AstraZeneca

| **Clinical Study Protocol** | |
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| Drug Substance | AZD1775 |
| Study Code | D6015C00003 |
| Version | 5 |
| Date | |

# A Phase Ib Study to Determine the Maximum Tolerated Dose (MTD) of AZD1775 Monotherapy in Patients with Locally Advanced or Metastatic Solid Tumours

**Sponsor:** ***AstraZeneca AB, 151 85 Södertälje, Sweden***

# VERSION HISTORY

| **Version 5.0,** | |
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| **Changes to the protocol are summarized below:** | **Rationale** |
| Section 4.3.2.3, Table 3, Table 4, and throughout the document:<br><br>A Final Protocol Visit (FPV) has been added for patients still on treatment. | This will allow patients still on treatment to continue to receive AZD1775 after the date of data cut-off if they are deriving clinical benefit, in the opinion of the investigator, and not fulfilling discontinuation criteria. |
| Section 4.3.2.3, Table 3, Table 4, and throughout the document:<br><br>Beyond the FPV, patients may continue to receive AZD1775 if they are deriving clinical benefit, in the opinion of the Investigator, and not fulfilling any of the discontinuation criteria. | This will allow patients still on treatment to continue to receive AZD1775 after the date of data cut-off if they are deriving clinical benefit, in the opinion of the investigator, and not fulfilling discontinuation criteria. |
| Section 4.3.2.3, Table 3, Table 4, Section 5.6.2, and throughout the document:<br><br>Beyond the FPV a plasma isolation blood sample for future biomedical research should be obtained at the time of AZD1775 discontinuation, if due to disease progression. | This will allow for future biomedical research to be conducted on ctDNA collected at the time of disease progression for all patients. |
| Table 3, Table 4, Table 5, Table 6<br><br>PK samples will no longer be required after implementation of Clinical Study Protocol (CSP) Version 5. | Since data will no longer be collected after the FPV, PK data is no longer needed. |
| Table 3 and Table 4<br><br>ECOG performance status will no longer be required after implementation of CSP Version 5. | Since data will no longer be required after the FPV, the ECOG data is no longer needed. |
| Table 3 and Table 4<br><br>The EOT visit is is **not** required for subjects continuing treatment | The FPV is only to be performed for patients who continue AZD1775 after the |

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| after the FPV. | implementation of CSP Version 5 and will align with the patient's next scheduled visit. |
| Section 6.4<br><br>Clarification of how SAEs will be reported after the FPV. | This confirms that SAEs will still be reported via the standard pharmacovigilance process even after the FPV. |
| Table 11<br><br>AZD1775 dose modifications for QTc interval prolongation has been updated per most recent PSSR. | This aligns the CSP with the most current PSSR guidelines. |
| **Version 4.0, 6 April 2017** | |
| **Changes to the protocol are summarized below:** | **Rationale** |
| Throughout document:<br><br>The dose expansion of the study design (Part B) has been removed.<br><br>A QD 5/2 weekly dosing schedule has been added to the study | The focus of the study has been returned to determining the correct dose level and dosing schedule |
| Throughout the document:<br><br>The number of patients to be enrolled on the study has been revised. | To accurately reflect the number of patients to be enrolled after removal of Part B and addition of the QD 5/2 weekly dosing schedule. |
| Throughout the document:<br><br>Introduction of new printed capsule formulation AZD1775 strengths (50mg, 75mg and 100mg) in addition to the existing plain capsule formulation AZD1775 strengths (25mg and 100mg). | A new drug formulation has been added and guidance on use of the formulation has been provided |
| Table 3, Table 4, Table 6, Section 5.4.1, and Section 6.7:<br><br>Additional PK sample collections were added when imaging is performed for response assessment, at the time of AEs possibly related to AZD1775 (unless the last dose of study drug was administered > 1 week prior to the event), and at the end of | To provide more PK information to the study. |

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| treatment or at the time of progression. | |
| Figures 1 -4, Table 4 and throughout the document:<br><br>The study design (Figures 1 and 3) has been updated and the treatment cohorts are shown in Table 1.<br><br>Dosing schedules for every cohort have been added in Figure 2 (BID Dosing Cohorts) and Figure 4 (QD Dosing Cohorts)<br><br>Study Plan and Assessments for the QD 5/2 Schedule (Table 4) has been revised to include QD 5/2 weekly dosing<br><br>The AZD1775 dosing cohorts table (Table 12) has been revised to show each dosing cohort. | These revisions were made to provide clarity for the investigational sites and investigators. |
| Throughout the document:<br><br>QTc intervals will be monitored throughout the study. Triplicate ECGs will be collected from all patients at baseline and on Day 1 of each treatment cycle. Guidance has been added in the event of QTc increases, changes from baseline or other related toxicities to Section 5.2.3.<br><br>Exclusion criteria #17 has been added<br><br>The acceptable methods for non-hormonal birth control has been clarified (Appendix G) | Revisions were made based on the newest PSSR language |
| Section 5.7 (moved to Appendix C) and Section 6.5:<br><br>A section on medication errors and overdose has been added (Section 6.5).<br><br>An appendix regarding genetic research (Appendix C) has been added and genetic research information has been moved from the body of the CSP (Section 5.7) to the appendix. | Revisions were made to align the CSP with the most recent CSP template. |
| Tables 7, Table 8 Table 11, and Section 6.7.1:<br><br>Dose reduction tables for BID and QD AZD1775 have been revised (Tables 7, Table 8 and Section 6.7.1).The AZD1775 Dose Modifications table (Table 11) has been revised. | To provide clarification on dose reductions and modifications |
| Throughout the document:<br><br>Minor clarifications and updates to improve readability, and | To improve readability of the document. |

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| minor grammatical errors corrections have been made throughout. | |

**Version 3.0, 08 November 2016**

Changes to the protocol are summarized below:

- **Section 1.2.3 Safety and Section 1.4 Benefit/risk and ethical assessment**

Have been changed to "~~Cardiac disorders (tachycardia, palpitations, QTc prolongation) and gastrointestinal haemorrhage were not observed frequently, but are considered to be important potential risks.~~ **Cardiac disorders (tachycardia, palpitations, QTc prolongation) were not observed frequently, but are considered to be important identified risks. Gastrointestinal haemorrhage is considered an important potential risk to be monitored closely as the programme progresses.**"

- **Section 1.5 Study Design, Synopsis, and Section 7.3**

Have been changed to "The preliminary effect of food on single dose pharmacokinetics (PK) of AZD1775 was assessed in approximately 12 patients on the BID schedule. **At least 6 patients to be enrolled on a QD schedule** ~~Patients~~ will receive a single oral dose of AZD1775 with 240 mL (8 oz) of water, once in the fasted state on Cycle 1 Day 1 and once following a high-fat meal on Cycle 2 Day 1."

- **Section 2.1 Primary objective and Synopsis:**

Has been changed to "To determine the MTD/RP2D of AZD1775 monotherapy administered QD (schedule 5/9, 14-day cycle or schedule 5/2, 21-day cycle) or BID **(5/9 schedule, 14-day cycle)** in patients with locally advanced or metastatic solid tumours." The outcomes measure has been changed to "The number and incidence of DLTs in the first cycle (21 days) of the QD 5/2 schedule, and the number and incidence of DLTs in the first 2 cycles (28 days) of the QD **or BID** 5/9 schedule."

- **Section 3.1 Inclusion criteria #6:**

Has been changed to "Baseline laboratory values within 7 ~~14~~ days of starting study drug".

- **Section 3.1 Inclusion criteria #7:**

Has been changed to "Female patients who are not of child-bearing potential and fertile females of childbearing potential who agree to use adequate contraceptive measures from 2 weeks prior to the study and until 1 month after study treatment discontinuation, who are not breastfeeding, and who have a negative serum or urine pregnancy test within 3 days prior to **and on the day of starting** ~~of~~ study

treatment."

- **Section 3.2 Exclusion criteria #3:**

Use of anti-cancer treatment drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of AZD1775.

- **Section 3.2 Exclusion criteria #4:**

The following exclusion criteria has been added: **"Use of an investigational drug during the past 30 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment."**

- **Section 3.2 Exclusion criteria #11:**

Has been changed to "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, or to be moderate to strong inhibitors/inducers of CYP3A4 which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study drug. The use of sensitive substrates of CYP3A4, such as atorvastatin, simvastatin and lovastatin are prohibited in this study. **As grapefruit and Seville oranges are moderate inhibitors of CYP3A4, these fruits or their products (including marmalade, juice, etc.) should be avoided while taking AZD1775.** Co-administration of aprepitant or fosaprepitant during this study is prohibited (see Appendix G)."

- **Table 1:**
  - Column header has been revised to Safety ~~FU[z]~~ & Response FU[z,aa] & Survival FU[bb] +/- 5 days
  - Footnote "l" has been changed to "PK samples for AZD1775 with food effect assessments will be collected on Cycle 1 Day 1, Cycle 1 Day 5 and Cycle 2 Day 1 pre-dose and at 1 hour, 2, 4, 6, 8, and 10 hours post-dose. ~~Triplicate ECGs will be obtained with 2-5 minutes apart coinciding with each food effect PK collection.~~"
  - Footnote "o" has been changed to "**Initial (i.e. b**~~B~~aseline**)** tumour imaging…"
  - The "plasma isolation samples collected" assessment, reference footnote has been changed from "**q**" to "**p**".
  - The footnote text "Previous individual patient genomic profile reports should be provided for this study" has been changed from footnote "c" to footnote "**x**".
  - Footnote "**u**" has been changed to: "All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO BID or granisetron (Kytril)

1 mg PO BID prior to each dose of AZD1775. **Additional doses of 5-HT3 antagonist may be used if needed.**"

- **Table 2:**
  - Column header has been revised to Safety ~~FU[ee]~~ & Response FU[cc,dd] & Survival FU[ee] +/- 5 days
  - Footnote **"c"** has been changed to: "Physical examinations will be done on Day 1 of each ~~14~~ **21-day** treatment cycle and at the end of treatment".
  - Footnote **"q"** has been changed to: "**Initial (i.e.** baseline**)** tumour imaging studies (e.g. computed tomography [CT] scan of the chest and abdomen/pelvis) will be performed within 28 days prior to the first dose of study drug (AZD1775) and will be repeated at the completion of **Cycle 3** ~~4~~ **(Week 9)** ~~8~~ within 7 days before starting **Cycle 4** ~~5~~ …"
  - Footnote "bb" has been removed from Cycle 3 Day 8, Cycle 4 Day 8, and Cycle 5 and beyond Day 8, and the text has been changed to: "**The haematology blood** ~~S~~**s**amples will be taken **before the patient takes their study medication on Cycle 1 Day 8 and Cycle 2 Day 8 only.** (**O**~~o~~n this day the patient should bring the study medication to the clinic and take as instructed by the treating physician)."
  - Footnote **"cc"** has been changed to: "Patients without evidence of undue toxicity may continue treatment with study drug until disease progression occurs as long as they are achieving clinical benefit and desire to continue therapy. **Please note, patients do not have to come into the clinic on Day 12 of any cycle.**"
- **Table 3:**
  - Column header has been revised to Safety ~~FU[bb]~~ & Response FU[**bb**,cc] & Survival FU[dd] +/- 5 days
  - Footnote "q" has been changed to "**Initial (i.e. b**~~B~~aseline**)** tumour imaging…**screening/**baseline"
- **Tables 1-3:**
  - Cycle 6 and beyond has been added to the tables
  - A line for antiemetic administration has been added to the tables
  - Column header has been revised to Safety ~~FU[ee]~~ & Response FU[**cc**,dd] & Survival FU[ee]
  - Footnote **"b"** has been removed from the screening "Pregnancy test if WoCBP" assessment.

- Footnote **"d"** has been changed to: "Vital signs (heart rate, systolic and diastolic blood pressure, respiration rate, weight, height [at screening only] and oral temperature) will be collected **at screening, baseline, and** on Day 1 of each cycle visit and at the end of treatment."

- Footnote **"e"** has been changed to: "Triplicate ECGs will be obtained at screening to confirm eligibility (see Section 5.2). Triplicate ECGs will be obtained 2-5 minutes apart before each PK **time point** collection. ~~as follows: Pre-dose and 2 hours on Cycle 1 Day 1 and Cycle 1 Day 5~~**.** Refer to Section 5.2.3."

- Footnote **"f"** has been changed to: "Haematologic samples **(2.7 mL)**~~(5 mL)~~ will be collected to measure complete blood count (CBC) with differential and platelets"

- Footnote **"g"** has been changed to: "Clinical chemistry samples **(2.7 mL)** ~~(5 mL)~~ will be collected to measure ~~glucose,~~ BUN, creatinine, sodium, potassium, chloride, calcium, ~~CO2,~~ alkaline phosphatase (ALP), AST, ALT, total bilirubin, ~~total protein~~ and albumin."

- Footnote **"i"** has been changed to: "Pregnancy tests will only be performed in women of childbearing potential **at screening**, within 3 days of study treatment, ~~and confirmed~~ prior to the first dose of study treatment on Day 1 **of each cycle,**~~. This will be repeated at the beginning of each treatment cycle~~ and **at** the EOT visit.

- Footnote "o" has been changed to "**Initial (i.e. b**~~B~~aseline**)** tumour imaging…"

- **Table 2 and 3:**
  - Footnote **"a"** has been changed to: "Signed informed consent may be obtained prior to the 28-day screening window, if required. **For patients on Part B,** the screening period will then start when the tumour sample is deemed acceptable by the central lab."

  - Footnote "**m**" has been changed to: "**QD DOSE ESCALATION:** PK samples for AZD1775 ~~non-food effect patients~~ will be collected on Cycle 1 Day 1 and Cycle 1 Day 5 pre-dose and at 1 hour, 2, 4, 6, 8, 10 and 24 hours post-dose. ~~Triplicate ECGs will be obtained with 2-5 minutes apart for each coinciding with the non-food effect PK timepoint collection as follows: pre-dose and post-dose at 2 hours on Cycle 1 Day 1 and Cycle 1 Day 5 at pre-dose, 1 hour, 2, 4, 6, 8, and 10 hours post-dose~~. On Cycle 5 Day, 5 **non-food effect PK samples will be taken pre-dose only** and then pre-dose **only** every 3-5 cycles. ~~Triplicate ECGs will be obtained with 2-5 minutes apart for each non-food effect PK time point collection.~~**"**

- Footnote "**n**" has been changed to: "For ~~6~~approximately 12 Patients AT MTD/RP2D: PK samples for AZD1775 ~~with food effect assessments~~ will be collected on Cycle 1 Day 1, Cycle 1 Day 5 and Cycle 2 Day 1 pre-dose and at 1 hour, 2, 4, 6, 8, and 10 hours post-dose. ~~Triplicate ECGs will be obtained with 2-5 minutes apart coinciding with each food effect PK collection.~~ **On Cycle 5 Day 5, PK samples will be taken pre-dose only and then pre-dose only every 3-5 cycles.** ~~PK collections will continue on Cycle 5 Day 5 pre-dose and then pre-dose every 3-5 cycles only.~~

- Footnotes "**o**" and "**p**" have the following text added: "**QD RP2D safety and food effect expansion patients only-"**

- Footnote "**q**" has been removed from the follow-up CT assessments.

- Footnote "**r**" has been changed to: "Blood samples will be taken for plasma isolation before dosing on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, **Cycle 4 Day 1**, and on Day 1 of every 2 cycles afterwards (e.g. Cycles **6**~~5~~, **8**~~7~~ [see Section 5.5])"and the table has been revised to show the change.

- Footnote "**v**" has been changed to: "AZD1775 should be taken under fasting conditions with 8 ounces of water approximately 2 hours before ~~and again 2 hours~~ **or** after food."

- Footnote **"w"** has been changed to: "All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO **QD** ~~BID~~ or granisetron (Kytril) 1 mg PO **QD** ~~BID~~ prior to each dose of AZD1775. If nausea and vomiting continue, a second dose of antiemetics can be taken 8 hours later if necessary. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose as a minimum on the first day dosing AZD1775 of every 3-5 days dosing period, unless contraindicated or not well-tolerated. Dexamethasone or the 5-HT3 antagonist may be given by IV as needed. Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known drug-drug interactions (see Section 6.7.3.2)."

- **Section 5.2:**

Has been changed to: "A physical examination, medical history (to capture previous treatment medications and response to each prior treatment regimen), concomitant medications recorded ≤**7**~~14~~ days prior to **initiation of treatment** ~~trial entry~~, ECOG PS, complete blood count (CBC) with differential and platelets, clinical chemistry, and **triplicate** 12-lead ECG should be done at screening."

- **Section 5.2.1:**

Has been changed to: "Pre-menopausal women of childbearing potential must have a negative urine or serum pregnancy test within ~~28~~**3** days prior to starting

study treatment on Day 1, and a confirmatory test will be performed before treatment at the start of each cycle and at the EOT visit. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately."

- **Section 5.2.3:**

Has been changed to: "~~A~~**Triplicate** 12-lead safety ECG**s**…

Triplicate ECGs will be obtained coinciding with the non-food effect PK collection **time points.** ~~as follows: pre-dose and post dose at 2 hours on Cycle 1 Day 1 and Cycle 1 Day 5 at pre-dose, 1 hour, 2, 4, 6, 8, 10, and 24 hours post-dose (QD schedule).~~

- **Table 4:**
  - The title has been changed to "**Part A** Pharmacokinetic sampling schedule for food effect ~~assessments~~ **patients (5/2 QD, and 5/9 QD or BID dosing schedules)** ~~during BID Dose Escalation (12 patients) and for 6-12 patients at the QD MTD/RP2D~~
  - The Cycle 1 Day 1 and Day 5 column has been split into two separate columns "Cycle 1 Day 1" and "Cycle 1 Day 5"
  - Footnote "b" ("Triplicate ECGs should be obtained to coincide with the food effect PK collections. The ECG assessments will be performed before the PK sample is collected.") has been added to pre-dose PK sample at Cycle 5 Day 5 and then every 3-5 cycles thereafter.

- **Table 5:**
  - The title has been changed to: "**Part A** Pharmacokinetic sampling schedule for non-food effect ~~population~~ **patients** (5/2 **QD** and 5/9 QD **and BID** dosing schedules)
  - A column "**Cycle 6 Days 3, 4, or 5 then every 3-5 cycles thereafter**" has been added.
  - A Footnote **"c"** has been added to Cycle 1 Day 2 and the text has been changed to: "24 hour sample collected **on Cycle 1 Day 2 and** Cycle 1 Day 6 (only for QD schedule)."

- **Table 6:**

The title has been changed to: "**Part B** Pharmacokinetic sampling schedule ~~for patients on Part B~~ (5/2 or 5/9 QD dosing schedule ~~on approximately 20 patients~~)

- **Section 6.3.3:**

One bullet point has been deleted: "~~Causality assessment in relation to module-specific combination treatments~~"

- **Table 7:**

The footnote has been changed to: If haematologic toxicity parameters do not recover within ~~28~~**21** days, the patient should be removed from the study treatment."

- **Section 6.7.3.2:**

Has been changed to: "For patients on BID dosing, all patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO **BID** ~~QD~~ or granisetron (Kytril) 1 mg PO BID prior to each dose of AZD1775."

- **Section 7.2.1:**

Has been changed to: "The AZD1775 dose levels to be evaluated are presented in Table 9. **It may be permitted to escalate the dose, in either of the QD dosing regimens, from dose level 1 to dose level 3, without exploring dose level 2, as long as it has been agreed to by the SRT upon reviewing all relevant safety and PK data up to that point. Any intermediate dosing may also be explored.**

- **Table 7:**
  - The QD dose levels have been changed from QD 1, QD 1a, QD 2 and QD 3 to QD 1, QD 2, QD 3, and QD 4.
  - Both BID dosing cohorts have been marked as complete.

- **Section 7.2.2:**

Has been changed to "Patients must complete Cycle 1 **(i.e. 21 days on the 5/2 schedule) or Cycle 1** and Cycle 2 **(i.e. 28 days on the 5/9 schedule)** safety evaluations ~~which will continue on Cycle 3 Day 1,~~ and must receive at least 80% of the planned dose to be considered evaluable. Patients receiving less than 80% of Cycle 1 dose **(21 days for the 5/2 schedule) or Cycle 1 and Cycle 2 dose** (28 days for the 5/9 Schedule~~, 42 days for the 5/2 Schedule~~) will be replaced unless they experienced a DLT confirmed by the SRT….

Cycle 1 **(for the 5/2 schedule)** and **Cycle 1 and** Cycle 2 **(for the 5/9 schedule)** data for each cohort will be reviewed by an SRT after completion of each dose level cohort. "

- **Section 7.3:**

Has been changed to: "**The preliminary effect of food on single dose pharmacokinetics (PK) of AZD1775 was assessed in approximately 12 patients on the BID schedule.** ~~During dose escalation, preliminary effect of food on single dose PK of AZD1775 will be assessed in 12 patients.~~ **At least 6 patients to be enrolled on a QD schedule will receive a single oral dose of AZD1775 with 240 mL (8 oz) of water, once in the fasted state on Cycle 1 Day 1 and once following a high-fat meal on Cycle 2 Day 1.** ~~An additional 6-12 patients may be evaluated for food effect at the RP2D/MTD dose for QD dosing, if necessary. In the food effect study, patients will receive a single oral dose of AZD1775 with 240 mL (8 fluid ounces) of water, once in the fasted state (Cycle 1~~

~~Day 1) and once following a high-fat meal (Cycle 2 Day 1).~~

The fasted condition requires patients to fast for ≥10 hours before AZD1775 dosing and continue until 4 hours post-dose on Cycle 1 Day 1. Patients may have glucose (sugar tablets) and/or juice (except for ~~grapefruit juices or~~ juices containing grapefruit or Seville oranges) if they have signs or symptoms of hypoglycaemia after they have received AZD1775 in the fasted state. Water will be restricted from 1 hour pre-dose until 1 hour post-dose, except for the water administered with AZD1775, and any drink provided as part of the meal in the fed portion of the study.

For the fed condition, patients will be required to fast for ≥10 hours prior to receiving AZD1775 and then resume fasting until 4 hours post-dose, with the exception of a high-fat meal that should be eaten in the 30 minutes prior to AZD1775 being administered on **Cycle 2 Day 1**. The AZD1775 capsule should be administered 30 minutes after the start of meal consumption. If the meal is not completed within 30 minutes, AZD1775 may still be administered so long as 75% of the meal has been consumed within 45 minutes of the start of the meal. If the patient vomits after eating the meal but before administration of AZD1775, investigators should contact the Medical Monitor for guidance regarding rescheduling administration of AZD1775 and subsequent AZD1775 should be administered with 240 mL (8 fluid ounces) of water. After PK assessments on **Cycle 2** Day 1, patients will continue to take the drug with a regular meal for the entire cycle to assess the effect of food on safety.

- **Section 7.8.2:**

Has been changed to: "The use of sensitive substrates of CYP3A4, such as atorvastatin, simvastatin and lovastatin are prohibited in this study. **Patients should stop using these substrates >14 days prior to initiation of study treatment** (see Appendix G)**.**

**"Grapefruit, Seville oranges and their products (e.g. juice, marmalade, etc.)"** have been added to the list of Prohibited Medication/Class of drug, and the additional information has been added "**As grapefruit and Seville oranges are moderate inhibitors of CYP3A4, these fruits or their products should be avoided while taking AZD1775.**"

- **Section 8.2**

"Subjects" has been changed to "patients" and the "efficacy analysis set" has been replaced by the "full analysis set".

- **Appendix G**

**Grapefruit and Seville oranges** have been added to the list of Moderate Cyp3A4 inhibitors.

Clarifications for improved readability, references updated, minor errors corrected, and minor

corrections were made for purpose of consistency.

