| **Synoptic Clinical Study Report** | |
|---|---|
| Drug Substance | [$^{14}$C]Adavosertib (AZD1775) |
| Study Code | D601HC00004 |
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# A Phase I, Open-Label, Non-Randomised Study of the Absorption, Distribution, Metabolism, and Excretion of Adavosertib After a Single Oral Dose of [$^{14}$C]Adavosertib to Patients with Advanced Solid Tumours

**Study dates:** First subject enrolled: 01 October 2021
Last subject last visit: 16 November 2021
The analyses presented in this report are based on a clinical data lock date of 16 September 2022

**Phase of development:** Phase I

**International Co-ordinating Investigator:** PPD

**Sponsor's Responsible Medical Officer:** Medical Monitor Name and Contact Information will be provided separately

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

# 2. SYNOPSIS

This study was prematurely terminated by AstraZeneca due to a strategic decision to discontinue the development program for adavosertib. AstraZeneca decided to close recruitment and initiate close-out activities for the study on 08 July 2022.

### Study centers

It was planned to recruit patients for enrolment in this study from 2 study sites in the United Kingdom (UK). However, patients were enrolled from only a single site, enrolling a total of 2 patients.

### Publications

None at the time of writing this report.

### Objectives and criteria for evaluation

**Table S1 Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To determine the mass balance of total radioactivity, including the routes and rates of elimination, following a single oral dose of CCI [$^{14}$C]adavosertib | • Collection of urine and fecal samples at regular intervals for analysis of total radioactivity to determine the following mass balance parameters:<br>– Amount excreted and cumulative amount excreted in urine, feces and total (urine and feces combined): Ae(urine), CumAe(urine), Ae(feces), CumAe(feces), Ae(total) and CumAe(total)<br>– Amount excreted and cumulative amount excreted in urine, feces and total (urine and feces combined) expressed as a percentage of the administered dose: fe(urine), Cumfe(urine), fe(feces), Cumfe(feces), fe(total) and Cumfe(total)<br>– CLR(urine)<br>– If available, vomit will be collected and analyzed for total radioactivity |

| Objectives | Endpoints |
|---|---|
| • To characterize the PK of adavosertib and total radioactivity following a single oral dose of CCI [$^{14}$C]adavosertib including the extent of distribution of total radioactivity into blood cells | • Collection of plasma and whole blood samples at pre-defined time-points for analysis of adavosertib (plasma only) and total radioactivity concentrations to determine the following PK parameters:<br>– Cmax, AUCinf, AUClast, tmax, λz, t½λz, CL/F, MRTinf, Vss/F, and Vz/F<br>– Ratio of AUCinf of plasma adavosertib relative to AUCinf of plasma total radioactivity<br>– Ratio of AUCinf of whole blood total radioactivity to AUCinf of plasma total radioactivity<br>– Additional PK parameters may have been determined where appropriate (eg, diagnostic parameters) (none were added)<br>• Collection of total urine samples at regular intervals for analysis of adavosertib to determine the following urine PK parameters:<br>– Ae(urine), CumAe(urine), fe(urine), Cumfe(urine), and CLR |
| **Secondary** | |
| • To assess the safety and tolerability of adavosertib following oral dosing in patients with advanced solid tumors | • Adverse events/Serious adverse events<br>• Vital signs<br>• Electrocardiograms<br>• Clinical chemistry/hematology/urinalysis |

Abbreviations: Ae = amount of unchanged adavosertib excreted into urine; AUC = area under plasma concentration-time curve; AUCinf = area under plasma concentration-time curve from time zero to infinity; AUClast = area under plasma concentration-time curve from zero to time of last quantifiable concentration; CL/F = Apparent total body clearance of drug from plasma after extravascular administration; CLR = renal clearance of adavosertib from plasma; Cmax = maximum observed plasma concentration; CumAe = cumulative Ae; Cumfe = cumulative fe; fe = Percentage of unchanged adavosertib excreted into urine; λz = terminal elimination rate constant; MRTinf = Mean Residence Time of the unchanged drug in the systemic circulation; PK = pharmacokinetic(s); t½λz = ; half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; tmax = time to reach peak or maximum observed concentration following drug administration; Vss/F = volume of distribution (apparent) at steady state following extravascular administration; Vz/F = apparent volume of distribution during the terminal phase after extravascular administration.

