taken with an adequate amount of water (ideally 240 mL) approximately 12 hours apart. If one of the 2 daily doses is missed, the dose should be taken as soon as possible, but not more than 6 hours after the missed dose. If the window is greater than 6 hours, the missed dose should be skipped and the next dose should be taken when scheduled.

Ativan, Phenergan and Compazine may be used prn for nausea/vomiting – please see list of restricted medication in Appendix H. However, if vomiting occurs after AZD1775 dosing, the dose should not be re-administered. Patients will be issued with a diary in which they must record the exact date and time the AZD1775 dose was taken, whether any food was consumed within 2 hours prior and 2 hours following AZD1775 administration, as well as any instances of vomiting.

If a patient misses more than 1 dose of AZD1775 on Day 1 or misses a dose of AZD1775 on Day 2, the patient will not receive treatment on Day 3 and no PK samples will be collected. Similarly, if the patient vomits within 3 hours following both AZD1775 doses on Day 1 and/or within 3 hours following one of the AZD1775 doses on Day 2, the patient will not receive treatment on Day 3 and no PK samples will be collected.

Patients will return to the study centre in the morning on Day 3. The final dose in the morning of Day 3 will be administered in the study centre. The visit should be scheduled such that the interval between the evening dose on Day 2 and the final morning dose will be as close to 12 hours as possible; the dosing interval must not be more than 18 hours. Patients will receive their final 225 mg dose of AZD1775 followed by the cocktail (caffeine [1 x 200 mg tablet], omeprazole [1 x 20 mg capsule] and midazolam [1 mL of 2 mg/mL syrup formulation]) with a combined amount of 240 mL of water. Patients should be administered Kytril (granisetron) 1 mg orally 30 minutes prior to administration of the AZD1775 capsules with a small amount of water. The date and time of granisetron administration will be documented in the eCRF. Administration of the cocktail should follow immediately after ingestion of AZD1775. The interval in which all 4 drugs are administered and ingested should be within 5 minutes. The midazolam syrup should not be held in the mouth but swallowed directly. The date and time of administration for AZD1775 and each of the 3 drugs will be recorded in the eCRF.

Patients should take all doses of cocktail drugs and/or AZD1775 after a fast of at least 2 hours. No food should be allowed for at least 2 hours post-dose. On Day -8 and the morning of Day 3, water is restricted from 1 hour before until 1 hour after cocktail substrates administration, excluding the 240 mL water required to take the cocktail substrates and study treatment, as well as the water required to swallow the Kytril (granisetron). Any changes from dosing schedule should be recorded in the eCRF. In case a patient vomits during any given treatment in both study parts (Day -8 Part A, Days 1 through 3), both the date and time of vomiting must be documented in the eCRF.

Part B:

On Day -1, each patient should be administered Kytril (granisetron) 1 mg orally with a small amount of water. Administration should be time-matched to the clock time for granisetron administration on Day 1 which is scheduled for 30 minutes prior to time of AZD1775 administration. Granisetron should be taken with a small amount of water. The date and time of granisetron administration will be documented in the eCRF. The date/time of dexamethasone administration (if applicable) will also be documented in the eCRF.

Each patient will receive 225 mg (3 x 75 mg capsules) AZD1775 orally bid in approximately 12-hour intervals over 2.5 days (Days 1 to 3). Patients should be administered Kytril (granisetron) 1 mg orally with a small amount of water 30 minutes prior to administration of each dose of AZD1775. Decadron (dexamethasone) 4 mg orally/IV may be given along with granisetron 30 minutes prior to the AZD1775 morning dose on Day 1 and may be continued to be used bid prn and/or given prior to each AZD1775 dose along with granisetron, if needed, potentially at a lower dose. If dexamethasone is given along with granisetron is it critical that consistent pre-treatment conditions are maintained in the mornings prior to all serial ECG collections (Day -1, Day 1, and Day 3; see Section 6.8.3).

The first dose in the morning of Day 1 and the final dose in the morning of Day 3 will be administered in the study centre. All other doses of AZD1775 and granisetron (and dexamethasone, if applicable) may be self-administered on an outpatient basis. The exact date and time of each dose administration will be recorded in the eCRF. The exact date and time

of granisetron (and dexamethasone, as appropriate) dose administrations prior to the morning dose on Days 1 and 3 will be recorded in the eCRF. Granisetron/dexamethasone administrations on other occasions will be reported under concomitant medication.

Patients should take the AZD1775 capsules after a fast of at least 2 hours and no food should be allowed for at least 2 hours post-dose. On the mornings of Day 1, Day 3 (and time-match on Day -1), water is restricted from 1 hour before until 1 hour after AZD1775 excluding the 240 mL water required to take the study treatment, as well as the water required to swallow the Kytril (granisetron). At all other times water can be allowed as desired. Doses should be taken approximately 12 hours apart. The AZD1775 capsules should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided, while the patient is in an upright position. If one of the 2 daily doses is missed, the dose should be taken as soon as possible, but not more than 6 hours after the missed dose. If the window is greater than 6 hours, the missed dose should be skipped and the next dose should be taken when scheduled.

Ativan, Phenergan and Compazine may be used prn for nausea/vomiting – please see list of restricted medication in Appendix H. However, if vomiting occurs after AZD1775 dosing, the dose should not be re-administered. Patients will be issued with a diary in which they must record the exact date and time the AZD1775 dose was taken, whether any food was consumed within 2 hours prior and 2 hours following AZD1775 administration, as well as any instances of vomiting.

Any changes from the dosing schedule should be recorded in the eCRF. In case a patient vomits during any given treatment (Days 1 through 3), both the date and time of vomiting must be documented in the eCRF.

7.3 Labelling

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. Specific dosing instructions will not be included on the label.

7.4 Storage

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

7.5 Compliance

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

Compliance will be assured by supervised administration of study treatment by the Investigator or his/her delegate. Date and time of the dose will be recorded in the eCRF.

7.6 Accountability

The study treatment provided for this study will be used only as directed in the CSP.

The study centre personnel will account for all study treatment dispensed to the patient. A diary recording dose of AZD1775 and granisetron taken and time and date needs to be given to patients who go home in between days on treatment.

Study centre personnel, if applicable, or the AstraZeneca monitor will account for all study treatment received at the study centre, unused study treatment and for appropriate destruction. Certificates of delivery and destruction should be signed.

7.7 Concomitant and other treatments

7.7.1 Permitted concomitant medications

Formal drug-drug interaction studies have not been performed with AZD1775. All medications received within 14 days before the first dose of study treatment, given concurrently with study treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications must be recorded in the appropriate sections of the eCRF.