**Version 2.0, 25 August2016**

Changes to the protocol are summarised below:

- The CSP contents have been placed into a new template.
- The CSP synopsis has been streamlined and condensed.
- Two additional dose escalation schedules are added to Part A:
    - Once daily (QD) 5/9 Dosing Schedule (14 day cycle; dosing on days 1 to 5, followed by no treatment on days 6-14)
    - QD 5/2 Dosing Schedule (21 day cycle; dosing on days 1-5, no treatment on days 6-7, then dosing again on days 8-12, followed by no treatment on days 13-21)
- The primary objective has been revised to include QD dosing.
- A dose expansion phase (Part B) is added to include ovarian cancer patients who progressed on a Poly (ADP-ribose) polymerase inhibitor (PARPi).
    - Added a primary objective for Part B to evaluate the clinical activity of AZD1775 monotherapy in patients who progressed on a PARPi ovarian cancer patients with a *BRCA* 1 or 2 mutation.
- An exploratory objective to collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response to AZD1775 (i.e., absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers is added. In addition, an optional Pharmacogenetic (PGx) sample will be requested from all patients who consent to this.
- To allow for any unforeseen discontinuations before the dose-limiting toxicity (DLT) period is completed, an extra patient may be enrolled and treated at each dose escalation cohort. Therefore, there may be a total of 4 patients (3+1) at the start of each cohort, provided that the 4$^{th}$ patient is able to start the first day of dosing within approximately 1 week of the 3$^{rd}$ patient in the same dose escalation cohort.
- The total enrolment for the study has increased to approximately 98 patients.
- Updated safety information, anti-emetic language and reproductive language based on the AZD1775 Investigator Brochure (version 14) is included.
- If a patient wishes to withdraw consent to both treatment and study assessment, they will be asked if they are willing to continue survival follow-up.

- Additional parameters of the physical examination have been added (including ears, eyes, nose and throat as well as spine and extremities in the musculoskeletal portion).

- A screening electrocardiogram (ECG) has been added

Clarifications for improved readability, references updated, minor errors corrected, and minor corrections were made for purpose of consistency.

**Version 1.0, 18 September 2015**

Initial creation

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

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.

# PROTOCOL SYNOPSIS

## A Phase Ib Study to Determine the Maximum Tolerated Dose (MTD) of AZD1775 Monotherapy in Patients with Locally Advanced or Metastatic Solid Tumours

**Principal Investigator**

**Study site(s) and number of patients planned**

This study will enrol and treat approximately 66 patients, at approximately three centres in the United States (US).

| Study period | | Phase of development |
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| Estimated date of first patient enrolled | Q4 2015 | 1 |
| Estimated date of last patient completed | Q3 2017 | 1 |

**Study design**

This is a Phase Ib multi-centre study investigating AZD1775 monotherapy in patients with locally advanced or metastatic solid tumours. The study will evaluate the safety and the Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D) of AZD1775 in patients for which standard therapy does not exist or has proven ineffective or intolerable. AZD1775 will be taken by mouth (PO) once a day (QD) or twice daily (BID) on a 5/9 dosing schedule every 14 days (dosing on days 1 to 5, followed by no treatment on days 6-14), or QD on a 5/2 dosing schedule every 21 days (dosing on days 1 to 5, no treatment on days 6-7, then dosing again on days 8 to 12, followed by no treatment on days 13-21), or QD on a 5/2 weekly dosing schedule every 21 days (dosing on days 1 to 5, no treatment on days 6-7, dosing on days 8 to 12, no treatment on days 13-14, dosing on days 15 to 19, followed by no treatment on days 20-21) as shown on Figure 3 and 4. Treatment cycles are 14 (schedule 5/9) or 21 (schedule 5/2) days. The patients already enrolled and treated on the BID schedule will continue as per Figures 1 and 2.

For patients on the BID dosing schedule, AZD1775 PO will be administered in approximate 12 hour intervals BID over 5 days (10 doses) on Days 1 through 5 followed by 9 days of no dosing. Treatment cycles will be repeated every 14 days.

For patients on the QD dosing schedule, the AZD1775 MTD will be determined through dose-escalation using a 3+3 cohort design. Initially, 3 patients will be enrolled and treated at the start of each cohort. However, to allow for any unforeseen discontinuations before the dose-limiting toxicity (DLT) period is completed, an extra patient may be enrolled and treated at each dose escalation cohort. Therefore, there may be a total of 4 patients (3 + 1) at the start of each cohort, provided that the 4$^{th}$ patient is able to start the first day of dosing within approximately 1 week of the 3$^{rd}$ patient in the same dose escalation cohort.

Initially, both the QD 5/9 and 5/2 dosing schedule cohorts will be run in parallel as shown in Figure 3. There will be an evaluation to determine whether to proceed with one or both dosing schedules after discussions during the safety/cohort review meeting have been completed. If there is 1 only DLT out of the first 3-4 DLT-evaluable patients, then further patients will be enrolled and treated to a total of 6 patients. Two or more DLTs out of 6 evaluable patients will have exceeded the maximum tolerated dose. A maximum of 10 dose escalations are anticipated in the determination of the MTD.

For an established MTD, a minimum of 12 patients will be enrolled and treated at the QD MTD/RP2D for safety evaluation. Of those, a minimum of 6 patients will be assessed for food effects. More than one dose level may be expanded with up to 12 patients per dose level to get further experience with the dosing schedules.

The preliminary effect of food on single dose pharmacokinetics (PK) of AZD1775 was assessed in approximately 12 patients on the BID schedule. At least 6 patients to be enrolled on the QD schedule will receive a single oral dose of AZD1775 with 240 mL (8 oz) of water, once in the fasted state on Cycle 1 Day 1 and once following a high-fat meal on Cycle 2 Day 1. Patients will be allowed to continue treatment with AZD1775 until evidence of disease progression, unacceptable toxicity, or other discontinuation criterion has occurred as described in Section 3.9. After review of the PK data from the food effect assessment, if it is agreed that the data supports no clinical relevant impact of food on the PK of AZD1775 and so recommended by the SRT and Astra Zeneca, the AZD1775 fasting/administration instructions in CSP Section 7.3 may be removed or discontinued.

Assuming a maximum of 10 QD dose escalation cohorts, approximately 40 evaluable patients are expected to be enrolled and treated in the QD dose escalation portion of the study, plus the 12 patients previously enrolled and treated in BID dose escalation cohorts. Therefore, it is expected that a total of approximately 52 evaluable patients may be enrolled and treated in the dose escalation part of this study. Furthermore, an additional 8 patients will be evaluated for safety (including a minimum of 6 evaluated for food effect) at the RP2D/MTD dose from the QD cohort. Approximately 6 patients may be added to replace non-evaluable patients. Therefore a total of approximately 66 patients are estimated to be treated in this study

Alternative dose level cohorts and/or schedules which may include reductions of dosing intervals may be guided by pharmacokinetic (PK) or pharmacodynamic (PD) evaluations as well as tolerability and may be evaluated before the MTD/RP2D is defined. Modified PK assessments would be defined to accommodate the investigation of alternative dose levels and/or schedules. The RP2D may be further explored through safety and efficacy cohorts organised by tumour type and molecular profile to evaluate anti-tumour activity.

Patients will be allowed to continue treatment with AZD1775 until evidence of disease progression, unacceptable toxicity, or other discontinuation criterion has occurred as described in Section 3.9.

**Objectives**

**Primary Objectives**

| **Primary Objective:** | **Outcome Measure:** |
|---|---|
| To determine the MTD/RP2D of AZD1775 monotherapy administered QD (schedule 5/9, 14-day cycle or schedule 5/2, 21-day cycle) or BID (schedule 5/9, 14-day cycle) in patients with locally advanced or metastatic solid tumours. | The number and incidence of DLTs in the first cycle (21 days) of the QD 5/2 schedule, and the number and incidence of DLTs in the first 2 cycles (28 days) of the QD or BID 5/9 schedule. |

**Secondary objectives**

| **Secondary Objective:** | **Outcome Measure :** |
|---|---|
| To evaluate the safety and tolerability of AZD1775 monotherapy in patients with locally advanced or metastatic solid tumours. | Treatment-emergent adverse events (TEAEs) and SAEs |
| To evaluate the preliminary anti-tumour activity of AZD1775 monotherapy in patients with locally advanced or metastatic solid tumours. | Best objective response (OR) to treatment will be assessed by dose level cohort according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Eisenhauer et al, 2009). |
| To evaluate the PK profile of AZD1775 monotherapy in patients with locally advanced or metastatic solid tumours. | PK parameters of AZD1775 |
| To evaluate the preliminary effect of a high-fat meal on the PK profile of AZD1775 monotherapy in patients with locally advanced or metastatic solid tumours. | PK parameters of AZD1775 |

| | |
|---|---|
| To characterise the effect of AZD1775 on QTc interval in patients with locally advanced or metastatic solid tumours. | QTc interval |

**Exploratory Objective:**

| Exploratory Objective: | Outcome Measure: |
|---|---|
| To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation to assess exploratory genetic biomarkers that may influence PK or response to AZD1775 (i.e., absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers. | Correlation of polymorphisms with variation in Pharmacokinetics (PK), Pharmacodynamics (PDx), PGx, safety or response observed, or cancer in subjects treated with AZD1775. |
| To identify genetic alterations from archived or recent tumour tissue and correlate with clinical outcomes. | Measurement of the presence of genetic alterations in tumours and correlation with response. |

**Target patient population**

Male or female patients aged 18 years or older with a histologically confirmed locally advanced or metastatic solid tumour, excluding lymphoma, for which standard therapy does not exist or has proven ineffective or intolerable. Patients must have measurable or non-measurable disease according to RECIST v1.1.

**Duration of treatment**

Patients will be allowed to continue AZD1775 as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.

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

AZD1775 is available as plain dry-filled capsules containing 25 mg or 100 mg of drug substance to provide a patient dose. AZD1775 is also available as printed dry-filled capsules containing 50 mg, 75mg or 100 mg of drug substance to provide a patient dose. Plain and printed capsule formulations are not to be combined to provide a patient dose.

Additional information about the investigational product (IP) may be found in the Investigator's Brochure (IB).

**Statistical considerations**

**Sample size**

The final sample size will depend on the number of DLTs and on the clinical activity observed at the different dose levels. In addition, any patients not evaluable (NE) for the Dose Escalation analysis set will be replaced in order to have the required number of patients evaluable for DLT

in each dose level. The expected number of patients on the dose escalation, is 52 patients (12 on the BID dosing schedule; and up to 40 on the QD dosing schedules) assuming 12 AZD1775 dose levels (two BID dose levels and up to 10 QD dose levels). An additional 8 patients will be enrolled and treated at the QD MTD/RP2D for safety evaluation. Note, a sample size of approximately 12 patients were initially assessed to evaluate the effect of a high-fat meal on the PK profile of AZD1775 monotherapy during dose-escalation on the BID schedule (i.e. the effect of food was assessed in all 12 patients on the BID dosing schedule). Of the 12 patients to be enrolled and treated at the QD MTD/RP2D, a minimum of 6 will be evaluated for food effect.

With 12 patients (4 patients in the dose escalation plus an additional 8 patients) enrolled and treated at the MTD/RP2D and approximately 6 additional patients to replace any non-evaluable patients, the total number of patients is approximately 66. However, the number of patients could be higher if more than twelve AZD1775 dose levels, alternative dosing schedules, or more cohorts are tested. In addition, more than one dose level may be expanded with up to 12 patients per dose level in order to get further experience with the dosing schedules.

**Methods**

No formal statistical testing will be conducted in this open-label Phase Ib study. Descriptive statistical and graphical displays will be used to summarise the safety data, PK data and preliminary anti-tumour activity data by dose level cohort (see Section 8).

A full description of the statistical methods and analyses will be provided in a statistical analysis plan (SAP).

**Food effect assessment**

For AZD1775, the natural log-transformed AUC and $C_{max}$ will be compared between treatments using a mixed effects analysis of variance model, in approximately 12 patients already assessed on the BID dosing schedule, and at least 6 patients to be assessed with the QD dosing schedule at the MTD/RP2D, (if conducted). Estimates of the mean difference between treatments and corresponding 90% confidence intervals (CI) will be calculated. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the geometric mean ratio and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs will be estimated and presented for each food condition. Additional AUCs will be analysed if appropriate.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| $AUC_{(0-t)}$ | Area under the curve from time zero to the time of last measureable concentration |
| BCRP | Breast cancer resistant protein |
| BID | Twice a day |
| *BRCA* | Breast cancer gene |
| CBC | Complete blood count |
| CI | Confidence interval |
| $C_{max}$ | Maximum observed plasma concentration |
| CR | Complete response |
| CrCl | Creatinine clearance |
| CSA | Clinical Study Agreement |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Event |
| ctDNA | Circulating tumour-derived DNA |
| DBL | Database lock |
| DDI | Drug-drug interaction |
| DHEA | Dehydroepiandrosterone |
| DLT | Dose-limiting toxicity |
| DMP | Data management plan |

| Abbreviation or special term | Explanation |
|---|---|
| EC | Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EOT | End of treatment |
| FDA | Food and Drug Administration |
| FFPE | Fixed-formalin paraffin-embedded |
| FPV | Final protocol visit |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| LMWH | Low molecular weight heparin |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| NCI | National Cancer Institute |
| NE | Not evaluable |
| NTL | Non-target lesion |
| NYHA | New York Heart Association |
| OR | Objective response |
| PARP | Poly (ADP-ribose) polymerase |
| PARPi | PARP inhibitor |
| PD | Progressive disease |
| PDx | Pharmacodynamics |
| PGx | Pharmacogenetics |
| PI | Principal Investigator |

| Abbreviation or special term | Explanation |
|---|---|
| PIS | Patient information sheet |
| PK | Pharmacokinetic |
| PO | By mouth |
| PR | Partial response |
| PS | Performance status |
| QD | Once daily |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate using Fridericia formula |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RP2D | Recommended Phase 2 Dose |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| Sarah Cannon | Sarah Cannon Development Innovations, LLC |
| SD | Stable disease |
| SDV | Source data verification |
| SRT | Safety review team |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| $t_{½}$ | Terminal elimination half-life |
| $\lambda z$ | Terminal elimination rate constant |
| TEAE | Treatment-emergent adverse event |
| TL | Target lesion |
| $t_{max}$ | Time of maximum concentration |
| ULN | Upper limit of normal |
| WoCBP | Women of childbearing potential |

# 1. INTRODUCTION

## 1.1 Background and rationale for conducting this study

Cell death or mutation can occur when DNA damage is not accurately repaired. Complex signalling networks regulate the integrity of the genome and initiate cell cycle arrest and repair and subsequent apoptotic responses if errors are detected. This allows the DNA to be repaired before the cell undergoes replication and/or division. Cancer cells undergo an array of genetic changes including mutations in the DNA repair pathways (Ashwell and Zabludoff 2008).

## 1.2 AZD1775

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 DNA metabolism and the DNA damage response (Coleman and Dunphy 1994; Parker and Piwnica-Worms 1992).

CDK1 (also called cell division cycle 2, 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. Therefore, it is anticipated that AZD1775 will have independent anti-tumour activity in the absence of added chemotherapy.

The tumour suppressor protein p53 regulates the G1 checkpoint. As the majority of human cancers harbour abnormalities in this pathway they become more dependent on S- and G2- phase checkpoints (Sherr 1996). Thus, S- and G2-checkpoint abrogation caused by inhibition of WEE1 may selectively sensitise p53-deficient cells to anti-cancer agents (Wang et al 2001.

*In vitro* experiments demonstrated that AZD1775 also sensitises tumour cells to cytotoxic effects of different DNA damaging agents, including chemotherapies. In xenograft models, anti-tumour efficacy of chemotherapy was significantly enhanced by AZD1775.

The early clinical development to date of AZD1775, administered in combination with a "standard of care" cytotoxic agent such as cisplatin, topotecan, carboplatin, or 5-fluouracil (5-FU), focused on the treatment of advanced solid tumours and also the treatment of p53 pathway deficient malignancies.

### 1.2.1 Clinical experience

As of 11 November 2016, approximately 551 patients have been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies, and 350 patients received AZD1775

as part of externally-sponsored scientific research. These patients have received single doses per cycle as high as 1300 mg of AZD1775 as monotherapy, 325 mg of AZD1775 in a single-dose regimen in combination with chemotherapy, and 325 mg twice a day (BID) in a multiple-dose regimen in combination with chemotherapy. Please refer to the current version of the AZD1775 Investigator's Brochure.

The completed or terminated early studies include:

**NCT 00648648:** a first-time-in-patients (FTIP), Phase I, dose-escalation study evaluating AZD1775 both as monotherapy and combination therapy with gemcitabine, cisplatin, or carboplatin in adult patients with advanced solid tumours (Part 1 & 2 only completed)

**NCT 010477007:** a Phase I, dose-escalation study evaluating AZD1775 as monotherapy (Part 1), combination therapy with 5-FU (Part 2), and combination therapy with 5 FU plus cisplatin (Part 3) in adult Japanese patients with advanced solid tumours was terminated early due to portfolio prioritisation in oncology at Merck after 3 patients had been enrolled in Part 1 and 8 patients had been enrolled in Part 2. Part 3 was not initiated.

**NCT 01076400:** a Phase I/IIa, dose-escalation study evaluating AZD1775 in combination with topotecan plus cisplatin in adult patients with cervical cancer was terminated early due to portfolio prioritisation in oncology at Merck after 7 patients had been enrolled in the dose-escalation part of the study. The Phase IIa part was not initiated.

**NCT 01748825:** a Phase I study of single-agent AZD1775, in patients with refractory solid tumours, sponsored by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program in collaboration with AstraZeneca and Merck. This study reported AZD1775 monotherapy activity in patients carrying *BRCA* mutations for the first time.

**NCT 02087176:** a lead-in Phase II multicentre, randomised, double-blind study comparing AZD1775 plus docetaxel with placebo plus docetaxel in previously treated patients with non-small-cell lung cancer (NSCLC).

**NCT 02087241:** a Phase II study of AZD1775 plus pemetrexed and carboplatin followed by a randomised comparison of pemetrexed and carboplatin with or without AZD1775 in patients with previously untreated stage IV non-squamous NSCLC.

In study **NCT 006486648**, of 176 evaluable patients who received AZD1775 (either single or multiple doses) as monotherapy or in combination with gemcitabine, cisplatin, or carboplatin, a partial response (PR) (confirmed and unconfirmed) was observed in 17 (9.7%) patients, and stable disease (SD) was observed in 94 (53.4%) patients (Ashwell and Zabludoff 2008; AZD1775 Investigator's Brochure [IB]).

Nine patients received AZD1775 monotherapy. Single ascending doses of AZD1775 up to 1300 mg were well tolerated; the maximum tolerated dose (MTD) was not established.

In study **NCT 010477007**, patients in Part 1 received single-cycle BID dosing of AZD1775 for 5 days at 1 of 2 dose levels as monotherapy. A cohort of 3 patients was enrolled at the starting dose level of AZD1775 65 mg BID and no serious adverse events (SAEs) were experienced.

In study **NCT 01748825**, patients received single-agent AZD1775 PO BID over 2.5 days per week for 2 weeks in 3-week treatment cycles. Twenty-five patients were enrolled to determine the MTD using a 3+3 design. The MTD was established at 225 mg by mouth (PO) BID for 5 doses on Weeks 1 and 2 of a 3-week schedule. Six patients with *BRCA*-mutated solid tumours were enrolled at the MTD. Partial responses were confirmed in two of the patients carrying *BRCA* mutations (ovarian cancer patient and head/neck cancer patient). Paired tumour biopsies were obtained from 5 patients treated at the MTD at baseline and after the 5$^{th}$ AZD1775 dose to determine the levels of pY15-Cdk and γH2AX. The biopsies showed a decrease in pY15-Cdk levels (2/5 paired biopsies). The same biopsies were analysed for increases in γH2AX, an indicator of DNA damage. Three of the 5 biopsy pairs showed an increase in γH2AX levels. DNA damage response was observed in this study through provided paired tumour biopsies (Do et al 2015).

Additional information may be found in the current version of the AZD1775 IB.

### 1.2.2 Pharmacokinetics

The pharmacokinetic (PK) data of AZD1775 following a single oral administration showed a moderate rate of absorption with a time of maximum concentration ($T_{max}$) occurring at 3 to 4 hours. Post-peak plasma concentrations declined essentially in a mono-exponential manner with a terminal elimination half-life ($t_{1/2}$) in the region of 10 hours. Exposure as measured by maximum plasma drug concentration observed ($C_{max}$) and area under the curve $AUC_{(0-\infty)}$ increased in a dose-proportional manner over the dose range of 325 to 1300 mg. Following single (100 to 325 mg) and multiple dose administrations of AZD1775 (25 to 325 mg BID and 100 to 200 mg once daily [QD]) with carboplatin, cisplatin, and gemcitabine, plasma exposure of AZD1775 was consistent with predictions based on the single-dose regimen. Preliminary investigation of drug-drug interactions (DDIs) in study NCT 00648648 suggests a 40-60% increase in the exposure of AZD1775 in the presence of aprepitant (moderate CYP3A4 inhibitor), but no effect with the concomitant administration of steroids (moderate CYP3A4 inducers). Preliminary studies also suggested that the Pre-marketed Oral Formulation of AZD1775 was similar to that of the Fit-For-Purpose formulation. Based on the preliminary comparison of the results of AZD1775 PK parameters at the 225 mg dose, PK estimates in Asian patients were 30-45% higher than in Western patients.

In the NCI PK study (PN011), QD doses of 200 mg to 300 mg have been evaluated without any DLTs. Preliminary PK data from the QD 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 $AUC_{0-24}$ on Day 5 at 200-250 mg QD dose is similar to that observed after BID dosing at 175 mg. At, 300 mg QD dose, the $AUC_{0-24}$ (22498 nM*h) on Day 5 exceeds the exposure observed after BID dosing at 200 mg (19632 nM*h). AZ data on file.

Further information on the PK and metabolism of AZD1775 is provided in the current version of the AZD1775 IB.

### 1.2.3 Safety

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/WBC count decreased, pancytopenia, myalgia, stomatitis, sepsis and transaminases elevation.

Refer to the IB for AZD1775 for information on the potential benefits and assessment of potential and known risks.

## 1.3 Rationale for study design

This Phase Ib study is designed to identify the MTD/Recommended Phase 2 Dose (RP2D) of AZD1775 administered as a single-agent in 14 or 21-day cycles to patients with locally advanced or metastatic solid tumours.

Selection of dose levels and schedules for evaluation in the study is guided by the PK data from study NCT 0174882 (see Section 1.2.2). AZD1775 will be administered orally once daily (QD), (or twice daily ([BID] for the patients already enrolled and treated on the BID schedule) on a QD 5/9 dosing schedule every 14 days (dosing on days 1-5, following by no treatment on days 6-14), or on a QD or BID 5/2 dosing schedule every 21 days (dosing on days 1 to 5, no treatment on days 6-7, then dosing again on days 8 to 12, followed by no treatment on days 13-21). The schedule will be repeated every 14 (schedule 5/9) or 21 days (schedule 5/2) (see Table 2, Table 3, and Table 4). Tumour assessments will be obtained approximately every 8 weeks. The safety, tolerability, PK parameters, and preliminary anti-tumour activity of AZD1775 will be assessed (see Table 2, Table 3, Table 4).

Alternative treatment schedules may be explored if preliminary data suggest these would be more appropriate. In the event alternative treatment schedules are explored, PK sampling times may be affected.

This study will provide an opportunity to further explore the safety and efficacy of a previously unexplored AZD1775 monotherapy schedule.

## 1.4 Benefit/risk and ethical assessment

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

Study **NCT 00648648** confirmed AZD1775 single-agent response is achievable. The optimal AZD1775 schedule and dose has not been confirmed and it is important to continue to evaluate this important agent and to determine the best dose and schedule for cancer patients.

See Section 1.2.3 for potential risks associated with AZD1775.

## 1.5 Study Design

This is a Phase Ib multi-centre study investigating AZD1775 monotherapy in patients with locally advanced or metastatic solid tumours. The study will evaluate the safety and the Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D) of AZD1775 in patients for which standard therapy does not exist or has proven ineffective or intolerable. AZD1775 will be taken by mouth (PO) once a day (QD) or twice daily (BID) on a 5/9 dosing schedule every 14 days (dosing on days 1 to 5, followed by no treatment on days 6-14), QD on a 5/2 dosing schedule every 21 days (dosing on days 1 to 5, no treatment on days 6-7, then dosing again on days 8 to 12, followed by no treatment on days 13-21), or QD on a 5/2 weekly dosing schedule every 21 days (dosing on days 1 to 5, no treatment on days 6-7, dosing on days 8 to 12, no treatment on days 13-14, dosing on days 15 to 19, followed by no treatment on days 20-21). Treatment cycles are 14 (schedule 5/9) or 21 (schedule 5/2) days. The patients already enrolled and treated on the BID schedule will continue on the assigned regimen. Dosing cohorts are shown in Table 1.

For patients currently on the BID dosing schedule (Figure 1 and Figure 2), AZD1775 PO will be administered in approximate 12 hour intervals BID over 5 days (10 doses) on Days 1 through 5 followed by 9 days of no dosing. Treatment cycles will be repeated every 14 days.

