Synoptic Clinical Study Report	
Drug Substance	Adavosertib (AZD1775)
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A Phase I, Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-Tumour Activity of Adavosertib (AZD1775) in Monotherapy and in Combination with Chemotherapy in Japanese Patients with Advanced Solid Tumours

Study dates: First patient enrolled: 24 June 2020
Last patient last visit: 22 September 2021
The analyses presented in this report are based on a clinical data lock date of 16 December 2022

Phase of development: Clinical pharmacology (I)

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

2. SYNOPSIS

Introduction

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. Therefore, Part B (combination with gemcitabine) was not initiated, and the clinical study report (CSR) was prepared in a synoptic format.

Study centre

One centre in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The objectives and endpoints are listed in Table 1 below.

Table 1 Objectives and Endpoints for Part A (Monotherapy)

Primary objective:	**Endpoint/variable:**
• To assess the safety and tolerability, describe any DLT for adavosertib	• AEs, DLTs, vital signs, ECG results, and laboratory parameters
Secondary objectives:	**Endpoints/variables:**
• To determine the PK profile of adavosertib	• Summary PK parameters for adavosertib, such as C_{max}, t_{max}, $AUC_{(0-24)}$ and C_{trough}
• To describe adavosertib's preliminary anti-tumour activity using the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1	• ORR, DCR, DoR, and PFS assessed based on RECIST v1.1 by investigator assessment

Abbreviations: AE = Adverse event; $AUC_{(0-24)}$ = area under the plasma concentration-time curve from zero to 24 hours; C_{max} = maximum plasma drug concentration observed; C_{trough} = trough plasma concentration; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetics; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, version 1.1; t_{max} = time of maximum plasma drug concentration observed.

Results for exploratory analyses are not reported in this CSR.

Study design

This was a Phase 1, open-label study to assess the safety, tolerability, pharmacokinetic (PK), and anti-tumour activity of adavosertib in monotherapy and in combination with gemcitabine in Japanese patients with advanced solid tumours.

The safety, tolerability, PK, and anti-tumour activities of adavosertib in combination with other agents could have been explored, as needed.

Adavosertib used as monotherapy and/or in combination with other agents was being developed as a potential treatment for multiple tumour types, therefore it was considered appropriate to assess tolerability of adavosertib in monotherapy and in combination with chemotherapy in Japanese patients.

Part A of the study consisted of dose escalation using adavosertib monotherapy. A safety review committee (SRC) evaluated emerging safety, tolerability, and PK profiles (if possible) to support dose escalation decisions. See Section 4 of Study Protocol in Appendix 16.1.1.

Part B (combination with gemcitabine) was not initiated since the study was terminated early.

Target population and sample size

Japanese patients ≥ 20 years old at the time of study entry, with histologically or cytologically documented locally advanced or metastatic solid tumour, excluding lymphoma, for which standard therapy did not exist or had proven ineffective or intolerable, and with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 or 1, predicted life expectancy ≥ 12 weeks were enrolled in Part A of the study. Additionally, tumours for which gemcitabine was expected to be effective, was necessary for enrolment in Part B of the study.

At least 3, or up to 6, evaluable Japanese patients with advanced solid tumours were enrolled in each cohort. Any patients not evaluable for dose-limiting toxicity (DLT) were to be replaced. Thus, the total number of patients was dependent on the available data in each cohort and the SRC's decision.

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

Adavosertib (AZD1775, provided by the Sponsor) was administered orally (PO) as 50, 75, or 100 mg capsules.

Batch numbers:
AZD1775 capsule 50 mg: KKAD
AZD1775 capsule 100 mg: PPAE
AZD1775 capsule 75 mg: SSAD

Duration of treatment

Patients were allowed to continue treatment with study drug until disease progression, intolerable toxicity, or until discontinuation criteria were met.

Patients in Part A (Monotherapy) received the treatment with study drug as described below:

Cohort 1: Adavosertib 250 mg PO once daily (QD) for five days ON and two days OFF for Week 1 and Week 2 of a 21-day cycle.

Cohort 2 onwards: Adavosertib PO QD for five days ON and two days OFF for Week 1 and Week 2 of a 21-day cycle.

The adavosertib dose in each cohort of Cohort 2 onwards was to be discussed based on emerging data and was to be determined when each cohort began.

Statistical methods

All analyses were performed on data entered into the study database to a data cut-off (DCO) date of 31 October 2022.