Premedication with anti-emetics is mandated. All patients must receive Kytril (granisetron) 1 mg orally bid 30 minutes prior to each dose of AZD1775. In addition, dexamethasone 4 mg orally may be given with each AZD1775 dose unless contraindicated or not well-tolerated, but only in Part B of the study. Ativan (lorazepam), Phenergan (promethazine), Compazine (prochlorperazine), and benzodiazepine (Part B only) may be used as additional anti-emetics if needed. The selected anti-emetic should also be administered under reference conditions (ie, Part A: Day -8 of Period 1; Part B: Day -1 at time-matched dosing time) to avoid a potential bias in treatment effect – please see list of restricted medication in Appendix H.

Please note: Emend **(**aprepitant) and fosaprepitant are not permitted due to known drug-drug interactions.

Certain medications (other than those that are prohibited in this protocol) may continue to be prescribed for co-morbidities or for new conditions that are diagnosed following the start of the study treatment, including but not limited to the following:

- Bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors (eg, denosumab).
- Patients requiring therapeutic warfarin or coumarin-derivative anticoagulants will be monitored with International Normalised Ratio (INR) and Prothrombin Time as clinically indicated.
- Low molecular weight heparin, rivaroxaban or equivalent anticoagulant therapy is permitted where clinically indicated.

- Any permitted medication known be a weak inducer/inhibitor of CYP3A4 should not be changed (adjusted or discontinued) within 1 week of commencement of treatment through collection of the last planned PK sample in Part B (Day 3, 24-hours) unless medically necessary. Exceptions are the H2-antagonists (cimetidine, ranitidine, famotidine, nizatidine, etc) which must be withheld for up to 96 hours at a time (24 hours prior to and following cocktail administration and 24 hours prior to the first, through 24 hours following the last AZD1775 administration in each study part) and antacids, which must be withheld for at least 3 hours prior to and 3 hours after AZD1775 administration.
- Any permitted medication known be a weak inducer/inhibitor of CYP1A2 or CYP2C19 should not be changed (adjusted or discontinued) within 2 weeks of commencement of treatment through collection of the last planned PK sample in Part A (Day 3, 24-hours) unless medically necessary.
- Any addition of medication known to be weak inducers or inhibitors of CYP3A4, CYP1A2, or CYP2C19 should be avoided during the study where possible.

7.7.2 Prohibited/restricted concomitant medication

The following treatments and the medications listed in Appendix H are prohibited or should be used with caution while in this study. Any further questions regarding concomitant treatments should be referred to the Medical Monitor.

Prohibited Medication/Class of Drug:	Usage:
Other investigational therapy Anticancer agents other than the study medications	If such agents are required for a patient, then the patient must first be withdrawn from the study
Drugs known to be moderate to strong inhibitors/inducers of CYP3A4 or sensitive CYP3A4 substrates or substrates of CYP3A4 with narrow therapeutic window. Such drugs include (but are not limited to): • Strong or moderate inhibitors of CYP3A4 include, but are not limited to, azole antifungals (ketoconazole, voriconazole and itraconazole), macrolide antibiotics (clarithromycin, erythromycin), calcium channel blockers (diltiazem, verapamil) and human immunodeficiency virus protease inhibitors (indinavir, nelfinavir and ritonavir) and nefazodone • Inducers of CYP3A4 include, but are not limited to, phenytoin, barbiturates and rifampicin • Substrates of CYP3A4 include, but are not limited to, statins (atorvastatin, lovastatin, simvastatin), midazolam, terfenadine, astemizole, cisapride and calcium channel blockers (felodipine, nisoldipine)	Prohibited within 2 weeks of first dose of cocktail drugs (Part A) through 2 weeks after the last dose AZD1775 in Part B
Drugs known to be moderate to strong inhibitors/inducers of CYP1A2. Any patient taking an oral contraceptive must be discussed with the Medical Monitor to ensure that there will be no interaction with the brand of oral contraceptive and cocktail of drugs prior to trial entry to confirm eligibility. For a list of drugs see Appendix H	Prohibited within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A
Drugs known to be moderate to strong inhibitors/inducers of CYP2C19. For a list of drugs see Appendix H	Prohibited within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A
Medication with a known risk of Torsades de Pointes (QT prolongation). For a list of drugs see Appendix H	Prohibited
Concomitant administration of proton pump inhibitors (omeprazole, lansoprazole, esomeprazole, panoprazole, etc)	Prohibited

Prohibited Medication/Class of Drug:	Usage:
H2-antagonists (cimetidine, ranitidine, famotidine, nizatidine)	Must be withheld for at least 24 hours prior to and following cocktail administration and 24 hours prior to and following AZD1775 administration.
Antacids	Must be withheld for at least 3 hours prior to and 3 hours following AZD1775 administration
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	Concomitant treatment with aprepitant and fosaprepitant is not allowable per protocol
Recent in vitro transporter studies have shown AZD1775 to be an inhibitor of the breast cancer resistance protein (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	The use of rosuvastatin is therefore prohibited in the current study
Herbal preparations including, but not limited to containing: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng	Herbal preparations are not allowed throughout the study (Angelica root [Bhai Zhi] throughout Part A, Day 4). Patients should stop using these herbal preparations 7 days prior to beginning study treatment (ie, first administration of cocktail [Part A Day -8]) with the exception of St John's wort which must be stopped 21 days prior to the first dose of AZD1775 and Angelica root which must be stopped 2 weeks prior to Day -8.
Metformin	Use of metformin is prohibited in this study as recent in vitro transporter data have shown AZD1775 is an inhibitor of MATE1 and MATE2K
Midazolam and/or omeprazole (or esomeprazole)	Prohibited from within 14 days of beginning study treatment (ie, first administration of cocktail [Part A Day -8]) through the last PK sample collected in Part A

Restricted Medication/Class of Drug:	Usage:
In vitro data suggests 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 a narrow therapeutic range
In vitro studies have shown that AZD1775 may be a substrate and inhibitor for human P glycoprotein (P-gp)	Caution should 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	Drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug. The exception to this restriction is rosuvastatin (discussed under prohibited medications) since modelling has predicted a substantial increase in the exposure of rosuvastatin when co-administered with AZD1775
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	Physicians should be vigilant when using substrates of CYP1A2 with a narrow therapeutic range

7.7.3 Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.8 Post study access to study treatment

Patients who have completed this study may continue to receive AZD1775 as a single agent in a CA study (D6014C00007), after a 4-day washout period, if they meet the inclusion/exclusion criteria and if in the opinion of their treating physician they could derive clinical benefit from continued treatment. Patients who discontinue early from this study will be considered by the Sponsor and treating physician on a case-by-case basis for enrolment into the CA study.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

Statistical analyses will be performed by QuintilesIMS using SAS® and, where appropriate, additional AstraZeneca approved and validated software. All code and datasets produced for this study should be compatible with version 9.4. A comprehensive Statistical Analysis Plan

(SAP) will be prepared by the QuintilesIMS biostatistician prior to first patient enrolment and any subsequent amendments will be documented, with final amendments completed prior to database lock.