For patients on the QD dosing schedule, the AZD1775 MTD will be determined through dose-escalation using a 3+3 cohort design. Initially, 3 patients will be enrolled and treated at the start of each cohort. However, to allow for any unforeseen discontinuations before the dose-limiting toxicity (DLT) period is completed, an extra patient may be enrolled and treated at each dose escalation cohort. Therefore, there may be a total of 4 patients (3 + 1) at the start of each cohort, provided that the 4$^{th}$ patient is able to start the first day of dosing within approximately 1 week of the 3$^{rd}$ patient in the same dose escalation cohort.

Initially, the QD 5/9 and 5/2 dosing schedule cohorts (Figure 3 and Figure 4) will be run in parallel. There will be an evaluation to determine whether to proceed with one or both dosing schedules after discussions during the safety/cohort review meetings have been completed. If there is 1 DLT out of the first 3-4 DLT-evaluable patients, then further patients will be enrolled and treated to a total of 6 patients. Two DLTs out of 6 evaluable patients will have exceeded the maximum tolerated dose.

A minimum of 12 patients (4 patients in the dose escalation plus an additional 8 patients) will be enrolled and treated at the QD MTD/RP2D for safety evaluation. Of those, a minimum of 6

patients will be assessed for food effects. More than one dose level may be expanded with up to 12 patients per dose level to get further experience with the dosing schedules.

The preliminary effect of food on single dose pharmacokinetics (PK) of AZD1775 was assessed in approximately 12 patients on the BID schedule. At least 6 patients to be enrolled on a QD schedule will receive a single oral dose of AZD1775 with 240 mL (8 oz) of water, once in the fasted state on Cycle 1 Day 1 and once following a high-fat meal on Cycle 2 Day 1. Patients will be allowed to continue treatment with AZD1775 until evidence of disease progression, unacceptable toxicity, or other discontinuation criterion has occurred as described in Section 3.9. After review of the PK data from the food effect assessment, if it is agreed that the data supports no clinically relevant impact of food on the PK of AZD1775 and so recommended by the SRT and Astra Zeneca, the AZD1775 fasting/administration instructions in Section 7.3 may be removed or discontinued.

Assuming a maximum of 10 QD dose escalation cohorts, approximately 40 evaluable patients are expected to be enrolled and treated in the QD dose escalation portion of the study, plus the 12 patients currently enrolled and treated in BID dose escalation cohorts. Therefore, it is expected that a total of approximately 52 evaluable patients may be enrolled and treated in the dose escalation part of this study. Furthermore, an additional 8 patients will be evaluated for safety (including a minimum of 6 evaluated for food effect) at the RP2D/MTD dose from the QD cohort. Approximately 6 patients may be added to replace non-evaluable patients. Therefore a total of approximately 66 patients are estimated to be treated in the study.

Alternative dose level cohorts and/or schedules which may include reductions of dosing intervals may be guided by pharmacokinetic (PK) or pharmacodynamic (PD) evaluations as well as tolerability and may be evaluated before the MTD/RP2D is defined. Modified PK assessments would be defined to accommodate the investigation of alternative dose levels and/or schedules. The RP2D may be further explored through safety and efficacy cohorts organised by tumour type and molecular profile to evaluate anti-tumour activity.

Patients will be allowed to continue treatment with AZD1775 until evidence of disease progression, unacceptable toxicity, or other discontinuation criterion has occurred as described in Section 3.9.

**Table 1 Dosing Cohorts**

| Cohort | Dose Level and Schedule |
|---|---|
| BID 1 | 125 mg PO BID |
| BID 2 | 150 mg PO BID |
| QD 1.1 | 200 mg PO QD on 5/9 schedule |
| QD 1.2 | 200 mg PO QD on 5/2 schedule |
| QD 2.1 | 250 mg PO QD on 5/9 schedule |
| QD 2.2 | 250 mg PO QD on 5/2 schedule |
| QD 2.3 | 250 mg PO QD on 5/2 weekly schedule |

**Table 1 Dosing Cohorts**

| Cohort | Dose Level and Schedule |
|---|---|
| QD 3.1 | 300 mg PO QD on 5/9 schedule |
| QD 3.2 | 300 mg PO QD on 5/2 schedule |
| QD 3.3 | 300 mg PO QD on 5/2 weekly schedule |
| QD 4.1 | 400 mg PO QD on 5/9 schedule |
| QD 4.2 | 400 mg PO QD on 5/2 schedule |

**Figure 1 Treatment Schema BID Dosing Schedule**

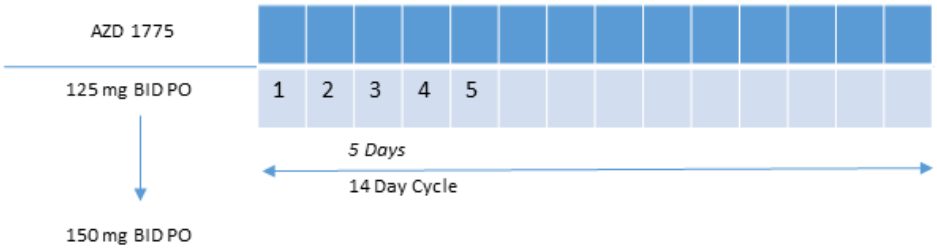



**Figure 2 BID Cohorts Dosing Schedules**

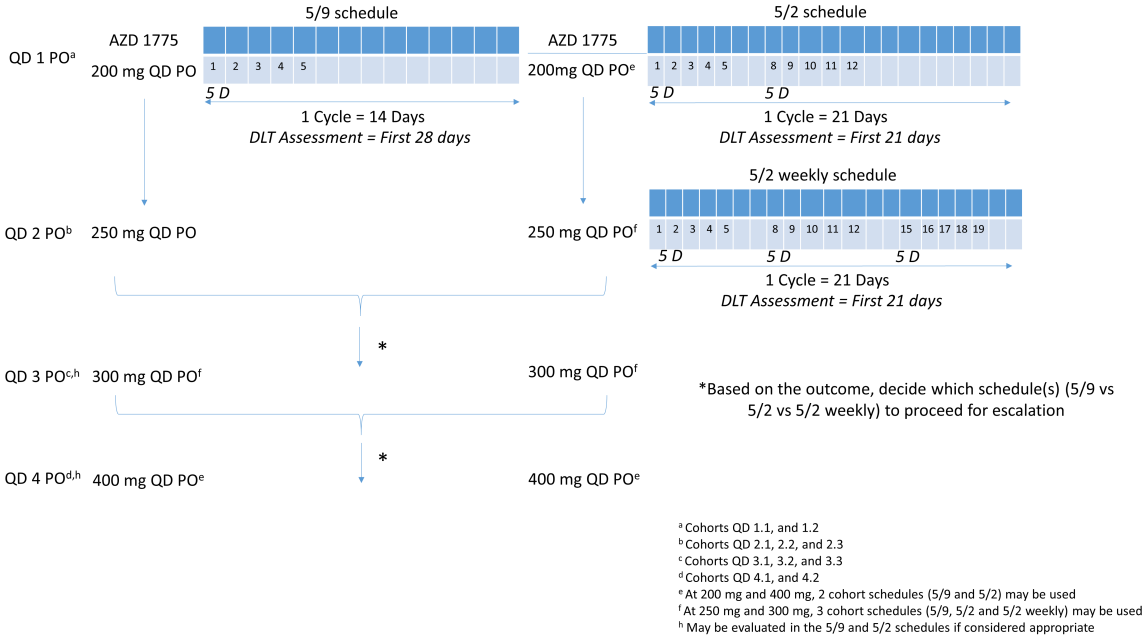
**Cohort BID 1 (AZD1775 PO 125mg BID)**

| Week | Week 1 | | | | | | | Week 2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| AZD1775 125 mg AM | X | X | X | X | X | | | | | | | | | |
| AZD1775 125 mg PM | X | X | X | X | X | | | | | | | | | |

**Cohort BID 2 (AZD1775 PO 155mg BID)**

| Week | Week 1 | | | | | | | Week 2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| AZD1775 150 mg AM | X | X | X | X | X | | | | | | | | | |
| AZD1775 150 mg PM | X | X | X | X | X | | | | | | | | | |

**Figure 3 Treatment Schema QD Dosing Schedules**




[a] Cohorts QD 1.1, and 1.2
[b] Cohorts QD 2.1, 2.2, and 2.3
[c] Cohorts QD 3.1, 3.2, and 3.3
[d] Cohorts QD 4.1, and 4.2
[e] At 200 mg and 400 mg, 2 cohort schedules (5/9 and 5/2) may be used
[f] At 250 mg and 300 mg, 3 cohort schedules (5/9, 5/2 and 5/2 weekly) may be used
[h] May be evaluated in the 5/9 and 5/2 schedules if considered appropriate

## Figure 4 QD Cohorts Dosing Schedules

Cohort QD 1.1 (AZD1775 PO 200mg QD 5/9 Schedule)

| Week | Week 1 | | | | | | | Week 2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| AZD 1775 200mg | X | X | X | X | X | | | | | | | | | |

Cohort QD 1.2 (AZD1775 PO 200mg QD 5/2 Schedule)

| Week | Week 1 | | | | | | | Week 2 | | | | | | | Week 3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| AZD1775 200 mg | X | X | X | X | X | | | X | X | X | X | X | | | | | | | | | |

Cohort QD 2.1 (AZD1775 PO 250mg QD 5/9 Schedule)

| Week | Week 1 | | | | | | | Week 2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| AZD 1775 250mg | X | X | X | X | X | | | | | | | | | |

Cohort QD 2.2 (AZD1775 PO 250mg QD 5/2 Schedule )

| Week | Week 1 | | | | | | | Week 2 | | | | | | | Week 3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| AZD1775 250 mg | X | X | X | X | X | | | X | X | X | X | X | | | | | | | | | |

Cohort QD 2.3 (AZD1775 PO 250mg QD 5/2 Weekly Dosing Schedule)

| Week | Week 1 | | | | | | | Week 2 | | | | | | | Week 3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| AZD1775 250 mg | X | X | X | X | X | | | X | X | X | X | X | | | X | X | X | X | X | | |

Cohort QD 3.1 (AZD1775 PO 300mg QD 5/9 Schedule)

| Week | Week 1 | | | | | | | Week 2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| AZD 1775 300mg | X | X | X | X | X | | | | | | | | | |

Cohort QD 3.2 (AZD1775 PO 300mg QD 5/2 Schedule)

| Week | Week 1 | | | | | | | Week 2 | | | | | | | Week 3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| AZD1775 300 mg | X | X | X | X | X | | | X | X | X | X | X | | | | | | | | | |

Cohort QD 3.3 (AZD1775 PO 300mg QD 5/2 Weekly Dosing Schedule)

| Week | Week 1 | | | | | | | Week 2 | | | | | | | Week 3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| AZD1775 300 mg | X | X | X | X | X | | | X | X | X | X | X | | | X | X | X | X | X | | |

Cohort QD 4.1 (AZD1775 PO 400mg QD 5/9 Schedule)

| Week | Week 1 | | | | | | | Week 2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| AZD 1775 400mg | X | X | X | X | X | | | | | | | | | |

Cohort QD 4.2 (AZD1775 PO 400mg QD 5/2 Schedule)

| Week | Week 1 | | | | | | | Week 2 | | | | | | | Week 3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| AZD1775 400 mg | X | X | X | X | X | | | X | X | X | X | X | | | | | | | | | |

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

| Primary Objective: | Outcome Measure: |
|---|---|
| To determine the MTD/RP2D of AZD1775 monotherapy administered QD (schedule 5/9, 14-day cycle or schedule 5/2, 21-day cycle) or BID (5/9 schedule, 14-day cycle) in patients with locally advanced or metastatic solid tumours. | The number and incidence of DLTs in the first cycle (21 days) of the QD 5/2 schedule, and the number and incidence of DLTs in the first 2 cycles (28 days) of the QD or BID 5/9 schedule. |

## 2.2 Secondary objectives

| Secondary Objective : | Outcome Measure : |
|---|---|
| To evaluate the safety and tolerability of AZD1775 monotherapy in patients with locally advanced or metastatic solid tumours. | Treatment-emergent adverse events (TEAEs) and SAEs |
| To evaluate the preliminary anti-tumour activity of AZD1775 monotherapy in patients with locally advanced or metastatic solid tumours. | Best objective response (OR) to treatment will be assessed by dose level cohort according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Eisenhauer et al 2009). |
| To evaluate the PK profile of AZD1775 monotherapy in patients with locally advanced or metastatic solid tumours. | PK parameters of AZD1775 |
| To evaluate the preliminary effect of a high-fat meal on the PK profile of AZD1775 monotherapy in patients with locally advanced or metastatic solid tumours. | PK parameters of AZD1775 |
| To characterise the effect of AZD1775 on QTc interval in patients with locally advanced or metastatic solid tumours. | QTc interval |

## 2.3 Exploratory Objective

| Exploratory Objective: | Outcome Measure: |
|---|---|
| To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic | Correlation of polymorphisms with variation in Pharmacokinetics (PK), Pharmacodynamics |

| | |
|---|---|
| variation to assess exploratory genetic biomarkers that may influence PK or response to AZD1775 (i.e., absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers. | (PDx), PGx, safety or response observed, or cancer in subjects treated with AZD1775. |
| To identify genetic alterations from archived or recent tumour tissue and correlate with clinical outcomes. | Measurement of the presence of genetic alterations in tumours and correlation with response. |

# 3. PATIENT SELECTION, ENROLMENT, 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 IC prior to any study-specific procedures.

2. Must be ≥18 years of age.

3. Any prior palliative radiation must have been completed at least 7 days prior to the start of study drugs, 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 0-1.

5. Ability to provide archival or fresh/recent tumour tissue for genomic analyses is required (see Section 5.6.1).

6. Baseline laboratory values within 7 days of starting study drug :

   - Absolute neutrophil count (ANC) ≥1500/μL
   - Haemoglobin (HgB) ≥9 g/dL with no blood transfusion in the past 28 days
   - 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) ≥45 mL/min, as calculated by the Cockcroft-Gault method (confirmation of creatinine clearance is only required when creatinine is > 1.5 x institutional ULN)

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

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

7. Female patients who are not of child-bearing potential and fertile females of childbearing potential who agree to use adequate contraceptive measures from 2 weeks prior to the study and until 1 month after study treatment discontinuation, who are not breastfeeding, and who have a negative serum or urine pregnancy test within 3 days prior to, and on the day of starting study treatment.

8. Male patients should be willing to abstain or use barrier contraception (i.e., condoms) for the duration of the study drug exposure and for 3 months after study treatment discontinuation.

9. Predicted life expectancy ≥12 weeks.

10. Willingness and ability to comply with all study and follow-up procedures.

11. 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.

12. Measurable or non-measurable- disease according to RECIST v1.1 or (Appendix E).

## 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 staff and/or staff at the study site)

2. Previous enrolment in the present study

3. Use of 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. Hormonal agents for prostate cancer are allowed provided that the dose has been unchanged for at least 3 months.

4. Use of an investigational drug during the past 30 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment.

5. Major surgical procedures ≤28 days of beginning study treatment, or minor surgical procedures ≤7 days. No waiting period required following port-a-cath or other central venous access placement.

6. Grade >1 toxicity from prior therapy (except alopecia or anorexia).

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

8. 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 the patient is receiving study medication. 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.

9. Palliative radiation therapy completed ≤7 days prior to the start of study drugs.

10. 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.

11. 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, or to be moderate to strong inhibitors/inducers of CYP3A4 which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study drug (see Appendix H).

12. Caution should be exercised when inhibitors or substrates of P-glycoprotein (P-gp), substrates of CYP1A2 with a narrow therapeutic range, sensitive substrates of CYP2C19 or CYP2C19 substrates with a narrow therapeutic range are administered with AZD1775.

13. Transporter studies (*in vitro*) have shown that AZD1775 is an inhibitor of breast cancer resistance protein (BCRP). Please refer to Appendix H for guidance on use of AZD1775 with BCRP substrates.

14. Patients should stop using herbal medications 7 days prior to first dose of study treatment. Please see section on prohibited concomitant medications and Appendix H for further details.

15. Any known hypersensitivity or contraindication to the components of the study drug AZD1775 (see Section 7.8).

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

    - Unstable angina pectoris
    - Congestive heart failure
    - Acute myocardial infarction
    - Conduction abnormality not controlled with pacemaker or medication
    - Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)

17. 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.

18. Mean resting corrected QTc interval using the Fridericia formula (QTcF) >450 msec/male and >470 msec/female (as calculated per institutional standards) obtained from 3 electrocardiograms (ECGs) 2-5 minutes apart at study entry, or congenital long QT syndrome.

19. Pregnant or lactating women.

20. Serious 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.

21. Presence of other active invasive cancers.

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

Procedures for withdrawal of incorrectly enrolled patients are described in Section 3.4.

## 3.3 Patient enrolment

Investigator(s) should keep a pre-screening log of patients considered for the study.

The Investigator(s) will:

1. Obtain signed ICF/PIS (patient information sheet) from the potential patient, or his/her guardian or legal representative before any study specific procedures are performed and obtain a patient identifier according to the instructions provided in the Study Reference Manual.

For inclusion in the optional exploratory pharmacogenetic (PGx) research patients must provide informed consent for pharmacogenetics research.

Exclusion from this pharmacogenetic 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 within 120 days of genetic sample collection

If a patient declines to participate in the optional exploratory pharmacogenetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study.

2. Provision of adequate tissue sample is mandatory for study eligibility. Molecular profile assessments may be performed on archived tumour or fresh tumour tissue taken for routine clinical purposes at baseline if archived tissues are unavailable. Please see details in the Laboratory Manual for tissue requirements.

3. Assign potential patient a unique patient/enrolment number.

4. Determine patient eligibility (See Section 3).

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

Human protection committee/Institutional Review Board (IRB) approval of this protocol and associated consent form(s) is required before any patient may be enrolled into the study.

## 3.4 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There will 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.

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

## 3.5 Methods for assigning treatment groups

Please refer to the Study Reference Manual for additional information.

## 3.6 Methods for ensuring blinding

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

## 3.7 Methods for unblinding

The study is open-label; therefore, unblinding procedures are not applicable.

## 3.8 Restrictions

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

**Female Patients**

- Women of childbearing potential (WoCBP) may be included only if acceptable contraception is in place for two weeks before study entry, for the duration of the study and for one month after the last dose of AZD1775 (see Appendix G for definitions of non-childbearing potential and acceptable contraceptive methods, including abstinence).

- WoCBP defined as: Women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

- All WoCBP must have a negative pregnancy test within 3 days of starting study treatment and confirmed prior to the start of study treatment on 1st day of dosing. This will be repeated prior to starting each treatment cycle and at the EOT Visit (see Table 2, Table 3, Table 4, and Appendix G).

**Male Patients**

- Males who are involved in the study must agree to avoid procreative sex and unprotected sex (i.e. using acceptable forms of contraception as described in Appendix G and must not donate sperm during the study and for 3 months after the last dose of AZD1775. Where the female partner is pregnant or not using effective birth control, men should abstain while in the study and for 3 months after the last dose of AZD1775.

- WoCBP who are partners of men participating in clinical studies of AZD1775 will also be required to use effective contraceptive measures (detailed in Appendix G)while their partner is on study drug and for 3 months thereafter.

- 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 while on AZD1775 or during the 3 months after stopping AZD1775.

## 3.9 Discontinuation of investigational product

Patients may be discontinued from AZD1775 in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event
- Confirmed disease progression
- Pregnancy
- Severe non-compliance with the study protocol
- Development of any study specific criteria for discontinuation
- Investigator decision
- Patient is lost to follow-up

### 3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, subjects are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.9), without prejudice to further treatment. A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 3.9); and all study drug should be returned by the subject.

If a subject is withdrawn from study, see Section 3.10.

## 3.10 Criteria for withdrawal

Reasons for withdrawal from the study:

- Withdrawal of consent
- Death
- Incorrectly enrolled or treated patient
- AE
- Patient is lost to follow-up

If a patient wishes to withdraw his/her consent to both treatment and study assessments, they should be asked if they are willing to continue with survival follow-up (which can be conducted by telephone). If a patient wishes to withdraw his/her consent to further participation in the study entirely, including survival follow-up, this should be clearly documented in the patient medical record and in the clinical study database (eCRF).

The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an analysis should be obtained by the site personnel by checking the patient's medical record, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can still be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

### 3.10.1 Screen failures

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

### 3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then their patient number cannot be reused. Withdrawn patients will not be replaced, unless they are deemed to be 'not evaluable' (see Section 7.2).

### 3.10.3 Lost to follow-up

Patients will be considered lost to follow-up only if contact was lost and could not be re-established by the time the study is completed, and there is insufficient information to determine the patient's status at that time.

Note: Patients who refuse to continue participation in the study, including phone contact, should be documented as 'withdrawal of consent' rather than 'lost to follow-up'. Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

## 3.11 Discontinuation of the study

The study may be stopped if, in the judgement 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 drug,
- 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 electronic case report form (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

The study plan and timing for procedures and assessments are described in Table 2, Table 3, and Table 4.

