# Clinical trial results:
# A Phase 2b, Open-label, Single-arm, Multi-centre Study Assessing the Efficacy and Safety of Adavosertib as Treatment for Recurrent or Persistent Uterine Serous Carcinoma (ADAGIO)

## Summary

| | |
|---|---|
| EudraCT number | 2020-000138-16 |
| Trial protocol | FR DE IT ES |
| Global end of trial date | 07 February 2023 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 13 October 2023 |
| First version publication date | 13 October 2023 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | D601HC00002 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04590248 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | AstraZeneca AB |
| Sponsor organisation address | Södertälje, Södertälj, Sweden, 151 85 |
| Public contact | Global Clinical Head, AstraZeneca Clinical Study Information Centre, +1 87724094 79, information.center@astrazeneca.com |
| Scientific contact | Global Clinical Head, AstraZeneca Clinical Study Information Centre, +1 87724094 79, information.center@astrazeneca.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 16 August 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 February 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of adavosertib by the assessment of objective response rate (ORR)

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation Good Clinical Practices (ICH-GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 30 November 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 55 |
| Country: Number of subjects enrolled | Spain: 22 |
| Country: Number of subjects enrolled | France: 18 |
| Country: Number of subjects enrolled | Italy: 10 |
| Country: Number of subjects enrolled | Canada: 4 |
| Worldwide total number of subjects | 109 |
| EEA total number of subjects | 50 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 30 |

| | |
|---|---|
| From 65 to 84 years | 78 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 28 sites in 5 countries (United States, Canada, France, Italy and Spain) from 30-November-2020 to 07-February-2023.

### Pre-assignment

Screening details:

Participants had been through a screening period of 28 days, followed by assessments as per schedule of activities.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Adavosertib |

Arm description:

Participants received adavosertib 300 mg administered orally, once daily on Days 1 to 5 followed by 2 days off and Days 8 to 12 (21 days treatment cycle).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Adavosertib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

The subjects received oral adavosertib 300 mg, once daily on Days 1 to 5 and Days 8 to 12 of a 21-day treatment cycle.- cross check with CSR if this was followed.

| **Number of subjects in period 1** | Adavosertib |
|---|---|
| Started | 109 |
| Completed | 90 |
| Not completed | 19 |
| Consent withdrawn by subject | 16 |
| Other | 2 |
| Lost to follow-up | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Adavosertib |
| Reporting group description: | |
| Participants received adavosertib 300 mg administered orally, once daily on Days 1 to 5 followed by 2 days off and Days 8 to 12 (21 days treatment cycle). | |

| Reporting group values | Adavosertib | Total | |
|---|---|---|---|
| Number of subjects | 109 | 109 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 30 | 30 | |
| From 65-84 years | 78 | 78 | |
| 85 years and over | 1 | 1 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 68.8 | | |
| standard deviation | ± 7.05 | - | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 109 | 109 | |
| Male | 0 | 0 | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Black African or American | 9 | 9 | |
| Asian | 1 | 1 | |
| White | 92 | 92 | |
| Other | 3 | 3 | |
| Missing | 4 | 4 | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 5 | 5 | |
| Not Hispanic or Latino | 98 | 98 | |
| Unknown or Not Reported | 6 | 6 | |

## End points

### End points reporting groups

| Reporting group title | Adavosertib |
|---|---|

Reporting group description:

Participants received adavosertib 300 mg administered orally, once daily on Days 1 to 5 followed by 2 days off and Days 8 to 12 (21 days treatment cycle).