All analyses and reporting were conducted by cohort and overall, for each part, where appropriate. Selected analyses and reporting were to be conducted for all parts combined, as appropriate. However, at DCO, Part B was not conducted. Therefore, the statistical analysis plan does not contain any analysis plan for Part B. The below mentioned general principles were followed throughout the study:

- Descriptive statistics were used for all variables, as appropriate. Continuous variables were summarised by the number of non-missing observations, mean, standard deviation (StdDev), median, upper and lower quartiles (as applicable), minimum, and maximum. For log-transformed data it was more appropriate to present geometric mean, coefficient of variation, median, minimum, and maximum. Categorical variables were summarised by frequency counts and percentages for each category.
- If data were available for < 3 patients, no summary statistics other than minimum, maximum and number of observations were presented.
- Unless otherwise stated, percentages were calculated out of the dose cohort total.
- For continuous data the mean and median were rounded to one additional decimal place compared to the original data. The StdDev was rounded to two additional decimal places compared to the original data. Minimum and maximum were displayed with the same accuracy as the original data.
- For categorical data, percentages were rounded to one decimal place.
- SAS® version 9.4 or above was used for all analyses.
- It was acceptable to present large numerical values in more appropriate units. For eg, an area under the plasma concentration-time curve (AUC) value of 123000 ng·h/mL was reported as 123 µg·h/mL instead.

The analysis sets used in this study were as listed in Table 2 below.

Table 2 Analysis Sets

Analysis Set	Definition
All Subjects Analysis Set	All patients who signed the informed consent form.
Safety Analysis Set	All patients who received at least one dose of adavosertib. Patients were evaluated according to the treatment received.
Dose-limiting Toxicity (DLT) Analysis Set	All patients who had completed the DLT evaluation period with sufficient dosing (See Section 6.6.2 of Study Protocol in Appendix 16.1.1).
Tumour Response Analysis Set	Patients who had non-missing tumour assessment data of measurable or non-measurable lesions at baseline and received at least 1 dose of adavosertib.
Pharmacokinetics (PK) Analysis Set	All patients who received at least 1 dose of adavosertib with at least 1 quantifiable plasma concentration for adavosertib or metabolites collected post dose without protocol deviations or events that would have affected the PK analysis.

Safety and tolerability evaluations included, but were not limited to, adverse events (AEs; including serious adverse events [SAEs]), deaths, DLTs, physical examinations, laboratory data, vital signs, and electrocardiograms (ECGs). The evaluations were descriptive using summary statistics. There was no formal statistical analysis of safety and tolerability data required for this study.

Exposure to study drug was listed for all patients. Relative dose intensity was summarised using medians, and quartiles as well as the minimum and maximum values.

An overall summary table of the number of patients experiencing each category of AE was produced. The AEs occurring after first study drug dose (Study Day 1) and within the 30-day follow-up period after discontinuation of study drug were considered as treatment-emergent adverse events (TEAEs). The number of patients experiencing TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 system organ class (SOC) and MedDRA preferred term (PT) were presented, with further splits by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade, possible relationship to study drug and AEs of Grade ≥ 3.

Separate tables were generated for DLTs and AEs leading to discontinuation, as well as modification, reduction, interruption, and SAEs - including number of SAEs and possible relationship to study drug. All AE data were listed appropriately. Episode-level summaries were also produced for the overall summary table and TEAE by SOC and PT.

All analyses related to anti-tumour activities of adavosertib were descriptive; no formal statistical testing was performed. Details of tumour assessment and response were listed for each patient, including information on lesion site, the method of assessment, diameter of lesion, sum of diameters of lesions, percent change from baseline, the calculated visit response, non-target lesions (NTLs), new lesions, best objective response (BOR), disease control rate (DCR), duration of response, and progression-free survival (PFS). Tumour response outcomes in terms of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) were presented for the Tumour Response Analysis Set and the subset of the Tumour Response Analysis Set with measurable disease at baseline. The objective response rate (ORR) was calculated based on the subset of the Tumour Response Analysis Set with measurable disease at baseline. The DCR was calculated based on the Tumour Response Analysis Set, while PFS was evaluated based on the Safety Analysis Set.

Plasma concentrations of adavosertib were summarised by nominal sample time, cohort and by analysis visit.