**Table 2 Study Plan and Assessments BID Schedule Closed to Enrollment**

| **Assessments** | **Screen (-28 days to 0)** | **Cycle 1** | | | **Cycle 2** | | | | | **Cycle 3** | | **Cycle 4** | | **Cycle 5** | | **Cycle 6 And beyond** | | **Every 8 wks (±7 days)[q]** | **EOT[r,s]** | **Safety & Response FU[z,aa];& Survival FU[bb] +/- 5 days** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **(cycle = 14 days [±1 day])** | | | | | | | | | | | | | | | | | | |
| | | Day | | | Day | | | | Day | | | Day | | Day | | **Day** | | | | |
| | Baseline | 1 | 5 | 8[z,aa] | 1 | 4 | 5 | 6 | 8[z,aa] | **1** | **5** | **1** | **5** | **1** | **5** | **1** | **3-5** | | | |
| Informed Consent | X[a] | | | | | | | | | | | | | | | | | | | |
| Medical history/ demographics | X | X[b] | | | | | | | | | | | | | | | | | | |
| Tumour genomic profiles[x] | X | | | | | | | | | | | | | | | | | | | |
| Physical examination[c] | X | X[b] | | | X | | | | | X | | X | | X | | X | | | X | |
| Vital signs[d] | X | X | | | X | | | | | X | | X | | X | | X | | | X | |
| ECOG PS | X | X[b] | | | X | | | | | X | | X | | X | | X | | | X | |
| Concomitant Medications | X | X | | | X | | | | | X | | X | | X | | X | | | X | X |
| AE evaluation[s] | | X | X | X | X | | X | | X | X | | X | | X | | X | | | X | X |
| Triplicate 12-lead ECG | X[b] | X[e] | X[e] | | X[m] | | | | | | | | | | | | | | | |
| Haematology[f] | X | X[b] | X | X | X | | X | | X | X | | X | | X | | X | | | X | |
| Chemistry[g] | X | X[b] | X | | X | | X | | | X | | X | | X | | X | | | X | |
| PT/PTT/INR[h] | X | | | | | | | | | | | | | | | | | | | |
| Pregnancy test if WoCBP[i] | X[i] | X[i] | | | X[i] | | | | | X[i] | | X[i] | | X[i] | | X[i] | | | X[i] | |

**Table 2 Study Plan and Assessments BID Schedule Closed to Enrollment**

| **Assessments** | **Screen (-28 days to 0)** | **Cycle 1** | | | **Cycle 2** | | | | | **Cycle 3** | | **Cycle 4** | | **Cycle 5** | | **Cycle 6 And beyond** | | **Every 8 wks (±7 days)** [q] | **EOT**[r,s] | **Safety & Response FU**[z,aa]**;& Survival FU**[bb] **+/- 5 days** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **(cycle = 14 days [±1 day])** | | | | | | | | | | | | | | | | | | |
| | | Day | | | Day | | | | Day | | | Day | | Day | | **Day** | | | | |
| | Baseline | 1 | 5 | 8[z,aa] | 1 | 4 | 5 | 6 | 8[z,aa] | **1** | **5** | **1** | **5** | **1** | **5** | **1** | **3-5** | | | |
| Archived or fresh tumour sample (required) | X[j] | | | | | | | | | | | | | | | | | | | |
| Optional Pharmacogenetic (PGx) blood sample | | X[y] | | | | | | | | | | | | | | | | | | |
| On-treatment tumour biopsy (required) | | | | | | X[j] | X[j] | X[j] | | | | | | | | | | | | |
| Plasma isolation sample | | X[p] | | | X[p] | | | | | X[p] | | | | X[p] | | X[p] | | | X[p] | |
| PK of AZD1775 | | X[l] | X[l] | | X[l] | | | | | | | | | | X[l] | | X[l] | | | |
| Food effect assessment | | X[m] | | | X[n] | | | | | | | | | | | | | | | |
| Tumour marker | X[w] | X[w] | | | X[w] | | | | | X[w] | | X[w] | | X[w] | | X[w] | | | X | |
| CT scan /MRI Chest | X[o] | | | | | | | | | | | | | | | | | X[o] | | X[o] |
| CT scan/ MRI Abdomen/Pelvis | X[o] | | | | | | | | | | | | | | | | | X[o] | | X[o] |
| Dispense AZD1775[k] | | X[m] | | | X[n] | | | | | X | | X | | X | | X | | | | |
| Antiemetics administration[u] | | X◆ | X | | X◆ | X | X | | | X◆ | X | X◆ | X | X◆ | X | X◆ | X | | | |
| AZD1775 administration[t,u,v] | | X◆ | X | | X◆ | X | X | | | X◆ | X | X◆ | X | X◆ | X | X◆ | X | | | |

## Table 2 Study Plan and Assessments BID Schedule Closed to Enrollment

| **Assessments** | **Screen (-28 days to 0)** | **Cycle 1** | | | **Cycle 2** | | | | | **Cycle 3** | | **Cycle 4** | | **Cycle 5** | | **Cycle 6 And beyond** | | **Every 8 wks (±7 days)** [q] | **EOT**[r,s] | **Safety & Response FU**[z,aa]**;& Survival FU**[bb] **+/- 5 days** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **(cycle = 14 days [±1 day])** | | | | | | | | | | | | | | | | | | |
| | | Day | | | Day | | | | Day | | | Day | | Day | | **Day** | | | | |
| | Baseline | 1 | 5 | 8[z,a a] | 1 | 4 | 5 | 6 | 8[z,a a] | **1** | **5** | **1** | **5** | **1** | **5** | **1** | **3-5** | | | |
| Review and/or collection dosing diary[k] | | | | | X | | | | | X | | X | | X | | | | | X | |

a Signed informed consent may be obtained prior to the 28-day screening window, if required. The screening period will then start when the tumour sample is deemed acceptable by the central lab.

b The screening/baseline medical history and demographics, physical examination, ECOG performance status, haematology, clinical chemistry, PT/PTT/INR, and triplicate ECGs should be done ≤7 days prior to initiation of treatment. If these assessments are performed within 72 hours of Cycle 1, Day 1 they do not need to be repeated prior to dosing on Cycle 1 Day 1. Scans to document measurable or evaluable disease should be performed ≤ 28 days prior to initiation of study treatment.

c Physical examinations will be done on Day 1 of each 14-day treatment cycle and at the end of treatment.

d Vital signs (heart rate, systolic and diastolic blood pressure, respiration rate, weight, height [at screening only] and oral temperature) will be collected at screening, baseline, and on Day 1 of each cycle visit and at the end of treatment.

e Triplicate ECGs will be obtained at screening to confirm eligibility (see Section 5.2), then Day 1 of each cycle. **Triplicate ECGs will be obtained 2-5 minutes apart before each PK time point collection.** Refer to Section 5.2.3.

f Haematologic samples (2.7 mL) will be collected to measure complete blood count (CBC) with differential and platelets. Samples should be taken and reviewed prior to administration of AZD1775.

g Clinical chemistry samples (2.7 mL) will be collected to measure BUN, creatinine, sodium, potassium, chloride, calcium, alkaline phosphatase (ALP), AST, ALT, total bilirubin, and albumin.

h PT/INR/PTT will be obtained at baseline. Repeat beginning of every cycle if patient is on Coumadin.

i Pregnancy tests will only be performed in women of childbearing potential at screening, within 3 days of study treatment, prior to the first dose of study treatment on Day 1 of each cycle, and at the EOT visit (See Section 3.8).

j An on-treatment tumour biopsy is required for all patients with easily accessible lesions within 12 hours of one of the last AZD1775 doses taken on Day 4 or 5 or within the first 12 hours of Day 6 in Cycle 2 unless medically contraindicated on the scheduled day in the opinion of the investigator. The exact timing of the biopsy relative to the first dose of AZD1775 should be noted as described in the Laboratory Manual.

k AZD1775 dosing compliance will be reviewed with the patient and documented at each visit. Dosing diaries will be collected at the beginning of each new cycle and at the end of treatment. The patient will be provided study medication to take home. Refer to Section 7.1 and 7.6.

l PK samples for AZD1775 with food effect assessments will be collected on Cycle 1 Day 1, Cycle 1 Day 5 and Cycle 2 Day 1 pre-dose and at 1 hour, 2, 4, 6, 8, and 10 hours post-dose. PK collections will continue on Cycle 5 Day 5 pre-dose and then pre-dose every 3-5 cycles. Note: beyond the PK for Cycle 5 Day 5, collections will be flexible for staff and patient convenience, and the PK may be collected once every 3, 4 or 5 cycles (instead of every 4 cycles) on

day 3, 4 or 5 (instead of day 5). All PK samples need to be collected within 10% of nominal time (±6 minutes for a 60 minute sample). Details for processing, handling and shipping specimens are in the Laboratory Manual. Refer to Section 5.6.

m The fasted condition requires patients to fast for ≥10 hours before AZD1775 dosing and continue until 4 hours post-dose on Cycle 1 Day 1. Patients may have glucose (sugar tablets) and/or juice (except for grapefruit juices or juices containing grapefruit or Seville oranges) if they have signs or symptoms of hypoglycaemia after they have received AZD1775 while in the fasted state. Water will be restricted from 1 hour pre-dose until 1 hour post-dose, except for the water administered with AZD1775, and any drink provided as part of the meal in the fed portion of the study (see Section 7.3).

n For the fed condition, which requires the consumption of a high-fat meal (see Section 7.3), patients will be required to fast for ≥10 hours prior to receiving AZD1775 until 4 hours post-dose, with the exception of a high-fat meal that should be eaten in the 30 minutes prior to AZD1775 being administered on Cycle 2 Day 1. The AZD1775 capsule should be administered 30 minutes after the start of meal consumption. If the meal is not completed within 30 minutes, AZD1775 may still be administered so long as 75% of the meal has been consumed within 45 minutes of the start of the meal (see Section 7.3).

o Initial (i.e. baseline) tumour imaging studies (e.g. computed tomography (CT) scan of the chest and abdomen/pelvis) will be performed within 28 days prior to the first dose of study drug (AZD1775) and will be repeated at the completion of Cycle 4 (Week 8) within 7 days before starting Cycle 5. Patients with measurable or non-measurable disease will be evaluated according the RECIST v1.1. Patients with progressive disease or unacceptable toxicity should be discontinued from the study; patients with stable disease or response to therapy will continue treatment. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at screening/baseline and during subsequent imaging procedures. Tumour imaging studies will be repeated every 4 cycles (8 weeks) to assess response.

p Blood samples will be taken for plasma isolation before dosing on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and on Day 1 of every 2 cycles afterwards (e.g. Cycles 5, 7 [see Section 5.5]).

q Patients without evidence of undue toxicity may continue treatment with study drug until disease progression as long as the investigator deems that the patient is deriving clinical benefit and desires to continue therapy.

r Patients discontinuing AZD1775 should be scheduled for an end of treatment (EOT) study visit as soon as possible after their last dose (<30 days after finishing study treatment). If treatment is discontinued during a study visit, the EOT visit does not need to be repeated. The reason for stopping treatment and date must be recorded in the electronic case report form (eCRF).

s All patients will be followed during the off-treatment period until all treatment related toxicity resolves, or for at least 30 days post-study drug discontinuation or until new therapy. This can be done via telephone contact at the Investigator's discretion. All concomitant medications received 30 days after the last dose of study medication(s) should be recorded in the medical record and eCRF.

t AZD1775 PO BID, over 5 days (10 doses), on Days 1-5 every 14 days. Fasting is required on Cycle 1 Day 1 for the food effect assessment portion of this study.

u All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO BID or granisetron (Kytril) 1 mg PO BID prior to each dose of AZD1775. Additional doses of 5-HT3 antagonist may be used if needed. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose as a minimum on the first day dosing AZD1775 of every 3-5 days dosing period, unless contraindicated or not well-tolerated. Dexamethasone or the 5-HT3 antagonist may be given by IV as needed. Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known drug-drug interactions (see Section 6.7.4.2).

v 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 ASCO guidelines. Patients should be instructed to take oral loperamide (Imodium) 2 mg every 2 hours until diarrhoea-free for at least 12 hours.

w When applicable, tumour markers that are elevated and are used by the investigator to monitor for tumour response will be collected at baseline, Day 1 of each cycle and at the end of treatment. The tumour marker analysis will be performed by a local laboratory.

x Previous individual patient genomic profile reports should be provided for this study.

y An optional Pharmacogenetics (PGx) sample will be obtained if the patient consents. If PGx blood sample is not collected at Cycle 1 Day 1, it can be collected any visit until the last study visit. This sample is **optional** and must be taken from patients who have provided informed consent for genetic sampling and analysis.

z PK samples will be collected when imaging is performed for response assessment and at the end of treatment or progression. aa Patients discontinuing from AZD1775 in the **absence** of PD should have CT scans performed every 3 months from the last dose of study drug until PD has been assessed by the Investigator or the patient begins a new course of cancer therapy or withdraws from the study. If PD has been assessed, patients will then be followed for survival.

bb Patients discontinuing from AZD1775 in the **presence** of PD will be followed every 3 months after the last dose of study drug for survival, until the last patient has discontinued study drug. The survival follow-up can be done by a medical record review or telephone call at the Investigator's discretion.

**Table 3 Study Plan and Assessments QD 5/9 Schedule Closed to Enrollment**

| **Assessments** | **Screen (-28 days to 0)** | **Cycle 1** | | | **Cycle 2** | | | | | **Cycle 3** | | **Cycle 4** | | **Cycle 5** | | **Cycle 6 and beyond** | | **Every 8 wks (±7 days)[s]** | **EOT[t,u,gg]** | **Safety & Response FU[s, cc];& Survival FU[dd]** +/- 5 days | **FPV[ff]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | (cycle = 14 days [±1 day]) | | | | | | | | | | | | | | | | | | | |
| | | **Day** | | | **Day** | | | | | **Day** | | **Day** | | **Day** | | **Day** | | | | | |
| | **Baseline** | **1** | **5** | **8[bb, cc]** | **1** | **4** | **5** | **6** | **8[bb, cc]** | **1** | **5** | **1** | **5** | **1** | **3-5** | **1** | **3-5[gg]** | | | | |
| Informed consent | X[a] | | | | | | | | | | | | | | | | | | | | |
| Medical history/ demographics | X | X[b] | | | | | | | | | | | | | | | | | | | |
| Tumour genomic profiles[z] | X | | | | | | | | | | | | | | | | | | | | |
| Physical examination[c] | X | X[b] | | | X | | | | | X | | X | | X | | X | | | X | | X |
| Vital signs[d] | X | X | | | X | | | | | X | | X | | X | | X | | | X | | X |
| ECOG PS | X | X[b] | | | X | | | | | X | | X | | X | | X[gg] | | | X | | |
| Concomitant medications[u] | X | X | | | X | | | | | X | | X | | X | | X | | | X | X | X |
| AE evaluation[ee] | | X | X | X | X | | X | | X | X | | X | | X | | X | | | X | X | X |
| Triplicate 12-lead ECG | X[b] | X[e] | X[e] | | X | | | | | X | | X | | X | | X | | | | | X |
| Haematology[f] | X | X[b] | X | X | X | | X | | X | X | | X | | X | | X | | | X | | X |
| Chemistry[g] | X | X[b] | X | X | X | | X | | X | X | | X | | X | | X | | | X | | X |
| PT/PTT/INR[h] | X | | | | | | | | | | | | | | | | | | | | |
| Pregnancy test if WoCBP[i] | X[i] | X[i] | | | X[i] | | | | | X[i] | | X[i] | | X[ii] | | X[ii] | | | X[i] | | X |
| Archived or fresh tumour sample (required) | X[j] | | | | | | | | | | | | | | | | | | | | |

**Table 3 Study Plan and Assessments QD 5/9 Schedule Closed to Enrollment**

| Assessments | Screen (-28 days to 0) | Cycle 1 | | | Cycle 2 | | | | | Cycle 3 | | Cycle 4 | | Cycle 5 | | Cycle 6 and beyond | | Every 8 wks (±7 days)[s] | EOT[t,u,gg] | Safety & Response FU[s, cc];& Survival FU[dd] +/- 5 days | FPV[ff] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | (cycle = 14 days [±1 day]) | | | | | | | | | | | | | | | | | | | |
| | | Day | | | Day | | | | | Day | | Day | | Day | | Day | | | | | |
| | Baseline | 1 | 5 | 8[bb, cc] | 1 | 4 | 5 | 6 | 8[bb, cc] | 1 | 5 | 1 | 5 | 1 | 3-5 | 1 | 3-5[gg] | | | | |
| Optional Pharmacogenetic (PGx) blood sample | | X[aa] | | | | | | | | | | | | | | | | | | | |
| On-treatment tumour biopsy (required) | | | | | | X[k] | X[k] | X[k] | | | | | | | | | | | | | |
| Plasma isolation sample | | X[r] | | | X[r] | | | | | X[r] | | X[r] | | X[r] | | X[r] | | | X[r] | | X[r] |
| PK of AZD1775[bb] | | X[m,n] | X[m,n] | | X[n] | | | | | | | | | | X[m,n] | | X[m,n,gg] | X[bb] | X[bb] | | |
| Food effect assessment **(At MTD/RP2D ONLY)** | | X[o] | | | X[p] | | | | | | | | | | | | | | | | |
| Tumour marker | X[y] | X[y] | | | X[y] | | | | | X[y] | | X[y] | | X[y] | | X[y] | | | X | | X |
| CT scan /MRI chest | X[q] | | | | | | | | | | | | | | | | | X[q] | | X | |
| CT scan/ MRI abdomen/pelvis | X[q] | | | | | | | | | | | | | | | | | X[q] | | X | |
| Dispense AZD1775[l] | | X[o] | | | X[p] | | | | | X | | X | | X | | X | | | | | X |
| Antiemetics administration[w] | | X ◆— | X | | X ◆— | X | X ◆ | | | X ◆ | X | X ◆ | X | X ◆ | X | X ◆ | X | | | | X |

**Table 3 Study Plan and Assessments QD 5/9 Schedule Closed to Enrollment**

| **Assessments** | **Screen (-28 days to 0)** | **Cycle 1** | | | **Cycle 2** | | | | | **Cycle 3** | | **Cycle 4** | | **Cycle 5** | | **Cycle 6 and beyond** | | **Every 8 wks (±7 days)[s]** | **EOT[t,u,gg]** | **Safety & Response FU[s], [cc];& Survival FU[dd]** | **FPV[ff]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | (cycle = 14 days [±1 day]) | | | | | | | | | | | | | | | | | | **+/- 5 days** | |
| | | **Day** | | | **Day** | | | | | **Day** | | **Day** | | **Day** | | **Day** | | | | | |
| | **Baseline** | **1** | **5** | **8[bb, cc]** | **1** | **4** | **5** | **6** | **8[bb, cc]** | **1** | **5** | **1** | **5** | **1** | **3-5** | **1** | **3-5[gg]** | | | | |
| AZD1775 administration[w,x, cc] | | X ◆—◆ | X | | X ◆—◆ | X | X | | | X ◆—◆ | X | X ◆—◆ | X | X ◆—◆ | X | X ◆—◆ | X | | | | X |
| Review and/or collection dosing diary[l] | | | | | X | | | | | X | | X | | X | | X | | | X | | X |

a Signed informed consent may be obtained prior to the 28-day screening window, if required.

b The screening/baseline medical history and demographics, physical examination, ECOG performance status, haematology, clinical chemistry, PT/PTT/INR, and triplicate ECGs should be done ≤7 days prior to initiation of treatment. If these assessments are performed within 72 hours of Cycle 1, Day 1 they do not need to be repeated prior to dosing on Cycle 1 Day 1. Scans to document measurable or evaluable disease should be performed ≤ 28 days prior to initiation of study treatment.

c Physical examinations will be done on Day 1 of each 14-day treatment cycle and at the end of treatment.

d Vital signs (heart rate, systolic and diastolic blood pressure, respiration rate, weight, height [at screening only] and oral temperature) will be collected at screening, baseline, and on Day 1 of each cycle visit, at the end of treatment, and the final protocol visit (FPV).

e Triplicate ECGs will be obtained at screening to confirm eligibility (see Section 5.2), then on Day 1 of each cycle. **Triplicate ECGs will be obtained 2-5 minutes apart before each PK time point collection.** Refer to Section 5.2.3.

f Haematologic samples (2.7 mL) will be collected to measure complete blood count (CBC) with differential and platelets. Samples should be taken and reviewed prior to administration of AZD1775.

g Clinical chemistry samples (2.7 mL) will be collected to measure BUN, creatinine, sodium, potassium, chloride, calcium, alkaline phosphatase (ALP), AST, ALT, total bilirubin, and albumin.

h PT/INR/PTT will be obtained at baseline. Repeat beginning of every cycle if patient is on Coumadin.

i Pregnancy tests will only be performed in women of childbearing potential at screening, within 3 days of study treatment, prior to the first dose of study treatment on Day 1 of each cycle, at the EOT visit and the FPV (see Section 3.8).

j Patients are required to provide an archival tumour sample or fresh/recent tumour sample to participate in the study (see Section 5.6). Refer to the Laboratory Manual for additional information around sample requirements.

k An on-treatment tumour biopsy is required for all patients with easily accessible lesions within 12 hours of one of the last AZD1775 doses taken on Day 4 or 5 or within the first 12 hours of Day 6 in Cycle 2 unless medically contraindicated on the scheduled day in the opinion of the investigator. The exact timing of the biopsy relative to the first dose of AZD1775 should be noted as described in the Laboratory Manual.

l AZD1775 dosing compliance will be reviewed with the patient and documented at each visit. Dosing diaries will be collected at the beginning of each new cycle and at the end of treatment. The patient will be provided study medication to take home. Refer to Section 7.1 and 7.6

m PK samples for AZD1775 non-food effect patients will be collected on Cycle 1 Day 1 and Cycle 1 Day 5 pre-dose and at 1 hour, 2, 4, 6, 8, 10 and 24 hours post-dose. On Cycle 5 Day 5, non-food effect PK samples will be taken pre-dose only and then pre-dose only every 3-5 cycles. Note: beyond the PK for Cycle 5 Day 5, collections will be flexible for staff and patient convenience, and the PK may be collected once every 3, 4 or 5 cycles (instead of every 4 cycles) on day 3, 4 or 5 (instead of day 5). All PK samples need to be collected within 10% of nominal time (±6 minutes for a 60 minute sample). Details for processing, handling and shipping specimens are in the Laboratory Manual. PK samples will no longer be required after implementation of CSP Version 5.

n **For approximately 12 Patients AT MTD/RP2D**: PK samples for AZD1775 will be collected on Cycle 1 Day 1, Cycle 1 Day 5 and Cycle 2 Day 1 pre-dose and at 1 hour, 2, 4, 6, 8, and 10 hours post-dose. On Cycle 5 Day 5, PK samples will be taken pre-dose only and then pre-dose only every 3-5 cycles. Note: beyond the PK for Cycle 5 Day 5, collections will be flexible for staff and patient convenience, and the PK may be collected once every 3, 4 or 5 cycles (instead of every 4 cycles) on day 3, 4 or 5 (instead of day 5). All PK samples need to be collected within 10% of nominal time (±6 minutes for a 60 minute sample). Details for processing, handling and shipping specimens are in the Laboratory Manual. Refer to Section 5.6. PK samples will no longer be required after implementation of CSP Version 5.

o **QD RP2D Safety and Food Effect expansion patients only-**The fasted condition requires patients to fast for ≥10 hours before AZD1775 dosing and continue until 4 hours post-dose on Cycle 1 Day 1. Patients may have glucose (sugar tablets) and/or juice (except for grapefruit juices or juices containing grapefruit or Seville oranges) if they have signs or symptoms of hypoglycaemia after they have received AZD1775 while in the fasted state. Water will be

restricted from 1 hour pre-dose until 1 hour post-dose, except for the water administered with AZD1775, and any drink provided as part of the meal in the fed portion of the study (see Section 7.3).

p **QD RP2D Safety and Food Effect expansion patients only-**For the fed condition, which requires the consumption of a high-fat meal (see Section 7.3, patients will be required to fast for ≥10 hours prior to receiving AZD1775 until 4 hours post-dose, with the exception of a high-fat meal that should be eaten in the 30 minutes prior to AZD1775 being administered on Cycle 2 Day 1. The AZD1775 capsule should be administered 30 minutes after the start of meal consumption. If the meal is not completed within 30 minutes, AZD1775 may still be administered so long as 75% of the meal has been consumed within 45 minutes of the start of the meal (see Section 7.3).

q Initial (i.e. baseline) tumour imaging assessments (e.g. computed tomography (CT) scan of the chest and abdomen/pelvis) will be performed within 28 days prior to the first dose of study drug (AZD1775) and repeated every 8 weeks (± 1 week) relative to the date of first dose until disease progression. Patients with measurable or non-measurable disease will be evaluated according to RECIST v1.1. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at screening/baseline and during subsequent imaging procedures.

r Blood samples will be taken for plasma isolation before dosing on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, and on Day 1 of every 2 cycles afterwards (e.g. Cycles 6, 8 [see Section 5.5]), EOT and FPV. Patients continuing treatment after FPV will have a plasma sample collected at the time the time of progression.

s Patients without evidence of undue toxicity may continue treatment with study drug until disease progression as long as the investigator deems that the patient is deriving clinical benefit and desires to continue therapy.

t Patients discontinuing AZD1775 should be scheduled for an end of treatment (EOT) study visit as soon as possible after their last dose (<30 days after finishing study treatment). If treatment is discontinued during a study visit, the EOT visit does not need to be repeated. The reason for stopping treatment and date must be recorded in the electronic case report form (eCRF). The EOT visit is **not** required for subjects continuing treatment after the FPV. The FPV should be considered as the patient's next cycle scheduled visit after the implementation of CSP Version 5.

u All patients will be followed during the off-treatment period until all treatment related toxicity resolves, or for at least 30 days post-study drug discontinuation or until new therapy. This can be done via telephone contact at the Investigator's discretion. All concomitant medications received 30 days after the last dose of study medication(s) should be recorded in the medical record and eCRF.

v AZD1775 PO QD, over 5 days, on Days 1-5 every 14 days. AZD1775 should be taken under fasting conditions with 8 ounces of water approximately 2 hours before or after food.

w All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO QD or granisetron (Kytril) 1 mg PO QD prior to each dose of AZD1775. If nausea and vomiting continue, a second dose of antiemetics can be taken 8 hours later, if necessary. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose as a minimum on the first day dosing AZD1775 of every 3-5 days dosing period, unless contraindicated or not well-tolerated. Dexamethasone or the 5-HT3 antagonist may be given by IV as needed. Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known drug-drug interactions (see Section 6.7.4.2).

x 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 ASCO guidelines. Patients should be instructed to take oral loperamide (Imodium) 2 mg every 2 hours until diarrhoea-free for at least 12 hours.

y When applicable, tumour markers that are elevated and are used by the Investigator to monitor for tumour response will be collected at baseline, Day 1 of each cycle, at the end of treatment and FPV. The tumour marker analysis will be performed by a local laboratory.

z Previous individual patient genomic profile reports should be provided for this study.

aa An optional Pharmacogenetics (PGx) sample will be obtained if the patient consents. If PGx blood sample is not collected at Cycle 1 Day 1, it can be collected any visit until the last study visit. This sample is **optional** and must be taken from patients who have provided informed consent for genetic sampling and analysis.

bb PK samples will be collected at time of AE possibly related to AZD1775 (unless the last dose of study drug was administered > 1 week prior to the event), when imaging is performed for response assessment and at the end of treatment or progression. PK samples will no longer be required after implementation of CSP Version 5.

cc Patients discontinuing from AZD1775 in the **absence** of PD should have CT scans performed every 3 months from the last dose of study drug until PD has been assessed by the Investigator or the patient begins a new course of cancer therapy or withdraws from the study. If PD has been assessed, patients will then be followed for survival.

dd Patients discontinuing from AZD1775 in the **presence** of PD will be followed every 3 months after the last dose of study drug for survival, until the last patient has discontinued study drug. The survival follow-up can be done by a medical record review or telephone call at the Investigator's discretion.

ee PK samples will also be collected at the time of AEs possibly related to AZD1775 (unless the last dose of study drug was administered > 1 week prior to the event)ff The FPV is to be performed only for patients who continue AZD1775 after the implementation of CSP Version 5. This FPV should be aligned with the patient's next scheduled visit. After the FPV, only serious adverse events, pregnancies, and overdoses will be collected until 30 (±7) days following the patient's last dose of AZD1775. Beyond the FPV, patients may continue to receive AZD1775 if they are deriving clinical benefit, in the opinion of the investigator, and not fulfilling any discontinuation criteria. Such patients are to be treated in accordance with local practice and as deemed appropriate by the Investigator to ensure continued safety monitoring of the patient while receiving the investigational product. The EOT and subsequent follow-up visits, are **not** required for patients continuing treatment after the FPV.

gg PK samples, ECOG performance status and EOT assessments will no longer be required after implementation of CSP Version 5.

