Synoptic Clinical Study Report	
Drug Substance	Adavosertib (AZD1775)
Study Code	D601HC00006
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A Phase I, Open-label, Non-randomised Study to Assess the Effect of Itraconazole (a CYP3A4 Inhibitor), Rifampicin (a CYP3A4 Inducer), and Omeprazole (a Proton Pump Inhibitor) on the Pharmacokinetics of a Single Oral Dose of Adavosertib in Patients with Advanced Solid Tumours

Study dates:	First subject enrolled: 28 June 2021 Last subject last visit: 01 June 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:	Not applicable.
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 centres

Eight sites in Spain and 8 sites in the United States (US) were selected for study participation. However, patients were enrolled from 1 study site in Spain and 3 study sites in the US, enrolling a total of 14 patients before termination of the study.

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 effect of itraconazole (Arm A)/rifampicin (Arm B)/omeprazole (Arm C) on the PK of adavosertib following oral dosing in patients with advanced solid tumours	• For each arm: adavosertib Cmax, AUCinf, and AUClast ratios of geometric means of test intervention (adavosertib + itraconazole/rifampicin/omeprazole) relative to reference intervention (adavosertib alone)
Secondary	
• To describe the PK parameters and the PK profiles for adavosertib when administered alone and in combination with itraconazole (Arm A)/rifampicin (Arm B)/omeprazole (Arm C)	• For each arm: adavosertib summary PK profiles and descriptive statistics of Cmax, AUCinf, AUClast, tmax, λz, t½λz, CL/F, Vss/F, and Vz/F (Additional PK parameters may be determined where appropriate) • Itraconazole (Arm A), rifampicin (Arm B), and omeprazole (Arm C) descriptive statistics of Ctrough
• To assess the safety and tolerability of adavosertib when dosed with itraconazole (Arm A), rifampicin (Arm B), and omeprazole (Arm C)	• AEs/SAEs • Vital signs • ECGs • Clinical chemistry/haematology/urinalysis

Abbreviations: AE = adverse event; AUCinf = area under plasma concentration-time curve (AUC) from time zero to infinity; AUClast = area under plasma concentration-time curve (AUC) from time zero to time of last quantifiable concentration; CL/F = Apparent total body clearance of drug from plasma after extravascular administration; Cmax = maximum observed plasma concentration; Ctrough = observed lowest drug concentration reached before the next dose is administered (for itraconazole, rifampicin, and omeprazole only); ECG = electrocardiogram; λz = terminal elimination rate constant; PK = pharmacokinetic(s); SAE = serious adverse event; 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 1, parallel, open-label, non-randomised, 3-arm (A, B, and C), drug-drug interaction (DDI) study to assess the effect of itraconazole (a cytochrome P450 3A4 [CYP3A4] inhibitor), rifampicin (a CYP3A4 inducer), and omeprazole (a proton pump inhibitor) on the pharmacokinetics (PK) of a single oral dose of adavosertib in patients with advanced solid tumours.

The study consisted of a screening period of up to 28 days (Day -28 to Day -1), an intervention period (12 days for Arm A and Arm C; 17 days for Arm B), and a follow-up end of treatment (EOT) visit (within 3 days after a 4-day washout period relative to the last dose of adavosertib).

Patients from all the 3 arms received 2 study interventions: a single oral dose of adavosertib alone, and a single oral dose of adavosertib administered concomitantly with either itraconazole, or rifampicin, or omeprazole, as stated below:

- Arm A: single dose of adavosertib CCI on Day 1, followed by once daily itraconazole CCI for 7 days from Days 5 to 11, with co-administration of adavosertib CCI and itraconazole CCI on Day 9.
- Arm B: single dose of adavosertib CCI on Day 1, followed by once daily rifampicin CCI for 13 days from Days 5 to 17, with co-administration of adavosertib CCI and rifampicin CCI on Day 14.
- Arm C: single dose of adavosertib CCI on Day 1, followed by once daily omeprazole CCI for 5 days from Days 5 to 9, with co-administration of adavosertib CCI and omeprazole CCI on Day 9.

Patients were to be fasted from at least 10 hours before the morning adavosertib dose on Day 1, Day 9 (in Arm A and Arm C), and Day 14 (in Arm B) until 4 hours post-dose. Water was to be allowed as desired except for 1 hour before and after adavosertib administration.

