Clinical Study Report Synopsis	
Drug Substance	Adavosertib (AZD1775)
Study Code	D601HC00009
Edition Number	1
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EudraCT Number	020-005413-41
NCT Number	NCT04949425

An Open-label, Non-randomised, Multicentre Study to Allow Continued Access to and Assess the Safety and Tolerability of Adavosertib for Patients with Advanced Solid Tumours Enrolled in Adavosertib Clinical Pharmacology Studies

Study dates:	First subject enrolled: 13 September 2021 Last subject last visit: 12 April 2022 The analyses presented in this report are based on a clinical data lock date of 06 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 Good Clinical Practice, including the archiving of essential documents.

This study was prematurely terminated by AstraZeneca due to a strategic business 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 centres

Eight sites in Spain, 2 sites in the United Kingdom (UK), and 5 sites in the United States (US) were selected for study participation. Of these, only 1 site in the UK and 1 site in the US enrolled at least 1 patient each.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of adavosertib following oral dosing of the capsule formulation in patients with advanced solid tumors	• Adverse events/Serious adverse events • Vital signs (blood pressure, pulse rate, and body temperature) • Clinical chemistry, urinalysis, and hematology assessments • Electrocardiograms • Dose interruptions, reductions, and withdrawals from treatment

Study design

This was an open-label, non-randomized study designed to provide continued access to adavosertib for eligible patients with advanced solid tumors who had previously completed an adavosertib clinical pharmacology study, and to investigate the safety and tolerability of a once daily monotherapy regimen of adavosertib in patients with advanced solid tumors.

Patients who completed one of the parent studies (D601HC00004 or D601HC00006) were eligible for this study after completing a washout period, and if the eligibility criteria specified in the protocol were met. Patients who discontinued early from the parent study were considered by the Sponsor and treating physician for participation in this study on a case-by-case basis.

During the study, patients were to continue to receive adavosertib as long as they were benefiting from treatment in the Investigator's opinion and did not meet any other discontinuation criteria.

Enrolment in this continued access (CA) study was to continue until all eligible patients in the parent studies had either enrolled in the CA study or discontinued from the parent study and declined to participate in the CA study. Safety assessments (physical examination, vital signs, electrocardiogram [ECG], blood samples for hematology and clinical chemistry, and monitoring of adverse events [AE]) were to be collected on all patients in the CA study until the last patient had completed their final patient visit, or for patients who discontinued study intervention before or at the final patient visit, at the 30-day safety Follow-up Visit (30 days after their last dose), whichever occurred later.

A data cut-off (DCO) was planned when the last patient enrolled had been on treatment for 2 months or had discontinued study intervention, whichever was earlier. However, due to the early termination of the study that cut-off point was not reached; instead, the data cut-off was considered to be the date of database lock (06 September 2022).

Patients who discontinued adavosertib were to be scheduled for an end of treatment (EoT) visit as soon as possible, and approximately within 7 days of their last dose of adavosertib. For patients who had to discontinue their study intervention at the next scheduled visit, this visit also acted as their EoT visit and they were also required to have the 30-day safety Follow-up Visit.

Target population and sample size

Male and female patients (of non-childbearing potential) aged ≥ 18 years (at the time of signing the informed consent) with locally advanced or metastatic solid tumor, having a life expectancy ≥ 12 weeks.

Patients must have participated in one of the adavosertib parent studies and not met any requirements to permanently discontinue treatment with adavosertib. The number of patients who enrolled into this CA study was dependent on the number of patients who completed one of the parent studies, who tolerated adavosertib in the parent study, who met the eligibility criteria for, and who were willing to participate in, this CA study.

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

Table S2 Investigational Products

Intervention name	Adavosertib (AZD1775)
Type	Drug
Dose formulation	Capsule
Unit dose strength	CCI [redacted]
Dosage level	CCI [redacted] once daily for 5 days followed by 2 days off for 2 weeks out of a 21-day cycle
Route of administration	Oral

Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the Sponsor
Batch and lot numbers:	CCI [redacted]
Packaging and labelling	Study intervention 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.

Duration of treatment

Adavosertib was administered at the dose of CCI [redacted] once daily on Days 1 to 5 and Days 8 to 12 of a 21-day cycle (ie, 5 days on and 2 days off for Weeks 1 and 2 of a 21-day cycle).