**Table 4 Study Plan and Assessments QD 5/2 Schedules Closed to Enrollment**

| Assessments | Screen (-28 days to 0) | Cycle 1 | | | | | | Cycle 2 | | | | | | | | Cycle 3, Cycle 4, Cycle 5 and beyond | | | | | | Every 9 wks (±7 days)[s] | EOT[t,u,kk] | Safety & Response FU[sdd]; & Survival FU[ee] +/- 5 days | FPV[jj] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | (cycle = 21 days [±1 day]) | | | | | | | | | | | | | | | | | | | | | | | |
| | | Day | | | | | | Day | | | | | | | | Day | | | | | | | | | |
| | Baseline | 1 | 5 | 8[bb,cc] | 12[cc] | 15 | 19 | 1 | 4 | 5 | 6 | 8[bb,cc] | 12[cc] | 15 | 19 | 1 | 5[kk] | 8[cc,kk] | 12[cc] | 15 | 19 | | | | |
| Informed consent | X[a] | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical history/ demographics | X | X[b] | | | | | | | | | | | | | | | | | | | | | | | |
| Tumour genomic profiles[z] | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical examination[c] | X | X[b] | | | | | | X | | | | | | | | X | | | | | | | X | | X |
| Vital signs[d] | X | X | | | | | | X | | | | | | | | X | | | | | | | X | | X |
| ECOG PS | X | X[b] | | | | | | X | | | | | | | | X[kk] | | | | | | | X | | |
| Concomitant medications | X | X | | | | | | X | | | | | | | | X | | | | | | | X | X | X |
| AE evaluation[ii] | | X | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | | X | X | X |
| Triplicate 12-lead ECG | X[b] | X[e] | X[e] | | | | | X | | | | | | | | X | X[hh] | | | | | | | | X |

**Table 4 Study Plan and Assessments QD 5/2 Schedules Closed to Enrollment**

| **Assessments** | **Screen (-28 days to 0)** | **Cycle 1** | | | | | | **Cycle 2** | | | | | | | | **Cycle 3, Cycle 4, Cycle 5 and beyond** | | | | | | **Every 9 wks (±7 days)[s]** | **EOT[t],[u, kk]** | **Safety & Response FU[sdd]; & Survival FU[ee] +/- 5 days** | **FPV[ij]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **(cycle = 21 days [±1 day])** | | | | | | | | | | | | | | | | | | | | | | |
| | | **Day** | | | | | | **Day** | | | | | | | | **Day** | | | | | | | | |
| | **Baseline** | **1** | **5** | **8[bb],[cc]** | **12[cc]** | **15** | **19** | **1** | **4** | **5** | **6** | **8[bb],[cc]** | **12[cc]** | **15** | **19** | **1** | **5[kk]** | **8[cc],[kk]** | **12[cc]** | **15** | **19** | | | | |
| Haematology[f] | X | X[b] | X | X[bb] | | X | | X | | X | | X[bb] | | X | | X | | X | | X | | | X | | X |
| Chemistry[g] | X | X[b] | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | | X | | X |
| PT/PTT/INR[h] | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy test if WoCBP[i] | X[i] | X[i] | | | | | | X[i] | | | | | | | | X[i] | | | | | | | X[i] | | X |
| Archived or fresh tumour sample (required) | X[j] | | | | | | | | | | | | | | | | | | | | | | | | |
| Optional pharmacogenetic (PGx) blood sample | | X[aa] | | | | | | | | | | | | | | | | | | | | | | | |
| On-treatment tumour biopsy (required) | | | | | | | | | X[k] | X[k] | X[k] | | | | | | | | | | | | | | |
| Plasma isolation sample | | X[r] | | | | | | X[r] | | | | | | | | X[r] | | | | | | | X[r] | | $X_r$ |

**Table 4 Study Plan and Assessments QD 5/2 Schedules Closed to Enrollment**

| Assessments | Screen (-28 days to 0) | Cycle 1 | | | | | | Cycle 2 | | | | | | | | Cycle 3, Cycle 4, Cycle 5 and beyond | | | | | | Every 9 wks (±7 days)[s] | EOT[t,u, kk] | Safety & Response FU[sdd]; & Survival FU[ee] +/- 5 days | FPV[ij] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | (cycle = 21 days [±1 day]) | | | | | | | | | | | | | | | | | | | | | | | |
| | | Day | | | | | | Day | | | | | | | | Day | | | | | | | | | |
| | Baseline | 1 | 5 | 8[bb, cc] | 12[cc] | 15 | 19 | 1 | 4 | 5 | 6 | 8[bb, cc] | 12[cc] | 15 | 19 | 1 | 5[kk] | 8[cc, kk] | 12[cc] | 15 | 19 | | | | |
| PK of AZD1775[cc] | | X[m, n] | X[m, n] | | | | | X[n] | | | | | | | | | | X[m,n, kk] | | | | X[cc] | X[cc] | | |
| Food effect assessment **(At MTD/RP2D ONLY)** | | X[o] | | | | | | X[p] | | | | | | | | | X[m. n, kk] | | | | | | | | |
| Tumour marker | X[y] | X[y] | | | | | | X[y] | | | | | | | | X[y] | | | | | | | X[y] | | X |
| CT scan /MRI chest | X[q] | | | | | | | | | | | | | | | | | | | | | X[q] | | X | |
| CT scan/ MRI abdomen/pelvis | X[q] | | | | | | | | | | | | | | | | | | | | | X[q] | | X | |
| Dispense AZD1775[l] | | X[o] | | | | | | X[p] | | | | | | | | X | | | | | | | | | X |
| Antiemetics administration[w,ff] | | X ◆ | X ◆ | X[ff] ◆ | X[ff] ◆ | X[ff] ◆ | X[ff] ◆ | X ◆ | X — | X ◆ | | X[ff] ◆ | X[ff] ◆ | X[ff] ◆ | X[ff] ◆ | X ◆ | X ◆ | X[ff] ◆ | X[ff] ◆ | X[ff] ◆ | X[ff] ◆ | | | | X |

**Table 4 Study Plan and Assessments QD 5/2 Schedules Closed to Enrollment**

| **Assessments** | **Screen (-28 days to 0)** | **Cycle 1** | | | | | | **Cycle 2** | | | | | | | | **Cycle 3, Cycle 4, Cycle 5 and beyond** | | | | | | **Every 9 wks (±7 days)[s]** | **EOT[t],[u, kk]** | **Safety & Response FU[sdd]; & Survival FU[ee] +/- 5 days** | **FPV[ij]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **(cycle = 21 days [±1 day])** | | | | | | | | | | | | | | | | | | | | | | |
| | | **Day** | | | | | | **Day** | | | | | | | | **Day** | | | | | | | | |
| | **Baseline** | **1** | **5** | **8[bb],[cc]** | **12[cc]** | **15** | **19** | **1** | **4** | **5** | **6** | **8[bb],[cc]** | **12[cc]** | **15** | **19** | **1** | **5[kk]** | **8[cc],[kk]** | **12[cc]** | **15** | **19** | | | | |
| AZD1775 administration[w,x,,gg] | | X ◆—◆ | X | X gg ◆—◆ | X gg | X gg ◆—◆ | X gg | X ◆———◆ | X | X | | X gg ◆—◆ | X gg | X gg ◆—◆ | X gg | X ◆—◆ | X | X gg ◆—◆ | X gg | X gg ◆—◆ | X gg | | | | X |
| Review and/or collection dosing diary[l] | | | | | | | | X | | | | | | | | X | | | | | | | X | | X |

a Signed informed consent may be obtained prior to the 28-day screening window, if required.

b The screening/baseline medical history and demographics, physical examination, ECOG performance status, haematology, clinical chemistry, PT/PTT/INR, and triplicate ECGs should be done ≤7 days prior to initiation of treatment. If these assessments are performed within 72 hours of Cycle 1, Day 1 they do not need to be repeated prior to dosing on Cycle 1 Day 1. Scans to document measurable or evaluable disease should be performed ≤ 28 days prior to initiation of study treatment.

c Physical examinations will be done on Day 1 of each 21-day treatment cycle and at the end of treatment.

d Vital signs (heart rate, systolic and diastolic blood pressure, respiration rate, weight, height [at screening only] and oral temperature) will be collected at screening, baseline, and on Day 1 of each cycle visit, at the end of treatment, and the FPV.

e Triplicate ECGs will be obtained at screening to confirm eligibility (see Section 5.2), then on Day 1 of each cycle. **Triplicate ECGs will be obtained 2-5 minutes apart before each PK timepoint collection.** Refer to Section 5.2.3.

f Haematologic samples (2.7 mL) will be collected to measure complete blood count (CBC) with differential and platelets. Samples should be taken and reviewed prior to administration of AZD1775.

g Clinical chemistry samples (2.7 mL) will be collected to measure BUN, creatinine, sodium, potassium, chloride, calcium, alkaline phosphatase (ALP), AST, ALT, total bilirubin, and albumin.

h PT/INR/PTT will be obtained at baseline. Repeat beginning of every cycle if patient is on Coumadin.

i Pregnancy tests will only be performed in women of childbearing potential at screening, within 3 days of study treatment, prior to the first dose of study treatment on Day 1 of each cycle, at the EOT visit, and the FPV (see Section 3.8).

j Patients are required to provide an archival tumour sample or fresh/recent tumour sample to participate in the study (see Section 5.6). Refer to the Laboratory Manual for additional information around sample requirements.

k An on-treatment tumour biopsy is required for all patients with easily accessible lesions within 12 hours of one of the last AZD1775 doses taken on Day 4 or 5 or within the first 12 hours of Day 6 in Cycle 2 unless medically contraindicated on the scheduled day in the opinion of the Investigator. The exact timing of the biopsy relative to the first dose of AZD1775 should be noted as described in the Laboratory Manual.

l AZD1775 dosing compliance will be reviewed with the patient and documented at each visit. Dosing diaries will be collected at the beginning of each new cycle and at the end of treatment. The patient will be provided study medication to take home. Refer to Section 7.1 and 7.6.

m PK samples for AZD1775 will be collected on Cycle 1 Day 1 and Cycle 1 Day 5 pre-dose and at 1 hour, 2, 4, 6, 8, 10 and 24 hours post-dose. On Cycle 5 Day 5 PK samples will be taken pre-dose only and then pre-dose only every 3-5 cycles. Note: beyond the PK for Cycle 5 Day 5, collections will be flexible for staff and patient convenience, and the PK may be collected once every 3, 4 or 5 cycles (instead of every 4 cycles) on day 3, 4 or 5 (instead of day 5). All PK samples need to be collected within 10% of nominal time (±6 minutes for a 60 minute sample). Details for processing, handling and shipping specimens are in the Laboratory Manual. PK samples will no longer be required after implementation of CSP Version 5.

n **For approximately 12 Patients AT MTD/RP2D**: PK samples for AZD1775 will be collected on Cycle 1 Day 1, Cycle 1 Day 5 and Cycle 2 Day 1 pre-dose and at 1 hour, 2, 4, 6, 8, and 10 hours post-dose. On Cycle 5 Day 5, PK samples will be taken pre-dose only and then pre-dose only every 3-5 cycles. Note: beyond the PK for Cycle 5 Day 5, collections will be flexible for staff and patient convenience, and the PK may be collected once every 3, 4 or 5 cycles (instead of every 4 cycles) on day 3, 4 or 5 (instead of day 5). All PK samples need to be collected within 10% of nominal time (±6 minutes for a 60 minute sample). Details for processing, handling and shipping specimens are in the Laboratory Manual. Refer to Section 5.6. PK samples will no longer be required after implementation of CSP Version 5.

o **QD RP2D safety and food effect expansion patients only-**The fasted condition requires patients to fast for ≥10 hours before AZD1775 dosing and continue until 4 hours post-dose on Cycle 1 Day 1. Patients may have glucose (sugar tablets) and/or juice (except for grapefruit juices or juices containing grapefruit or Seville oranges) if they have signs or symptoms of hypoglycaemia after they have received AZD1775 while in the fasted state.

Water will be restricted from 1 hour pre-dose until 1 hour post-dose, except for the water administered with AZD1775, and any drink provided as part of the meal in the fed portion of the study (see Section 7.3).

p **QD RP2D safety and food effect expansion patients only-**For the fed condition, which requires the consumption of a high-fat meal (see Section 7.3), patients will be required to fast for ≥10 hours prior to receiving AZD1775 until 4 hours post-dose, with the exception of a high-fat meal that should be eaten in the 30 minutes prior to AZD1775 being administered on Cycle 2 Day 1. The AZD1775 capsule should be administered 30 minutes after the start of meal consumption. If the meal is not completed within 30 minutes, AZD1775 may still be administered so long as 75% of the meal has been consumed within 45 minutes of the start of the meal (see Section 7.3).

q Initial (i.e. baseline) tumour imaging assessments (e.g. computed tomography (CT) scan of the chest and abdomen/pelvis) will be performed within 28 days prior to the first dose of study drug (AZD1775) and repeated every 9 weeks (± 1 week) relative to the date of first dose until disease progression. Patients with measurable or non-measurable disease will be evaluated according to RECIST v1.1. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at screening/baseline and during subsequent imaging procedures.

r Blood samples will be taken for plasma isolation before dosing on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, and on Day 1 of every 2 cycles afterwards (e.g. Cycles 6, 8 [see Section 5.5]), EOT and FPV. Patients continuing treatment after FPV will have a plasma sample collected at the time the time of progression.

s Patients without evidence of undue toxicity may continue treatment with study drug until disease progression as long as the investigator deems that the patient is deriving clinical benefit and desires to continue therapy.

t Patients discontinuing AZD1775 should be scheduled for an end of treatment (EOT) study visit as soon as possible after their last dose (<30 days after finishing study treatment). If treatment is discontinued during a study visit, the EOT visit does not need to be repeated. The reason for stopping treatment and date must be recorded in the electronic case report form (eCRF). The EOT visit is is **not** required for subjects continuing treatment after the FPV. The FPV should be considered as the patient's next cycle day 1 scheduled visit after the implementation of CSP Version 5.

u All patients will be followed during the off-treatment period until all treatment related toxicity resolves, or for at least 30 days post-study drug discontinuation or until new therapy. This can be done via telephone contact at the Investigator's discretion. All concomitant medications received 30 days after the last dose of study medication(s) should be recorded in the medical record and eCRF.

v AZD1775 PO QD on Days 1-5 and Days 8-12 every 21 days. AZD1775 should be taken under fasting conditions with 8 ounces of water approximately 2 hours before or after food.

w All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO QD or granisetron (Kytril) 1 mg PO QD prior to each dose of AZD1775. If nausea and vomiting continue, a second dose of antiemetics can be taken 8 hours later, if necessary. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose as a minimum on the first day dosing AZD1775 of every 3-5 days dosing period, unless contraindicated or not well-tolerated. Dexamethasone or the 5-HT3 antagonist may be given by IV as needed. Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known drug-drug interactions (see Section 6.7.4.2).

x 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 ASCO guidelines. Patients should be instructed to take oral loperamide (Imodium) 2 mg every 2 hours until diarrhoea-free for at least 12 hours.

y When applicable, tumour markers that are elevated and are used by the Investigator to monitor for tumour response will be collected at baseline, Day 1 of each cycle, at the end of treatment and FPV. The tumour marker analysis will be performed by a local laboratory.

z Previous individual patient genomic profile reports should be provided for this study.

aa An optional Pharmacogenetics (PGx) sample will be obtained if the patient consents. If PGx blood sample is not collected at Cycle 1 Day 1, it can be collected any visit until the last study visit. This sample is **optional** and must be taken from patients who have provided informed consent for genetic sampling and analysis.

bb The haematology blood samples will be taken **before the patient takes their study medication** on Cycle 1 Day 8 and Cycle 2 Day 8. (On this day the patient should bring the study medication to the clinic and take as instructed by the treating physician).

cc PK samples will be collected at time of AE possibly related to AZD1775 (unless the last dose of study drug was administered > 1 week prior to the event), when imaging is performed for response assessment and at the end of treatment or progression. PK samples will no longer be required after implementation of CSP Version 5.

dd Patients discontinuing from AZD1775 in the **absence** of PD should have CT scans performed every 3 months from the last dose of study drug until PD has been assessed by the Investigator or the patient begins a new course of cancer therapy or withdraws from the study. If PD has been assessed, patients will then be followed for survival.

bb Patients discontinuing from AZD1775 in the **presence** of PD will be followed every 3 months after the last dose of study drug for survival, until the last patient has discontinued study drug. The survival follow-up can be done by a medical record review or telephone call at the Investigator's discretion.

ff Antiemetics will be taken on the same days of AZD1775 dosing, therefore patients in QD Cohorts 1.2, 2.2, 3.2, and 4.2 will take antiemetics on a 5/2 dosing schedule (days 1-5, 8-12 every21 day-cycle; no treatment on days 6-7 and 13-21). Patients in QD Cohorts 2.3 and 3.3 will take antiemetics on a 5/2 weekly dosing schedule (days 1-5, 8-12 **and 15-19** every 21-day cycle; no treatment on days 6-7, 13-14, and 20-21)

gg Patients in QD Cohorts 1.2, 2.2, 3.2, and 4.2 will take AZD1775 on a 5/2 dosing schedule (days 1-5, 8-12 every21 day-cycle; no treatment on days 6-7 and 13-21). Patients in QD Cohorts 2.3 and 3.3 will take AZD1775 on a 5/2 weekly dosing schedule (days 1-5, 8-12 **and 15-19** every 21-day cycle; no treatment on days 6-7, 13-14, and 20-21). See Figure 3 and Figure 4.

hh Triplicate ECG should be done on Cycle 3 and beyond Day 5 ONLY on days that PK samples are to be collected. See footnotes m and n and Section5.4 for further details.

ii PK samples will also be collected at the time of AEs possibly related to AZD1775 (unless the last dose of study drug was administered > 1 week prior to the event)

jj The FPV is to be performed only for patients who continue AZD1775 after the implementation of CSP Version 5. This FPV should be aligned with the patient's next scheduled visit. After the FPV, only serious adverse events, pregnancies, and overdoses will be collected until 30 (±7) days following the patient's last dose of AZD1775. Beyond the FPV, patients may continue to receive AZD1775 if they are deriving clinical benefit, in the opinion of the investigator, and not fulfilling any discontinuation criteria. Such patients are to be treated in accordance with local practice and as deemed appropriate by the Investigator to ensure continued safety monitoring of the patient while receiving the investigational product. The EOT and subsequent follow-up visits, are **not** required for patients continuing treatment after the FPV.

kk PK samples, ECOG performance status and EOT assessments will no longer be required after implementation of CSP Version 5.

## 4.1 Enrolment/screening period

Procedures will be performed according to the Study Plan described in Table 2, Table 3, and Table 4. The screening period begins once the patient has signed the informed consent.

Consent may be taken prior to the 28-day window if required. The screening period will then start when the tumour sample is deemed acceptable by the central lab.

Subjects will be considered in screening/enrolment period until all screening assessments are completed and eligibility is confirmed.

## 4.2 Treatment period

A patient is defined as being on-study if they are continuing to have any study data collected, if the patient is receiving study specific treatment, is being followed for efficacy after discontinuation of protocol specific treatment, or is in follow-up (see Table 2, Table 3, and Table 4).

## 4.3 Follow-up period

Patients discontinuing study treatment should be scheduled for an End of Treatment (EOT) visit as soon as possible after their last dose. At that visit all assessments listed in the EOT visit column in Table 2, Table 3, and Table 4 will be performed. If treatment is discontinued during a study visit, the EOT visit does not need to be repeated. The reason for stopping treatment and the date must be recorded in the eCRF.

### 4.3.1 30-day safety evaluation

After discontinuation from study treatment, patients must be followed for AEs for 30 days, after their last dose (see Section 6) or until new cancer therapy is started, whichever is shorter. This can be done via telephone contact at the Investigator's discretion. All concomitant medications received up to 30 days after the last dose of study medication should be recorded in the medical record and eCRF.

All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical records and as a comment in the eCRF.

All patients who have Grade 3 or 4 laboratory abnormalities (per NCI CTCAE v4.03 [http://ctep.cancer.gov]) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless in the opinion of the investigator it is not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patient's medical records and as a comment on the eCRF.

### 4.3.2 Follow-up period

#### 4.3.2.1 Follow-up for patients who discontinue treatment prior to disease progression

Patients discontinuing from AZD1775 in the absence of PD should have progression-free survival (PFS) CT assessments performed according to Table 2, Table 3, and Table 4 until PD has been assessed by the Investigator. If PD has been assessed, patients will then be followed for survival.

#### 4.3.2.2 Follow-up for patients who discontinue treatment due to disease progression

Patients with documented disease progression will be followed every 3 months for survival status (e.g., date and cause of death). Patients may be contacted during outpatient visits or by telephone. Information pertaining to the type and dates of administered post-treatment therapy will be collected when available (see Table 2, Table 3, and Table 4).

#### 4.3.2.3 Final Protocol Visit and Beyond

The Final Protocol Visit (FPV) requirement applies only to patients who continue AZD1775 after the implementation of the Clinical Study Protocol (CSP) Version 5. Patients should return to the clinic soon after the CSP Version 5 is implemented in order to be re-consented on the associated updated ICF.

Beyond the FPV, patients may continue to receive AZD1775 if they are deriving clinical benefit, in the opinion of the Investigator, and not fulfilling any of the discontinuation criteria. Such patients are to be treated in accordance with local practice and as deemed appropriate by the Investigator to ensure continued safety monitoring of the patient while receiving the investigational product. It is recommended to continue observing ongoing patients at the frequency indicated within the study plans as described in Table 3 and Table 4. Restrictions regarding concomitant medications (refer to Section 7.8.2) will be followed while the patient is receiving AZD1775. A change in AZD1775 dose/schedule should only occur for safety reasons, based on the Investigator's judgement, and should generally follow the approach for dose reduction and discontinuation as described in this protocol. Combining AZD1775 with other anti-cancer therapy is not allowed.

If a patient is no longer receiving benefit from AZD1775 beyond the FPV in the opinion of the treating physician, then the study drug should be stopped. The Investigator will inform AstraZeneca when a patient discontinues the study drug. Patients must return unused medication during routine clinic visits, and drug accountability information must continue to be collected in patient source documents until the patient discontinues treatment. In addition, provided that a patient gives proper informed consent, a plasma isolation (ctDNA) blood sample for future biomedical research should be obtained at the time of AZD1775 discontinuation, if due to disease progression. Patients will continue to be monitored for all SAEs, pregnancies, and overdoses for 30 days after the last dose of the investigational product.

# 5. STUDY ASSESSMENTS

The Sarah Cannon Development Innovations, LLC (Sarah Cannon) Trial Master electronic data capture (EDC) system will be used for data collection and query handling. The investigator will ensure that data are promptly and accurately recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

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

## 5.1 Efficacy assessments

### 5.1.1 Tumour assessments

RECIST v1.1 criteria will be used to assess patient response to treatment. The RECIST v1.1 guidelines for measurable, non-measurable, target lesions (TL) and non-target lesions (NTL) and the objective tumour response criteria (Complete Response [CR], Partial Response [PR], Stable Disease [SD] or progressive disease [PD]) are presented in Appendix E.