Study population

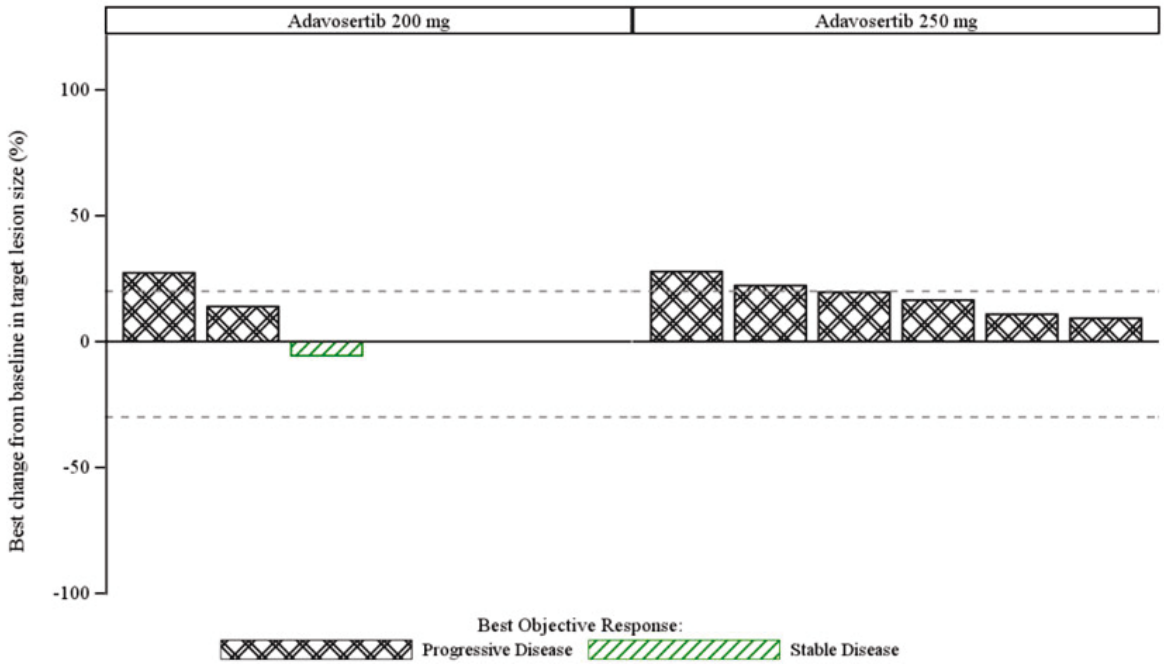
- A total of 10 patients were enrolled in Part A of the study, out of which, 1 patient did not meet eligibility criteria, did not receive treatment, and was not included in any analysis set except for All Subjects Analysis Set. Out of the 9 patients who received treatment, 3 patients received 200 mg adavosertib (200 mg cohort), while 6 patients received 250 mg adavosertib (250 mg cohort).
- All patients were Asian, a majority were female (6 out of 9 patients, 66.67%), while most were in the age group of <65 years (7 out of 9 patients, 77.8%). The mean (StdDev) age, weight, height, and body mass index were 56.4 years (9.53 years), 53.43 kg (9.959 kg), 161.74 cm (6.238 cm), and 20.43 kg/m^2 (3.731 kg/m^2) respectively.
- The patients presented with Stage I through IV (American Joint Committee on Cancer Staging) at screening, with primary tumour location in the pancreas (1 patient), ovary (2 patients), uterus (2 patients), testis (1 patient), or “other” (1 patient each, with intrahepatic cholangiocarcinoma, melanoma, and gallbladder cancer). A majority (7 out of 9 patients) had unassessable tumour grade at screening, with histology types including endometrioid: adenoacanthoma in 2 patients, as well as 1 patient each, with adenocarcinoma, adenocarcinoma (NOS), cholangiocarcinoma (intrahepatic), mucinous, serous cystadenocarcinoma, and “other”, while histology of 1 patient could not be determined.
- All patients had received previous anti-cancer therapy, with a median of 3 previous regimens, ranging from a minimum of 2 to maximum of 13 previous regimens.
- All patients had ECOG PS of 0 (8 out of 9 patients, 88.9%) or 1 (1 out of 9 patients, 11.1%) at baseline.
- All 9 patients discontinued treatment, due to worsening of condition under investigation (2 patients in the 200 mg cohort and all 6 patients in the 250 mg cohort) or ‘Other’ reason (1 patient in the 200 mg cohort).

- All 9 patients were subsequently withdrawn from the study after Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1.1) assessment, due to PD (2 patients in the 200 mg cohort and all 6 patients in the 250 mg cohort) or physician decision (1 patient in the 200 mg cohort).