Patients were screened within 14 days of Day 1 of the treatment period. During screening, patients underwent an appropriate washout period after the last dose of adavosertib in the parent clinical pharmacology study and before receiving the first dose of adavosertib in this CA study. The minimum duration of the washout period was dependent on the parent clinical pharmacology study in which the patient participated (7 days, except for patients on itraconazole in the parent study for whom it was 14 days).

Patients were to continue to receive adavosertib as long as they were benefiting from treatment in the Investigator's opinion and did not meet any other discontinuation criteria.

Statistical methods

Determination of Sample Size:

The number of patients who enrolled in this study was dependent on the number of patients who completed the parent studies, who tolerated adavosertib in the parent study, who meet the eligibility criteria for this CA study, and who were willing to participate in this CA study.

Analysis Sets:

- Enrolled: All patients who sign the Informed Consent form (ICF).
- Safety analysis set: All patients who receive at least 1 dose of adavosertib in this study.

Presentation and Analysis of Safety Data:

As per study protocol, analysis of safety variables was to be performed using descriptive statistics, with categorical variables summarized by number of subjects (n) and percentages, and continuous variables summarized using n, mean, standard deviation, minimum, median,

and maximum. Furthermore, number and percentages of patients with serious adverse events (SAEs), AEs with outcome of death, AEs leading to intervention discontinuation or interruption, and withdrawal from the study were to be summarized. All safety data were also to be presented in data listings.

Due to early study termination and the limited number of patients enrolled, no summary statistics were performed, and safety data were presented by individual patient listings only.

Adverse events were coded using version 24.1 of the Medical Dictionary for Regulatory Activities. Listings of AEs included timing of events, Common Terminology Criteria for Adverse Events (CTCAE) grading, seriousness, action taken with the study intervention, Investigator causality assessment, and outcome of event(s). The results of laboratory assessment (hematology and clinical chemistry), vital signs, and ECG parameters were also listed by patient and analysis visit.

No imputation of missing data was planned.

Study population

A total of 4 patients were screened for study eligibility; of these 1 was a screening failure. The PPD who met the entry requirements in the study and were assigned to study intervention were from 2 centers in 2 countries (UK and US). All assigned patients were exposed to study intervention. All assigned and treated patients had study intervention permanently discontinued and were prematurely withdrawn from the study (1 patient PPD due to an AE [neutropenic sepsis] and 2 patients PPD due to Investigator decision). None of the patients completed the study.

Age of the 3 enrolled patients ranged from PPD. All patients were PPD

Protocol deviations

Important protocol deviations were reported as follows:

- Patient PPD: the patient did not re-consent to the updated version of the ICF, did not have laboratory tests (hematology and clinical chemistry) performed as planned at one study visit, had an SAE which was not reported within the 24 hours maximum timeframe, and did not have EoT visit within 7 days of the last dose of adavosertib.
- Patient PPD: general assessment by telephone to assess AEs and concomitant medications was not performed at C1D3 and/or C2D3.
- Patient PPD: urinalysis (dipstick) was not performed as planned at one study visit, and EoT visit was not performed within 7 days of the last dose of adavosertib.

Summary of safety results

- The 3 treated patients experienced a total of 30 AEs during the study.
- There were no AEs with outcome of death. A total of 3 SAEs were reported for 1 patient:
  - Patient PPD experienced SAEs of thrombocytopenia (CTCAE Grade 4) on study Day 14, and neutropenic sepsis (CTCAE Grade 3) and anemia (CTCAE Grade 2) on Day 15. On Day 14, the patient also reported non-serious events of pyrexia (CTCAE Grade 1), decreased appetite, and hypalbuminemia (both CTCAE Grade 2). The events occurring on Day 14 led to decision of study intervention interruption. On Day 15, the decision to permanently discontinue the study intervention was made due to the SAE of neutropenic sepsis. All SAEs and AEs resolved, with the exception of anemia for which the outcome was reported as ongoing at the end of the study. All events were assessed by the Investigator as possibly related to the study intervention.
- For PPD AEs led to permanent study intervention discontinuation (neutropenic sepsis for Patient PPD and nausea for patient PPD. Both patients also experienced AEs requiring drug interruption. In addition, for Patien PPD, the dose of study intervention was reduced due to an AE of dehydration which was considered by the Investigator to be CTCAE Grade 1; the event resolved.
- Twenty-eight out of the 30 reported events were considered by the Investigator as CTCAE Grade 1 or CTCAE Grade 2; 1 event was CTCAE Grade 3 (neutropenic sepsis), and 1 CTCAE Grade 4 (thrombocytopenia), both events were reported for Patient PPD.
- Of the total, 22 events were assessed by the Investigator as possibly related to the administration of the study intervention. Of these:
  - There were 13 CTCAE Grade 1 events (dysgeusia, fatigue, pyrexia, 2 events of diarrhea, dehydration, nausea, neck pain, dizziness, dyspepsia, asthenia, headache, and decreased appetite),
  - There were 7 CTCAE Grade 2 events (anemia, decreased appetite, hypoalbuminemia, blood creatinine increased, asthenia, hypotension, and dehydration),
  - There were 1 CTCAE Grade 3 event (neutropenic sepsis) and 1 CTCAE Grade 4 event (thrombocytopenia).
- The outcome for all 30 events was reported as resolved without sequelae, with the exception of 4 events (anemia, dysgeusia, fatigue, and dehydration) for which the outcome was reported as not recovered/not resolved. Follow-up information received post-database lock reported that at the end of the study the event of dehydration resolved and the events of anemia, dysgeusia, and fatigue were ongoing.
- Laboratory tests reported as being higher or lower than the predefined reference ranges for all 3 enrolled patients were:
  - Hematology:

- Low erythrocytes:
  - Patient PPD at Screening, on C1D1, C1D8, Unscheduled visit, and EoT,
  - Patient PPD on C1D15, C2D1, and EoT,
  - Patient PPD on C2D1, C5D1, and C6D1,
- Low hematocrit:
  - Patient PPD at Screening, on C1D1, Unscheduled visit, and EoT,
  - Patient PPD at C1D15 and EoT,
  - Patient PPD on C1D1, C2D1, C3D1, C4D1, C5D1, C5D8, and C6D1,
- Low hemoglobin:
  - PatientPPD at Screening, on C1D1, Unscheduled visit, and EoT,
  - Patient PPD on C1D15, C2D1, and EoT,
  - Patient PPD at Screening, on C1D1, C1D15, C2D1, C2D5, C2D8, C2D15, C3D1 C3D8, C4D1 C4D8, C5D1, C5D8, and C6D1,
- Low lymphocytes:
  - Patient PPD at Screening, on C1D1, and Unscheduled visit,
  - Patient PPD on C1D8,
  - Patient PPD on C1D5, C1D8, C2D5, C2D8, C2D15, C3D8, C4D1, C4D8C5D1, C5D8, C6D1, and EoT,
- High neutrophils:
  - Patient PPD on C1D5 and C1D8,
  - Patient PPD on C1D15 and C1D8,
  - Patient PPD on C1D5 and C1D8.

– Clinical chemistry:

- High creatinine:
  - Patient PPD on C1D5,
  - Patient PPD at Screening, on C1D1, C1D5, C1D8, C1D15, C2D1, and EoT,
  - Patient PPD on C1D15, C2D8, and C2D15,
- High urea nitrogen:
  - Patient PPD on C1D5, C1D8, and Unscheduled visit,
  - Patient PPD on C1D5 and C1D8,
  - Patient PPD on C1D5, C2D8, and C2D15.

- Two patients had abnormal laboratory tests results reported as AEs. All events were assessed by the Investigator as related to the study intervention, were non-serious, and all resolved:
  – Patien PPD reported hypoalbuminemia (CTCAE Grade 2), and thrombocytopenia (CTCAE Grade 4), both requiring interruption of study

intervention, and anemia (CTCAE Grade 2) for which action taken with study intervention was reported as not applicable,

  - Patient PPD experienced blood creatinine increased (CTCAE Grade 2) for which study intervention dose was not changed.

- Two patients had abnormal vital signs reported as AEs. All events were assessed by the Investigator as related to the study intervention, were non-serious, and resolved:
  - Patient PPD reported pyrexia (CTCAE Grade 1) requiring interruption of study intervention,
  - Patient PPD experienced hypotension (CTCAE Grade 2) for which study intervention was interrupted.
- Whilst some ECG abnormalities were reported, no clinically significant results were observed on a patient level. No AEs associated to ECG parameters were reported during the study.

Conclusion

This study was prematurely terminated due to a strategic business decision after 3 patients were dosed with adavosertib.

- The safety profile in this study was consistent with the established safety profile of adavosertib, with no new safety findings identified. The adverse events were generally manageable and tolerable.