8.2 Sample size estimate

No formal sample size estimation has been conducted. The number of patients is based on the careful clinical consideration to gain adequate information on the primary endpoints while exposing as few patients as possible to study procedures. The study has been sized to provide an estimate of the difference between the PK parameters of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole), and CYP3A (midazolam) in the presence and absence of AZD1775. Based on an estimate of within-patient standard deviation (SD) of 0.294 and assuming a true interaction effect of 100%, 20 evaluable patients would provide 80% power to show that the 90% confidence interval (CI) for the AZD1775 effect lies entirely below 2.67, ie, would rule out a 167% increase of exposure in the presence of AZD1775. Enrolment of approximately 30 patients with a target of 20 evaluable patients to complete both parts of this study is considered adequate and sufficient to meet the objectives of this study.

Additional patients may be enrolled in Part A if necessary to ensure at least 20 evaluable patients complete both study parts.

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set (not applicable)

8.3.2 Safety analysis set

The safety analysis set will include all patients who received at least 1 dose of study treatment (AZD1775 or cocktail drug). Patients will be evaluated according to the treatment received.

8.3.3 PK analysis set

Part A: The PK analysis set includes all dosed patients who have at least 1 quantifiable plasma concentration for any of the cocktail drugs (or metabolites) or AZD1775 collected post-dose without protocol deviations or events that would affect the PK analysis.

Part B: The PK analysis set includes all dosed patients who have at least 1 quantifiable plasma concentration for AZD1775 collected post-dose without protocol deviations or events that would affect the PK analysis.

Important protocol deviations or events include changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PK. Examples include, but may not be limited to, vomiting following oral dosing occurring within the timeframe of 2 times the median time to reach maximum plasma concentration (t_{max}) of each analyte of interest, sample processing errors that lead to inaccurate bioanalytical results, incomplete dose administered, incomplete PK profile collected, and/or use of disallowed concomitant medication or changes in medications. In the case of an important protocol deviation or event, affected PK data collected will be excluded from the summaries and

statistical analyses, but will still be reported in the study result listings. Important protocol deviations will be listed and summarised in the CSR.

The PK profiles of patients who vomit close to 2 times median t_{max} of an analyte of interest will be evaluated on a case-by-case basis as to whether inclusion of the patient data for the affected period in the summaries and statistical analyses may be acceptable for this study.

8.3.4 Pharmacodynamic analysis set

The pharmacodynamic (PD) analysis set for Part B includes all dosed patients who have at least 1 evaluable time-matched PD endpoint (QTcF on Day -1 and Day 1 or 3) after first administration of AZD1775 without protocol deviations or events that would affect the PD analysis.

8.4 Outcome measures for analyses

Outcome measures for analyses are presented in Table 5.

Table 5 Outcome measures

Analysis	Measure
Primary	**Pharmacokinetic endpoints** Part A Plasma AUC, AUC_{0-t}, and C_{max} for cocktail parent compounds (midazolam, omeprazole, and caffeine) **Pharmacodynamic endpoints** Part B dECG intervals (QTcF) for absolute values and time-matched change from baseline
Secondary	**Pharmacokinetic endpoints** Plasma t_{max}, $t_{½}$, λ_z, CL/F, and V_z/F for cocktail parent compounds (midazolam, omeprazole, and caffeine) Plasma AUC, AUC_{0-t}, t_{max}, C_{max}, $t_{½}$, and λ_z for cocktail metabolites (1'-hydroxy-midazolam, 5-hydroxy-omeprazole, and paraxanthine) and the AUC and C_{max} ratios in relation to parent compound Plasma AZD1775 Day 1: Part B only: AUC_{0-12}, t_{max}, and C_{max} Plasma AZD1775 Day 3: Parts A & B: AUC_{0-12}, t_{max}, C_{max}, C_{min}, C_{avg}, CL_{ss}/F and FI; Part B only: $RAUC_{0-12}$ and RC_{max}

Analysis	Measure
	Pharmacodynamic endpoints
	dECG intervals (heart rate, RR, PR, QRS, QTcB, QTcF and QT) for absolute values and time-matched change from baseline; changes in ECG morphology
	Safety endpoints
	Assessment of AEs, graded by CTCAE (version 4.03), physical examination, vital signs (blood pressure, pulse rate and body temperature), standard 12-lead ECG, evaluation of laboratory parameters (clinical chemistry and haematology)

λ_z: Elimination rate constant; AEs: adverse events; AUC: area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}: area under the plasma concentration-time curve from time zero to the time "t" of the last quantifiable concentration; C_{avg}: average concentration over a dosing interval; CL/F: apparent clearance; CL_{ss}/F: apparent clearance at steady state; C_{max}: maximum plasma drug concentration; C_{min}: minimum plasma drug concentration; CTCAE: Common Terminology Criteria for Adverse Events; dECG: digital electrocardiogram; ECG: electrocardiogram; FI: fluctuation index over a dosing interval; PR: ECG interval measured from the onset of the P wave to the onset of the QRS complex; QRS: ECG interval measured from the onset of the QRS complex to the J point; QT interval: ECG interval measured from the onset of the QRS complex to the end of the T wave; QTc: QT interval corrected for heart rate; QTcB: QT interval corrected for heart rate according to Bazett's formula; QTcF: QT interval corrected for heart rate using Fridericia's formula; $RAUC_{0-12}$: accumulation ratio for AUC_{0-12}; RC_{max}: accumulation ratio for C_{max}; RR: time between corresponding points on 2 consecutive R waves on ECG; t_{max}: time to reach maximum plasma concentration; $t_{½,}$: terminal half-life; V_z/F: apparent volume of distribution.

8.4.1 Pharmacokinetics

The sample bioanalysis will be performed by a third party on behalf of AstraZeneca. The merging of PK concentration data with actual PK sampling times will be performed by QuintilesIMS Data Management. The PK parameter calculations from the plasma concentration data for AZD1775 and cocktail substrates/metabolites and preparation of summary figures will be the responsibility of the pharmacokineticist at QuintilesIMS Early Clinical Development, Overland Park, Kansas, United States. The PK summaries, individual patient figures, and data listings, as well as the statistical analysis of the PK variables, will be the responsibility of the QuintilesIMS biostatistician.

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® version 6.4, or higher, (Certara, L.P., Princeton, New Jersey, United States) and/or SAS® version 9.1, or higher (SAS Institute, Inc., Cary, North Carolina, United States). The actual sampling times will be used in the final PK parameter calculations. All descriptive and inferential statistical computations will be performed using SAS® version 9.1, or higher.