Summary of efficacy results

- No patient showed response at DCO of 31 October 2022.
- The DCR (CR+PR+SD) was 1 out of 3 (33.3%) patients in the 200 mg cohort and 0 out of 6 (0%) patients in the 250 mg cohort.
- One patient in the 200 mg cohort (PPD) showed BOR of SD at ≥8 weeks, while all other patients showed BOR of PD.
- In the 200 mg cohort, disease progression was reported in terms of RECIST v1.1 progression in the NTLs only, for both patients, with median PFS of 2.10 months (80% CI=0.79-NC).
- In the 250 mg cohort, disease progression was reported in terms of RECIST v1.1 progression in the target lesions (TLs) for 2 patients (33.3%), in the NTLs for 1 patient (16.7%), and due to new lesions noted for 3 patients (50.0%), with median PFS of 1.08 months (80% CI = 0.99-2.14).
- Mean best percentage change (StdDev) in TL size from baseline was 11.8% (16.55%) in the 200 mg cohort and 17.7% (7.02%) in the 250 mg cohort. One patient showed reduction (PPD) of -5.6% in tumour size in the 200 mg cohort.

Figure 1 **Target Lesion Size, Best Percentage Change Waterfall Plot (Tumour Response Analysis Set, Patients with Measurable Disease at Study Entry)**



Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
Reference lines represent +20%/-30% change in tumour size.
Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.
Source: Figure 14.2.1.4.2

Summary of pharmacokinetic results

- Adavosertib was steadily absorbed following both, first and fifth dosing of QD doses for 5 days; median time to reach maximum concentration (t_{max}) ranged from 2.08 to 4.03 hours after first dose and 1.90 to 2.82 hours after fifth dose, across two treatment cohorts (200 or 250 mg QD doses).
- Adavosertib was slowly eliminated; mean terminal elimination half-life ($t_{1/2\lambda z}$) were approximately 7.30 to 7.36 hours after first dose and 8.88 to 10.55 hours after fifth dose, generally similar between treatment cohorts.
- Accumulation of adavosertib in plasma following multiple QD doses for 5 days was generally minimal; mean accumulation ratios based on area under the concentration-time curve from zero to 24 hours [$AUC_{(0-24)}$] ranged from 1.63 to 1.73 across two treatment cohorts.
- As dose increased from 200 to 250 mg, systemic exposure to adavosertib increased in slightly more than dose-proportional manner; a 1.25-fold increase in dose resulted in 1.70- and 1.65-fold increases in geometric mean of maximum plasma drug concentration observed (C_{max}) and $AUC_{(0-24)}$, respectively, after first dose and 1.38- and 1.62-fold increases in geometric mean C_{max} and $AUC_{(0-24)}$, respectively, after fifth dose.

Summary of safety results

- In the 200 mg cohort, there was no difference in median values for total and actual duration of adavosertib exposure. The median total and actual duration was 1.54 months (minimum = 0.4 months, maximum = 1.8 months), while mean (StdDev) total and actual duration was 1.24 months (0.739 months).
- In the 250 mg cohort, the total duration was slightly higher than the actual duration of adavosertib exposure. The median total duration was 0.97 months (minimum = 0.4 months, maximum = 1.9 months), while the median actual duration was 0.95 months (minimum = 0.4 months, maximum = 1.8 months). Similarly, the mean (StdDev) total duration was 1.13 months (0.580 months), while mean (StdDev) actual duration was 1.11 months (0.559 months). This was due to higher proportion of patients in the 250 mg cohort with dose modifications (ie, either an interruption or dose reduction) during the study compared with patients in the 200 mg cohort.
- Mean (StdDev) values for relative dose intensity was 100% (0%) in the 200 mg cohort and 96.67% (5.578%) in the 250 mg cohort.
- A total of 8 out of 9 patients (88.9%) overall reported at least 1 AE, including all 3 patients (100%) in the 200 mg cohort and 5 out of 6 patients (83.3%) in the 250 mg cohort.
- The most commonly reported AEs at the PT level overall, were nausea (reported by 8 out of 9 patients [88.9%] overall), followed by decreased appetite, constipation, diarrhoea,

vomiting, and platelet count decreased (4 patients each, [44.4%] overall). The most commonly reported AEs at the PT level in the 200 mg cohort were nausea (3 patients), followed by diarrhoea and hypoalbuminaemia (2 patients, each). The most commonly reported AEs at the PT level in the 250 mg cohort were nausea (5 patients), followed by vomiting and decreased appetite (4 patients, each).