The same method of assessment of tumour burden used at baseline (CT scans or magnetic resonance imaging [MRI] of the chest and abdomen/pelvis) must be used at each subsequent follow-up assessment (see Table 2, Table 3, and Table 4). Tumour imaging studies will be repeated every 8 weeks (± 1 week) relative to date of first dose for patients on the QD 5/9 treatment schema and every 9 weeks (± 1 week) relative to date of first dose for patients on the QD 5/2 treatment schema to assess response until objective disease progression as defined by RECIST v1.1 or withdrawal from study.

Categorisation of objective tumour response assessment will be based on the RECIST v1.1 criteria of response: CR, PR, SD and PD. Target lesion progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of longest diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, or SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

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

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

It is important to follow the assessment schedule as closely as possible.

## 5.2 Safety assessments

A physical examination, medical history (to capture previous treatment medications and response to each prior treatment regimen), concomitant medications recorded ≤7 days prior to starting treatment, ECOG PS, complete blood count (CBC) with differential and platelets, clinical chemistry, and triplicate 12-lead ECG should be done at screening and prior to dosing on Day 1 of each cycle. Assessments at other time points are indicated in the study plan.

Vital signs (resting heart rate, blood pressure, temperature) and weight will be recorded at screening and at times shown in the study plan.

The following are additional AZD1775 project related assessments that should be carried out in addition to any standard protocol monitoring such as routine haematology/biochemistry, vital signs, and physical examinations.

### 5.2.1 Laboratory safety assessments

Blood samples for standard monitoring and determination of haematology and clinical chemistry safety will be taken at the times indicated in the Study Plan (see Table 2, Table 3, and Table 4).

Additional safety samples may be collected as clinically indicated and at the discretion of the Investigator. The date and results (values and units) will be recorded on the appropriate eCRF.

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

The following laboratory variables will be measured as a minimum (some of these variables may be measured at baseline only):

**Laboratory Safety Variables**

| Haematology (2.7 mL whole blood sample) | Clinical chemistry (2.7 mL serum or plasma sample) | Coagulation (1.8 mL sample) | Pregnancy test |
|---|---|---|---|
| B-Haemoglobin | S/P-Albumin | B-PT or INR with PTT | Blood or urine |
| B-Leukocyte | S/P-Alanine transaminase (ALT) | | |
| B-Haematocrit | S/P-Aspartate transaminase (AST) | | |

| | |
|---|---|
| B-Red blood cell count | S/P-Alkaline phosphatase (ALP) |
| B-Absolute leukocyte differential count | S/P-Bilirubin, total |
| Neutrophils | S/P-Calcium, total |
| Lymphocytes | S/P-Creatinine |
| Monocytes | S/P-Chloride |
| Basophils | S/P-Potassium |
| Eosinophils | S/P-Sodium |
| B-Platelet count | S/P-Urea nitrogen or blood urea nitrogen |

Pre-menopausal women of childbearing potential must have a negative urine or serum pregnancy test within 3 days prior to starting study treatment on Day 1, and a confirmatory test will be performed before treatment at the start of each cycle and at the EOT visit. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

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 6.3.6.

In case a patient shows an AST or ALT ≥3 x ULN and total bilirubin ≥2 x ULN please referto Appendix D 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; abdomen, skin, head and neck (including ears, eyes, nose and throat); lymph nodes and thyroid; and respiratory, cardiovascular, 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). Performance status will be assessed using the ECOG performance status criteria (see Study Plan Table 2, Table 3, and Table 4).

### 5.2.3 Electrocardiogram

Triplicate 12-lead safety ECGs (paper ECG printout of 10 seconds for Investigator review) will be taken at screening and prior to dosing on Day 1 of each cycle (see Table 2, Table 3, and Table

4, and Section 3.2). Triplicate ECGs should also be obtained to coincide with the non-food and food effect PK collections described in Table 2, Table 3 and Table 4. The triplicate ECG assessments must be performed before the PK sample is collected.

Triplicate ECG recordings should be taken within an approximate 5-minute period. QTc interval will be calculated using the Fridericia formula (per institutional standards) obtained from the 3 ECGs performed 2-5 minutes apart at study entry.

Additional ECGs may be taken at any other time the Investigator deems necessary for safety during the administration period. The patients will rest for at least 10 minutes before the start of each recording 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 the recording time point.

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 ECG 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 ECG 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 ).

Attention should be paid to any detected increases in QTc interval. Patients who develop a single resting value of QTc interval of >450 msec/male and >470 msec/female or a shift from baseline of 60ms should stop taking AZD1775. Dosing can be resumed at a reduced dose (see section 6.7.3) after return of the resting QTc interval to pre-treatment status has been confirmed and correction of possible electrolyte imbalance has been made.

Monitoring of QTc, checking and correction of abnormal electrolyte levels and renal function are advised, especially in case of severe/prolonged diarrhoea. If QTc increases markedly from baseline, but stays below the above limits, a cardiologist's advice should be sought.

The concomitant use of ondansetron (known to prolong the QTc interval in rare cases, per labelling) should be taken into account when interpreting QTc changes.

### 5.2.4 Vital signs

Vital signs to be assessed include: resting heart rate, blood pressure, temperature and weight. Height will be measured at the screening visit only. Vital signs and weight should be obtained Day 1 of each treatment cycle (see Table 2, Table 3, and Table 4).

### 5.2.5 Tumour markers

An elevated tumour marker (e.g. CA-125, CEA, PSA, etc.) that is used by the investigator to monitor for tumour response will be collected at baseline, Day 1 of each cycle, and at the end of treatment. The results will be recorded in the eCRF. The tumour marker analysis will be performed by a local laboratory.

## 5.3 Other assessments

### 5.3.1 Patient reported outcomes

Not applicable.

## 5.4 Pharmacokinetics

### 5.4.1 Collection of samples for AZD1775 PKs

Pharmacokinetic samples for AZD1775 (2 mL) will be collected throughout the study as indicated below. The date and actual time of the PK sample is to be recorded in the medical records and eCRF. Samples will be obtained at the time points indicated in Table 5 and Table 6.

**Table 5 Pharmacokinetic sampling schedule for food effect patients**

| Time relative to first dose in cycle | Cycle 1 Day 1 | Cycle 1 Day 5 | Cycle 2 Day 1 | Cycle 5 Day 5 and then every 3-5 cycles thereafter[a] [d] | At response assessment (+/- 24 hrs) | At time of AEs possibly related to AZD1775 | At end of treatment or progression (+/- 24 hrs) |
|---|---|---|---|---|---|---|---|
| Pre-dose | X[b] | X[b] | X[b] | X[b] | | | |
| 1 hour | X[b] | X[b] | X[b] | - | | | |
| 2 hours | X[b] | X[b] | X[b] | - | | | |
| 4 hours | X[b] | X[b] | X[b] | - | | | |
| 6 hours | X[b] | X[b] | X[b] | - | | | |
| 8 hours | X[b] | X[b] | X[b] | - | | | |
| 10 hours | X[b] | X[b] | X[b] | - | | | |
| Unscheduled | | | | | X | X[c] | X |

[a] Beyond the PK for Cycle 5 Day 5, collections will be flexible and may be obtained once every 3, 4 or 5 cycles (instead of 4 cycles) on day 3, 4 or 5 (instead of day 5).
[b] Triplicate ECGs should be obtained to coincide with the food effect PK collections. The triplicate ECG assessments will be performed before the PK sample is collected.
[c] Unless the last dose of study drug was administered > 1 week prior to the event (See Section 6.7).
[d] PK samples will no longer be required after implementation of CSP Version 5.

**Table 6 Pharmacokinetic sampling schedule for non-food effect patients**

| Time relative to first dose in cycle | Cycle 1 Day 1 | Cycle 1 Day 5 | Cycle 5 Day 5 | Cycle 6 Day 3, 4, or 5then every 3-5 cycles thereafter[a] [e] | At response assessment (+/- 24 hrs) | At time of AEs possibly related to AZD1775 | At end of treatment or progression (+/- 24 hrs) |
|---|---|---|---|---|---|---|---|
| Pre-dose | X[b] | X[b] | X[b] | X[b] | | | |
| 1 hour | X[b] | X[b] | - | | | | |
| 2 hours | X[b] | X[b] | - | | | | |
| 4 hours | X[b] | X[b] | - | | | | |
| 6 hours | X[b] | X[b] | - | | | | |
| 8 hours | X[b] | X[b] | - | | | | |
| 10 hours | X[b] | X[b] | - | | | | |
| 24 hours | X[b,c] | X[b,c] | | | | | |
| Unscheduled | | | | | X | X[d] | X |

[a] Beyond the PK for Cycle 5 Day 5, collections will be flexible and may be obtained once every 3, 4 or 5 cycles (instead of every 4 cycles) on day 3, 4 or 5 (instead of day 5).
[b] Triplicate ECGs should be obtained to coincide with the non-food effect PK collections. The ECG assessments will be performed before the PK sample is collected.
[c] 24 hour sample collected on Cycle 1 Day 2 and Cycle 1 Day 6 (only for QD schedule).
[d] Unless the last dose of study drug was administered > 1 week prior to the event (See Section 6.7).
[e] PK samples will no longer be required after implementation of CSP Version 5.

All PK samples need to be collected within 10% of the nominal time (± 6 minutes for a 60 minute sample) to be protocol compliant. Pre-dose samples can be collected any time prior to dosing. The timing of the PK samples may be adjusted during the study, dependent on emerging data and in order to ensure appropriate characterization of the plasma concentration-time profiles.

If a patient misses any doses of AZD1775 a day prior to PK sampling, the Medical Monitor should be contacted as to any effect of the missed doses and potential changes required on the timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as per study plan, relative to baseline assessments.

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

PK samples will also be collected when imaging is performed for response assessment, at the time of AEs possibly related to AZD1775 (unless the last dose of study drug was administered > 1 week prior to the event), and at the end of treatment or at the time of progression.

### 5.4.2 Storage and destruction of pharmacokinetic samples

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

Any pharmacokinetic sample remaining after analysis for AZD1775 may be used for exploratory drug-drug interaction (DDI), metabolite, or biomarker analyses. Any results from such analyses may be reported separately from the CSR.

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

Incurred sample reproducibility analyses, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

Any residual back-up PK samples will be disposed of after the CSR is finalized.

## 5.5 Pharmacodynamics (PDx)

### 5.5.1 Repeat Biopsies

This study is designed in part to provide evidence of proof of mechanism (POM). For the Wee1 inhibitor AZD1775, this means to demonstrate that following treatment of patients there is a measurable decrease from baseline in readouts of activity of the Wee1 kinase.

The baseline Wee1 pharmacodynamic (PD) marker, pCDK1 (pCDC2), will be retrospectively assessed from the baseline biopsy. A post-treatment biopsy will then be taken after first dose on day 2 or day 3 of the first cycle of treatment.

These paired biopsies will be considered evaluable for POM if assessable by Immunohistochemistry (IHC) for the biomarker above and if the concurrent pharmacokinetic (PK) blood sample is consistent with the patient having had adequate pharmacological exposure to AZD1775.

We estimate that we would need at least 7 patients with evaluable paired biopsies in order to have confidence in an assessment of POM (see statistical calculations below).

A patient showing the target decrease of 50% or more (evaluated as number of cells showing positive staining in post vs pre dose) in pCDK1 will be considered a pharmacodynamic responder. This value is based on preclinical data correlating with anti-tumour efficacy, using the

same assay to be used on clinical samples. We have set a POM target value of 50% of patients having a pharmacodynamic response in their tumour biopsy. With n=7 biopsies, we would accept having established POM if 4 out the 7 biopsies show the desired biomarker change.

### 5.5.2 Storage re-use, and destruction of pharmacodynamic samples

The primary pharmacodynamic (PD) samples will be kept in the AZ Biobank for 15 years for future needs.

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. The results of any investigation will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

## 5.6 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory.

Biological samples (e.g., archived tumour samples and ctDNA) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

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

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

### 5.6.1 Archived or fresh/recent tumour tissue required for correlative studies

All patients are required to provide archival or fresh tumour samples for study participation. The tumour samples will preferably be in the form of a block. If this is not possible, then up to 20 slides will be requested depending on the tumour type. Studies on these tumour tissues may include, but are not limited to, the analysis of genetic aberrations in the tumour that may be associated with response or resistance to AZD1775. Please see the Laboratory Manual for additional information around tumour requirements.

If the tumour tissue sample is insufficient for molecular analysis, the investigative site will be informed and additional tissue will be requested (refer to the Laboratory Manual).

The patients' molecular profiles will be established using a Sponsor-approved method and clinical laboratory (see Laboratory Manual).

A full report of the molecular biomarker panel will subsequently be made available to investigators upon individual request.

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

### 5.6.2 Plasma isolation samples

Blood samples (20 mL) will be drawn to enable plasma isolation pre-dose as indicated in Table 2, Table 3, and Table 4, at the end of treatment, at the FPV, and at disease progression for patients continuing treatment after FPV. The plasma may be analysed for biomarkers including, but not limited to, changes in cytokine levels as well as the presence of cell-free DNA in the blood, or circulating tumour-derived DNA (ctDNA). The studies on ctDNA may include, but are not limited to, determination of the amount of ctDNA in the blood and whether certain tumour-derived aberrations such as mutations are present and change after treatment with AZD1775.

### 5.6.3 On-treatment tumour biopsy

An on-treatment tumour biopsy is required for all patients with surface accessible lesions within 12 hours of one of the last AZD1775 doses taken on Day 4 or 5 or within the first 12 hours of Day 6 in Cycle 2 (Day 4 through 6) unless medically contraindicated on the scheduled day in the opinion of the investigator. The exact timing of the biopsy relative to the first dose of AZD1775 should be noted as described in the Laboratory Manual. Studies may include, but are not limited to, analysis of the downstream effects of Wee1 inhibition such as changes in the levels of phosphorylation of the Wee1 kinase substrate CDC2.

For the Wee1 inhibitor AZD1775, this means to demonstrate that following treatment of patients there is a measurable decrease from baseline in readouts of activity of the Wee1 kinase via analysis of the levels of phosphorylated CDC2 (pCDC2) in tumour samples. The collection of baseline and on-treatment biopsies is essential to guarantee the comparison of pCDC2 levels before and during treatment and to provide evidence that patients receive a biologically active dose.

### 5.6.4 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

### 5.6.5 Labelling and shipment of biological samples

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

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

### 5.6.6 Chain of custody of biological samples

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

The PI at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (when appropriate).

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

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

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

### 5.6.7 Withdrawal of Informed Consent for donated biological samples

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

The PI:

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

AstraZeneca or its designee ensures the central laboratory(is) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

AstraZeneca ensures that biological samples are destroyed at the end of a specified period as described in the informed consent.

# 6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

## 6.1 Definition of adverse events

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

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

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected. Any deterioration of disease targeted in the study and associated symptoms should not be regarded as an adverse event.

## 6.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., 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/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the CSP.

## 6.3 Recording of adverse events

### 6.3.1 Time period for collection of adverse events

Adverse events will be collected throughout the study, from informed consent until 30 days after the end of the last investigational product administration.

SAEs will be recorded from the time of informed consent and should be reported to Sarah Cannon Safety Department as described in Section 6.4.

Following discontinuation of study treatment, SAEs considered related to study procedures should continue to be collected while patients are followed-up for disease progression.

For each patient who discontinues study treatment for a reason other than disease progression:

– Follow-up information on all ongoing AEs should continue to be collected until the survival follow-up.

– SAEs considered related to study procedures must continue to be collected and reported using standard SAE timelines and process until the end of progression follow-up (i.e., disease progression).

– All deaths must continue to be collected after progression and during the survival follow-up.

### 6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study (after the EOT visit) are followed up by the 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) 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 Sarah Cannon.

### 6.3.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date 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
- Causality rating against AZD1775 (yes or no)
- Action taken with regard to AZD1775
- 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
- Reason AE is serious
- 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(s)
- Description of AE.

The grading scales found in the revised CTCAE Version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria should be utilized that converts mild, moderate, and severe events. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

### 6.3.4 Causality collection

The Investigator will assess causal relationship between AZD1775 and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study 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 to the CSP.

### 6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient, reported in response to the open question from the study personnel, or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of a diagnosis is preferred (when possible) to the recording of 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.

They 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 should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment unless clearly due to the progression of disease under study.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical rather than the laboratory term (e.g., 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 an AST or ALT ≥ 3xULN, together with total bilirubin ≥ 2xULN 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 potential Hy's Law cases. Prompt reporting of cases meeting Hy's law criteria (via SAE expedited reporting system) is required for compliance with regulatory guidelines. The investigator is responsible for, without delay, determining whether a patient meets potential Hy's law (PHL) criteria.

### 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 IP is being studied. It may be an increase in the severity of the disease

under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events which are unequivocally due to disease progression should not be reported as an AE during the study.

Events including diagnosis or signs and symptoms or the abnormal results of an investigation including those leading to hospitalization, which constitute or result from:

a) 'unequivocal progression' (i.e., representative of overall disease status change, not a single lesion increase) of non-measurable/non-target disease,

**or**

b) progression of malignancy under study (target disease) as determined per RECIST 1.1 criteria, should not be reported as AEs or SAEs.

Progression of the malignancy under study, including signs and symptoms of progression, should not be reported as a serious adverse events. Hospitalizations due to signs and symptoms of disease progression should not be reported as serious adverse events.

### 6.3.9 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious AE 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 a SAE during the study.

- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported 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 a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

## 6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the AZD1775 or to the study procedure(s). All SAEs will be recorded in the eCRF. For patients continuing after the FPV (see Section 4.3.2.3), SAEs should be determined per protocol and must continue to be reported via the standard pharmacovigilance process (in paper) as stated below. For medical emergencies, refer to Section 6.4 below.

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

The designated Sarah Cannon representative works with the Investigator to ensure that all the necessary information is provided within 24 hours of investigator awareness.

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 (i.e., immediately but no later than 24 hours) of when he or she becomes aware of it.

SAE information will be sent via secure e-mail connection or via fax. The Sarah Cannon Safety Department standard paper SAE Report with supporting relevant source documents (e.g. history and physical [H&P], hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event) will be attached and sent via:

1. Secure email (Sarah Cannon SAE mailbox: CANN.SAE@SCRI-Innovations.com) or by

2. Fax (Sarah Cannon safety fax number): + 1-866-807-4325

Transmission of the SAE report Form should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Sarah Cannon Safety Department as soon as it is available; these reports should be submitted using the Sarah Cannon SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual. The appointed study Medical Monitor works with the Investigator to ensure that all the necessary information is provided to the Sarah Cannon Safety Department **within 24 hours of investigator awareness**.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB. For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately.

AstraZeneca or their representative will provide Regulatory Authorities, Ethics Committees

(ECs), IRBs and PIs with clinical safety updates/reports according to local requirements.

Where appropriate, full details of the AE reporting process should be described in a Safety Handling Plan for the study.

## 6.5 Medication error and overdose

### 6.5.1 Medication error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for the study drug(s) 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 site staff or patient.

Medication error includes situations where an error has:

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were identified that could have led to an error

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

- Drug name confusion
- Dispensing error e.g., 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 e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g., kept in the fridge when it should be at room temperature
- Wrong patient received the medication
- Wrong drug administered to patient

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

- Patient accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose see Section 6.5.2)

- 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 AZ product

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

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the Sarah Cannon representatives within 1 day, i.e., immediately but no later than 24 hours of when he or she becomes aware of it. The Sarah Cannon representative works with the Investigator to ensure that all relevant information is completed within 1 to 5 calendar days if there is an SAE associated with the medication error (see Section 6.2) and within 30 days for all other medication errors.

### 6.5.2 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 CRF module.

If an overdose of AZD1775 occurs in the course of the study, then the Investigator or other site personnel will inform the Sarah Cannon Safety Department immediately or **no later than 24 hours** of when he or she becomes aware of it. All overdoses of AZD1775 have to be reported by completing an Overdose Form. The Sarah Cannon Safety Department representative works with the Investigator to ensure that all relevant information is provided.

For overdoses associated with SAE, standard reporting timelines apply (see Section 6). For other overdoses, reporting should be done within 24 hours.

Additional PK samples should be collected for any AE possibly related to AZD1775; please refer to Section 5.4 for further guidance.

## 6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Sarah Cannon Safety Department.

### 6.6.1 Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then Investigators or other site personnel inform the Sarah Cannon Safety Department immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The Sarah Cannon Safety Department representative works with the Investigator to ensure that all relevant information is provided.

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 three months following the last dose of study treatment.

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 Management of IP related toxicities

Toxicity will be assessed utilising the NCI CTCAE v4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), unless otherwise specified.

Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. Additional unscheduled PK samples should be collected for any AE

possibly related to AZD1775. The date and time of last study drug administration should be collected and recorded on an 'Unscheduled PK' sample eCRF page. The additional PK samples should not be taken if the last dose of study drug(s) was administered > 1 week prior to the event.

A maximum of 2 dose reductions for AZD1775 will be allowed. Patients requiring >2 dose reductions will be discontinued from the study drug.

There are different doses and schedules being evaluated currently. Dose should be reduced to a previous dose level for a toxicity. Patients starting at 125 mg BID can be dose reduced to 125 mg QD if needed for management of toxicity. Patients on 150 mg BID can be dose reduced to 125 mg BID and potentially 150 mg QD if needed for management of toxicity. Patients on 200 mg QD can be dose reduced to 150 mg QD and potentially 125 mg QD if needed for management of toxicity.

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

### 6.7.1 Dose modifications and guidance

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of study, as appropriate. Dose reductions and holds are allowed as clinically indicated by the treating physician and if in line with Table 9 and Table 10. For each patient, a maximum of 2 dose reductions will be allowed as presented in Table 7 and Table 8.

**Table 7 AZD1775 BID (Cohorts BID 1 and 2) Dose Level Reductions[a]**

| | AZD1775 STARTING DOSE | AZD1775 -1 DOSE LEVEL |
|---|---|---|
| AZD1775 BID regimens | 125 mg BID | TBD[b] |
| | 150 mg BID | TBD[b] |

a Full details of the AZD1775 BID regimens are provided in Figure 1and Figure 2.
b If dose reduction required below 150 or 125 mg, this is to be discussed on a case by case basis with Medical monitor

**Table 8 AZD1775 QD (Cohorts QD 1.1, 1.2, 2.1, 2.2, 2.3, 3.1, 3.2, 3.3, 4.1, 4.2) Dose Level Reductions[a]**

| | AZD1775 STARTING DOSE | AZD1775 -1 DOSE LEVEL | AZD1775 -2 DOSE LEVEL |
|---|---|---|---|
| AZD1775 QD regimens | 200 mg QD | TBD[b] | TBD[b] |
| | 250 mg QD | TBD[b] | TBD[b] |
| | 300 mg QD | 250 mg QD[b] | TBD[b] |

**Table 8 AZD1775 QD (Cohorts QD 1.1, 1.2, 2.1, 2.2, 2.3, 3.1, 3.2, 3.3, 4.1, 4.2) Dose Level Reductions[a]**

| | AZD1775 STARTING DOSE | AZD1775 -1 DOSE LEVEL | AZD1775 -2 DOSE LEVEL |
|---|---|---|---|
| | 400 mg QD | 300 mg QD | 250 mg QD[b] |

a Full details of the AZD1775 QD regimens are provided in Figure 3 and Figure 4.
b If dose reduction required below 250 mg , this is to be discussed on a case by case basis with Medical Monitor

### 6.7.2 Dose modifications due to haematologic toxicity

Complete blood counts (CBC) will be obtained for all patients at the beginning of each treatment cycle (Day 1). If haematologic toxicity occurs (see Table 9), treatment should be held and ANC and platelets should be monitored weekly until recovery.

**Table 9 Cycle Day 1 Haematologic Dose Modifications**

| Treatment Day Blood Counts and Toxicity | | | |
|---|---|---|---|
| **ANC** | | **Platelets** | **Action** |
| ≥1000/µL | And | ≥75,000/µL | No dose modification or interruption |
| <1000/µL | Or | <75,000/µL | Delay by 1 week intervals until recovery |

If haematologic toxicity parameters do not recover within 21 days, the patient should be removed from the study treatment.