Where possible the following PK parameters will be determined for AZD1775 (both study parts), cocktail drugs (midazolam, omeprazole and caffeine), and cocktail metabolites (1'-hydroxy-midazolam, 5-hydroxy-omeprazole and paraxanthine) following dosing:

- Drug cocktail (Part A only):
  - Parent analytes:
    - Area under the plasma concentration-time curve from time zero to infinity (AUC)
    - Area under the plasma concentration-time curve from time zero to the time "t" of the last quantifiable concentration (AUC_{0-t})
    - Maximum plasma concentration (C_{max})
    - Time to maximum plasma concentration (t_{max})
    - Terminal half-life ($t_{½}$)
    - Elimination rate constant (λ_z)
    - Apparent clearance (CL/F)
    - Apparent volume of distribution (V_z/F)
  - Metabolites:
    - AUC
    - AUC_{0-t}
    - t_{max}
    - C_{max}
    - $t_{½}$
    - λ_z
    - Metabolite/parent AUC ratio
    - Metabolite/parent C_{max} ratio
  - AZD1775:
    - Day 1:
    - Part B only:
      - Area under the plasma concentration-time curve from time zero to 12 hours (AUC_{0-12})

- t_{max}
- C_{max}

- Day3:
- Parts A & B:
  - AUC_{0-12}
  - t_{max}
  - C_{max}
  - Minimum plasma concentration (C_{min})
  - Average concentration over a dosing interval (C_{avg})
  - Apparent clearance at steady state (CL_{ss}/F)
  - Fluctuation index over a dosing interval (FI)
- Part B only:
  - Accumulation ratio for AUC_{0-12} ($RAUC_{0-12}$) (Day 3/Day 1)
  - Accumulation ratio for C_{max} (RC_{max}) (Day 3/Day 1)

Additional PK parameters may be determined if deemed appropriate.

8.4.2 Pharmacodynamics

Pharmacodynamic endpoints from the dECG assessments will include: conduction intervals (heart rate, RR, PR, QRS, QTcF, QTcB, QTcF and QT) for absolute values and time-matched change from baseline, and changes in ECG morphology. All PD analyses will be performed on the PD analysis set.

8.4.3 Safety

The assessment of safety will be based on the analyses of AEs, vital signs, dECGs, physical examinations as well as laboratory safety assessments. All safety analyses will be performed on the safety analysis set.

8.5 Methods for statistical analyses

8.5.1 General considerations for pharmacokinetic and pharmacodynamic data

All data received will be presented in data listings. Pharmacokinetic summaries will be presented for patients in the PK analysis set, as defined in Section 8.3. Pharmacodynamic

summaries will be presented for patients in the PD analysis set, as defined in Section 8.3. Data from patients excluded from the PK and/or PD analysis set will be included in the data listings, but not in the summaries.

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, arithmetic mean, standard deviation (SD), median, minimum and maximum values. Additionally, for PK endpoints, geometric means, geometric coefficient of variation (%GCV), geometric SD (back transformed), geometric mean – geometric SD (back transformed) and geometric mean + geometric SD (back transformed) will be reported for PK variables (concentrations and all PK parameters, except for t_{max} for which only median and range will be presented).

The PK data will be presented by study part, analyte, and treatment or study day.

Digital ECG data from this study may be pooled with data from another study(ies) and analysed by AstraZeneca using statistical methods and PK/PD modelling to evaluate the effect of AZD1775 concentration on QTc (mainly QTcF interval). The methodology and results for these analyses will be described and reported separately from this protocol and CSR.

8.5.2 Analysis of the primary variable(s)

Part A:

The natural log transformed pharmacokinetic parameters (C_{max}, AUC and AUC_{0-t}) of cocktail parent compounds will be analysed using a linear mixed effects model with a fixed effect for treatment and a random effect for subject. Estimates of the mean difference between treatments (AZD1775 + cocktail substrate compared to cocktail substrate alone) and corresponding 90% confidence intervals (CIs) will be calculated. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs. Interpretation of the results will be based on the size of the treatment ratio and associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs will be estimated and presented by treatment.

Part B:

A plasma concentration to QT (C-QT) relationship analysis will be conducted using a linear mixed model in which the placebo-corrected (Day -1-corrected) change from baseline in QTcF is the dependent variable and the AZD1775 plasma concentration obtained on Day 1 and Day 3 is the independent variable. Hysteresis and departures from a linear relationships will be examined. Additional C-QT relationships other than the linear relationship may be explored if supported by data. A detailed plan of this analysis will be presented as part of the statistical analysis plan. The results for the C-QT analysis will be part of the CSR for this study.

The dECG intervals (absolute values and time-matched change from baseline) will be listed and summarised using descriptive statistics (n, mean, SD, percentage coefficient of variance

[%CV], median, minimum, and maximum). The QTcF outliers are defined as QTcF values following dosing that are greater than 450 ms or are increases from baseline greater than 30 ms. QTcF outliers will be highlighted in the data listings and summarised using the following categories: values that are 450 ms or less, greater than 450 ms to 480 ms; greater than 480 ms to 500 ms; and greater than 500 ms; or are increases from baseline of 30 ms or less, greater than 30 ms to 60 ms; and greater than 60 ms.

For QTcF, figures will be generated for the mean time-matched change from baseline values on Days 1 and Day 3.

Figures for mean time-matched change from baseline QTcF values versus AZD1775 mean concentrations (time-matched with QTcF) on Days 1 and Day 3 will also be generated.

8.5.3 Analysis of the secondary variable(s)

Part A:

The natural log transformed pharmacokinetic parameters (AUC, AUC_{0-t}, and C_{max}) of cocktail metabolites will be analysed using a linear mixed effects model with a fixed effect for treatment and a random effect for subject. Estimates of the mean difference between treatments (AZD1775 + cocktail substrate compared to cocktail substrate alone) and corresponding 90% CIs will be calculated. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs will be estimated and presented by treatment.

Part B:

To assess the extent of accumulation of AZD1775, a linear mixed effects model using the natural log transformed AUC_{0-12} or C_{max} as the response variable, day as a fixed effect and subject as a random effect will be performed. Estimates of the mean difference between days (Day 3 compared to Day 1) and corresponding 90% CIs will be calculated. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs will be estimated and presented by day.

Results for AUC_{0-12} and C_{max} obtained after AZD1775 administration on Day 3 in Part B will be compared with those obtained on Day 3 in Part A to probe for potential effects by the cocktail drugs and to obtain an estimate of intra-subject variability following multiple dose administration. All evaluable data for Part A and Part B will be included in the analysis. To assess the potential effects of the cocktail drugs on AZD1775 exposure, a linear mixed effects model using the natural log transformed AUC_{0-12} or C_{max} as the response variable, study part as a fixed effect and subject as a random effect will be performed. Estimates of the mean difference between study parts (Part A, Day 3 compared to Part B, Day 3) and corresponding 90% CIs will be calculated. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs.