Patients remained at the study site until 24 hours after the dose of adavosertib, during which PK blood samples and other safety assessments were collected.

Patients who completed the study were allowed further access to adavosertib in a continued access study (D601HC00009) if the study was open and was enrolling at the site, they met the eligibility and in the opinion of their treating physician they were deriving clinical benefit from continued treatment. All patients who were not to enroll in the continued access study were to be asked to return to the study site 30 (±7) days after the last dose of adavosertib for a final follow-up visit (end of study [EOS] visit).

Target population and sample size

Male (either surgically sterile or using an acceptable method of contraception) and/or female patients (either post-menopausal, or surgically sterile, or using one highly effective form of birth control), aged ≥ 18 years (at the time of signing the informed consent form [ICF]), with locally advanced or metastatic solid tumour, excluding lymphoma, and having a predicted life expectancy ≥ 12 weeks.

Approximately 24 patients were planned to be enrolled in Arm A and 24 patients in Arm B, to achieve 20 evaluable PK patients per arm. Approximately 22 patients were planned to be enrolled in Arm C, to achieve 18 evaluable PK patients. However, only 7 male and 7 female patients were enrolled into the study.

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

Table S2 Investigational Products

Intervention name	Adavosertib (AZD1775)	Itraconazole	Rifampicin	Omeprazole
Type	Drug	Drug	Drug	Drug
Dose formulation	Capsule	Capsule	Capsule	Capsule
Unit dose strength(s)	CCI	CCI	CCI	CCI
Dosage level(s)	CCI single dose, followed by CCI (on Day 9 in Arm A) or CCI (on Day 14 in Arm B and on Day 9 in Arm C)	CCI once daily for 7 days in Arm A only	CCI once daily for 13 days in Arm B only	CCI once daily for 5 days in Arm C only
Route of administration	Oral	Oral	Oral	Oral
Use	Experimental	Challenge agent	Challenge agent	Challenge agent
IMP and NIMP	IMP	NIMP	NIMP	NIMP
Sourcing	Provided centrally by the sponsor	Provided by Parexel	Provided by Parexel	Provided by Parexel
Batch/Lot Number(s)	CCI	CCI	CCI	CCI

Intervention name	Adavosertib (AZD1775)	Itraconazole	Rifampicin	Omeprazole
Packaging and labelling	Study intervention was provided in high-density polyethylene bottle. Each bottle was labelled as required per country requirement.	Study intervention was provided in commercially available package.	Study intervention was provided in commercially available package.	Study intervention was provided in commercially available package.

a: Though adavosertib was provided in unit dose strengths of CCI and CCI, only CCI dose strength was used during the study.

Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational medicinal product; US = United States.

Duration of treatment

The patients in Arm A (adavosertib and itraconazole) and Arm C (adavosertib and omeprazole) received the treatment for 12 days while the patients in Arm B (adavosertib and rifampicin) received the treatment for 17 days.

Statistical methods

The below methods reflect the actual methods followed for the study due to premature study termination. No summary statistics were performed, the safety measurements and PK concentration 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 3-arm, drug-drug interaction study in patients with advanced solid tumors, to provide an estimate of the difference between adavosertib PK parameters in the presence and absence of concomitant itraconazole (Arm A), rifampicin (Arm B), and omeprazole (Arm C).

The aim was to enroll 24 patients in Arm A and 24 patients in Arm B, to achieve 20 evaluable patients in each arm. Approximately 22 patients were to be enrolled in Arm C, to achieve 18 evaluable patients.

It was expected that the proposed sample size would give adequate information on the effect of itraconazole, or rifampicin, or omeprazole on the exposure of adavosertib, while exposing as few participants as possible to study procedures. 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. Classification into safety and PK analysis sets were conducted prior to database lock. The analysis sets were defined as below:

- The **Enrolled Set**: all patients who signed the informed Consent Form (ICF).
- The **Safety Analysis Set**: all patients who received at least 1 dose of study intervention (adavosertib).
- The **PK Analysis Set**: all dosed patients who have at least 1 reportable post-dose plasma concentration without Clinical Study Protocol (CSP) deviations or events that would affect the PK analysis.

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 for the PK analysis set. No summary statistics were performed, and no graphical representation plots were constructed due to limited number of subjects enrolled in each arm before termination.

Presentation of safety data:

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. 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 using version 25.0 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).

Study population

A total of 14 patients with solid tumors were screened for study eligibility. Of these, 4 were screening failures, 4 patients withdrew their consent, 1 patient was withdrawn by the Investigator, and 5 patients who met the entry requirements in the study were assigned to study intervention.

At the time when the study was terminated prematurely by the sponsor, 5 patients had been treated with study intervention. Of these, 4 patients completed the study per protocol, and 1 patient was prematurely withdrawn as per Investigator decision on Day 14 of the study.

Age of the 5 (3 male and 2 female) enrolled patients ranged from 37 to 70 years. Four patients were White and for 1 patient the race was not recorded. The baseline body mass index (BMI) ranged from 19.9 to 35.3 kg/m^2. The patients were from 4 study sites in 2 countries (US and Spain).

Protocol deviations

Important protocol deviations were reported in the study as follows:

- Patient PPD: physical examination was not completed prior to the first dose of adavosertib (anywhere between Day -1 to pre-dose of Day 1); local laboratory urinalysis was not performed at one study visit; rifampicin PK pre-dose sample (Arm B) was not collected within expected time window prior to dosing on Day 14, Day 15, Day 16 and/or Day 17.
- Patient PPD: PK sample at 0.75-hour post-dose (Arm A, Arm B, and Arm C) was not collected within 10% of the nominal time (+/- 6 minutes for a 60-minute sample).
- Patient PPD: the Visit Date V7D8 was not within the visit window 4 day since visit V6D4 (Arm A and Arm C).
- Patient PPD: physical examination was not completed prior to the first dose of adavosertib (anywhere between Day -1 to pre-dose of Day 1); rifampicin PK sample pre-dose (Arm B) was not collected within expected time window prior to dosing on Day 14, Day 15, Day 16 and/or Day 17.

Summary of pharmacokinetic results

Effects of itraconazole (strong CYP3A4 inhibitor) on adavosertib PK: Two subjects were dosed in the Arm A (PPD). The plasma concentrations of adavosertib were higher in the presence of itraconazole as compared to adavosertib alone (Day 1 vs Day 9) in most of the post-dose time points and increase was less than 2 folds (Appendix 16.2.6). However, due to limited number of subjects, no statement or conclusion could be derived about potential DDI.

Effects of rifampicin (strong CYP3A4 inducer) on adavosertib PK: Two subjects were dosed in the Arm B (PPD). The plasma concentrations of adavosertib were decreased from <20% to >80% in post-dose time points as compared to adavosertib alone (Day 1 vs Day 14), suggesting a potential impact of strong CYP3A4 inducer on the adavosertib exposure (Appendix 16.2.6). However, due to limited number of subjects, no statement or conclusion could be derived about potential DDI.

Effects of omeprazole (a proton pump inhibitor) on adavosertib PK: Only 1 subject was dosed in the Arm C (PPD). The plasma concentrations of adavosertib appeared to be similar in majority of the post-dose time points as compared to adavosertib alone (Day 1 vs Day 9), suggesting, minimum potential impact on omeprazole on adavosertib exposure

(Appendix 16.2.6). However, due to limited number of subjects, no statement or conclusion could be derived about potential DDI.

Summary of safety results

- Out of the 5 treated patients, 3 patients experienced 3 AEs (1 AE each) during the study. The details are as below:
  - The AE of hypotension for Patient PPD was considered by the investigator to be mild in intensity (CTCAE Grade 1) and presented on Day 15. The outcome of the AE was ongoing at the end of the study.
  - The AE of blood creatinine increased for Patient PPD was considered by the investigator to be mild in intensity (CTCAE Grade 1) and was reported as starting 23 days prior to administration of the study intervention. The outcome of the AE was recovered at the end of the study.
  - The AE of white blood cell count decreased for Patient PPD was considered by the investigator to be mild in intensity (CTCAE Grade 1) and presented on Day 6. The outcome of the AE was recovered at the end of the study.
  - All 3 AEs were considered by the investigator as non-serious and not related to administration of the study intervention.
  - No action was taken for any of the AEs with regards to the study intervention.
- There were no serious adverse events (SAEs) reported for any of the treated patients.
- There were no AEs with outcome of death.
- Out of range results were reported for 5 treated patients for various laboratory finding, as below:

Patient	Laboratory Parameter (unit)	Reference range	Screening	Day −1	Day 8	Day 13	End of Treatment	End of Study
PPD	High Alkaline Phosphatase (µkat/L)	0.58345 to 1.75035	1.98373					
	High Calcium (mmol/L)	2.1457 to 2.5449				2.56985	2.5948	
	Low Creatinine (µmol/L)	44.2 to 79.56				39.78		36.244
	Low Urea Nitrogen (mmol/L)	7.14 to 17.136		5.4978		4.4982		
	Low Partial Thromboplastin Time (sec)	26 to 39					25	
	High Eosinophils ($\times 10^9$/L)	0 to 0.5					0.6	

Patient	Laboratory Parameter (unit)	Reference range	Screening	Day −1	Day 8	Day 13	End of Treatment	End of Study
	Low Erythrocytes ($\times 10^{12}$/L)	3.8 to 5.1					3.57	3.7
	High Neutrophils ($\times 10^{9}$/L)	1.8 to 7.6						8.6
PPD	High Alanine Aminotransferase (µkat/L)	0 to 0.53344			0.55011			
	High Alkaline Phosphatase (µkat/L)	0.65013 to 1.95039	2.63386	2.6672	2.8339		3.25065	
	High Calcium (mmol/L)	2.17065 to 2.56985	2.5948				2.7445	
	High Creatinine (µmol/L)	50.388 to 88.4	91.052	91.052	99.008		94.588	
	High Partial Thromboplastin Time (sec)	24 to 33			34			
PPD	High Albumin (g/L)	29 to 44		45				
	High Creatinine (µmol/L)	67.184 to 112.268	160.888	151.164	141.44		151.164	
	Low Potassium (mmol/L)	3.5 to 5.2	3.2					
	Low Erythrocytes ($\times 10^{12}$/L)	4.14 to 5.8	3.56	3.8	3.54		3.51	
	Low Hematocrit (Ratio)	0.375 to 0.51	0.354		0.337		0.332	
	Low Hemoglobin (g/L)	130 to 177	117	124	115		110	
PPD	High Albumin (g/L)	29 to 44		45				
	High Creatinine (µmol/L)	67.184 to 112.268 (Day −1); 70.72 to 114.92 (Day 8)		117.572	122.876			
	High Prothrombin Time (sec)	9.4 to 12.5 (Day 8); 9.1 to 12 (End of Treatment)			12.6		13.5	
	Low Hematocrit (Ratio)	0.375 to 0.51					0.355	
	Low Hemoglobin (g/L)	130 to 177	128				115	
	Low Lymphocytes ($\times 10^{9}$/L)	0.7 to 3.1 (Day −1 and End of		0.6	0.7		0.6	

Patient	Laboratory Parameter (unit)	Reference range	Screening	Day −1	Day 8	Day 13	End of Treatment	End of Study
		Treatment); 2.5 to 10.5 (Day 8)						
PPD	Low Albumin (g/L)	34 to 50	32	32			33	31
	High Alkaline Phosphatase (µkat/L)	0.8335 to 2.26712				2.3338		2.3338
	Low Calcium (mmol/L)	2.12075 to 2.51995				2.0459		
	High Chloride (mmol/L)	97 to 107	108	110		108	109	
	High Sodium (mmol/L)	136 to 145		148		146	146	
	High Urea Nitrogen (mmol/L)	2.499 to 6.426		7.497		7.14	7.497	6.783
	High Partial Thromboplastin Time (sec)	27.1 to 35.9	39.1					39.2
	Low Erythrocytes ($\times 10^{12}$/L)	4.7 to 6.1	4.69				4.67	4.28
	Low Hematocrit (Ratio)	0.4 to 0.5						0.379
	Low Hemoglobin (g/L)	140 to 180	128	130		135	129	121
	Low Leukocytes ($\times 10^{9}$/L)	4.8 to 10.8	4.36	3.97		3.68	4.4	4.15
	Low Lymphocytes ($\times 10^{9}$/L)	1.2 to 3.4	0.63	0.88		0.88	0.53	0.75

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:

- Adavosertib plasma concentrations appeared to be increased in the presence of itraconazole, decreased in the presence of rifampicin, and remained unaltered in the presence of omeprazole in majority of post-dose time points. However, due to very limited number of subjects data, no conclusion about potential DDI could be derived.
- Adavosertib was overall well tolerated when dosed with itraconazole, rifampicin or omeprazole in this study. No new or unexpected safety signals were identified based on the limited safety data observed.