**Table 10 Neutropenia, Infection, Febrile Neutropenia Dose Modifications and Management**

| **Any Day** | |
|---|---|
| **Grade 3 neutropenic fever** (ANC <1000/μL + Temperature ≥101°F [38.5°C]) or neutropenic infection<br>**Documented infection with Grade 3 neutropenia** (ANC <1000/μL)<br>**Grade 4 neutropenia**<br>(ANC <500/μL >7 days)<br>**Grade 4 thrombocytopenia** (platelet count <25,000/μL >7 days) | **Hold dose until recovery.**<br>**Then, upon resuming dosing, reduce AZD1775 to the next lower dose level[a].** |
| **Grade 4 febrile neutropenia or Grade 4 infection with neutropenia** (both defined as septic shock)<br>**Thrombocytopenic haemorrhage** (gross occult bleeding) associated with a platelet count <50,000/μL | **Discontinue treatment and follow for disease progression.** |

a No more than two dose reductions will be allowed for any patient. Patients requiring additional dose modifications due to toxicity will discontinue study treatment.

### 6.7.3 Non-haematologic toxicity dose modifications

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of investigational product, as appropriate. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician.

Dose reductions of AZD1775 should be considered if the toxicity is considered to be related to AZD1775. Dose re-escalation is not permitted.

In general, if a patient experiences a G1/G2 non-haematological toxicity, no dose modification is required (except QTc prolongation, see table below). If a patient experiences a G3 or G4 toxicity which is not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and/or the dose reduced, and supportive therapy administered as required. Any patient who develops a Grade 3 or 4 non-haematologic toxicity that does not resolve to ≤ Grade 1 within 21 days should be removed from the study treatment unless approved by the Medical Monitor.

**Table 11 AZD1775 dose modifications for QTc interval prolongation**

| **Electrocardiogram QT corrected interval prolonged** | |
|---|---|
| QTc Value | AZD1775 |

**Table 11 AZD1775 dose modifications for QTc interval prolongation**

| **Electrocardiogram QT corrected interval prolonged** | |
|---|---|
| QTc 450-480 ms (males) or 470-480 ms (females) | Hold. Once QTc interval has returned to pretreatment status and correction of possible electrolyte imbalance has been made, resume at next lower dose level. |
| QTc 481-500 ms | Hold. Seek cardiologist advice, patient may resume at next lower dose level if cardiologist agrees. |
| QTc ≥ 501 ms | Discontinue treatment. Seek cardiologist advice. |
| Shift from baseline of ≥ 60ms | Discontinue treatment. Seek cardiologist advice. |

### 6.7.4 Non-haematologic toxicity management guidelines

#### 6.7.4.1 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) 4mg should be administered at the first onset of diarrhoea and then 2mg every 2 hours until diarrhoea-free for at least 12 hours. The first dose of loperamide could be lowered to 2mg if the diarrhoea is recurrent and if, in the opinion of the treating physician, the diarrhoea is not severe.

Patients should be instructed to notify the Investigator or research staff for the occurrence of blood 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 (i.e., 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 hospitalized for IV hydration and correction of electrolyte imbalances.

#### 6.7.4.2 Nausea and vomiting (mandatory antiemetic prophylaxis)

For patients on BID dosing, all patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO BID or granisetron (Kytril) 1 mg PO BID prior to each dose of AZD1775. Additional doses of 5-HT3 antagonist may be used if needed. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose as a minimum on the first day of dosing AZD1775 of every 3-5 days dosing period, unless contraindicated or not well-tolerated. Dexamethasone may be continued on further days of dosing, potentially at a lower dose. Dexamethasone or the 5-HT3 antagonist may be given by IV as needed.

For patients on QD dosing, all patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO QD or granisetron (Kytril) 1 mg PO QD prior to each dose of AZD1775. If nausea and vomiting continue, a second dose of antiemetics can be taken 8 hours later if necessary. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose unless contraindicated or not well-tolerated. Dexamethasone or the 5-HT3 antagonist may be given by IV as needed.

Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy.

**Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known DDIs.**

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

Suitable alternative medications may be used, with adequate justification, in those studies where the use of any of the above medications might interfere with other study procedures or are deemed insufficient.

#### 6.7.4.3 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.

## 6.8 Study governance and oversight

A Safety Review Team (SRT) will be established by Sarah Cannon for this study. Reviewers may include the study PI, Medical Monitor, Lead Biostatistician, Safety Director, Safety Lead, Clinical Data Analyst, Clinical Project Manager, and Sponsor representatives. The roles and responsibilities of the SRT and the Medical Monitor are described in the Dose Escalation Plan.

Once there are at least 3 evaluable patients (see Section 7.2.4) at a dose level the SRT will review and assess all available safety data and any other relevant data from the cohort to make a decision on how the study should proceed. Any dose interruptions and reductions will be taken into account. When available, emerging PK data for plasma exposure and safety will be evaluated to inform the dose escalation or dosing regimen decisions.

The decision may be to:

3. Proceed with dose escalation – refer to Section 7.2.1

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

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

6. Stop the dose escalation part of the study

7. Evaluate alternative dosing schedules.

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

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

The decisions and decision-making of the SRT on the next dose level will be documented and provided to the Investigators prior to dosing any new patients.

The timing and frequency of safety evaluations may be revised, in consultation with the SRT, in response to emerging data.

# 7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

## 7.1 AZD1775

| Investigational product | Dosage form and strength |
|---|---|
| AZD1775 | 25 mg and 100 mg plain capsules*<br>50 mg, 75 mg and 100 mg printed capsules* |

*Other dosage form(s) and/or strength(s) may also be used if necessary due to dosage adjustments and/or supply

Plain and printed capsule formulations must not be combined to provide a patient dose. Patients receiving the plain capsule formulation will continue to receive the plain capsule strengths, while those receiving the printed capsule formulation will continue to receive the printed capsule strength. AZD1775 should be taken with 8 ounces of water approximately 2 hours before or 2 hours after food. If a patient misses one of the two daily doses according to schedule, the dose should be taken as soon as possible, but not more than 6 hours after the missed dose was scheduled. If greater than 6 hours, the missed dose should be skipped and the patient should take the next dose when scheduled.

If vomiting occurs after a patient takes the AZD1775 dose, the patient should be instructed not to retake the dose, but to wait until the next scheduled dose of AZD1775. If no dose is scheduled for the following day, the dose will not be 'made up'. If vomiting persists, the patient should contact the Investigator.

## 7.2 AZD1775 treatment regimen

### 7.2.1 Dose escalation guidelines

The MTD of AZD1775 monotherapy (dose to be determined) PO QD or BID (for the patients already enrolled on the BID schedule) when administered on a 5/9 Dosing Schedule every 14 days (dosing on days 1 to 5, followed by no treatment on days 6-14), a 5/2 Dosing Schedule every 21 days (dosing on days 1 to 5, no treatment on days 6-7, then dosing again on days 8 to 12, followed by no treatment on days 13-21), or a 5/2 weekly dosing schedule every 21 days (dosing on days 1 to 5, no treatment on days 6-7, dosing on days 8 to 12, no treatment on days 13-14, dosing on days 15 to 19, followed by no treatment on days 20-21) will be defined in this dose escalation phase. Treatment cycles are 14 or 21 days. Patients will continue to receive

treatment with AZD1775 until disease progression, intolerable toxicity, or discontinuation criteria have been m-et.

Initially, 3 patients will be enrolled and treated at the start of each cohort. However, to allow for any unforeseen discontinuations before the dose-limiting toxicity (DLT) period is completed, an extra patient may be enrolled and treated at each dose escalation cohort. Therefore, there may be a total of 4 patients (3 + 1) at the start of each cohort, provided that the 4th patient is able to start the first day of dosing within approximately 1 week of the 3rd patient in the same dose escalation cohort.

The DLT evaluation period will be 21 days (for patients on both QD 5/2 Schedules, and the BID dosing Schedule) or 28 days (for patients on the QD 5/9 Schedule). If there is 1 DLT out of the first 3-4 DLT-evaluable patients, then further patients will be enrolled and treated to a total of 6 patients. Two DLTs out of 6 evaluable patients will have exceeded the maximum tolerated dose.

The AZD1775 dose levels to be evaluated are presented in Table 12. It may be permitted to escalate the dose in either of the QD dosing regimens, from dose level 1 to dose level 3, without exploring dose level 2, as long as it has been agreed to by the SRT upon reviewing all relevant safety and PK data up to that point. Any intermediate dosing may also be explored. Evaluable patients are those who meet the minimum treatment and safety evaluation requirements of the study (see Table 2, Table 3, and Table 4) and/or those who experience a DLT during Cycle 1 and/or Cycle 2.

**Table 12 AZD1775 Dosing Cohorts**

| Cohort | AZD1775 | Number Patients |
|---|---|---|
| BID1 | 125 mg PO BID[a,b] | 3-6 patients (completed) |
| BID 2 | 150 mg PO BID[a,b] | 3-6 patients (completed) |
| QD 1.1 and QD 1.2 | 200 mg PO QD[c,d,e,f] | 3-6 patients in each dosing schedule |
| QD 2.1, QD 2.2, and QD 2.3 | 250 mg PO QD[c,d,e,f] | 3-6 patients in each dosing schedule |
| QD 3.1, QD 3.2, and QD 3.3 | 300 mg PO QD[c,d,e,g] | 3-6 patients in each dosing schedule |
| QD 4.1, and QD 4.2 | 400 mg PO QD[c,d,g] | 3-6 patients in each dosing schedule |

[a] AZD1775 taken in 12-hour intervals
[b] AZD1775 taken Days 1-5; Rest, i.e., no treatment Days 6-14
[c] Cohorts QD 1.1, 2.1, 3.1, and 4.1-5/9 schedule: Dosing on days 1 to 5, every 14 days (no treatment on days 6-14)
[d] Cohorts QD 1.2, 2.2, 3.2, and 4.2-5/2 schedule : Dosing on days 1 to 5, and days 8 to12, every 21 days (no treatment on days 6-7 and 13-21)
[e] Cohorts QD 2.3 and 3.3-5/2 weekly schedule : Dosing on days 1 to 5, days 8 to 12, and days 15-19 every 21 days (no treatment on days 6-7, 13-14, and 20-21)

[f] May be evaluated in 5/9 (Cohorts QD 1.1 and 2.1), 5/2 (Cohorts 1.2, and 2.2), and 5/2 weekly (Cohort 2.3) regimens in parallel as shown in Figure 4
[g] May be evaluated in 5/9 (Cohorts QD 3.1, and 4.1), 5/2 (Cohorts 3.2 and 4.2), and 5/2 weekly (Cohort 3.3) regimens in parallel if considered appropriate.

Dose escalation will occur in accordance with the following rules:

- Up to 6 patients will be enrolled and treated in each cohort, and must be deemed evaluable.
- If one of the first 3 patients enrolled and treated in a given cohort experiences a DLT, at least 3 additional patients will be enrolled in that cohort.
- If less than one-third of evaluable patients in a given cohort experiences a DLT (i.e., fewer than 0 of 3 or 1 of 6), escalation may proceed to the next higher dose level.
- If a DLT is observed in one-third or more of evaluable patients (e.g., 2 or more of up to 6 evaluable patients), the dose at which this occurs will be considered not tolerated, and the MTD will have been exceeded.
- The highest dose level(s) at which less than one-third of evaluable patients (0 of 3 patients or 1 of 6 patients) experience a DLT will be declared the MTD.
- Dose escalation will continue until identification of the MTD.
- Intra-patient dose escalation is not permitted.

Alternative dose levels, cohorts and/or schedules which may include reductions of dose interval treatment schedules may be guided by PK or PDx evaluations as well as tolerability and may be evaluated before the MTD/RP2D is defined. Modified PK assessments would be defined to accommodate the investigation of alternative dose levels and/or schedules.

The AZD1775 monotherapy dose will be selected by the SRT upon review of the safety and PK data.

### 7.2.2 Dose-limiting toxicity

Dose-limiting toxicities will be evaluated during the first 28 days (5/9 Schedule), or first 21 days (both 5/2 Schedules) of AZD1775 monotherapy treatment. If appropriate the DLT observation period can be extended by up to 2 weeks in case of treatment delay due to study drug-related AE. Toxicity will be graded according to the NCI CTCAE v4.03.

Patients must complete Cycle 1 (i.e. 21 days on either 5/2 schedule) or Cycle 1 and Cycle 2 (i.e. 28 days on the 5/9 schedule) safety evaluations and must receive at least 80% of the planned dose to be considered evaluable. Patients receiving less than 80% of Cycle 1 dose (21 days for the 5/2 schedule) or Cycle 1 and Cycle 2 dose (28 days for the 5/9 Schedule) will be replaced unless they experienced a DLT confirmed by the SRT.

Dose-limiting toxicities are defined as any of the following toxicities not attributable to the disease or disease-related process under investigation, that occur from the first dose of study treatment up to the last day of Cycle 2 (first 28 days) for the 5/9 Schedule, or the last day of Cycle 1 (first 21 days) for the 5/2 Schedule, and that meet at least 1 of the criteria below:

1. Haematologic toxicity ≥ Grade 4 for more than 7 days including infection with febrile neutropenia

2. Grade 3 thrombocytopenia associated with Grade ≥2 bleeding

3. Haematologic toxicity ≥ Grade 4 neutropenia or thrombocytopenia for more than 7 days, or Grade 4 Infection with febrile neutropenia, or Grade 3 neutropenic fever, or Grade 3 thrombocytopenia associated with Grade ≥ 2 bleeding.

4. Non-haematologic toxicity ≥ Grade 3

5. Liver function tests (LFTs), Grade ≥3 total bilirubin, hepatic transaminase ALT or AST or ALP lasting >48 hours, or any change in liver functions tests consistent with Hy's Law (see Appendix D.)

6. Any other toxicity that is clinically significant and/or unacceptable that does not respond to supportive care, results in a disruption of dosing schedule of more than 7 days, or is judged to be a DLT by the investigator in collaboration with the medical monitor.

A DLT excludes:

- Nausea, vomiting, or diarrhoea that responds to supportive care
- Isolated laboratory change of any grade without clinical sequelae or clinical significance
- Alopecia of any grade

Cycle 1 (for both 5/2 schedules) and Cycle 1 and Cycle 2 (for the 5/9 schedule) data for each cohort will be reviewed by an SRT after completion of each dose level cohort. Participating sites will be informed of the findings and of the next cohort to be evaluated as soon as possible.

### 7.2.3 Reporting a DLT

Any DLT occurring in a patient during that occur from the first dose of study treatment up to the last day of Cycle 2 (first 28 days) for the 5/9 Schedule, or the last day of Cycle 1 (first 21 days) for either 5/2 Schedule of a dose-escalation cohort must be reported to the Medical Monitor by the Investigator or designee with 24 hours of first knowledge, and to Sarah Cannon Safety Department as an SAE when appropriate (see Section 6.4).

### 7.2.4 Determination of MTD/RP2D

The patient population used to determine the MTD/RP2D will consist of patients who have met the minimum safety evaluation requirements of the study, and/or who have experienced a DLT from the first dose of study treatment up to the last day of Cycle 2 (first 28 days) for the 5/9 Schedule, or the last day of Cycle 1 (first 21 days) for either 5/2 Schedule. Minimum safety requirements will be met if during Cycle 1 (for both 5/2 Schedules) and Cycles 1 and 2 (for the 5/9 Schedule) of treatment the patient receives a minimum of 80% of treatment doses of AZD1775, completes the safety evaluations (see Table 2, Table 3, and Table 4), and is observed for at least 28 days. Patients who do not meet these minimum safety evaluation and treatment requirements and who do not experience a DLT will be replaced.

Treatment dose will be considered non-tolerated and dose escalation will cease if 2 or more of 6 evaluable patients experience a DLT at a dose level.

A minimum of 12 patients will be treated at the MTD/RP2D. More than one dose level may be expanded with up to 12 patients per dose level to get further experience with the dosing schedule with AZD1775.

## 7.3 Effect of food on PK and safety

The preliminary effect of food on single dose pharmacokinetics (PK) of AZD1775 was assessed in approximately 12 patients on the BID schedule. At least 6 patients to be enrolled on a QD schedule will receive a single oral dose of AZD1775 with 240 mL (8 oz) of water, once in the fasted state on Cycle 1 Day 1 and once following a high-fat meal on Cycle 2 Day 1. The study will be conducted using the Food and Drug Administration (FDA) standard high-fat meal which should have a total of approximately 800 to 1000 kcal, with approximately 50% of the caloric content made up from fat (See Appendix I).

The fasted condition requires patients to fast for ≥10 hours before AZD1775 dosing and continue until 4 hours post-dose on Cycle 1 Day 1. Patients may have glucose (sugar tablets) and/or juice (except for juices containing grapefruit or Seville oranges) if they have signs or symptoms of hypoglycaemia after they have received AZD1775 in the fasted state. Water will be restricted from 1 hour pre-dose until 1 hour post-dose, except for the water administered with AZD1775, and any drink provided as part of the meal in the fed portion of the study.

For the fed condition, patients will be required to fast for ≥10 hours prior to receiving AZD1775 and then resume fasting until 4 hours post-dose, with the exception of a high-fat meal that should be eaten in the 30 minutes prior to AZD1775 being administered on Cycle 2 Day 1. The AZD1775 capsule should be administered 30 minutes after the start of meal consumption. If the meal is not completed within 30 minutes, AZD1775 may still be administered so long as 75% of the meal has been consumed within 45 minutes of the start of the meal. If the patient vomits after eating the meal but before administration of AZD1775, Investigators should contact the Medical Monitor for guidance regarding rescheduling administration of AZD1775 and subsequent AZD1775 should be administered with 240 mL (8 fluid ounces) of water. After PK assessments on Cycle 2 Day 1, patients will continue to take the drug with a regular meal for the entire cycle to assess the effect of food on safety.

After review of the PK data, if it is agreed that the data supports no clinically relevant impact of food on the PK of AZD1775 and so recommended by the SRT and AstraZeneca, the AZD1775 fasting/administration instructions in Section 7.3 may be removed or no longer observed.

## 7.4 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.

The label will include the following information: Name of the Sponsor, Study Code, 'For Clinical Trial Use Only' and/or other market specific requirements.

Distinct labels will also allow for the AZD1775 plain and printed capsule formulations to be easily distinguishable for dispensing.

## 7.5 Storage

All study drugs (AZD1775) should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

The dispensing and retention of reserve samples of IP will be performed with the Food and Drug Administration (FDA) Code of Federal Regulations 21, Part 320 Bioavailability and Bioequivalence requirements.

## 7.6 Compliance

AZD1775 dosing compliance will be reviewed with the patient at the beginning of each new treatment cycle. Patients will be given a supply of study medication to take home. All patients will be required to complete a Dosing Diary, which must be returned to the clinic for review at each visit. The patient should be instructed to record each date and time the dose was taken on the dosing diary. If a dose is missed, the reason must be noted in the diary. A copy of the Dosing Diary is provided in the study reference materials.

The administration of all study drugs (AZD1775) should be recorded in the appropriate sections of the Case Report Form (CRF).

## 7.7 Accountability

The study drug (AZD1775) provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Patients must return all unused medication and empty containers to the Investigator.

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

## 7.8 Concomitant and other treatments

### 7.8.1 Permitted concomitant medications

All concomitant medications received within 14 days before the first dose of study medication and 30 days after the last dose of study medication should be recorded. Concomitant medications must be recorded in the appropriate sections of the eCRF.

| Supportive Medication/Class of drug: | Usage: |
|---|---|
| Anti-emetics (excluding aprepitant [Emend] and fosaprepitant) | Premedication with anti-emetics is mandatory (excluding aprepitant [Emend] and fosaprepitant) as presented in Section 6.7.4.2 |
| Loperamide (Imodium) | Loperamide (Imodium) is required at the first onset of diarrhoea according to ASCO guidelines (see Section6.7.4.1. |
| Medications including but not limited to the following:<br>• Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g. denosumab).<br>• Patients requiring therapeutic warfarin or coumadin-derivative anticoagulants will be monitored with INR and Prothrombin Time (PT) as clinically indicated.<br>• Low molecular weight heparin, rivaroxaban, or equivalent anticoagulant therapy is permitted where clinically indicated.<br>• Patients may receive treatment with megestrol acetate when prescribed for appetite stimulation. | Medications may be administered for maintenance of existing conditions prior to study enrolment or for a new condition that develops while on study. |

### 7.8.2 Prohibited and restricted concomitant medications

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

| Prohibited Medication/Class of drug: | Additional Information |
|---|---|
| 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. |

| Prohibited Medication/Class of drug: | Additional Information |
|---|---|
| Concomitant treatment with aprepitant and fosaprepitant is not allowable per protocol until further evaluation.<br>Potent or moderate inhibitors or inducers of CYP3A4, sensitive CYP3A4 substrates, and CYP3A4 substrates with a narrow therapeutic window should be avoided until additional data on drug-drug interaction becomes available. | No formal clinical drug interaction studies have been performed with AZD1775. An exploratory assessment of the effect of aprepitant on AZD1775 exposure in oncology patients suggests that there is a drug interaction between AZD1775 and aprepitant, as exposure to AZD1775 increased by ~60% when aprepitant was co-administered with AZD1775. The observed increase in AZD1775 exposure is likely the result of CYP3A4 inhibition by aprepitant. This increase in exposure is statistically significant. At the selected MTDs, this increase may also be of clinical importance.<br>The use of sensitive substrates of CYP3A4, such as atorvastatin, simvastatin and lovastatin are prohibited in this study. Patients should stop using these substrates > 14 days prior to initiation of study treatment (see Appendix H). |
| Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. | Patients should stop using these herbal medications 7 days prior to first dose of AZD1775. |
| Avoid concomitant use of strong CYP3A inhibitors and moderate CYP3A inhibitors. | See Appendix H |
| Grapefruit, Seville oranges and their products (e.g. juice, marmalade, etc.) | As grapefruit and Seville oranges are moderate inhibitors of CYP3A4, these fruits or their products should be avoided while taking AZD1775. |

| 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 narrow therapeutic range.<br>Refer to Appendix H for a list of sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range |

| Restricted Medication/Class of drug: | Usage: |
|---|---|
| AZD1775 has been shown to be a weak inducer of CYP1A2 *in vitro* with a maximum measured response between donors of 39.9% to 93.1% (at 10 μM) and 18.6% to 32.5% (at 5 μM) of the positive control omeprazole (50 μM), respectively. Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low. | Be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range. |
| Inhibitors or substrates of P-gp | 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 (see Appendix H) |
| Substrates of Multidrug and Toxin Extruder 1 (MATE1) and MATE2K of these transporters (e.g. cimetidine, acyclovir, fexofenadine) | Caution should be used when administering substrates of MATE1 and MATE2K of these transporters (e.g. cimetidine, acyclovir, fexofenadine) as the clinical relevance of AZD1775 inhibition of the MATE pathway is not known in these compounds. |
| Metformin | Metformin should be used with caution. AZD1775 has been shown to be an inhibitor of MATE1 and MATE2K transporters. A drug interaction with substrates of either transporter cannot be ruled out, the most important substrate known to date being metformin. |
| BCRP substrates with narrow therapeutic index | Recent *in vitro* transporter studies have shown AZD1775 to be an inhibitor of BCRP (IC50 5.1 μM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins, such as rosuvastatin. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug. |

### 7.8.3 Palliative radiotherapy

Patients may receive palliative radiotherapy during the study only for local pain control, and only if in the opinion of the treating Investigator the patient does not have disease progression. The radiation field cannot encompass a target lesion. Radiation to a target lesion is considered progressive disease and the patient should be removed from study treatment.

### 7.8.4 Other concomitant treatment

Medication other than those described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

# 8. STATISTICAL ANALYSES

## 8.1 Sample size estimate

The final sample size will depend on the number of DLTs and on the clinical activity observed at the different dose levels. In addition, any patients not evaluable (NE) for the Dose Escalation analysis set will be replaced in order to have the required number of patients evaluable for DLT in each dose level. The expected number of evaluable patients on the dose escalation, is 52 patients (12 on the BID dosing schedule; and up to 40 on the QD dosing schedules) assuming 12 AZD1775 dose levels (two BID dose levels and up to 10 QD dose levels for each schedule). A minimum of 12 patients (4 patients in the dose escalation plus an additional 8 patients) will be enrolled and treated at the QD MTD/RP2D. A sample size of approximately 12 patients was assessed to evaluate the effect of a high-fat meal on the PK profile of AZD1775 monotherapy during dose-escalation on the BID schedule. Of the 12 patients enrolled and treated at the QD MTD/RP2D, a minimum of 6 will be evaluated for food effect.