Additionally, back transformed geometric means together with 95% CIs will be estimated and presented by study part. Furthermore, an estimate of intra-subject variability following multiple dose administration will be estimated and presented.

The dECG intervals (absolute values and time-matched change from baseline) will be listed and summarised using descriptive statistics (n, mean, SD, %CV, median, minimum, and maximum) by time and study day.

The QT and QTcB/QTcF outliers are defined as QT and QTcB/QTcF values following dosing that are greater than 450 ms or are increases from baseline greater than 30 ms. Outliers will be highlighted in the data listings and summarised using the same categories as for QTcF described under the primary analysis.

8.5.4 Demographic and safety analyses

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, mean, SD, median, minimum, and maximum values. Where appropriate, assessments will be summarised by treatment. All data will be summarised and listed appropriately.

The number of patients screened and included in the safety analysis set will be summarised. Demographic and baseline characteristics will be summarised and listed for the safety analysis set.

Treatment duration will be summarised. Treatment duration is based on the dates of first and last dose.

Study day will be calculated as follows:

- Days prior to first dose: Study day = date – first dose date.
- Days on or after first dose: Study day = date – first dose date +1.

Where day part is missing from the date, but is required in the calculation of time to first dose, day part will be imputed as 01, ie, the first of the month. Otherwise no imputations will be made for any missing data, unless agreed by the study team.

Safety analyses will be presented using the safety analysis set and will be done by means of descriptive statistics. Safety profiles will be assessed in terms of AEs, vital signs (including blood pressure, pulse rate and body temperature), laboratory data (clinical chemistry and haematology), and physical examinations.

Appropriate summaries of AEs, laboratory data, and vital signs will be produced. Adverse events will be summarised separately for the two study parts.

The number of patients experiencing AEs following administration of AZD1775 capsules as well as the number of AEs experienced will be summarised by treatment and overall. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system of nomenclature (Preferred Term [PT] and System Organ Class[SOC]) and will be summarised by presenting the number and percentage of patients having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. Furthermore, a summary for SAEs and summaries by severity and relationship to study treatment will be presented. Most frequent AEs and drug-related AEs will also be provided. Adverse events reported before administration of AZD1775 capsules will be listed only and be referred to as "pre-treatment".

All percentages will be based on the number of patients in the safety analysis set.

Adverse events reported before administration of AZD1775 capsules will be listed only and be referred to as "pre-treatment". A treatment emergent AE will be defined as an AE with the start date and time on or after the dosing in the first treatment period up to (and including) EoS visit (for patients who do not enrol in to the open-label CA study) or EoT visit (for patients who enrol in to the open-label CA study).

All AE data will be listed for all patients. In addition, SAEs and AEs that led to withdrawal or death, and treatment-related AEs will be listed.

Any AE that occurs during a washout between study parts will be attributed to the treatment given in the preceding study part. Unresolved AEs at the end of washout period that worsens in severity following treatment administration in treatment period 2 will be counted as a new AE.

AEs will also be listed by patient.

Patient death due to any cause and patients with AEs leading to study treatment discontinuation will be listed and summarised, as appropriate.

The proportion of patients that discontinue study treatment due to treatment-emergent AEs will be summarised by treatment.

Laboratory data (clinical chemistry and haematology) will be summarised and listed. Shift tables will be provided for selected tests, where shift from baseline to the worst value within each treatment and overall will be summarised. Laboratory data outside the reference ranges should be indicated in the listings.

Concomitant medications will be summarised by the coded terms. The number of patients receiving a medication will be summarised overall and for each treatment. A medication taken during the course of the study is considered concomitant. A patient is only counted once if receiving the medication more than once.

Vital signs will be listed and summarised over time by treatment arms and overall. Changes from baseline will also be summarised. Notable values and changes will be tabulated.

Descriptive statistics (n, mean, SD, median, minimum, and maximum values) of the dECG parameters will be presented by treatment group and overall, at the screening visit.

Physical examination findings will be displayed in a descriptive manner for each patient.

The impact of any important protocol deviations, missing data, and the use of concomitant medication on the robustness of study results will be investigated and any methods employed to deal with these will be documented.

Additional tables, figures, or listings may be produced to aid interpretation.

Further details of summaries of the safety data will be given in the SAP.

8.5.5 Subgroup analysis (Not applicable)

8.5.6 Interim analysis

No interim analysis is planned for this study.

8.5.7 Sensitivity analysis (Not applicable)

8.5.8 Exploratory analysis

Methods and results of exploratory analyses, including for polymorphisms of absorption, distribution, metabolism and excretion (ADME)-related genes, urine 1β-hydroxy deoxycholic acid as a CYP3A4 biomarker, and population PK/PD modelling, will be described and reported separately.

9. STUDY AND DATA MANAGEMENT

This study will be managed by QuintilesIMS, on behalf of AstraZeneca, and QuintilesIMS will act as the AstraZeneca representative.

9.1 Training of study centre personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational personnel and also train them in any study specific procedures and the WBDC system(s) utilised.

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

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

9.2 Monitoring of the study

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

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

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

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

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

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

9.2.3 Archiving of study documents

The Principal Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the Last Patient Last Visit of the last patient undergoing the study' ie, when the last patient has his or her EoT or EoS visit.

The study is expected to start in Q3 2017 and to end by Q1 2018.

The study may be terminated at individual study 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.

9.4 Data management

Data management will be performed by QuintilesIMS, AstraZeneca Data Management Centre personnel or other party, according to the Data Management Plan (DMP). Adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the World Health Organisation Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre or other party. The data collected through third party sources will be obtained and reconciled against study data.

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 DMP. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The study DMP will describe in greater detail the methods used to collect, check, and process clinical data. It will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

All decisions on the evaluability of the data from each individual patient must be made and documented. Following database lock, required amendments to the database due to critical errors will only be allowed with the appropriate supporting documentation. Non-critical errors will not result in amendments to the database but will be captured via the appropriate documentation. The data will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed and locked, clean file will be declared and the final database will be locked. A copy of the eCRF will be archived at the study centre when the study has been closed.

Serious adverse event reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the study centre.

Data management of genotype data

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca. Any genotype data generated in this study will be stored in the AstraZeneca genotyping database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research will be reported separately from the CSR for the main study.

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

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Subject data protection

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

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

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or the 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.

10.3 Ethics and regulatory review

An Ethics Committee (synonymous to IRB and Independent Ethics Committee, hereafter referred to as EC) should approve the final CSP, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study centre personnel.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. The EC should approve all advertising used to recruit patients for the study. AstraZeneca or its representative

should approve any modifications to the ICF that are needed to meet local requirements. If required by local regulations, the protocol should be re-approved by the EC annually.