**Study design**

This was a Phase I, open-label, non-randomized study in patients with advanced solid malignancies.

Patients were assessed for study eligibility prior to admission to the study site during a 28-day screening period. A pharmacokinetics (PK) evaluable patient was defined as a patient who received the whole dose of [$^{14}$C]adavosertib, did not vomit at or before median 2 × time to reach peak or maximum observed concentration following drug administration (tmax), and completed the scheduled PK sampling allowing the estimation of desired PK parameters. The collected PK samples from a patient who was not considered to be PK evaluable were to be analyzed accordingly. All available data were listed but were not necessarily part of the final PK summary statistical calculation.

Each patient was admitted to the study site pre-dose on Day -1 and remained at the study site until at least Day 8 (168 hours post-dose). Patients received a single administration of CCI [$^{14}$C]adavosertib as an oral solution on Day 1. During this study, whole blood, plasma, urine, feces, and vomit samples (if presented) were collected at various time points to characterize the absorption, distribution, metabolism, excretion (ADME), and PK of adavosertib.

Measurement of the total radioactivity recovered from the first patient was performed immediately following Day 8. Based on the recovery of the radioactivity from the first patient, the residential period for urine and fecal collections for subsequent patients could be adjusted to allow for recovery of at least 90% of the total radioactivity for each patient and/or until less than 1% of the administered dose was recovered in urine and/or feces within a 24-hour period.

After patients completed this ADME study, they were allowed further access to adavosertib in a continued access study (D601HC00009) if the study was open and enrolling at the site, they met the inclusion/exclusion criteria, and in the opinion of their treating physician they could derive clinical benefit from continued treatment.

**Target population and sample size**

Male and female patients aged ≥ 18 years (at the time of signing the informed consent) with histologically or cytologically documented, locally advanced or metastatic solid tumor, excluding lymphoma, and having a predicted life expectancy ≥ 12 weeks.

Approximately 8 patients were planned to be enrolled to achieve a minimum of 4 PK evaluable patients.

### Treatment compliance

The study was terminated prematurely after 2 patients had been enrolled. Both patients received their dose of study intervention and completed the study.

Patients received the dose of study intervention at the site, directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic was recorded in the source documents and recorded in the electronic Case Report Form (eCRF). The dose of study intervention and study patient identification was confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

### Investigational product and comparator(s): dosage, mode of administration and batch numbers

**Table S2 Investigational Products**

| | |
|---|---|
| **Intervention name** | [$^{14}$C]Adavosertib (AZD1775) Oral Solution, CCI [redacted] |
| **Type** | Drug |
| **Dose formulation** | Solution |
| **Unit dose strength** | CCI [redacted] |
| **Dosage level** | Single dose |
| **Route of administration** | Oral |
| **Use** | Experimental |
| **IMP and NIMP** | IMP |
| **Sourcing** | Provided centrally by the Sponsor |
| **Batch/Lot Number(s):** | CCI [redacted] |
| **Packaging and labelling** | Study intervention was provided in high-density polyethylene bottle. Each bottle was labelled as required per country requirement. |

Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational medicinal product;
CCI [redacted]

### Duration of treatment

The duration of the residential period was evaluated following treatment of the first patient and could have been adjusted to ensure recovery of at least 90% of the total radioactivity following the dose of [$^{14}$C]adavosertib and/or until less than 1% of dose is recovered in urine and/or feces within a 24-hour period. Each enrolled patient was to be in-patient at the Site from Day -1 to Day 8 to receive a single dose of [$^{14}$C]adavosertib on Day 1.