With the addition of 12 patients (4 patients in the dose escalation plus an additional 8 patients) patients enrolled and treated at the MTD/RP2D and approximately 6 additional patients to replace any non-evaluable patients, the total number of patients is approximately 66. However, the number of patients could be higher if more than six AZD1775 dose levels, alternative dosing schedules, or more cohorts are tested. In addition, more than one dose level may be expanded with up to 12 patients per dose level to get further experience with the dosing schedules.

## 8.2 Definitions of analysis sets

### 8.2.1 All patients set

The All Patients Set will include all patients who have signed the informed consent form (i.e. screening failures plus patients enrolled and treated). The All Patients Set will be used to list the patient accountability, AEs, and deaths on study.

### 8.2.2 Full analysis set

The Full Analysis Set will include all patients who have received at least one (non-zero) dose of study treatment. Patients who were replaced for assessment of DLT due to noncompliance will still be included in the Full Analysis Set, if they meet the above criteria.

### 8.2.3 Per protocol analysis set

The Per Protocol Analysis Set (PPS) is a subset of the Full Analysis Set (FAS) excluding subjects having an important protocol deviation. Those protocol deviations deemed to have an important impact on the analysis of study endpoints and leading to the exclusion of a subject will

be identified prior to database lock. This analysis set may be used for analyses of efficacy endpoints if appropriate.

### 8.2.4 Dose-limiting toxicity analysis set

The DLT Analysis Set will include all patients in the dose escalation phase who received at least 80% of the AZD1775 dose and completed the minimum safety evaluation requirements during the first 28 days (5/9 Schedule) or 21 days (either 5/2 Schedule) of treatment or who experienced a DLT during the first 28 days (5/9 Schedule) or 21 days (either 5/2 Schedule) of treatment regardless of the amount of drug received.

The patients in the DLT analysis set will be used for the determination of the MTD of AZD1775.

Refer to the SAP for additional information.

### 8.2.5 Pharmacokinetic analysis set

The PK Analysis Set will include all patients who receive AZD1775 and have provided at least one PK sample. If a patient has a major protocol deviation that affects the evaluability of the PK profile, then the patient will not form part of the PK Analysis Set.

Major protocol deviations 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 time frame of 2 times the median time of maximum concentration ($t_{max}$); sample processing errors that lead to inaccurate bioanalytical results; incomplete dose administered; incomplete PK profile collected; and/or use of disallowed concomitant medication. In the case of a major protocol deviation, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Major deviations will be listed and summarised in the CSR.

## 8.3 Outcome measures for analyses

### 8.3.1 Tumour response

Patients will undergo regular tumour assessments until documented objective disease progression as defined by RECIST v1.1. At each restaging visit the RECIST data for a patient will be assigned a response of CR, PR, SD, or PD depending on the status of the disease compared with baseline and previous assessments (see Appendix E).

The objective response rate (ORR) is defined as the number of patients with a confirmed best objective response (OR) of CR or PR divided by the number of patients in the full analysis set. Similarly, the disease control rate (DCR) is defined as the percentage of patients in the full analysis set with a confirmed best objective response of CR or PR, or a best objective response of SD.

Progression of TL will be calculated in comparison with what the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of

progression, tumour response (CR, PR, or SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

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

For TL measurements, if ≤1/3 of the TL sizes are missing (either not evaluable or not read, or the scan was not done) then a scaling up rule will be applied as follows:

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

- If >1/3 of lesions recorded at baseline are missing, then the TL response will be NE. However, if the sum of non-missing TL diameters would result in PD (i.e., if using a value of 0 for missing lesions, the sum of diameters has still increased by >20% or more compared with the smallest sum of diameters on study, and has an absolute increase ≥5 mm) PD takes precedence over NE.

A visit response of CR will not be allowed if any of the TL data are missing.

Progression of non-target lesions is outlined below:

| Visit Responses | Description |
|---|---|
| Complete Response (CR) | Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis). |
| Progressive Disease (PD) | Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy. |
| Non-CR/Non-PD | Persistence of one or more NTLs with no evidence of progression. |

| Visit Responses | Description |
|---|---|
| Not Evaluable (NE) | Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit.<br><br>Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met. |
| Not Applicable (NA) | Only relevant if there are no NTLs at baseline |

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

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

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

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

The overall visit response will be based upon the overall visit response as reported by the investigator, with TL, NTL and new lesion information provided and listed as supportive information.

### 8.3.2 Changes in tumour size

Percent changes in tumour size from baseline will also be determined for patients with measurable disease at baseline and is derived at each visit as the % change in the sum of the diameters of TLs. % change = [(post baseline TL sum – baseline TL sum) / baseline TL sum] *100.

### 8.3.3 Exposure to investigational product

The total time on study treatment, as well as total exposure to study treatment and the amount delivered relative to the intended amount will be summarised. The number of patients with interruption and reductions to the dose intensity of AZD1775 will also be summarised.

### 8.3.4 Adverse events, laboratory changes, vital signs

Safety profiles will be assessed in terms of DLTs, AEs, SAEs, laboratory data, vital signs, and ECG data that will be collected for all patients. Treatment-emergent AEs (TEAEs) are defined as any AE which initiates on or after the first day of study drug up through 30 days after study drug discontinuation.

## 8.4 Methods for statistical analyses

In this open-label, Phase Ib study, no formal hypothesis testing will be conducted. Descriptive statistical and graphical displays will be employed to assess the safety, PK data, and preliminary anti-tumour activity by dose level cohort.

A comprehensive description of the statistical analyses and data summaries for this study will be documented in a Statistical Analysis Plan (SAP).

The study will have a primary data cut-off for the primary analysis (see Section 9.3). Following the primary analysis data cut-off, no further statistical analysis of the data will be conducted. All safety data collected after the primary analysis and up to (and including) the last of the FPVs will be listed and/or summarised as appropriate. A CSR addendum will be prepared to include such data.

### 8.4.1 Demographic and baseline data

Baseline characteristics of the patients, including demography, medical history, disease characteristics, and prior therapies will be listed for each patient and summarised by dose level cohort.

### 8.4.2 Exposure

Exposure to AZD1775 (i.e., total amount of study drug received) will be listed and summarised by dose level cohort. Total exposure, time on study drug, and dose intensity will be summarised, along with the number and percentage of patients with at least one dose interruption and at least one dose reduction. Reason for discontinuation of study treatment will be summarised.

### 8.4.3 Safety

Dose-limiting toxicities will be summarised by dose level cohort using the DLT analysis set. Additionally the following minimum data summaries will be presented by dose level cohort using the full analysis set:

- TEAEs of any CTCAE grade – summarised by MedDRA preferred term and system organ class and CTCAE maximum grade

- SAEs
- Deaths summarised by primary cause
- Laboratory parameters (hematology and chemistry), vital signs, ECG data and concomitant medications including evaluations for potential DILI

### 8.4.4 Efficacy

Anti-tumour activity will be summarized using the full analysis set.

### 8.4.5 Best objective response

The best objective response to treatment via RECIST v1.1 and Investigator assessment will be summarised by dose level cohort.

The best objective response (BOR) per subject will be derived as the best response recorded from the start of treatment until disease progression, death or subsequent cancer therapy (taking as reference for progressive disease the smallest measurements recorded since treatment started) using the Investigator reported objective response per time point. See Appendix E for how objective visit responses will be recorded.

Objective Response Rate (ORR) is the proportion of patients whose confirmed best objective response is complete response (CR) or partial response (PR). Confirmation must occur at least 4 weeks later.

Only patients with measurable disease will be included in the analysis of ORR. Patients without measureable disease at baseline will be excluded in the analysis of ORR.

The following rules will be used to determine the best objective response in each patient, assuming Assessment 1 is Baseline/Pre-treatment tumour assessment, and assessments are performed every 8 weeks on the BID and QD 5/9 Schedule or 9 weeks on either of the 5/2 Schedules.

| Assessment 2 | Assessment 3 | Assessment 4 | Best Objective Response |
|---|---|---|---|
| PD | - | - | PD |
| CR, PR, SD | PD | - | SD |
| UNK | PD | - | PD |
| CR, PR or SD | UNK | PD or UNK | SD |
| SD or UNK | CR, PR or SD | PD | SD |
| UNK | UNK | PD | PD |

| Assessment 2 | Assessment 3 | Assessment 4 | Best Objective Response |
|---|---|---|---|
| PR | SD(1) | PD | SD |
| PR | CR or PR | PD or UNK | PR |
| PR | SD | PR | PR |
| PR | UNK | PR | PR |
| CR | CR | PD | CR |
| CR | UNK | CR | CR |

(1) Only if the increase in diameter from Assessment 2 to Assessment 3 does not qualify for PD

- **Objective Response Rate (ORR)** = Proportion of patients with a confirmed best objective response of CR or PR.

### 8.4.6 Progression-free survival

Progression-free survival (PFS) is defined as the time from date of first dose of AZD1775 until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression.

The PFS will be censored in the following scenarios:

- If the patient has neither PD nor death, the PFS will be censored at last tumour assessment with CR, PR, or SD. Patient cannot be censored at "NE".

- If patient had PD or Death occurred more than 53 days for the BID or QD 5/2 schedule or 35 days for the 5/9 schedule (2.5 tumour assessment intervals) after previous tumour assessment with CR, PR or SD, the PFS will be censored at the date of previous tumour assessment with CR, PR, or SD.

- If the patient does not have post baseline tumour assessment nor death within 53 days for the BID or QD 5/2 schedule or 35 days for the 5/9 schedule after randomisation/enrolment, the PFS will be censored at Day 1.

PFS (in days) is calculated as:

(Date of death of documented Progression or Censoring) – (Date of randomization) +1

To apply the cut-off date to PFS is to exclude those Tumour assessments after cut-off date and anti-cancer therapy date after cut-off date in the analysis.

Progression-free survival will be derived based on scan/assessment dates not visit dates. If RECIST assessments/scans contributing towards a particular visit are performed on different dates then the date of progression will be determined based on the earliest of the dates of the component that triggered the progression. With regard to censoring, a patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

### 8.4.7 Changes in target lesions

Waterfall plots indicating the best percentage change from baseline in the sum of longest diameters of TL will be produced for the dose level cohorts.

Spider Plots charting change in tumour size across visits will be produced. It will include all visits, including unscheduled.

### 8.4.8 Pharmacokinetics

Pharmacokinetics will be summarised as per the PK analysis set.

All plasma concentration data for AZD1775 and derived PK parameters will be summarised and presented according to AstraZeneca standards as described in the SAP.

### 8.4.9 Timing of analyses

A formal review of safety and PK data by the SRT will occur at the end of each dose escalation cohort prior to opening the next dose level cohort.

The final analysis will take place when patients completed protocol specified follow-up or at an earlier time if deemed appropriate by the SRT and/or AstraZeneca.

## 8.5 Evaluation and calculation of variables by AstraZeneca or delegate

### 8.5.1 Calculation or derivation of pharmacokinetic variables

**Pharmacokinetic analysis:** For AZD1775 concentration data will be performed by Covance on behalf of AstraZeneca. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

When possible the following PK parameters will be determined:

- $C_{max}$
- $C_{8hr\ or}\ C_{10hr}$
- Time to $C_{max}$ ($t_{max}$)
- Time of last detectable concentration ($t_{last}$)
- Terminal half-life ($t½\lambda z$)

- Area under the plasma concentration-time curve from zero to 10 hours ($AUC_{(0-10)}$) from zero to the time of the last measurable concentration ($AUC_{(0-t)}$), and from zero to 24 hours ($AUC_{(0-24)}$).

- $C_{trough}$

The $C_{max}$ and $t_{max}$ parameters will be determined by inspection of the concentration time profiles. Where possible the terminal elimination rate constant (λz) will be calculated by log linear regression of the terminal portion of the concentration-time profiles when there are sufficient data and the terminal elimination half-life (t½λz) will be calculated as 1n2/λz. The area under the concentration-time curve up to the last quantifiable sample ($AUC_{[0-t]}$) and the $AUC_{(0-10)}$ will be calculated using the linear up, log down trapezoidal rule. Where appropriate, the $AUC_{(0-t)}$ will be extrapolated to infinity using λz to obtain AUC. The apparent oral steady state clearance $CL_{ss}/F$ following multiple dosing will be determined from the ratio of dose/$AUC_{(0-24)}$. The apparent volume of distribution ($V_z/F$) will be determined from the CL/F divided by λz, as appropriate.

**Assessment of food effect:** For AZD1775 natural log-transformed AUC and $C_{max}$ will be compared between treatments using a mixed effects analysis of variance model. Estimates of the mean difference between treatments and corresponding 90% confidence intervals (CI) will be calculated. The mean differences and the CIs will be back transformed to the original scale in order to give estimates of the geometric mean ratio and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs will be estimated and presented for each food condition. Additional AUCs will be analysed if appropriate.

## 8.6 Pharmacokinetics/Pharmacodynamic Analysis

The plasma concentration data for AZD1775 may be analysed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allows. A population PDx approach will be used to investigate the relationship between PK and selected primary, secondary and/or exploratory endpoints, where deemed appropriate. Results may be reported separately from the CSR for the main study.

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

# 9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

## 9.1 Training of study site personnel

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

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

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

## 9.2 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (SDV [a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study]) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., 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 designee will be available between visits if the Investigator(s) or other staff at the centre need 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 PI at each centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this 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 designee and the PI should be in place before any study-related procedures can take place or patients are enrolled.

### 9.2.3 Archiving of study documents

The 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 visit of the last subject undergoing the study'.

There will be a data cut-off for preparation of a CSR. Any patients still receiving AZD1775 at the time of the primary data cut-off will complete a FPV, which should align with the next scheduled visit following implementation of the CSP Version 5. Refer to Section 4.3.2.3 for further information regarding the FPV.

Patients continuing beyond FPV (Section 4.3.2.3) will continue to be monitored for all SAEs, pregnancies, and overdoses for 30 days after the last dose of the investigational product. Investigators must report SAEs, overdoses, and pregnancies to the AstraZeneca representative in accordance with Sections 6.4, 6.5, and 6.6, and continue to maintain study drug accountability as long as patients are receiving treatment with the study drug. The study is expected to start in Q4 2015 and end by the last visit of the last patient undergoing the study.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD1775.

## 9.4 Data management

Data management will be performed by Sarah Cannon according to the Data Management Plan (DMP). Data will be entered in the EDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests, and assessments specified in the protocol into the EDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the EDC system will be immediately saved to a central database and changes tracked to provide an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. 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. The PI is responsible for signing the eCRF but this can be delegated to a trained Investigator. The eCRF is signed electronically as per the eCRF instructions.

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool (e.g., Interactive Web Response System [IWRS], etc.) will be tested and validated as needed. The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to the World Health Organisation (WHO) Drug Dictionary. All coding will be performed by AstraZeneca or delegate.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail. All decisions on the evaluability of the data from each individual patient must have been made and documented. Following DBL, 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 site when the study has been closed.

**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 Committee on Harmonization (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

## 10.2 Patient 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 a patient, 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 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.

## 10.3 Ethics and regulatory review

An EC or IRB should approve the final study protocol, 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 site staff.

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

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

The AstraZeneca designee 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/IRB annually.

Before enrolment of any patient into the study, the final study protocol, 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.

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

The AstraZeneca designee will provide Regulatory Authorities, EC/IRBs, and PIs with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), when relevant.

Each PI is responsible for providing the EC/IRB with reports of any SUSARs from any other study conducted with the investigational product. The AstraZeneca designee will provide this information to the PI so that he/she can meet these reporting requirements.

## 10.4 Informed consent

The PI(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, and 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 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/IRB.

## 10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Medical Science Director, Medical Monitor, 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/IRB and, if applicable, the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

The AstraZeneca designee will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to ECs/IRBs see Section 10.3.

If a protocol amendment requires a change to a centre's ICF, the AstraZeneca designee and the centre's EC/IRB 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/IRB.

## 10.6 Audits and inspections

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

# 11. LIST OF REFERENCES

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# 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 adverse event (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 (e.g., hepatitis that resolved without hepatic failure).

**Hospitalisation**

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., 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. These should usually be considered as serious.

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

Examples of such events are:

- 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 (e.g., 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**

The following factors should be considered 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?

- Dechallenge 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.

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

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

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. 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 (e.g., 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 e.g., 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 collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Exploratory genetic research in this study will focus on, but not be limited to, the study of genes/genetic variations that may influence PK or response to AZD1775 (i.e., absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, 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.

## Genetic Research Plan and Procedures

### Selection of genetic research population

### Study selection record

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

### Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the CSP **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 subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects 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, approximately 10 mL, will be obtained from the subjects at prior to the first dose of AZD1775. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn prior to the first dose of AZD1775, it may be taken at any visit until the last study visit. Only one sample should be collected per subject 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 subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject 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.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the subject enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. 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.

### Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 7.3 of the main CSP.

### Informed consent

The genetic component of this study is optional and the subject 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 subject 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 subject and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the subject 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 subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

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

### Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as Hospitals, Academic Organization or Health Insurance Companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

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 subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan will be prepared where appropriate.

# Appendix D Actions Required in Cases of Combined Increases of Aminotransferase and Total Bilirubin – Hy-s Law

## Introduction

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

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

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

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

## Definitions

### Potential Hy's Law (PHL)

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

### Hy's Law (HL)

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

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

## Identification of Potential Hy's Law Cases

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

- ALT ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

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

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the 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 Investigator will without delay:

- Determine whether the patient meets PHL criteria by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

**Follow-up**

**Potential Hy's Law Criteria not met**

If the patient does not meet PHL criteria the 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 CSP.

**Potential Hy's Law Criteria met**

If the patient does meet PHL criteria the Investigator will:

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

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

**Review and Assessment of Potential Hy's Law Cases**

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

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

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

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

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

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

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply
    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

**Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment**

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

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

- Determine if there has been a significant change in the patients' condition compared with the last visit where PHL criteria were met.
    - If there is no significant change no action is required
    - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in this Appendix

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

**Actions Required for Repeat Episodes of Potential Hy's Law**

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

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment. If No: follow the process described in Potential Hy's Law Criteria of this Appendix

If Yes:

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

- If there is no significant change no action is required

- If there is a significant change follow the process described in Section 4.2 of this Appendix

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

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

## INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D6015C00003 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

## DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

**Measurable:**

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

**Non-measurable:**

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

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

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

**Special Cases:**

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

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

**Target lesions:**

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

**Non-Target lesions:**

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

**METHODS OF ASSESSMENT**

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

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

**Summary of methods of assessments**

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

**CT and MRI**

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

In the D6015C00003 study it is recommended that CT examinations of the chest, abdomen, and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination

with intravenous (IV) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

**Clinical Examination**

In the D6015C00003 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

**Chest x-ray**

In the D6015C00003 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

**Plain x-ray**

In the D6015C00003 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

**Ultrasound**

In the D6015C00003 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

**Endoscopy and laparoscopy**

In the D6015C00003 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

**Tumour Markers**

In the D6015C00003 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

**Cytology and histology**

In the D6015C00003 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease.

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

**Isotopic bone scan**

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

In the D6015C00003 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

**FDG-PET Scans**

In the D6015C00003 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

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

**TUMOUR RESPONSE EVALUATION**

**Schedule of evaluation**

Baseline assessments should encompass chest, abdomen and pelvis and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. Follow-up assessments will be performed every 8-9 weeks (depending on the dosing schedule) +/- 1 week window interval after start of treatment until objective disease progression as defined by RECIST 1.1, or withdrawal from study Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

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

**Target Lesions (TA)**

**Documentation of target lesions**

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

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

**Special cases:**

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

### Evaluation of target lesions

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

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

### Non-Target Lesions

### Evaluation of non-target lesions

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

**Evaluation of non-target lesions**

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

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

**New Lesions**

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

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

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

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

**Symptomatic Deterioration**

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

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

**Evaluation of objective visit response**

The objective visit response will be derived using the algorithm shown below.

**Objective visit response**

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

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

## CONFIRMATION OF RESPONSE

In the D6015C00003 study, imaging for confirmation of response (CR or PR) should be performed at next scheduled visit (certainly no less than 4 weeks) following the date the criteria for response were first met.

## SPECIFICATIONS FOR RADIOLOGIAL IMAGING

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

## CT Scans

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

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

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

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

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

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

minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

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

**MRI Scans**

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

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

**FDG-PET Scans**

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

**PET/CT Scans**

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

recommended because the PET portion of the CT introduces additional data that may bias an Investigator if it is not routinely or serially performed.

## REFERENCES

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

# 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 Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods

## DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL

**Women of Child Bearing Potential (WoCBP)** - Women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

**Women NOT of Childbearing Potential -** Women who are permanently or surgically sterilized or postmenopausal (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 (e.g. 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 postmenopausal 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 postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.

## 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 (e.g. less than 1 percent per year) when used consistently and correctly.

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for at least 1 month after last dose of study drug, or they must totally/truly abstain from any form of sexual intercourse (see below).

## ACCEPTABLE NON-HORMONAL BIRTH CONTROL METHODS INCLUDE:

- Total/True sexual abstinence: Abstinence is only acceptable as ‘total/true abstinence’, when the subject refrains from any form of sexual intercourse and this is in line with

his/her usual and/or preferred lifestyle. This must continue for the total duration of the trial and for at least 1 month after the last dose of study drug for female subjects/3 months after the last dose for male subjects. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the 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
- IUD PLUS male condom, provided coils are copper-banded

**ACCEPTABLE HORMONAL METHODS:**

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone-based pill.
- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin / EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom.

**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 except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing Intra-Uterine Devices (IUDs)
- Fertility awareness methods
- Coitus interruptus

# Appendix H 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 uM). Caution should therefore be exercised when AZD1775 is coadministered with agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with a narrow therapeutic range.

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

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

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

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

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

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

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

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

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

# CYP3A4 Inhibitors

## Strong

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

## Moderate

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

**Weak**

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

**CYP3A4 Inducers (Strong and Moderate)**

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

**CYP3A4 Inducers (Weak)**

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

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

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

**CYP2C19 Sensitive Substrates or Substrates with a Narrow Therapeutic Range**

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

## CYP1A2 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Alosetron
Caffeine
Duloxetine
Melatonin
Ramelteon
Tacrine
Theophylline
Tizanidine

### P-gp Substrates

Colchicine
Digoxin
Fexofenadine
Indinavir
Paclitaxel
Toptecan
Vincristine

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

## P-gp Inhibitors (Strong)

Cyclosporine
Elacridar
Erythromycin
Itraconazole
Ketocoanzole
LY335979Quinidine
Ritonavir
Valspodar
Verapamil

## BCRP Substrates

Daunorubicin
Doxorubicin
Rosuvastatin
Sulfasalazine
Topotecan

# Appendix I High Fat Guidance

## High-fat meal

In accordance with Food and Drug Administration (FDA) guidance (Food and Drug Administration 2002), the high-fat meal should have a total of approximately 800 to 1000 kcal, with approximately 50% of the calorific content made up from fat. The meal should therefore derive approximately 150, 250 and 500 to 600 kcal from protein, carbohydrate and fat respectively, as shown in Table 1.

The exact composition of the meal may vary as long as the totals are within 5% of those detailed.

**Table 1 High-fat meal (Food and Drug Administration 2002)**

| | **Protein** | **kcal** | **Fat** | **kcal** | **Carbo-hydrate** | **kcal** | **Total kcal** |
|---|---|---|---|---|---|---|---|
| 150 mL whole milk (3% fat) | 4.9 | 19.6 | 5.7 | 51.3 | 10 | 40 | 110.9 |
| 45 g cereal (cornflake) | 3.9 | 15.6 | 0.8 | 5.8 | 15 | 60 | 81.4 |
| ½ a slice of fried bread | 1.5 | 6 | 10.3 | 92.7 | 10 | 40 | 138.7 |
| 60 g lean black bacon (2 rashers) | 19.7 | 78.8 | 13.4 | 120.6 | | | 199.4 |
| 1 lightly fried egg | 8.5 | 34 | 11.2 | 100.8 | | | 134.8 |
| 3 slices of toast | 6.9 | 27.9 | 1.5 | 13.5 | 30 | 120 | 161.1 |
| 30 g of butter | | | 16 | 144 | | | 144 |
| 200 mL decaf tea/coffee with milk from allowance | | | | | | | |
| **Totals** | 45.4 | **181.6** | 58.9 | **528.7** | 65 | **260** | **970.3** |
| **% of total kcal** | | **19** | | **54** | | **27** | |
| **FDA guidelines** | | **150** | | **500-600** | | **250** | **800-1000** |

# REFERENCES

**Food and Drug Administration 2002**
U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies. December 2002.

# SIGNATURE PAGE

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