Before enrolment of any patient into the study, the final CSP, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations. AstraZeneca or its representative will handle the distribution of any of these documents to the national regulatory authorities. AstraZeneca or a delegate will provide Regulatory Authorities, ECs and Investigators with safety updates/reports according to local requirements.

Each Investigator is responsible for providing the EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study treatment. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Investigator(s) at each study centre will:

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

10.5 Changes to the Clinical Study 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 study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised CSP).

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

AstraZeneca will distribute any subsequent amendments and new versions of the CSP to each Investigator. For distribution to EC see Section 10.3.

If a protocol amendment requires a change to a study centre's ICF, AstraZeneca and the study centre's EC are to approve the revised ICF before the revised form is used.

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

10.6 Audits and inspections

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

11. LIST OF REFERENCES

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Sherr CJ. Cancer cell cycles. Science 1996; 274: 1672-7.

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Wang Y, Li J, Booher RN, Kraker A, Lawrence T, Leopold WR, et al. Radiosensitization of p53 Mutant Cells by PD0166285, a Novel G2 Checkpoint Abrogator. Cancer Res 2001; 61: 8211-7.

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the patient 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 patient'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 patient 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 jeopardise the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious.

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

These medical events should usually be considered as serious:

- 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 patient 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 recognised 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.

Appendix B 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.

Appendix C Genetic Research

Rationale and Objectives

AstraZeneca intends to perform genetic research in the AZD1775 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD1775. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD1775 and/or agents used in combination or as comparators but also susceptibility to advanced solid tumours for which AZD1775 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

The objective of this research is to collect and store DNA for future exploratory research into the impact of genes/genetic variations and polymorphisms of (ADME)-related genes on the absorption, distribution, metabolism, and excretion of AZD1775.

The results of this pharmacogenetic research will be reported separately and will not form part of the Clinical Study Report (CSR).

Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant.
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.9 of the main CSP.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at the screening visit. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at screening, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patients last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory personnel working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access within the relevant sample tracking system. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent or when the patient has requested disposal/destruction of collected samples not yet analysed.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main CSP.

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

Subject data protection

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

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

Data management

Any genotype data generated in this study will be stored in the AstraZeneca genotyping database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse the samples.

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

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

Statistical Methods and Determination of Sample Size

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

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

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

The Principal 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 study treatment.

The Principal 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) ≥3 x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥2 x ULN 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 ≥3 x ULN **together with** TBL ≥2 x ULN, where no other reason, other than the study treatment, 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 (ie, 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 ≥3 x ULN

- AST ≥3 x ULN
- TBL ≥2 x ULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Principal Investigator (also sent to AstraZeneca representative).

The Principal Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Principal Investigator will:

- Notify the AstraZeneca representative.
- Request a repeat of the test (new blood draw) by the central laboratory.
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the Principal Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

The Principal 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 Principal Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- 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 Principal Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment).
- Notify the AstraZeneca representative who will then inform the central Study Team.

The Study Physician contacts the Principal 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 Principal 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 eCRF 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

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the I Principal 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 study medication. 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 Principal 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 an 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 AstraZeneca standard processes.

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

- 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 Principal 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 in Section 4 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 Principal 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 Principal 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 eg, chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 3.

If No: follow the process described in Section 4 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 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 Principal Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

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

Appendix E Definition of women of childbearing potential and acceptable contraceptive methods

1. Definition of women of childbearing potential

Women of childbearing potential (WoCBP):

Women between menarche and menopause who have not been permanently or surgically sterilised and are capable of procreation.

Women NOT of childbearing potential:

Women who are permanently or surgically sterilised or post-menopausal (definitions below):

Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

- Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (eg, undergo pregnancy testing etc, as required by the study protocol).
- Women will be considered postmenopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    - Women under 50 years old will be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.
    - Women over 50 years of age will be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.

2. Acceptable contraception methods

Highly effective method of birth control is defined in Note 3 in ICH Guidance M3 (Nonclinical Safety Studies for the conduct of Human Clinical trials for Pharmaceuticals) as one that results in a low failure rate (eg, less than 1 percent per year) when used consistently and correctly.

Note that women should have been stable on their chosen method of birth control during screening (or consent) before entering the trial. Generic names and examples of trade names are given. As trade names may vary, Investigators should check the generic name of any contraception to ensure suitability.

Acceptable contraception methods are:

- Total/true abstinence: when the subject refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for 3 months after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial], and withdrawal are not acceptable methods of contraception).
- Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia).
- Tubal occlusion plus male condom.
- Intra-uterine Device (IUD) - provided coils are copper-banded, plus male condom.
- Intra-uterine system (IUS) Levonorgestrel Intra Uterine System (eg, Mirena), plus male condom.
- Medroxyprogesterone injections (Depo-Provera) plus male condom.
- Etonogestrel implants (eg, Implanon, Norplan) plus male condom.
- Normal and low dose combined oral contraceptive pills, plus male condom.
- Norelgestromin / ethinylestradiol transdermal system plus male condom.
- Intravaginal device (eg ethinylestradiol and etonogestrel) plus male condom.
- After completion of Part A, Day 4, oral contraceptives containing Cerazette (desogestrel) plus male condom. Cerazette is currently the only highly efficacious progesterone based pill.

3. Unacceptable contraception methods

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives (COCs).
- All progesterone only pills. Cerazette is not permitted within 2 weeks of beginning study treatment (ie, first administration of cocktail drugs in Part A) but is permitted after completion of the PK collections in Part A, Day 4.
- All barrier methods, if intended to be used alone.
- Non-copper containing Intra-Uterine Devices (IUDs).

- Fertility awareness methods.
- Coitus interruptus.

Appendix F 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.

Appendix G Eastern Cooperative Oncology group (ECOG) performance status

Table G1 ECOG Performance Status

Patient ability	Score
Fully active, able to carry on all pre-disease performance without restriction	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work	1
Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	3
Completely disabled, unable to carry out any self-care and confined totally to bed or chair	4

Appendix H Prohibited 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 effected by drugs which 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 (Kinact 0.061/min, Ki 6.04 μM). The full impact of the time dependent inhibition is currently unknown, however, modelling data has predicted an 8 to 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. 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.

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 (eg, 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 Principal 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.

Medication which could adversely affect gastrointestinal motility or transit (for example: diphenoxylate, metoclopramide, cisapride, tegaserod, erythromycin) are discouraged. Use of the aforementioned medications by patients with any of these conditions could affect the PK profile and exposure of AZD1775, thus leading to the primary objectives of this study not being met due to atypical gastrointestinal transit. Note that the use of loperamide is permitted for treatment of diarrhoea as described in Section 6.8.2.

