



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
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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
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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
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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			
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			
Units: years			
arithmetic mean	68.8		
standard deviation	± 7.05	-	
Sex: Female, Male			
Units: Participants			
Female	109	109	
Male	0	0	
Race/Ethnicity, Customized			
Units: Subjects			
Black African or American	9	9	
Asian	1	1	
White	92	92	
Other	3	3	
Missing	4	4	
Ethnicity (NIH/OMB)			
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), $\geq 30\%$ 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: 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: 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: 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: 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: 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: 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: 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 parameter.	
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)
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

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

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 Management 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