- No AEs leading to discontinuation of treatment were reported in the study.
- No deaths were reported in the study.
- A total of 2 out of 9 patients (22.2%) overall, both from the 250 mg cohort, reported SAEs, including Grade 3 febrile neutropenia (2 patients) and Grade 4 platelet count decreased (1 patient). All 3 SAEs were assessed by the investigator as possibly related to study drug and all 3 SAEs were resolved as of DCO.
- A total of 4 out of 9 patients (44.4%) overall, reported CTCAE Grade ≥3 AEs that were assessed by the investigator as possibly related to the study drug. In the 200 mg cohort, 1 out of 3 patients (33.3%) reported one Grade 3 hypoalbuminaemia that was assessed by the investigator as possibly related to study drug, while no Grade 4 events were reported. In the 250 mg cohort, 3 out of 6 patients (50%) reported CTCAE Grade ≥3 AEs that were assessed by the investigator as possibly related to study drug, including:
  - Grade 4 events: neutropenia, white blood cell count decreased, platelet count decreased (SAE), and neutrophil count decreased (1 patient, each)
  - Grade 3 events: febrile neutropenia, and anaemia (2 patients, each) and white blood cell count decreased, lymphocyte count decreased, and decreased appetite (1 patient, each).
- In the 200 mg cohort, 1 patient reported dose modification ie, dose interruption (due to AE), while no dose reduction was reported. In the 250 mg cohort, 4 patients reported dose modification, including 3 patients with dose interruption and 1 patient with dose reduction (See footnote e in Table 3).
- The AEs that led to dose modification were reported by 4 out of 9 patients (44.4%) overall (see Table 3 footnotes), including:
  - One patient in the 200 mg cohort reported an AE of pelvic abscess that led to dose interruption.
  - One patient in the 250 mg cohort reported an AE of platelet count decreased that led to dose interruption and dose reduction. The same patient reported an SAE of febrile neutropenia that led to dose reduction.
  - One patient in the 250 mg cohort reported an AE of anaemia and an SAE of platelet count decreased, both events led to dose interruption. Another patient in the 250 mg cohort reported AE of decreased appetite that led to dose interruption.

Table 3 Number of patients with adverse events in any category - patient level (Safety Analysis Set)

AE Category	Number (%) of patients [a] Adavosertib 200 mg (N=3)	Adavosertib 250 mg (N=6)	Total (N=9)
Any AE	3 (100)	5 (83.3)	8 (88.9)
Any AE possibly related to treatment [b]	3 (100)	5 (83.3)	8 (88.9)
Any AE of CTCAE grade 3 or higher	1 (33.3)	3 (50.0)	4 (44.4)
Any AE of CTCAE grade 3 or higher, possibly related to treatment [b]	1 (33.3)	3 (50.0)	4 (44.4)
Any AE with outcome = death	0	0	0
Any AE with outcome = death, possibly related to treatment [b]	0	0	0
Any SAE (including events with outcome = death)	0	2 (33.3)	2 (22.2)
Any SAE (including events with outcome = death), possibly related to treatment [b]	0	2 (33.3)	2 (22.2)
Any SAE leading to discontinuation of treatment	0	0	0
Any SAE leading to discontinuation of treatment, possibly related to treatment [b]	0	0	0
Any AE leading to discontinuation of treatment	0	0	0
Any AE leading to dose modification of treatment	1 (33.3)	3 (50.0)	4 (44.4)
Any AE leading to dose reduction of treatment	0	1 (16.7) [c]	1 (11.1)
Any AE leading to dose interruption of treatment	1 (33.3) [d]	2 (33.3) [e]	3 (33.3)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] As assessed by the investigator.

[c] A single patient reported multiple dose reductions in the 250 mg cohort: Patient PPD reported dose interruption and dose reduction due to AE of platelet count decreased. The same patient reported another dose reduction due to SAE of febrile neutropenia.

[d] A single patient reported multiple dose interruptions in the 200 mg cohort: Patient PPD reported dose interruption twice due to AE (pelvic abscess).

[e] A total of 3 patients reported multiple dose interruptions in 250 mg cohort: Patient PPD reported dose interruption twice due to AEs (AE of anaemia and SAE of platelet count decreased). Patient PPD reported dose interruption twice: once due to AE (decreased appetite) and once due to 'other' reason (site circumstance). Additionally, Patient PPD reported dose interruption due to 'other' (patient convenience) and is not counted in this table.