AZD1775 has pH-dependent solubility and absorption is therefore potentially affected by gastric pH. Proton pump inhibitors (omeprazole, lansoprazole, esomeprazole, pantoprazole, etc) are prohibited. Antacids must be withheld for 3 hours prior to and 3 hours following AZD1775 administration and H2-antagonists (cimetidine, ranitidine, famotidine, nizatidine, etc) must be withheld for up to 96 hours at a time (24 hours prior to and following cocktail administration and 24 hours prior to the first, through 24 hours following the last AZD1775 administration in each study part).

Part A of this study evaluates the effect of AZD1775 on the PK of omeprazole (CYP2C19 substrate) and caffeine (CYP1A2 substrates). Drugs known to be moderate to strong inhibitors/inducers of CYP1A2 or CYP2C19 are therefore prohibited for use in the current study through the collection of the last PK sample in Part A (Day 4 of Part A). Weak inducers/inhibitors of CYP1A2 and CYP2C19 are permitted as long as patient is on a stable regimen with no dose adjustment within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A.

Note that the subsequent tabulation may include medications in more than 1 category. The most restricted usage for these medications will apply with exception of cimetidine, ranitidine, and famotidine which will follow the restrictions for the H2-antagonists.

Table H1 Prohibited and restricted medication

Category	Drug name	Usage
CYP3A4 Inhibitors - Strong	Boceprevir	Prohibited
	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	
CYP3A4 Inhibitors - Moderate	ACT-178882	Prohibited
	Amprenavir	
	Aprepitant	
	Atazanavir	
	Casopitant	
	Cimetidine	
	Ciprofloxacin	
	Crizotinib	
	Cyclosporine	
	Darunavir	

Category	Drug name	Usage
	Diltiazem	
	Dronedarone	
	Erythromycin	
	FK1706	
	Fluconazole	
	Fosamprenavir	
	Grapefruit juice	
	Imatinib	
	Ledipasvir	
	Lomitapide	
	Netupitant	
	Schisandra sphenanthera	
	Tofisopam	
	Verapamil	
CYP3A4 Inhibitors - Weak	Almorexant	Should not be changed within 1 week of dose administration in Part A (Day -8) through collection of the last planned PK sample in Part B unless medically necessary. Any addition of medication should be avoided during the treatment period where possible.
	Alprazolam	
	AMD070	
	Amiodarone	
	Amlodipine	
	Atorvastatin	
	Azithromycin	
	Berberine	
	Bicalutamide	
	Blueberry juice	
	Chlorzoxazone	
	Cilostazol	
	Cimetidine	
	Clotrimazole	
	Cranberry juice	
	Cyclosporine	
	Daclatasvir	
	Delavirdine	
	Everolimus	
	Faldaprevir	
	Fluvoxamine	
	Fosaprepitant (IV)*	*Fosaprepitant is prohibited
	Ginkgo	

Category	Drug name	Usage
	Goldenseal	
	GSK1292263	
	GSK2248761	
	Isoniazid	
	Ivacaftor	
	Lacidipine	
	I Linagliptin	
	Lomitapide	
	M100240	
	Nilotinib	
	Oral contraceptives (Estradiol, Ethinylestradiol; Etonogestrel; levonorgestrel)	
	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	Prohibited
	Bosentan	
	Carbamazepine	
	Efavirenz	
	Enzalutamide	

Category	Drug name	Usage
	Etravirine	
	Genistein	
	Lersivirine	
	Lopinavir	
	Mitotane	
	Modafinil	
	Nafcillin	
	Phenobarbital	
	Phenytoin	
	Rifabutin	
	Rifampin	
	Ritonavir	
	Semagacestat	
	St John's Wort	
	Talviraline	
	Thioridazine	
	Tipranavir	
CYP3A4 Inducers – Weak	Amprenavir	Should not be changed within 1 week of dose administration in Part A (Day -8) through collection of the last planned PK sample in Part B unless medically necessary. Any addition of medication should be avoided during the treatment period where possible. **Aprepitant is prohibited
	Aprepitant**	
	Armodafinil	
	AZD 7325	
	Bexarotene	
	Boceprevir	
	Brivaracetam	
	Clobazam	
	Danshen	
	Dexamethasone	
	Echinacea	
	Eslicarbazepine	
	Garlic	
	Gingko	
	Ginseng	
	Glycyrrhizin	
	LCL161	

Category	Drug name	Usage
	Methylprednisolone	
	Nevirapine	
	Oritavancin	
	Oxcarbazepine	
	PA-824	
	Pioglitazone	
	Pleconaril	
	Prednisone	
	Quercetin	
	Raltegravir	
	Ritonavir	
	Rufinamide	
	Sorafenib	
	Stribild	
	Sulfinpyrazone	
	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	Prohibited
	Alfentanil	
	Alfuzosin	
	Almorexant	
	Alpha-Dihydroergocryptine	
	Aplaviroc	
	Amiodarone	
	Aprepitant	
	Astemizole	
	Atazanavir	

Category	Drug name	Usage
	Atorvastatin	
	Avanafil	
	Bexarotine	
	BIRL 355	
	Bortezomib	
	Bosutinib	
	Brecanavir	
	Brotizolam	
	Budesonide	
	Buspirone	
	Capravirine	
	Carbamazepine	
	Casopitant	
	Cisapride,	
	Conivaptan	
	Cyclophosphamide	
	Cyclosporine	
	Danoprevir	
	Darifenacin	
	Darunavir	
	Dasatinib	
	Diergotamine	
	Dihydroergotamine	
	Disopyramide	
	Dronedarone	
	Docetaxol	
	Dofetilide	
	Doxorubicin	
	Ebastine	
	Eletriptan	
	Elvitegravir	
	Eplerenone	
	Ergotamine	
	Erlotinib	
	Etoposide	
	Everolimus	
	Felodipine	

Category	Drug name	Usage
	Fentanyl	
	Fluticasone	
	Gefitinib	
	Halofantrine	
	Ibrutinib	
	Ifosfamide	
	Imatinib	
	Indinavir	
	Ironotecan	
	Ivacaftor	
	Ixabepilone	
	L-771,688	
	Lapatinib	
	Levomethadyl (LAAm)	
	Lomitapide	
	Lopinavir	
	Lovastatin	
	Lumefantrine	
	Lurasidone	
	Maraviroc	
	Midazolam	
	Midostaurin	
	Mosapride	
	Neratinib	
	Nilotinib	
	Nisoldipine	
	Paclitaxel	
	Pazopanib	
	Perospirone	
	Pimozide	
	Propafenone	
	Propofol	
	Quetiapine	
	Quinidine	
	Ranolazine	