### Statistical methods

The below methods reflect the actual methods followed for the study due to premature study termination. No summary statistics were performed and the safety measurements, PK

concentrations and radioactivity data were presented in data listings only. For the full set of planned statistical methods, refer to the Statistical Analysis Plan (SAP).

Determination of sample size:

This was a study to adequately characterize the ADME and PK of a single oral dose of CCI [$^{14}$C]adavosertib in patients with advanced solid tumors, whilst exposing as few patients as possible to study procedures. The aim was to recruit approximately 8 patients with a minimum number of 4 PK evaluable patients.

No formal sample size calculation was performed. As per previous similar studies, a sample size of 4 to 6 patients was considered to be an adequate number for the purpose of this study; however, due to the early termination of the study, this planned sample size (number of evaluable patients) was not reached.

Analysis sets:

Analysis sets included the Enrolled Set, the Safety Analysis Set, and the PK Analysis Set. Definitions of these analysis sets are provided in the SAP.

Presentation of data for mass balance evaluation:

The urine and feces total radioactivity concentration and parameter data were presented in the data listings. No summary statistics were performed and no graphical representation plots were constructed.

Presentation of pharmacokinetic data:

Data listings of PK sample collection times, as well as derived sampling time deviations, and all reportable concentrations were presented for adavosertib and total radioactivity for each specimen type for the safety analysis set. No summary statistics were performed and no graphical representation plots were constructed.

Presentation of safety data:

The results of safety assessments (which included adverse events [AEs], weight, and laboratory evaluations) were listed. The listings of laboratory evaluations included the reference range to identify results below or above the normal reference range.

Adverse events were coded by preferred term (PT) and system organ class (SOC) using the medical dictionary for regulatory activities (MedDRA) Version 24.1 and classified by severity using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

**Study population**

A total of 2 patients with solid tumors were screened for study eligibility; there were no screening failures. The 2 enrolled patients were from the same study center. Both enrolled patients received their full dose of study intervention (CCI as a single dose) and completed the study.

The 2 patients were PPD of age; both were PPD, PPD, and had a baseline body mass index (BMI) of PPD respectively. Both patients had solid tumors with primary location in the PPD, with primary tumors PPD and no spread to PPD. The tumors for Patient PPD were reported as not having metastasized (M0), while for Patient PPD the distant metastases were not measurable PPD.

**Protocol deviations**

For both enrolled patients the following important protocol deviation was reported.

- Initial lack of details in patient source document regarding the informed consent process.

This protocol deviation did not have any direct impact on the study's results.

**Summary of pharmacokinetic results**

**Summary of PK results**

- After oral administration of [$^{14}$C]adavosertib, the maximum plasma concentration in Patient PPD and Patient PPD was observed at 3 hours post-dose (664 ng/mL) and 2 hours post-dose (814 ng/mL), respectively. Following tmax, the plasma concentrations declined in both patients and were detectable until 36 hours post-dose.
- Following oral administration of [$^{14}$C]adavosertib, the maximum radioactivity in plasma was observed in Patient PPD (964 ngEg/g) and Patient PPD (965 ngEg/g) at 3 hours and 1.5 hours post-dose, respectively. The plasma radioactivity declined steadily after attaining maximum level in both patients and fell below the limit of detection at 48 hours and 24 hours post-dose in Patients PPD and PPD, respectively, suggesting administered [$^{14}$C]adavosertib and its metabolites have been eliminated from the body.
- For Patient PPD, the total recovery of radioactivity in urine was 15.87% of the dose, with 14.84% recovered in the first 24 hours post-dose. For Patient PPD, 15.70% of the dose was recovered in the urine, with 14.95% recovered in the first 24 hours post-dose.
- For Patient PPD, at total of 78.5% of the dose was recovered in the feces, with 3.77% of the dose recovered from Patient PPD (feces collection was limited for this patient which could have impacted the total radioactivity recovery estimation, therefore, this patient was considered non-evaluable for PK analysis set).

- Overall, total recoveries of radioactive dose in urine and feces were 94.39% and 19.4% from Patients PPD and PPD, respectively.