### Primary: Objective response rate (ORR)

| End point title | Objective response rate (ORR)[1] |
|---|---|

End point description:

Per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 for target lesions (TLs) and assessed by computed tomography (CT) or magnetic resonance imaging (MRI): confirmed Complete response (CR), Disappearance of all target lesions; confirmed Partial response (PR), >=30% decrease in the sum of the diameters of TL, as determined by Blinded Independent Central Review (BICR), taking as reference the baseline sum of diameters. The number of participants analysed is based on patients with measurable disease at baseline.

| End point type | Primary |
|---|---|

End point timeframe:

up to 75 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was performed for this outcome measure.

| End point values | Adavosertib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 104 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 26.0 (17.9 to 35.5) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression free survival (PFS)

| End point title | Progression free survival (PFS) |
|---|---|

End point description:

The time from first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdraws from study drug or receives another anticancer therapy prior to progression. PFS was assessed per RECIST v1.1 using CT or MRI scans by BICR.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 75 weeks

| End point values | Adavosertib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 109 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.8 (2.60 to 3.94) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Depth of response

| End point title | Depth of response |
|---|---|

End point description:

Depth of response is defined as best percentage change from baseline in target lesion size, which is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. A negative change denotes a reduction in target lesion size.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 75 weeks

| End point values | Adavosertib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: Percentage change | | | | |
| arithmetic mean (standard deviation) | -20.8 (± 31.60) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of response (DoR)

| End point title | Duration of response (DoR) |
|---|---|

End point description:

The time from the date of first documented response until date of documented progression per RECIST v1.1 as assessed by BICR, or death in the absence of disease progression

| End point type | Secondary |
|---|---|

End point timeframe:

up to 75 weeks

| End point values | Adavosertib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: Months | | | | |
| median (full range (min-max)) | 4.7 (1.4 to 10.5) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival rate at 6 months (PFS6)

| End point title | Progression Free Survival rate at 6 months (PFS6) |
|---|---|

End point description:

The progression free survival rate was assessed at 6 months by Kaplan-Meier estimate per RECIST v1.1.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 6 months

| End point values | Adavosertib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 109 | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | 18.1 (10.42 to 27.55) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Disease control rate (DCR)

| End point title | Disease control rate (DCR) |
|---|---|

End point description:

The percentage of participants who have a best overall response of confirmed response (CR) or partial response (PR) or who have stable disease for at least 5 weeks after start of treatment, based on BICR.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 75 weeks

| End point values | Adavosertib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 109 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 51.4 (41.6 to 61.1) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall survival (OS)

| End point title | Overall survival (OS) |
|---|---|

End point description:

The time from date of first dose until the date of death due to any cause.
Here, arbitrary value 9999.9999 represents not applicable.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 75 weeks

| End point values | Adavosertib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 109 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9.6 (8.28 to 9999.9999) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Lowest concentration (Ctrough) of adavosertib

| End point title | Lowest concentration (Ctrough) of adavosertib |
|---|---|

End point description:

Lowest plasma concentration of adavosertib was evaluated as pharmacokinetic paramerter.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 1, Day 5 and Cycle 2, Day 5 (pre-dose) (each cycle is 21 days)

| End point values | Adavosertib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 109 | | | |
| Units: nanomole (nM) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Day 5 | 307.2 (± 105.6) | | | |
| Cycle 2 Day 5 | 328.7 (± 70.3) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum concentration (Cmax) of adavosertib

| End point title | Maximum concentration (Cmax) of adavosertib |
|---|---|

End point description:

Maximum plasma concentration of adavosertib was evaluated as pharmacokinetic parameter.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 1, Day 5 and Cycle 2, Day 5 (2 hours post-dose) (each cycle is 21 days)

| End point values | Adavosertib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 109 | | | |
| Units: nM | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Day 5 | 1115.9 (± 82.1) | | | |
| Cycle 2 Day 5 | 1356.5 (± 59.3) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with treatment emergent adverse events (AEs)

| End point title | Number of participants with treatment emergent adverse events (AEs) |
|---|---|

End point description:

The number of participants with treatment emergent adverse events (AEs) were assessed as variable of safety and tolerability.