Notes: This table includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of study drug. Patients who had an AE leading to discontinuation of treatment post the DCO date, were to be reset to the action taken at the DCO date using the dosing information. Patients who had a maximum CTCAE Grade 5 post DCO, were to be reset to unknown at the DCO date. However, no patients in either cohort fulfilled this requirement.

MedDRA version 25.0.

Abbreviations: AE = adverse events; CTCAE = Common Terminology Criteria for Adverse Events (version 5.0); DCO = data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of patients in treatment group; SAE = serious adverse event.
Source: Table 14.3.2.1, Appendix 16.2.5.1.

- As per Study Protocol version 6.0, if less than one-third of patients experienced a DLT in the cohort, that dose level was to be declared tolerable. While no DLT was reported in the 200 mg cohort, DLTs of Grade 3 febrile neutropenia were reported by 2 out of 6 patients in the 250 mg cohort (PPD and PPD). As per protocol, monotherapy with 250 mg adavosertib was therefore confirmed as not tolerable.
- No clinically meaningful changes in mean values over time were noted for any laboratory parameter. Shift changes of ≥2 CTCAE grade levels between Grade 0 and Grade 4 were noted for up to 2 patients in both cohorts. Of these, shift of ≥2 CTCAE grade levels to Grade 3 was noted in the 200 mg cohort for aspartate aminotransferase and albumin (1/3 patients, each). Additionally, shift of ≥2 CTCAE grade levels to Grade 3 was noted in the 250 mg cohort for leukocytes, aspartate aminotransferase and alanine aminotransferase (1/6 patients, each) as well as haemoglobin (1/4 patients). Shift of ≥2 CTCAE grade levels to Grade 4 was noted in the 200 mg cohort for alanine aminotransferase (1/3 patients). Shift of ≥2 CTCAE grade levels to Grade 4 was noted in the 250 mg cohort for leukocytes and platelets (1/6 patients, each) as well as neutrophils (2/6 patients).
- No abnormal and clinically significant changes were noted in ECG parameters. No clinically meaningful changes were noted in vital signs data.

Conclusions

No RECIST v1.1 response was observed, the main AEs were haematological or gastrointestinal in nature, and no new safety signals were noted for adavosertib in this study. Monotherapy with 200 mg adavosertib was considered tolerable as no DLTs were reported in the 200 mg cohort, while monotherapy with 250 mg adavosertib was considered as not tolerable as per protocol, considering 2 out of 6 patients reporting DLTs. Following both, first and fifth dosing of QD doses for 5 days, adavosertib was steadily absorbed with median t_{max} ranging from 1.90 to 4.03 hours and then slowly eliminated from plasma, with mean $t_{1/2\lambda z}$ of about 7.30 to 10.55 hours. As dose increased from 200 to 250 mg, systemic exposure to adavosertib increased in slightly more than dose-proportional manner.

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5. ETHICS

This section is not required in a synoptic CSR. See Study Protocol in Appendix 16.1.1.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This section is not required in a synoptic CSR. See Study Protocol in Appendix 16.1.1.

7. INTRODUCTION

This section is not required in a synoptic CSR. See Study Protocol in Appendix 16.1.1.

8. STUDY OBJECTIVES AND ENDPOINTS

This section is not required in a synoptic CSR. See Study Protocol in Appendix 16.1.1.

9. STUDY DESIGN AND PROCEDURES

This section is not required in a synoptic CSR. See Study Protocol in Appendix 16.1.1.

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This section is not required in a synoptic CSR. See Synopsis.

14. SUMMARY TABLES AND FIGURES, LISTINGS, AND NARRATIVES

14.1 Demographic, baseline, concomitant medication, and other subject-specific characteristics

This section is provided as separate file(s).

14.2 Efficacy evaluation data

This section is provided as separate file(s).

14.3 Safety evaluation data

This section is provided as separate file(s).

14.3.1 Exposure

14.3.2 All adverse events

14.3.3 Deaths

No deaths were reported in this study.

14.3.4 Serious adverse events

For narratives of serious adverse events (SAEs) other than death, see Section 16.2.7.3.

14.3.5 Discontinuation of investigational product due to adverse events

No discontinuation of study drug due to adverse events (AEs) were reported in this study.

14.3.6 Other significant adverse events

No other significant AEs were reported in this study.

14.3.7 Clinical laboratory evaluation

14.3.8 Vital signs, ECG, physical findings, and other observations

14.4 Patient narratives

This section is provided as separate file(s).

15. REFERENCE LIST

This section is not required in a synoptic CSR. See Study Protocol in Appendix 16.1.1.