**Summary of safety results**

- The 2 enrolled patients experienced a total of 3 AEs (2 events of constipation and 1 event of anemia) during the study.
  - The 2 AEs of constipation (PPD were both considered by the Investigator to be mild in intensity (CTCAE Grade 1) and presented on Day 2.
  - The AE of anemia for Patient PPD was considered by the Investigator to be moderate in intensity (CTCAE Grade 2) and was reported as starting 10 days prior to administration of the study intervention.
  - All 3 AEs were considered by the Investigator as non-serious and not related to administration of the study intervention; the outcome of all events was considered as ongoing at the end of the study.
  - No action was taken for any of the AEs with regards to the study intervention as only a single dose of CCI [$^{14}$C]adavosertib was administered.
- There were no serious adverse events (SAEs) reported during the study.
- There were no AEs with outcome of death.
- There were no AEs leading to study intervention discontinuation or discontinuation from the study.
- No vomiting was reported for any of the patients.
- Although out of range results were reported for both patients for various laboratory findings, none were considered by the Investigator to be clinically significant, and none were reported as AEs. Out of range laboratory findings included:

| Patient | Laboratory Parameter (unit) | Reference range | Screening | Day -1 | Day 8 | Follow-up Visit |
|---|---|---|---|---|---|---|
| PPD | Low Calcium (µmol/L) | 2.2 to 2.6 | | 2.12 | 2.18 | |
| | high Chloride (mmol/L) | 95 to 108 | | | 111 | 109 |
| | High Potassium (mmol/L) | 3.5 to 5.3 | | | 5.4 | |
| | Low Erythrocytes ($\times 10^{12}$/L) | 3.8 to 5.8 | | 3.46 | 3.17 | 3.21 |
| | Low Hematocrit (ratio) | 0.37 to 0.47 | | 0.345 | 0.322 | 0.333 |
| | Low Hemoglobin (g/L) | 115 to 165 | | | 99 | 106 |
| | Low Lymphocytes ($\times 10^{9}$/L) | 1.5 to 4 | 1.3 | 1.2 | 1.4 | 1.4 |

| Patient | Laboratory Parameter (unit) | Reference range | Screening | Day -1 | Day 8 | Follow-up Visit |
|---|---|---|---|---|---|---|
| PPD | High Alkaline Phosphatase (µkat/L) | 0.5001 to 2.1671 | 3.43402 | 3.60072 | 3.85077 | 3.73408 |
| | Low Alanine Aminotransferase (µkat/L) | 0.1667 to 0.81683 | 0.11669 | | | |
| | Low Erythrocytes ($\times 10^{12}$/L) | 3.8 to 5.8 | 3.25 | 3.3 | 3.22 | 3.52 |
| | Low Hematocrit (ratio) | 0.37 to 0.47 | 0.29 | 0.287 | 0.285 | 0.315 |
| | Low Hemoglobin (g/L) | 115 to 165 | 90 | 90 | 90 | 97 |
| | Low Lymphocytes ($\times 10^9$/L) | 1.5 to 4 | | 1.4 | | |
| | High Neutrophils ($\times 10^9$/L) | 2 to 7.5 | 7.9 | 8.4 | | |
| | High Platelets ($\times 10^9$/L) | 150 to 400 | 588 | 727 | 572 | 664 |

## Conclusion(s)

This Clinical Study Report (CSR) is presented in a synoptic format as the study was prematurely terminated by AstraZeneca due to a strategic decision to discontinue the development program for adavosertib. In this study:

- The PK data collected during this study was overall consistent with the adavosertib human PK observed in other clinical studies with adavosertib.
- The safety profile in this study was overall consistent with the established safety profile of adavosertib. In the 2 patients with advanced or metastatic solid tumors enrolled in this study, single doses of [$^{14}$C]adavosertib (AZD1775) demonstrated an acceptable safety profile and were well tolerated with no new or unexpected safety signals identified during the study.