CTCAE: Common Terminology Criteria for Adverse Events
PRTT: Possibly Related to Treatment
SAE: Serious Adverse Event
IP: Investigational Product

The adverse events reported here were treatment emergent.

| End point type | Secondary |
|---|---|

End point timeframe:

From baseline to post-treatment follow-up (30 days after last dose), approximately up to 114 weeks

| **End point values** | Adavosertib | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 109 | | | |
| Units: Participants | | | | |
| Any AE | 109 | | | |
| Any AE PRTT | 106 | | | |
| Any AE with outcome = death | 4 | | | |
| Any AE with outcome = death, PRTT | 1 | | | |
| Any AE of CTCAE grade 3 or higher | 75 | | | |
| Any AE of CTCAE grade 3 or higher, PRTT | 66 | | | |
| Any AE leading to discontinuation of IP | 19 | | | |
| Any AE leading to discontinuation of IP, PRTT | 16 | | | |
| Any SAE (IEW outcome = death) | 50 | | | |
| Any SAE (IEW outcome = death), PRTT | 29 | | | |
| Any SAE leading to discontinuation of IP | 10 | | | |
| Any SAE leading to discontinuation of IP, PRTT | 8 | | | |
| Any AE leading to dose modification of IP | 79 | | | |
| Any AE leading to dose reduction of IP | 62 | | | |
| Any AE leading to dose interruption of IP | 72 | | | |
| Any AE leading to dose interruption PRTT | 62 | | | |
| Any AE leading to dose reduction PRTT | 60 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline to post-treatment follow-up (30 days after last dose), approximately up to 114 weeks

Adverse event reporting additional description:

All adverse events during the trial are reported.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Adavosertib |

Reporting group description:

Participants received adavosertib 300 mg administered orally, once daily on Days 1 to 5 followed by 2 days off and Days 8 to 12 (21 days treatment cycle).

| **Serious adverse events** | Adavosertib | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 53 / 109 (48.62%) | | |
| number of deaths (all causes) | 47 | | |
| number of deaths resulting from adverse events | 3 | | |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 3 / 109 (2.75%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 2 / 109 (1.83%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General disorders and administration site conditions | | | | |
| Fatigue | | | | |
| subjects affected / exposed | 3 / 109 (2.75%) | | | |
| occurrences causally related to treatment / all | 2 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gait disturbance | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Generalised oedema | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malaise | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oedema | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oedema peripheral | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyrexia | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 109 (3.67%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | | |
| occurrences causally related to treatment / all | 2 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 4 / 109 (3.67%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorder | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|---|---|---|---|
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 109 (3.67%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|---|---|---|---|
| Anaemia | | | | |
| subjects affected / exposed | 3 / 109 (2.75%) | | | |
| occurrences causally related to treatment / all | 2 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thrombocytopenia | | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal disorders | | | | |
| Abdominal pain | | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Duodenal ulcer | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 4 / 109 (3.67%) | | | |
| occurrences causally related to treatment / all | 3 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Constipation | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal pain lower | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastritis | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestinal obstruction | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestine perforation | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal haemorrhage | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vomiting | | | | |
| subjects affected / exposed | 5 / 109 (4.59%) | | | |
| occurrences causally related to treatment / all | 5 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal and urinary disorders | | | | |
| Acute kidney injury | | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematuria | | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary retention | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Biliary sepsis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Kidney Infection | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 5 / 109 (4.59%) | | |
| occurrences causally related to treatment / all | 4 / 5 | | |
| deaths causally related to treatment / all | 1 / 1 | | |

| | | | |
|---|---|---|---|
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Adavosertib | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 109 / 109 (100.00%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 15 / 109 (13.76%) | | |
| occurrences (all) | 22 | | |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 20 / 109 (18.35%) | | |
| occurrences (all) | 26 | | |
| Fatigue | | | |
| subjects affected / exposed | 43 / 109 (39.45%) | | |
| occurrences (all) | 66 | | |
| Asthenia | | | |
| subjects affected / exposed | 45 / 109 (41.28%) | | |
| occurrences (all) | 72 | | |
| Pyrexia | | | |
| subjects affected / exposed | 7 / 109 (6.42%) | | |
| occurrences (all) | 8 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | | |
| occurrences (all) | 6 | | |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | | |
| occurrences (all) | 6 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 19 / 109 (17.43%) | | |
| occurrences (all) | 21 | | |
| Cough | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | | |
| occurrences (all) | 8 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 9 / 109 (8.26%) | | |
| occurrences (all) | 9 | | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 12 / 109 (11.01%) | | |
| occurrences (all) | 16 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 22 / 109 (20.18%) | | |
| occurrences (all) | 40 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 16 / 109 (14.68%) | | |
| occurrences (all) | 31 | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | | |
| occurrences (all) | 9 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 27 / 109 (24.77%) | | |
| occurrences (all) | 40 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 14 / 109 (12.84%) | | |
| occurrences (all) | 18 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 23 / 109 (21.10%) | | |
| occurrences (all) | 31 | | |