Category	Drug name	Usage
	Ridaforolimus	
	Romidepsin	
	Saquinavir	
	Sildenafil	
	Simeprevir	
	Simvastatin	
	Sirolimus	
	Tacrolimus	
	Temsirolimus	
	Terfenadine	
	Ticagrelor	
	Theoophylline	
	Thioridazine	
	Thiotepa	
	Tilidine	
	Tipranavir	
	Tolvaptan	
	Triazolam	
	Tretinoin	
	Ulipristal	
	Vardenafil	
	Vicriviroc	
	Voclosporin	
CYP1A2 Inducers – Moderate	Cigarette smoking	Prohibited within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A
	Phenytoin	
	Rifampin	
	Ritonavir	
	Teriflunomide	
CYP1A2 Inducers – Weak	Aminoglutethimide	Weak inducers of CYP1A2 are permitted as long as patient is on a stable regimen with no dose adjustment within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A unless medically necessary. Any addition of medication should be avoided during the treatment period where possible
	Carbamazepine	
	Montelukast	
	Moricizine	
	Nelfinavir	
	Omeprazole	
	Phenobarbital	
	Sulfinpyrazone	

Category	Drug name	Usage
	Tanshinone IIA	
	Terbutaline	
	Topranavir and ritonavir	
	Valproic acid	
CYP1A2 Inhibitors - Strong	Angelica root – Bhai Zhi	Prohibited within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A
	Ciprofloxacin	
	Clinafloxacin	
	Enoxacin	
	Fluvoxamine	
	Oltipraz	
	Rofecoxib	
	Zafirlukast	
CYP1A2 Inhibitors - Moderate	3,4-methylene-dioxymethamphetamine (MDMA)	Prohibited within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A
	Etintidine	
	Genistein	
	Idrocilamide	
	Methoxsalen	
	Mexiletine	
	Certain Oral contraceptives (Any patient taking an oral contraceptive must be discussed with the Medical Monitor to ensure that there will be no interaction with the brand of oral contraceptive and cocktail of drugs prior to trial entry to confirm eligibility.)	
	Osilodrostat	
	Phenylpropanolamine	
	Pipemidic acid	
	Propafenone	
	Propranolol	
	Troleandomycin	
	Vemurafenib	

Category	Drug name	Usage
CYP1A2 Inhibitors - Weak	Acyclovir Allopurinol Antofloxacin Artemisinin Caffeine Cimetidine Curcumin Daidzein Deferasirox Disulfiram Echinacea Famotidine Glecaprevir and pibrentasvir Grapefruit juice Geprafloxacin Hormone replacement therapy Interferon alpha Interferon beta Norfloxacin Pefloxacin Peginterferon alpha-2a Piperine Safinamide Simeprevir Sirukumab Terbinafine Thiabendazole Ticlopidine Verapamil Viloxazine Zileiton	Weak inhibitors of CYP1A2 are permitted as long as patient is on a stable regimen with no dose adjustment within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A unless medically necessary. Any addition of medication should be avoided during the treatment period where possible.
CYP2C19 Inducers – Strong and moderate	Dicloxacillin Enzalutamide Lopinavir and ritonavir Paritaprevir and ritonavir and ombitasvir Rifampin Tipranavir and ritonavir	Prohibited within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A

Category	Drug name	Usage
CYP2C19 Inducers - Weak	Artemisinin Atazanavir and ritonavir Carbamezapine Dicloxacillin Efavirenz Enzalutamide Gingko Glycyrrhizin Lopinavir and ritonavir Paritaprevir and ritonavir and ombitasvir Paritaprevir and ritonavir and ombitasvir and dasabuvir Sirukumab St John's Wort extract Tocilizumab Yin Zhi Huang	Weak inducers of CYP2C19 are permitted as long as patient is on a stable regimen with no dose adjustment within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A unless medically necessary. Any addition of medication should be avoided during the treatment period where possible.
CYP2C19 Inhibitors - Strong	Flucanazole Fluvoxamine Ticlopidine	Prohibited within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A
CYP2C19 Inhibitors - Moderate	Esomeprazole Fluoxetine Moclobemide Omeprazole Voriconazole	Prohibited within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A
CYP2C19 Inhibitors - Weak	Allicin (garlic derivative) Armodafinil Carbamazepine Cimetidine Etravirine Felbamate Human growth hormone (rhGH) Ketoconazole Oral contraceptives	Weak inhibitors of CYP2C19 are permitted as long as patient is on a stable regimen with no dose adjustment within 2 weeks of first dose of cocktail drugs (Part A) through Day 4 of Part A

Category	Drug name	Usage
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	Caution
CYP1A2 Sensitive Substrates or Substrates with a Narrow Therapeutic Range	Alosetron Caffeine Duloxetine Melatonin Ramelteon Tacrine Theophylline Tizanidine	Caution
Proton pump inhibitors	Esomeprazole Lansoprazole Omeprazole Pantoprazole	Prohibited
Antacids		Must be withheld for at least 3 hours prior to and 3 hours following AZD1775 administration
Inhibitors of acid secretion such as H2-antagonists	Cimetidine Famotidine Nizatidine Ranitidine	Must be withheld for at least 24 hours prior to and following cocktail administration and 24 hours prior to and following AZD1775 administration.

Category	Drug name	Usage
P-gp Substrates	Colchicine	Caution
	Digoxin	
	Fexofenadine	
	Indinavir	
	Paclitaxel	
	Toptecan	
	Vincristine	
P-gp Inhibitors (Strong)	Cyclosporine	Caution
	Elacridar	
	Erythromycin	
	Itraconazole	
	Ketocoanzole	
	LY335979	
	Quinidine	
	Ritonavir	
	Valspodar	
	Verapamil	
BCRP Substrates	Rosuvastatin	Prohibited
BCRP Substrates	Daunorubicin	Caution
	Doxorubicin	
	Sulfasalazine	
	Topotecan	
Medication with a known risk of Torsades de Pointes (QT elongation)	Amiodarone	Prohibited
	Anagrelide	
	Arsenic trioxide	
	Azithromycin	
	Chlorquine	
	Cilostazol	
	Ciprofloxacin	
	Citalopram	
	Clarithromycin	
	Cocaine	
	Disopyramide	
	Dofetilide	
	Domperidone	
	Donepezil	
	Dronedarone	

Category	Drug name	Usage
	Droperidol	
	Erythromycin	
	Escitalopram	
	Flecainide	
	Fluconazole	
	Grepafloxacin	
	Halofantrine	
	Haloperidol	
	Ibutilide	
	Levofloxacin	
	Levomepromazine	
	Methadone	
	Moxifloxacin	
	Ondansetron	
	Oxaliplatin	
	Papaverine HCL	
	Pentamide	
	Pimozide	
	Procainamide	
	Propofol	
	Quinidine	
	Sevoflurane	
	Sotalol	
	Sulpiride	
	Thioridazine	
	Vandetanib	

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