| | | | |
|---|---|---|---|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 28 / 109 (25.69%) | | |
| occurrences (all) | 39 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | | |
| occurrences (all) | 6 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 14 / 109 (12.84%) | | |
| occurrences (all) | 19 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 17 / 109 (15.60%) | | |
| occurrences (all) | 19 | | |
| Dizziness | | | |
| subjects affected / exposed | 11 / 109 (10.09%) | | |
| occurrences (all) | 17 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 74 / 109 (67.89%) | | |
| occurrences (all) | 155 | | |
| Leukopenia | | | |
| subjects affected / exposed | 8 / 109 (7.34%) | | |
| occurrences (all) | 15 | | |
| Neutropenia | | | |
| subjects affected / exposed | 26 / 109 (23.85%) | | |
| occurrences (all) | 48 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 27 / 109 (24.77%) | | |
| occurrences (all) | 40 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 39 / 109 (35.78%) | | |
| occurrences (all) | 55 | | |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 71 / 109 (65.14%) | | |
| occurrences (all) | 140 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 8 / 109 (7.34%) | | |
| occurrences (all) | 8 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 13 / 109 (11.93%) | | |
| occurrences (all) | 13 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 73 / 109 (66.97%) | | |
| occurrences (all) | 146 | | |
| Constipation | | | |
| subjects affected / exposed | 45 / 109 (41.28%) | | |
| occurrences (all) | 58 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 16 / 109 (14.68%) | | |
| occurrences (all) | 22 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 34 / 109 (31.19%) | | |
| occurrences (all) | 45 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 10 / 109 (9.17%) | | |
| occurrences (all) | 11 | | |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 7 / 109 (6.42%) | | |
| occurrences (all) | 7 | | |
| Dysuria | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | | |
| occurrences (all) | 6 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 16 / 109 (14.68%) | | |
| occurrences (all) | 20 | | |
| Myalgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 109 (6.42%) | | |
| occurrences (all) | 7 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 6 / 109 (5.50%) | | |
| occurrences (all) | 9 | | |
| Back pain | | | |
| subjects affected / exposed | 12 / 109 (11.01%) | | |
| occurrences (all) | 12 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 16 / 109 (14.68%) | | |
| occurrences (all) | 19 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 27 / 109 (24.77%) | | |
| occurrences (all) | 39 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 18 / 109 (16.51%) | | |
| occurrences (all) | 21 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 10 / 109 (9.17%) | | |
| occurrences (all) | 18 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 21 / 109 (19.27%) | | |
| occurrences (all) | 27 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 17 / 109 (15.60%) | | |
| occurrences (all) | 27 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 10 / 109 (9.17%) | | |
| occurrences (all) | 11 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 30 July 2020 | The protocol was revised to address the FDA recommendations. Section 8.3, Adverse events and serious adverse events was updated to reflect changes in the haematologic toxicity dose modifications management and to provide additional clarity on the management of non-haematologic toxicities, with detailed information on dose modifications for the management of gastrointestinal (GI) toxicities. Section 4.1 Overall design and section 8.6.1.1 Tumour tissue, were updated to clarify that all diagnostic tumor tissue samples should be submitted, not only if the diagnostic sample is different from the biomarker sample. Section 4.1 Overall design, Figure 2 was updated to reflect a change in tumor assessment frequency. Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis and Appendix J Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis were added to include guidance on how the study could continue in the event of a serious disruption. Section 9.5.1 Safety Review Committee was updated to add additional detail regarding the Safety Review Committee. Appendix A Guidelines for Evaluation of Objective Tumour Response using RECIST v1.1 Criteria (Response Evaluation Criteria in Solid Tumours), was updated to remove reference to CT/MRI of the liver and adrenal glands, as this is not applicable for this study. |
| 20 April 2021 | The protocol was revised to address the recommendations of the Safety Review Committee. Additional safety haematology and clinical chemistry assessment, review of the Toxicity Management Guidelines for participants with CTCAE Grade 4 infection with Grade 4 neutropenia, to allow participants who recover and have clear clinical benefit that outweighs the risks to continue dosing (at a reduced dose), only after sponsor approval and additional guidance in Toxicity Management Guidelines for the G-CSF use in severe neutropenia were the 3 recommendations which were reflected through the updates made to sections 1.3 Schedule of activities, section 8.2.4. Clinical Safety Laboratory Assessments and section 8.3.13.1 Haematologic Toxicity Dose Modifications. Section 8 was updated in view of the additional laboratory assessments required, to increase the amount of blood collected from each participant accordingly. |
| 08 November 2021 | The protocol was revised in line with the urgent safety measures implemented, based on a preliminary analysis which identified an association between reduced renal function and the risk of Grade 4 neutropenia. Section 1.3 Schedule of Activities and section 8.2.4 Clinical Safety Laboratory Assessments updated to include creatinine clearance calculation at each study visit where clinical chemistry is assessed. Section 2.3.1 Risk Assessment was updated to include sepsis as an identified risk. Section 5.1 Inclusion criteria was updated with the threshold for creatinine clearance. Section 5.2 Exclusion criteria was updated with supplemental exclusion criteria relating to infection. Section 8.3.13 Mangement of Adavosertib related toxicities, was updated with Toxicity management guidelines for Blood neutrophil count decrease and for moderate/severe renal impairment (low creatinine clearance). Gastrointestinal toxicity management (title was updated) and renal function monitoring reference were also added in the same section. |

| | |
|---|---|
| 03 March 2022 | Additional risk mitigation strategies were implemented through this protocol amendment following the safety events of sepsis cases. Sections 1.1 Synopsis, 1.2 Schema, 1.3 Schedule of activities, 4.1 Overall design, 6.1 Study intervention administered, 6.6 Dose modification and Figure 2 Study flow chart were updated with the starting dose being changed from 300mg to 250 mg QD adavosertib for the remaining participants to be recruited to the study. Two cohorts were defined Cohorts A and B: Cohort A with participants dosed at starting dose of 300mg QD, and Cohort B with participants dosed at a starting dose of 250 mg QD. No further participants would be enrolled to Cohort A. The relevant sections were updated to provide clarity on the data from which primary analysis and final analysis will be arrived at and also to include eligibility criteria and cohort A and cohort B. Section 1.3 Schedule of Activities and section 8 Study Assessments and Procedures were updated with additional safety on-site visits. Section 4 Study Design was updated with rationale for starting dose of 250mg QD adavosertib for Cohort B and end of study definition in view of introduction of Cohort B. Section 5.1 Inclusion criteria 11 was updated to clarify the definition of postmenopausal women and section 5.2 Exclusion criteria 4 was updated for participants with refractory nausea and vomiting. Section 5.3.3 Contraception was updated to include permanent sterilization as a highly effective method of contraception.Table 9 Dose Levels for Adavosertib was updated for dose reduction levels for new starting dose of 250mg QD. Section 7.1.2 Study Intervention Interruption was updated to clarify onset of 21-day drug interruption period. Section 8.3.13 Management of Adavosertib-related Toxicities, was updated with Toxicity Management Guidelines. Section 9.4 Statistical Analyses was updated to reflect that efficacy and safety endpoints will be summarised by starting dose. |
| 20 May 2022 | Throughout the protocol all reference to Cohorts (A and B), and 250 mg dose was removed. Section 8.3.13 Management of Adavosertib-related Toxicities, was updated with Toxicity Management Guidelines. The final analysis data cut-off was removed from section 4 Overall design, section 8 Study assessments and Procedures and section 9 Statistical considerations. Section 4.4 was updated with end of study definition. Section 9.4 Statistical Analyses was updated to reflect the removal of Cohort B. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported