Clinical trial results:
A Multicentre Phase II Study of Adavosertib plus Chemotherapy in Patients with Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Summary

EudraCT number	2015-000886-30
Trial protocol	GB NL
Global end of trial date	13 December 2018

Results information

Result version number	v1 (current)
This version publication date	05 April 2023
First version publication date	05 April 2023

Trial information

Trial identification

Sponsor protocol code	D6010C00004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02272790
WHO universal trial number (UTN)	-
Other trial identifiers	Sarah Cannon Development Innovations, LLC: GYN 49

Notes:

Sponsors

Sponsor organisation name	AstraZeneca, Global Medicines Development - Oncology
Sponsor organisation address	City House, 132-134 Hills Road, Cambridge, United Kingdom, CB2 1PG
Public contact	Pejvack Motlagh, MD, AstraZeneca, +44 0 7384 799 850, pejvack.motlagh@astrazeneca.com
Scientific contact	Pejvack Motlagh, MD, AstraZeneca, +44 0 7384 799 850, pejvack.motlagh@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	04 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 December 2018
Global end of trial reached?	Yes
Global end of trial date	13 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the objective response rate (ORR) of AZD1775 in combination with carboplatin, paclitaxel, gemcitabine, or pegylated liposomal doxorubicin (PLD) in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Protection of trial subjects:

The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH) Good Clinical Practice guidance, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Precautions were taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject.

An Institutional Review Board (IRB) or Ethics Committee reviewed and approved the study protocol, as well as the Informed Consent Form document and other written information provided to the subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 84
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	94
EEA total number of subjects	1

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	59
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multi-center study was conducted at 20 sites: 18 in the USA, 1 in Canada, and 1 in The Netherlands. Ninety-four (94) patients received treatment. The first patient started treatment on 2 Feb 2015; the final patients were still receiving treatment and were censored at the time of database lock on 14 Dec 2018.

Pre-assignment

Screening details:

One hundred twenty-six (126) patients consented and underwent screening; 94 patients passed screening, whereas 32 patients failed screening tests and were not eligible. The Full Analysis Set consists of 94 patients.

Period 1

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

Blinding implementation details:

The study was not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Adavosertib 175 mg orally QD on Days 1, 2, 8, 9, 15, and 16 of 28 day cycles. Gemcitabine 800 mg/m² IV on Days 1, 8, and 15 of 28 day cycles.

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

Dosage and administration details:

Adavosertib 175 mg orally QD on Days 1, 2, 8, 9, 15, and 16 of 28 day cycles.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine 800 mg/m² IV on Days 1, 8, and 15 of 28 day cycles.

Arm title	Arm B

Arm description:

Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3, 8-10, and 15-17 of 28 day cycles. Paclitaxel 80 mg/m² IV on Days 1, 8, and 15 of 28 day cycles.

Arm type	Experimental

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	Taxol
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 80 mg/m² IV on Days 1, 8, and 15 of 28 day cycles.

Investigational medicinal product name	Adavosertib
Investigational medicinal product code	Adavosertib
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3, 8-10, and 15-17 of 28 day cycles.

Arm title	Arm C

Arm description:

Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3 of 21 day cycles. Carboplatin AUC 5 IV on Day 1 of 21 day cycles.

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin AUC 5 IV on Day 1 of 21 day cycles.

Investigational medicinal product name	Adavosertib
Investigational medicinal product code	Adavosertib
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3 of 21 day cycles.

Arm title	Arm C2

Arm description:

Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3, 8-10, and 15-17 of 21 day cycles. Carboplatin AUC 5 IV on Day 1 of 21 day cycles.

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

Dosage and administration details:

Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3, 8-10, and 15-17 of 21 day cycles.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	Paraplatin
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin AUC 5 IV on Day 1 of 21 day cycles.

Arm title	Arm D-175 mg

Arm description:

Adavosertib 175 mg orally BID (5 doses over 3 days) on Days 1-3 of 28 day cycles. Pegylated liposomal doxorubicin 40 mg/m² IV on Day 1 of 28 day cycles.

Arm type	Experimental
Investigational medicinal product name	Pegylated Liposomal Doxorubicin
Investigational medicinal product code	
Other name	PLD
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pegylated liposomal doxorubicin 40 mg/m² IV on Day 1 of 28 day cycles.

Investigational medicinal product name	Adavosertib
Investigational medicinal product code	Adavosertib
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Adavosertib 175 mg orally BID (5 doses over 3 days) on Days 1-3 of 28 day cycles.

Arm title	Arm D-225 mg

Arm description:

Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3 of 28 day cycles. Pegylated liposomal doxorubicin 40 mg/m² IV on Day 1 of 28 day cycles.

Arm type	Experimental
Investigational medicinal product name	Pegylated Liposomal Doxorubicin
Investigational medicinal product code	
Other name	PLD
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pegylated liposomal doxorubicin 40 mg/m² IV on Day 1 of 28 day cycles.

Investigational medicinal product name	Adavosertib
Investigational medicinal product code	Adavosertib
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3 of 28 day cycles.

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	9	38	23
Completed	9	38	23

Number of subjects in period 1	Arm C2	Arm D-175 mg	Arm D-225 mg
Started	12	6	6

Completed	12	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Adavosertib 175 mg orally QD on Days 1, 2, 8, 9, 15, and 16 of 28 day cycles. Gemcitabine 800 mg/m² IV on Days 1, 8, and 15 of 28 day cycles.	
Reporting group title	Arm B
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3, 8-10, and 15-17 of 28 day cycles. Paclitaxel 80 mg/m² IV on Days 1, 8, and 15 of 28 day cycles.	
Reporting group title	Arm C
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3 of 21 day cycles. Carboplatin AUC 5 IV on Day 1 of 21 day cycles.	
Reporting group title	Arm C2
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3, 8-10, and 15-17 of 21 day cycles. Carboplatin AUC 5 IV on Day 1 of 21 day cycles.	
Reporting group title	Arm D-175 mg
Reporting group description:	
Adavosertib 175 mg orally BID (5 doses over 3 days) on Days 1-3 of 28 day cycles. Pegylated liposomal doxorubicin 40 mg/m² IV on Day 1 of 28 day cycles.	
Reporting group title	Arm D-225 mg
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3 of 28 day cycles. Pegylated liposomal doxorubicin 40 mg/m² IV on Day 1 of 28 day cycles.	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	9	38	23
Age categorical Units: Subjects			
Adults (18-64 years)	5	26	14
≥ 65 years	4	12	9
Age Continuous Units: years			
arithmetic mean	58.6	60.9	62.1
standard deviation	± 9.75	± 8.16	± 11.29
Sex: Female, Male Units: Subjects			
Female	9	38	23
Male	0	0	0
Age, Categorical Units: Subjects			
< 65	5	26	14
≥ 65	4	12	9
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	5	0

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	4	2
White	7	24	20
More than one race	0	0	0
Unknown or Not Reported	0	5	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	6	2
Not Hispanic or Latino	8	31	21
Unknown or Not Reported	0	1	0
ECOG Performance Status			
ECOG Performance Status: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory, able to carry out light or sedentary work; 2 = Ambulatory and capable of all self care but unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, cannot carry on any self care. Totally confined to bed or chair; 5 = Dead.			
Units: Subjects			
PS = 0	5	19	13
PS = 1	4	19	10
PS = 2	0	0	0
PS = 3	0	0	0
PS = 4	0	0	0
Local or Regional Recurrence Units: Subjects			
Yes	5	26	17
No	4	12	6
Distant Metastases Units: Subjects			
Yes	3	29	11
No	6	9	12
Histology Units: Subjects			
Serous Epithelial Carcinoma	9	33	21
Endometrioid Carcinoma	0	1	0
Clear Cell Epithelial Carcinoma	0	2	1
Transitional Cell/Brenner Carcinoma	0	0	0
Squamous Cell Epithelial Carcinoma	0	0	0
Undifferentiated Epithelial Carcinoma	0	0	0
Mucinous Epithelial Carcinoma	0	0	0
Mixed Epithelial Carcinoma	0	1	0
Missing	0	1	1
Histological Grade Units: Subjects			
G1 - Well Differentiated	1	1	0
G2 - Moderately Differentiated	0	1	1
G3 - Poorly Differentiated	5	28	15
G4 - Undifferentiated	0	3	2
GX - Grade cannot be assessed or Not Applicable	2	3	3
Missing	1	2	2
Stage at Initial Diagnosis			

Units: Subjects			
IC	0	1	0
IIC	0	0	0
III	0	1	1
IIIA	0	1	0
IIIB	0	2	0
IIIC	6	14	14
IV	3	18	8
Missing	0	1	0
Metastatic Disease			
Units: Subjects			
Yes	7	37	19
No	2	1	4
Prior Systemic Therapy			
Units: Subjects			
Yes	9	38	23
No	0	0	0
Number of prior treatment regimens			
Units: Subjects			
No. of subjects with no prior treatment regimens	0	0	0
No. of subjects with 1 prior treatment regimen	3	12	8
No. of subjects with 2 prior treatment regimens	6	16	9
No. of subjects with 3 prior treatment regimens	0	10	6
No. of subjects with >3 prior treatment regimens	0	0	0
Disease setting for most recent prior regimen			
Units: Subjects			
Adj/Neoadj in Localized disease (Stage I or II)	0	1	0
Adjuvant in advanced disease (Stage III or IV)	4	14	13
Neoadjuvant in advanced disease (Stage III or IV)	0	3	2
Metastatic	5	19	8
Missing	0	1	0
Best overall response to most recent prior regimen			
Units: Subjects			
Complete Response (CR)	0	0	0
Partial Response (PR)	0	2	1
Non-CR/Non-PD	0	1	0
Stable Disease (SD)	2	4	1
Progressive Disease (PD)	2	9	5
Not Evaluable	0	1	0
Not Applicable	5	21	16
Reason most recent prior regimen ended			
Units: Subjects			
Completed planned treatment	4	14	10
Progressive Disease	5	19	10

Toxicity	0	3	1
Other	0	2	2
Prior Surgery Units: Subjects			
Yes	8	35	22
No	1	3	1
Prior Radiotherapy Units: Subjects			
Yes	0	1	0
No	9	37	23
Region of Enrollment Units: Subjects			
United States	7	30	23
Canada	2	7	0
Netherlands	0	1	0
Time from 1st positive biopsy for disease to consent for this study (mean) Units: Weeks			
arithmetic mean	52.0	70.9	62.3
standard deviation	± 11.83	± 46.42	± 24.68
Time from 1st positive biopsy for disease to consent for this study (median) Units: Weeks			
median	49.9	54.9	54.1
full range (min-max)	35.9 to 77.1	31.4 to 250.4	30.0 to 113.6
Time from local/regional recurrence to consent for this study (mean)			
Sixty-seven (67) patients has a local or regional recurrence.			
Units: Weeks			
arithmetic mean	12.2	34.3	20.6
standard deviation	± 14.98	± 51.20	± 20.23
Time from local/regional recurrence to consent for this study (median)			
Sixty-seven (67) patients has a local or regional recurrence.			
Units: Weeks			
median	6.1	18.6	16.6
full range (min-max)	3.0 to 38.9	0.6 to 200.4	1.6 to 70.6
Time from end of most recent prior systemic therapy to consent for this trial (mean) Units: Weeks			
arithmetic mean	11.0	14.4	10.5
standard deviation	± 9.54	± 15.45	± 7.81
Time from end of most recent prior systemic therapy to consent for this trial (median) Units: Weeks			
median	5.4	6.9	6.9
full range (min-max)	2 to 25	1 to 82	0 to 27
Weight (mean) Units: Kilograms			
arithmetic mean	73.5	73.2	75.7
standard deviation	± 21.56	± 15.89	± 19.25

Weight (median) Units: Kilograms			
median	69.6	69.6	71.5
full range (min-max)	47.6 to 124.1	47.4 to 117.6	44.8 to 114.0
Systolic Blood Pressure (mean) Units: mmHg			
arithmetic mean	130.0	125.2	127.7
standard deviation	± 15.23	± 13.37	± 10.65
Systolic Blood Pressure (median) Units: mmHg			
median	130.0	126.5	128.0
full range (min-max)	109.0 to 153.0	100.0 to 159.0	110.0 to 153.0
Diastolic Blood Pressure (mean) Units: mmHg			
arithmetic mean	76.2	76.7	74.8
standard deviation	± 10.96	± 7.74	± 8.03
Diastolic Blood Pressure (median) Units: mmHg			
median	78.0	78.0	75.0
full range (min-max)	62.0 to 90.0	59.0 to 93.0	61.0 to 95.0
Body Surface Area (mean) Units: m²			
arithmetic mean	1.8	1.8	1.8
standard deviation	± 0.25	± 0.19	± 0.22
Body Surface Area (median) Units: m²			
median	1.8	1.8	1.8
full range (min-max)	1.5 to 2.3	1.4 to 2.3	1.4 to 2.3
Age Continuous | Units: years			
median	63.0	60.0	62.0
full range (min-max)	46 to 72	45 to 76	34 to 85

Reporting group values	Arm C2	Arm D-175 mg	Arm D-225 mg
Number of subjects	12	6	6
Age categorical Units: Subjects			
Adults (18-64 years)	8	3	3
≥ 65 years	4	3	3
Age Continuous Units: years			
arithmetic mean	60.3	57.3	61.0
standard deviation	± 6.96	± 14.58	± 7.16
Sex: Female, Male Units: Subjects			
Female	12	6	6
Male	0	0	0
Age, Categorical Units: Subjects			
< 65	8	3	3
≥ 65	4	3	3

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	10	6	6
More than one race	0	0	0
Unknown or Not Reported	2	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	0	1
Not Hispanic or Latino	10	5	5
Unknown or Not Reported	0	1	0
ECOG Performance Status			
ECOG Performance Status: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory, able to carry out light or sedentary work; 2 = Ambulatory and capable of all self care but unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, cannot carry on any self care. Totally confined to bed or chair; 5 = Dead.			
Units: Subjects			
PS = 0	4	1	3
PS = 1	8	5	3
PS = 2	0	0	0
PS = 3	0	0	0
PS = 4	0	0	0
Local or Regional Recurrence Units: Subjects			
Yes	9	4	6
No	3	2	0
Distant Metastases Units: Subjects			
Yes	12	5	5
No	0	1	1
Histology Units: Subjects			
Serous Epithelial Carcinoma	12	4	6
Endometrioid Carcinoma	0	0	0
Clear Cell Epithelial Carcinoma	0	1	0
Transitional Cell/Brenner Carcinoma	0	0	0
Squamous Cell Epithelial Carcinoma	0	0	0
Undifferentiated Epithelial Carcinoma	0	0	0
Mucinous Epithelial Carcinoma	0	1	0
Mixed Epithelial Carcinoma	0	0	0
Missing	0	0	0
Histological Grade Units: Subjects			
G1 - Well Differentiated	2	0	0
G2 - Moderately Differentiated	0	0	0
G3 - Poorly Differentiated	9	5	3

G4 - Undifferentiated	0	1	1
GX - Grade cannot be assessed or Not Applicable	1	0	2
Missing	0	0	0
Stage at Initial Diagnosis Units: Subjects			
IC	0	0	0
IIC	0	1	0
III	0	0	0
IIIA	0	1	0
IIIB	0	1	0
IIIC	4	1	5
IV	8	2	1
Missing	0	0	0
Metastatic Disease Units: Subjects			
Yes	12	5	6
No	0	1	0
Prior Systemic Therapy Units: Subjects			
Yes	12	6	6
No	0	0	0
Number of prior treatment regimens Units: Subjects			
No. of subjects with no prior treatment regimens	0	0	0
No. of subjects with 1 prior treatment regimen	4	3	2
No. of subjects with 2 prior treatment regimens	5	3	4
No. of subjects with 3 prior treatment regimens	2	0	0
No. of subjects with >3 prior treatment regimens	1	0	0
Disease setting for most recent prior regimen Units: Subjects			
Adj/Neoadj in Localized disease (Stage I or II)	0	1	0
Adjuvant in advanced disease (Stage III or IV)	4	3	1
Neoadjuvant in advanced disease (Stage III or IV)	2	0	1
Metastatic	6	2	4
Missing	0	0	0
Best overall response to most recent prior regimen Units: Subjects			
Complete Response (CR)	0	1	2
Partial Response (PR)	1	0	1
Non-CR/Non-PD	0	0	0
Stable Disease (SD)	2	1	0
Progressive Disease (PD)	4	1	2
Not Evaluable	0	0	0
Not Applicable	5	3	1

Reason most recent prior regimen ended Units: Subjects			
Completed planned treatment	5	3	2
Progressive Disease	7	2	3
Toxicity	0	1	1
Other	0	0	0
Prior Surgery Units: Subjects			
Yes	11	6	6
No	1	0	0
Prior Radiotherapy Units: Subjects			
Yes	0	0	0
No	12	6	6
Region of Enrollment Units: Subjects			
United States	12	6	6
Canada	0	0	0
Netherlands	0	0	0
Time from 1st positive biopsy for disease to consent for this study (mean) Units: Weeks			
arithmetic mean	86.1	61.4	65.8
standard deviation	± 55.67	± 23.88	± 20.82
Time from 1st positive biopsy for disease to consent for this study (median) Units: Weeks			
median	74.9	62.9	71.1
full range (min-max)	25.1 to 241.0	30.6 to 87.4	41.1 to 90.0
Time from local/regional recurrence to consent for this study (mean)			
Sixty-seven (67) patients has a local or regional recurrence.			
Units: Weeks			
arithmetic mean	47.0	39.3	5.2
standard deviation	± 57.13	± 27.78	± 3.61
Time from local/regional recurrence to consent for this study (median)			
Sixty-seven (67) patients has a local or regional recurrence.			
Units: Weeks			
median	15.4	37.7	5.6
full range (min-max)	0.9 to 177.9	7.6 to 74.3	0.4 to 10.0
Time from end of most recent prior systemic therapy to consent for this trial (mean) Units: Weeks			
arithmetic mean	15.4	12.9	13.4
standard deviation	± 15.12	± 11.36	± 12.08
Time from end of most recent prior systemic therapy to consent for this trial (median) Units: Weeks			
median	9.4	10.5	12.2
full range (min-max)	2 to 53	2 to 32	1 to 36

Weight (mean) Units: Kilograms			
arithmetic mean	70.6	70.2	65.7
standard deviation	± 9.45	± 14.11	± 8.61
Weight (median) Units: Kilograms			
median	67.7	68.2	67.8
full range (min-max)	56.9 to 85.1	56.2 to 95.1	51.1 to 74.4
Systolic Blood Pressure (mean) Units: mmHg			
arithmetic mean	122.3	125.2	127.5
standard deviation	± 6.40	± 17.22	± 9.35
Systolic Blood Pressure (median) Units: mmHg			
median	121.0	120.0	126.5
full range (min-max)	115.0 to 137.0	112.0 to 159.0	113.0 to 142.0
Diastolic Blood Pressure (mean) Units: mmHg			
arithmetic mean	74.4	73.0	78.7
standard deviation	± 8.26	± 6.66	± 6.02
Diastolic Blood Pressure (median) Units: mmHg			
median	73.5	74.0	77.5
full range (min-max)	62.0 to 87.0	63.0 to 83.0	73.0 to 89.0
Body Surface Area (mean) Units: m²			
arithmetic mean	1.8	1.8	1.7
standard deviation	± 0.13	± 0.18	± 0.10
Body Surface Area (median) Units: m²			
median	1.7	1.7	1.7
full range (min-max)	1.6 to 2.0	1.6 to 2.1	1.5 to 1.8
Age Continuous | Units: years			
median	58.5	58.5	60.5
full range (min-max)	52 to 76	40 to 72	54 to 70

Reporting group values	Total		
Number of subjects	94		
Age categorical Units: Subjects			
Adults (18-64 years)	59		
≥ 65 years	35		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	94		
Male	0		

Age, Categorical Units: Subjects			
< 65	59		
≥ 65	35		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	5		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	8		
White	73		
More than one race	0		
Unknown or Not Reported	8		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12		
Not Hispanic or Latino	80		
Unknown or Not Reported	2		
ECOG Performance Status			
ECOG Performance Status: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory, able to carry out light or sedentary work; 2 = Ambulatory and capable of all self care but unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, cannot carry on any self care. Totally confined to bed or chair; 5 = Dead.			
Units: Subjects			
PS = 0	45		
PS = 1	49		
PS = 2	0		
PS = 3	0		
PS = 4	0		
Local or Regional Recurrence Units: Subjects			
Yes	67		
No	27		
Distant Metastases Units: Subjects			
Yes	65		
No	29		
Histology Units: Subjects			
Serous Epithelial Carcinoma	85		
Endometrioid Carcinoma	1		
Clear Cell Epithelial Carcinoma	4		
Transitional Cell/Brenner Carcinoma	0		
Squamous Cell Epithelial Carcinoma	0		
Undifferentiated Epithelial Carcinoma	0		
Mucinous Epithelial Carcinoma	1		
Mixed Epithelial Carcinoma	1		
Missing	2		
Histological Grade			

Units: Subjects			
G1 - Well Differentiated	4		
G2 - Moderately Differentiated	2		
G3 - Poorly Differentiated	65		
G4 - Undifferentiated	7		
GX - Grade cannot be assessed or Not Applicable	11		
Missing	5		
Stage at Initial Diagnosis			
Units: Subjects			
IC	1		
IIC	1		
III	2		
IIIA	2		
IIIB	3		
IIIC	44		
IV	40		
Missing	1		
Metastatic Disease			
Units: Subjects			
Yes	86		
No	8		
Prior Systemic Therapy			
Units: Subjects			
Yes	94		
No	0		
Number of prior treatment regimens			
Units: Subjects			
No. of subjects with no prior treatment regimens	0		
No. of subjects with 1 prior treatment regimen	32		
No. of subjects with 2 prior treatment regimens	43		
No. of subjects with 3 prior treatment regimens	18		
No. of subjects with >3 prior treatment regimens	1		
Disease setting for most recent prior regimen			
Units: Subjects			
Adj/Neoadj in Localized disease (Stage I or II)	2		
Adjuvant in advanced disease (Stage III or IV)	39		
Neoadjuvant in advanced disease (Stage III or IV)	8		
Metastatic	44		
Missing	1		
Best overall response to most recent prior regimen			
Units: Subjects			
Complete Response (CR)	3		
Partial Response (PR)	5		
Non-CR/Non-PD	1		

Stable Disease (SD)	10		
Progressive Disease (PD)	23		
Not Evaluable	1		
Not Applicable	51		
Reason most recent prior regimen ended			
Units: Subjects			
Completed planned treatment	38		
Progressive Disease	46		
Toxicity	6		
Other	4		
Prior Surgery			
Units: Subjects			
Yes	88		
No	6		
Prior Radiotherapy			
Units: Subjects			
Yes	1		
No	93		
Region of Enrollment			
Units: Subjects			
United States	84		
Canada	9		
Netherlands	1		
Time from 1st positive biopsy for disease to consent for this study (mean)			
Units: Weeks			
arithmetic mean			
standard deviation	-		
Time from 1st positive biopsy for disease to consent for this study (median)			
Units: Weeks			
median			
full range (min-max)	-		
Time from local/regional recurrence to consent for this study (mean)			
Sixty-seven (67) patients has a local or regional recurrence.			
Units: Weeks			
arithmetic mean			
standard deviation	-		
Time from local/regional recurrence to consent for this study (median)			
Sixty-seven (67) patients has a local or regional recurrence.			
Units: Weeks			
median			
full range (min-max)	-		
Time from end of most recent prior systemic therapy to consent for this trial (mean)			
Units: Weeks			
arithmetic mean			
standard deviation	-		
Time from end of most recent prior			

systemic therapy to consent for this trial (median) Units: Weeks median full range (min-max)	-		
Weight (mean) Units: Kilograms arithmetic mean standard deviation	-		
Weight (median) Units: Kilograms median full range (min-max)	-		
Systolic Blood Pressure (mean) Units: mmHg arithmetic mean standard deviation	-		
Systolic Blood Pressure (median) Units: mmHg median full range (min-max)	-		
Diastolic Blood Pressure (mean) Units: mmHg arithmetic mean standard deviation	-		
Diastolic Blood Pressure (median) Units: mmHg median full range (min-max)	-		
Body Surface Area (mean) Units: m² arithmetic mean standard deviation	-		
Body Surface Area (median) Units: m² median full range (min-max)	-		
Age Continuous | Units: years median full range (min-max)	-		

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set included all patients who received at least one dose of study treatment.

Reporting group values	Full Analysis Set		
Number of subjects	94		
Age categorical Units: Subjects			
Adults (18-64 years)	59		
≥ 65 years	35		
Age Continuous Units: years			
arithmetic mean	60.7		
standard deviation	± 9.30		
Sex: Female, Male Units: Subjects			
Female	94		
Male	0		
Age, Categorical Units: Subjects			
< 65	59		
≥ 65	35		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	5		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	8		
White	73		
More than one race	0		
Unknown or Not Reported	8		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12		
Not Hispanic or Latino	80		
Unknown or Not Reported	2		
ECOG Performance Status			
ECOG Performance Status: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory, able to carry out light or sedentary work; 2 = Ambulatory and capable of all self care but unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, cannot carry on any self care. Totally confined to bed or chair; 5 = Dead.			
Units: Subjects			
PS = 0	45		
PS = 1	49		
PS = 2	0		
PS = 3	0		
PS = 4	0		
Local or Regional Recurrence Units: Subjects			
Yes	67		
No	27		
Distant Metastases Units: Subjects			
Yes	65		

No	29		
Histology Units: Subjects			
Serous Epithelial Carcinoma	85		
Endometrioid Carcinoma	1		
Clear Cell Epithelial Carcinoma	4		
Transitional Cell/Brenner Carcinoma	0		
Squamous Cell Epithelial Carcinoma	0		
Undifferentiated Epithelial Carcinoma	0		
Mucinous Epithelial Carcinoma	1		
Mixed Epithelial Carcinoma	1		
Missing	2		
Histological Grade Units: Subjects			
G1 - Well Differentiated	4		
G2 - Moderately Differentiated	2		
G3 - Poorly Differentiated	65		
G4 - Undifferentiated	7		
GX - Grade cannot be assessed or Not Applicable	11		
Missing	5		
Stage at Initial Diagnosis Units: Subjects			
IC	1		
IIC	1		
III	2		
IIIA	2		
IIIB	3		
IIIC	44		
IV	40		
Missing	1		
Metastatic Disease Units: Subjects			
Yes	86		
No	8		
Prior Systemic Therapy Units: Subjects			
Yes	94		
No	0		
Number of prior treatment regimens Units: Subjects			
No. of subjects with no prior treatment regimens	0		
No. of subjects with 1 prior treatment regimen	32		
No. of subjects with 2 prior treatment regimens	43		
No. of subjects with 3 prior treatment regimens	18		
No. of subjects with >3 prior treatment regimens	1		
Disease setting for most recent prior regimen			

Units: Subjects			
Adj/Neoadj in Localized disease (Stage I or II)	2		
Adjuvant in advanced disease (Stage III or IV)	39		
Neoadjuvant in advanced disease (Stage III or IV)	8		
Metastatic	44		
Missing	1		
Best overall response to most recent prior regimen Units: Subjects			
Complete Response (CR)	3		
Partial Response (PR)	5		
Non-CR/Non-PD	1		
Stable Disease (SD)	10		
Progressive Disease (PD)	23		
Not Evaluable	1		
Not Applicable	51		
Reason most recent prior regimen ended Units: Subjects			
Completed planned treatment	38		
Progressive Disease	46		
Toxicity	6		
Other	4		
Prior Surgery Units: Subjects			
Yes	88		
No	6		
Prior Radiotherapy Units: Subjects			
Yes	1		
No	93		
Region of Enrollment Units: Subjects			
United States	84		
Canada	9		
Netherlands	1		
Time from 1st positive biopsy for disease to consent for this study (mean) Units: Weeks			
arithmetic mean	68.0		
standard deviation	± 38.93		
Time from 1st positive biopsy for disease to consent for this study (median) Units: Weeks			
median	54.9		
full range (min-max)	25.1 to 250.4		
Time from local/regional recurrence to consent for this study (mean)			
Sixty-seven (67) patients has a local or regional recurrence.			
Units: Weeks			

arithmetic mean	28.6		
standard deviation	± 41.11		
Time from local/regional recurrence to consent for this study (median)			
Sixty-seven (67) patients has a local or regional recurrence.			
Units: Weeks			
median	13.0		
full range (min-max)	0.4 to 200.4		
Time from end of most recent prior systemic therapy to consent for this trial (mean)			
Units: Weeks			
arithmetic mean	13.1		
standard deviation	± 12.75		
Time from end of most recent prior systemic therapy to consent for this trial (median)			
Units: Weeks			
median	7.6		
full range (min-max)	0 to 82		
Weight (mean)			
Units: Kilograms			
arithmetic mean	72.8		
standard deviation	± 16.12		
Weight (median)			
Units: Kilograms			
median	69.7		
full range (min-max)	44.8 to 124.1		
Systolic Blood Pressure (mean)			
Units: mmHg			
arithmetic mean	126.1		
standard deviation	± 12.16		
Systolic Blood Pressure (median)			
Units: mmHg			
median	126.0		
full range (min-max)	100.0 to 159.0		
Diastolic Blood Pressure (mean)			
Units: mmHg			
arithmetic mean	75.8		
standard deviation	± 7.99		
Diastolic Blood Pressure (median)			
Units: mmHg			
median	76.0		
full range (min-max)	59.0 to 95.0		
Body Surface Area (mean)			
Units: m^2			
arithmetic mean	1.8		
standard deviation	± 0.19		
Body Surface Area (median)			
Units: m^2			
median	1.7		
full range (min-max)	1.4 to 2.3		
Age Continuous |			

Units: years			
median	60.0		
full range (min-max)	34 to 85		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Adavosertib 175 mg orally QD on Days 1, 2, 8, 9, 15, and 16 of 28 day cycles. Gemcitabine 800 mg/m² IV on Days 1, 8, and 15 of 28 day cycles.	
Reporting group title	Arm B
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3, 8-10, and 15-17 of 28 day cycles. Paclitaxel 80 mg/m² IV on Days 1, 8, and 15 of 28 day cycles.	
Reporting group title	Arm C
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3 of 21 day cycles. Carboplatin AUC 5 IV on Day 1 of 21 day cycles.	
Reporting group title	Arm C2
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3, 8-10, and 15-17 of 21 day cycles. Carboplatin AUC 5 IV on Day 1 of 21 day cycles.	
Reporting group title	Arm D-175 mg
Reporting group description:	
Adavosertib 175 mg orally BID (5 doses over 3 days) on Days 1-3 of 28 day cycles. Pegylated liposomal doxorubicin 40 mg/m² IV on Day 1 of 28 day cycles.	
Reporting group title	Arm D-225 mg
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3 of 28 day cycles. Pegylated liposomal doxorubicin 40 mg/m² IV on Day 1 of 28 day cycles.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set included all patients who received at least one dose of study treatment.	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]
End point description:	
Objective response rate is defined as the proportion of patients achieving a complete or partial tumour response according to RECIST v1.1 criteria.	
End point type	Primary
End point timeframe:	
Throughout the duration of the study (up to 19 months)	
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: The study protocol did not specify statistical analysis for this primary endpoint.	

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants	1	11	7	8

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants	2	1		

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 Disease Control Rate is defined as the proportion of patients achieving a complete response (CR), partial response (PR), or stable disease (SD) according to RECIST v1.1 criteria.

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants	3	27	19	12

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants	3	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:

Duration of Response (DoR) is defined as the time from first documented tumour response until the date of documented progression or death from any cause.

End point type	Secondary

End point timeframe:

Throughout the duration of the study, approximately 19 months.

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	11	7	8
Units: Months				
median (confidence interval 95%)	4.4 (0 to 99999.9)	12.0 (3.7 to 99999.9)	0 (0 to 99999.9)	10.4 (5.8 to 99999.9)

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: Months				
median (confidence interval 95%)	0 (0 to 99999.9)	0 (0 to 99999.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (Median, 80% CI)

End point title	Progression Free Survival (Median, 80% CI)

End point description:

Progression-free survival (PFS) was defined as the elapsed time from date of first dose of adavosertib until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdrew from therapy or received another anti-cancer therapy prior to progression. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment. Progression-free survival was derived based on scan/assessment dates, not visit dates.

End point type	Secondary

End point timeframe:

Throughout the Study, Approximately 4 years

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Months				
median (confidence interval 80%)	1.7 (1.6 to 5.5)	5.5 (3.8 to 7.1)	4.2 (3.9 to 5.6)	12.0 (8.6 to 13.1)

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Months				
median (confidence interval 80%)	2.7 (1.7 to 99999.9)	0 (0 to 99999.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (Median, 95% CI)

End point title	Progression Free Survival (Median, 95% CI)

End point description:

Progression-free survival (PFS) was defined as the elapsed time from date of first dose of adavosertib until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdrew from therapy or received another anti-cancer therapy prior to progression. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment. Progression-free survival was derived based on scan/assessment dates, not visit dates.

End point type	Secondary

End point timeframe:

Throughout the Study, Approximately 4 years

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Months				
median (confidence interval 95%)	1.7 (0.3 to 5.5)	5.5 (3.7 to 7.4)	4.2 (2.8 to 8.9)	12.0 (2.7 to 99999.9)

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Months				
median (confidence interval 95%)	2.7 (0.5 to 99999.9)	0 (0 to 99999.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (Median, 80% CI)

End point title	Overall Survival (Median, 80% CI)

End point description:

Overall survival (OS) was defined as the elapsed time from the date of first dose of adavosertib until death due to any cause. Any patient not known to have died at the time of the analysis was censored based on the last recorded date on which the patient was known to be alive.

End point type	Secondary

End point timeframe:

Throughout the Study, Approximately 4 years

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Months				
median (confidence interval 80%)	16.0 (6.7 to 99999.9)	99999.9 (15.6 to 99999.9)	8.9 (8.0 to 99999.9)	19.2 (12.4 to 19.2)

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Months				
median (confidence interval 80%)	3.8 (2.0 to 6.2)	0 (0 to 99999.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (Median, 95% CI)

End point title	Overall Survival (Median, 95% CI)

End point description:

Overall survival (OS) was defined as the elapsed time from the date of first dose of adavosertib until death due to any cause. Any patient not known to have died at the time of the analysis was censored based on the last recorded date on which the patient was known to be alive.

End point type	Secondary

End point timeframe:

Throughout the Study, Approximately 4 years

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Months				
median (confidence interval 95%)	16.0 (2.2 to 99999.9)	99999.9 (11.6 to 99999.9)	8.9 (8.0 to 99999.9)	19.2 (12.4 to 19.2)

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Months				
median (confidence interval 95%)	6.2 (2.0 to 99999.9)	0 (0 to 99999.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Gynecologic Cancer Intergroup (GCIG) CA-125 Response

End point title	Gynecologic Cancer Intergroup (GCIG) CA-125 Response

End point description:

The GCIG CA-125 response is defined as the proportion of patients achieving a 50% reduction in CA-125 levels from baseline, if baseline level is ≥2 x the upper limit of normal (ULN) within 2 weeks prior to starting treatment. Response must be confirmed and maintained for at least 28 days.

End point type	Secondary

End point timeframe:

Throughout the study, approximately 4 years

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	28	15	11
Units: Percent				
number (confidence interval 90%)	25.0 (4.6 to 60.0)	53.6 (36.6 to 69.9)	26.7 (9.7 to 51.1)	63.6 (35.0 to 86.5)

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Percent				
number (confidence interval 90%)	25.0 (1.3 to 75.1)	25.0 (1.3 to 75.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-emergent adverse events (TEAEs).

End point title	Treatment-emergent adverse events (TEAEs).

End point description:

The number and proportion of patients experiencing at least one treatment-related adverse event (TEAE). Severity Grade 1 = Mild; Severity Grade 2 = Moderate; Severity Grade 3 = Severe; Severity Grade 4 = Life Threatening; Severity Grade 5 = Fatal

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants				
Participants with at least one TEAE Grade 1.	0	2	0	0
Participants with at least one TEAE Grade 2.	1	1	5	0
Participants with at least one TEAE Grade 3.	2	19	10	4
Participants with at least one TEAE Grade 4.	6	15	8	8
Participants with at least one TEAE Grade 5.	0	1	0	0

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants				
Participants with at least one TEAE Grade 1.	0	0		
Participants with at least one TEAE Grade 2.	3	4		
Participants with at least one TEAE Grade 3.	3	0		
Participants with at least one TEAE Grade 4.	0	2		
Participants with at least one TEAE Grade 5.	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-emergent adverse events (TEAEs) Related to Adavosertib

End point title	Treatment-emergent adverse events (TEAEs) Related to Adavosertib

End point description:

The number and proportion of patients experiencing at least one treatment-related adverse event (TEAE) related to adavosertib.

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants				
Participants with at least one TEAE Grade 1.	0	3	2	0
Participants with at least one TEAE Grade 2.	1	4	5	0
Participants with at least one TEAE Grade 3.	3	16	7	4
Participants with at least one TEAE Grade 4.	5	14	8	8
Participants with at least one TEAE Grade 5.	0	1	0	0

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants				
Participants with at least one TEAE Grade 1.	0	0		
Participants with at least one TEAE Grade 2.	5	4		
Participants with at least one TEAE Grade 3.	1	0		
Participants with at least one TEAE Grade 4.	0	2		
Participants with at least one TEAE Grade 5.	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-emergent adverse events (TEAEs) Related to Chemotherapy

End point title	Treatment-emergent adverse events (TEAEs) Related to Chemotherapy

End point description:

The number of patients experiencing at least one treatment-related adverse event (TEAE) related to chemotherapy.

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants				
Participants with at least one TEAE Grade 1.	0	4	0	0
Participants with at least one TEAE Grade 2.	1	5	6	0
Participants with at least one TEAE Grade 3.	3	13	8	4
Participants with at least one TEAE Grade 4.	5	15	8	8
Participants with at least one TEAE Grade 5.	0	1	0	0

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants				
Participants with at least one TEAE Grade 1.	0	0		
Participants with at least one TEAE Grade 2.	5	4		
Participants with at least one TEAE Grade 3.	1	0		
Participants with at least one TEAE Grade 4.	0	2		
Participants with at least one TEAE Grade 5.	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Serious Adverse Events

End point title	Serious Adverse Events

End point description:

The number of patients experiencing at least one serious adverse event (SAE).

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants				
Pts. with ≥ one serious TEAE related to AZD1775.	0	8	9	7
Pts. with ≥ one serious TEAE related to Chemo.	0	8	9	7

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants				
Pts. with ≥ one serious TEAE related to AZD1775.	1	1		
Pts. with ≥ one serious TEAE related to Chemo.	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Serious Adverse Events Leading to Death

End point title	Serious Adverse Events Leading to Death

End point description:

The number of patients experiencing at least one serious adverse event (SAE) leading to death.

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants				
No. with STEAE related to AZD1775 leading to death	0	1	0	0
No. with STEAE related to chemo leading to death	0	1	0	0

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants				
No. with STEAE related to AZD1775 leading to death	0	0		
No. with STEAE related to chemo leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-Related Adverse Events Related to Adavosertib Leading to Treatment Discontinuation

End point title	Treatment-Related Adverse Events Related to Adavosertib Leading to Treatment Discontinuation

End point description:

The number of patients experiencing at least one treatment-related adverse event related to adavosertib leading to treatment discontinuation.

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants	0	6	5	1

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-Related Adverse Events Related to Adavosertib Leading to Dose Reduction

End point title	Treatment-Related Adverse Events Related to Adavosertib Leading to Dose Reduction

End point description:

The number of patients experiencing at least one treatment-related adverse event related to adavosertib leading to dose reduction.

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants	2	18	5	11

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-Related Adverse Events Related to Adavosertib Leading to Treatment Interruption

End point title	Treatment-Related Adverse Events Related to Adavosertib Leading to Treatment Interruption

End point description:

The number of patients experiencing at least one treatment-related adverse event related to adavosertib leading to treatment interruption.

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants	8	30	10	11

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-Related Adverse Events Related to Chemotherapy Leading to Treatment Discontinuation

End point title	Treatment-Related Adverse Events Related to Chemotherapy Leading to Treatment Discontinuation

End point description:

The number of patients experiencing at least one treatment-related adverse event related to chemotherapy leading to treatment discontinuation.

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants	0	6	5	1

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-Related Adverse Events Related to Chemotherapy Leading to Dose Reduction

End point title	Treatment-Related Adverse Events Related to Chemotherapy Leading to Dose Reduction

End point description:

The number of patients experiencing at least one treatment-related adverse event related to chemotherapy leading to dose reduction.

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants	6	19	8	11

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-Related Adverse Events Related to Chemotherapy Leading to Treatment Interruption

End point title	Treatment-Related Adverse Events Related to Chemotherapy Leading to Treatment Interruption

End point description:

The number of patients experiencing at least one treatment-related adverse event related to chemotherapy leading to treatment interruption.

End point type	Secondary

End point timeframe:

Throughout the duration of the study (up to 19 months)

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Participants	8	28	12	9

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Single Dose Adavosertib Cmax

End point title	Single Dose Adavosertib Cmax[2]

End point description:

Maximum plasma concentration of adavosertib after a single oral dose (Cycle 1 Day 1) in combination with IV infusion of commonly used chemotherapy agents, including gemcitabine, paclitaxel, and carboplatin.

End point type	Secondary

End point timeframe:

8 hours

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Single Dose Cmax was only calculated in Arms B and C. Sufficient data were not available to calculate this parameter in other arms.

End point values	Arm B	Arm C		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: nM				
geometric mean (geometric coefficient of variation)	533.8 (± 37.29)	556.6 (± 56.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Multiple Dose Adavosertib Cmax

End point title	Multiple Dose Adavosertib Cmax[3]

End point description:

Maximum plasma concentration of adavosertib after a multiple oral doses (Cycle 1 Day 3) in combination with IV infusion of 40 mg/m² pegylated liposomal doxorubicin.

End point type	Secondary

End point timeframe:

3 Days

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Multiple dose pharmacokinetics were calculated only in Arm D-175 mg and Arm D-225 mg.

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	2		
Units: nM				
geometric mean (geometric coefficient of variation)	4135 (± 65.8)	23530 (± 30.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as the elapsed time from the date of first dose of adavosertib until death due to any cause. Any patient not known to have died at the time of the analysis was censored based on the last recorded date on which the patient was known to be alive.

End point type	Secondary

End point timeframe:

Throughout the Study, Approximately 4 years

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Months				
median (confidence interval 90%)	16.0 (2.2 to 99999.9)	99999.9 (11.6 to 99999.9)	8.9 (6.5 to 99999.9)	19.2 (12.4 to 19.2)

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Months				
median (confidence interval 90%)	6.2 (2.0 to 99999.9)	0 (0 to 99999.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Single Dose Adavosertib tmax

End point title	Single Dose Adavosertib tmax[4]

End point description:

The time to reach maximum plasma concentration of adavosertib after a single oral dose (Cycle 1 Day 1) in combination with IV infusion of commonly used chemotherapy agents, including gemcitabine, paclitaxel, and carboplatin.

End point type	Secondary

End point timeframe:

8 hours

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Single Dose tmax was only calculated in Arms B and C. Sufficient data were not available to calculate this parameter in other arms.

End point values	Arm B	Arm C		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: hours				
median (full range (min-max))	4.08 (1.97 to 8.00)	3.15 (1.75 to 4.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

Progression-Free Survival (PFS) was defined as the elapsed time from the date of first dose of adavosertib until confirmed progressive disease or death due to any cause.

End point type	Secondary

End point timeframe:

Throughout the Study, Approximately 4 years

End point values	Arm A	Arm B	Arm C	Arm C2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	23	12
Units: Months				
median (confidence interval 95%)	1.7 (0.3 to 5.5)	5.5 (3.7 to 7.4)	4.2 (2.8 to 8.9)	12.0 (2.7 to 99999.9)

End point values	Arm D-175 mg	Arm D-225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Months				
median (confidence interval 95%)	2.7 (0.5 to 99999.9)	0 (0 to 99999.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study, approximately 19 months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Adavosertib 175 mg orally QD on Days 1, 2, 8, 9, 15, and 16 of 28 day cycles. Gemcitabine 800 mg/m² IV on Days 1, 8, and 15 of 28 day cycles.	
Reporting group title	Arm B
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3, 8-10, and 15-17 of 28 day cycles. Paclitaxel 80 mg/m² IV on Days 1, 8, and 15 of 28 day cycles.	
Reporting group title	Arm D-175 mg
Reporting group description:	
Adavosertib 175 mg orally BID (5 doses over 3 days) on Days 1-3 of 28 day cycles. Pegylated liposomal doxorubicin 40 mg/m² IV on Day 1 of 28 day cycles.	
Reporting group title	Arm C2
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3, 8-10, and 15-17 of 21 day cycles. Carboplatin AUC 5 IV on Day 1 of 21 day cycles.	
Reporting group title	Arm D-225 mg
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3 of 28 day cycles. Pegylated liposomal doxorubicin 40 mg/m² IV on Day 1 of 28 day cycles.	
Reporting group title	Arm C
Reporting group description:	
Adavosertib 225 mg orally BID (5 doses over 3 days) on Days 1-3 of 21 day cycles. Carboplatin AUC 5 IV on Day 1 of 21 day cycles.	

Serious adverse events	Arm A	Arm B	Arm D-175 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)	17 / 38 (44.74%)	2 / 6 (33.33%)
number of deaths (all causes)	5	12	3
number of deaths resulting from adverse events	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 9 (11.11%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 38 (2.63%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic Reaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Chest Pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet Count Decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil Count Decreased			

subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Gastrointestinal Stoma Complication			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion Related Reaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient Ischaemic Attack			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	3 / 38 (7.89%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			

subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			

subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	1 / 38 (2.63%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			
subjects affected / exposed	2 / 9 (22.22%)	3 / 38 (7.89%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	1 / 38 (2.63%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin Ulcer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flank Pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 9 (0.00%)	3 / 38 (7.89%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney Infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cellulitis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver Abscess			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic Sepsis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Paraspinal Abscess			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Device Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 38 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm C2	Arm D-225 mg	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)	1 / 6 (16.67%)	12 / 23 (52.17%)
number of deaths (all causes)	2	0	9
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic Reaction			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Chest Pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			

subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet Count Decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil Count Decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Gastrointestinal Stoma Complication			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion Related Reaction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient Ischaemic Attack			

subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	4 / 23 (17.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	5 / 12 (41.67%)	0 / 6 (0.00%)	3 / 23 (13.04%)
occurrences causally related to treatment / all	5 / 6	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			

subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin Ulcer			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Flank Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney Infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver Abscess			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic Sepsis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraspinal Abscess			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			

subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Device Infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 Diabetes Mellitus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A	Arm B	Arm D-175 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	38 / 38 (100.00%)	6 / 6 (100.00%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 9 (33.33%)	2 / 38 (5.26%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 9 (11.11%)	4 / 38 (10.53%)	0 / 6 (0.00%)
occurrences (all)	3	11	0
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 9 (0.00%)	3 / 38 (7.89%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Blood Creatinine Increased			

subjects affected / exposed	0 / 9 (0.00%)	3 / 38 (7.89%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Neutrophil Count Decreased			
subjects affected / exposed	4 / 9 (44.44%)	13 / 38 (34.21%)	0 / 6 (0.00%)
occurrences (all)	16	64	0
Platelet Count Decreased			
subjects affected / exposed	2 / 9 (22.22%)	7 / 38 (18.42%)	0 / 6 (0.00%)
occurrences (all)	10	12	0
Weight Decreased			
subjects affected / exposed	1 / 9 (11.11%)	3 / 38 (7.89%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
White Blood Cell Count Decreased			
subjects affected / exposed	2 / 9 (22.22%)	11 / 38 (28.95%)	1 / 6 (16.67%)
occurrences (all)	10	64	1
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 9 (11.11%)	4 / 38 (10.53%)	1 / 6 (16.67%)
occurrences (all)	1	4	1
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	2 / 38 (5.26%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	1 / 9 (11.11%)	8 / 38 (21.05%)	0 / 6 (0.00%)
occurrences (all)	1	8	0
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 9 (0.00%)	8 / 38 (21.05%)	0 / 6 (0.00%)
occurrences (all)	0	14	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 9 (33.33%)	24 / 38 (63.16%)	3 / 6 (50.00%)
occurrences (all)	12	82	4
Thrombocytopenia			
subjects affected / exposed	1 / 9 (11.11%)	9 / 38 (23.68%)	0 / 6 (0.00%)
occurrences (all)	3	12	0
Neutropenia			

subjects affected / exposed	4 / 9 (44.44%)	12 / 38 (31.58%)	1 / 6 (16.67%)
occurrences (all)	14	25	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 9 (33.33%)	23 / 38 (60.53%)	3 / 6 (50.00%)
occurrences (all)	5	33	6
Oedema, Peripheral			
subjects affected / exposed	0 / 9 (0.00%)	10 / 38 (26.32%)	0 / 6 (0.00%)
occurrences (all)	0	10	0
Pyrexia			
subjects affected / exposed	4 / 9 (44.44%)	8 / 38 (21.05%)	1 / 6 (16.67%)
occurrences (all)	4	11	3
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	2 / 9 (22.22%)	2 / 38 (5.26%)	1 / 6 (16.67%)
occurrences (all)	3	2	1
Abdominal Pain			
subjects affected / exposed	2 / 9 (22.22%)	8 / 38 (21.05%)	1 / 6 (16.67%)
occurrences (all)	2	12	2
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	4 / 38 (10.53%)	2 / 6 (33.33%)
occurrences (all)	1	4	2
Diarrhoea			
subjects affected / exposed	3 / 9 (33.33%)	31 / 38 (81.58%)	1 / 6 (16.67%)
occurrences (all)	3	67	1
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)	3 / 38 (7.89%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Stomatitis			
subjects affected / exposed	0 / 9 (0.00%)	3 / 38 (7.89%)	2 / 6 (33.33%)
occurrences (all)	0	3	4
Nausea			
subjects affected / exposed	5 / 9 (55.56%)	23 / 38 (60.53%)	4 / 6 (66.67%)
occurrences (all)	9	49	5
Gastrointestinal Reflux Disease			

subjects affected / exposed	0 / 9 (0.00%)	4 / 38 (10.53%)	3 / 6 (50.00%)
occurrences (all)	0	4	3
Vomiting			
subjects affected / exposed	4 / 9 (44.44%)	19 / 38 (50.00%)	3 / 6 (50.00%)
occurrences (all)	7	41	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 9 (0.00%)	5 / 38 (13.16%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	10 / 38 (26.32%)	0 / 6 (0.00%)
occurrences (all)	1	12	0
Epistaxis			
subjects affected / exposed	1 / 9 (11.11%)	2 / 38 (5.26%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Oropharyngeal Pain			
subjects affected / exposed	1 / 9 (11.11%)	2 / 38 (5.26%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Nasal Congestion			
subjects affected / exposed	0 / 9 (0.00%)	5 / 38 (13.16%)	0 / 6 (0.00%)
occurrences (all)	0	7	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 9 (22.22%)	1 / 38 (2.63%)	1 / 6 (16.67%)
occurrences (all)	4	1	1
Alopecia			
subjects affected / exposed	0 / 9 (0.00%)	6 / 38 (15.79%)	1 / 6 (16.67%)
occurrences (all)	0	6	1
Rash			
subjects affected / exposed	3 / 9 (33.33%)	2 / 38 (5.26%)	1 / 6 (16.67%)
occurrences (all)	3	2	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)	6 / 38 (15.79%)	1 / 6 (16.67%)
occurrences (all)	1	6	1
Musculoskeletal and connective tissue disorders			

Back Pain			
subjects affected / exposed	1 / 9 (11.11%)	6 / 38 (15.79%)	1 / 6 (16.67%)
occurrences (all)	1	6	1
Arthralgia			
subjects affected / exposed	2 / 9 (22.22%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Pain in Extremity			
subjects affected / exposed	1 / 9 (11.11%)	4 / 38 (10.53%)	0 / 6 (0.00%)
occurrences (all)	1	4	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	6 / 38 (15.79%)	0 / 6 (0.00%)
occurrences (all)	0	6	0
Bone Pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 38 (2.63%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	0 / 9 (0.00%)	6 / 38 (15.79%)	1 / 6 (16.67%)
occurrences (all)	0	9	1
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	2 / 9 (22.22%)	7 / 38 (18.42%)	1 / 6 (16.67%)
occurrences (all)	3	9	1
Hypokalaemia			
subjects affected / exposed	1 / 9 (11.11%)	4 / 38 (10.53%)	1 / 6 (16.67%)
occurrences (all)	1	6	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 9 (0.00%)	6 / 38 (15.79%)	0 / 6 (0.00%)
occurrences (all)	0	18	0
Hyperglycaemia			
subjects affected / exposed	1 / 9 (11.11%)	6 / 38 (15.79%)	1 / 6 (16.67%)
occurrences (all)	2	12	1
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	3 / 38 (7.89%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Hypophosphataemia			

subjects affected / exposed	0 / 9 (0.00%)	3 / 38 (7.89%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Hyponatraemia			
subjects affected / exposed	1 / 9 (11.11%)	4 / 38 (10.53%)	0 / 6 (0.00%)
occurrences (all)	7	6	0
Hypomagnesaemia			
subjects affected / exposed	1 / 9 (11.11%)	8 / 38 (21.05%)	0 / 6 (0.00%)
occurrences (all)	1	13	0

Non-serious adverse events	Arm C2	Arm D-225 mg	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	6 / 6 (100.00%)	23 / 23 (100.00%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	3
Blood Creatinine Increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	2
Neutrophil Count Decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	5 / 23 (21.74%)
occurrences (all)	0	0	17
Platelet Count Decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	5 / 23 (21.74%)
occurrences (all)	0	1	19
Weight Decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
White Blood Cell Count Decreased			

subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	4 / 23 (17.39%)
occurrences (all)	0	1	17
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	4 / 12 (33.33%)	0 / 6 (0.00%)	3 / 23 (13.04%)
occurrences (all)	4	0	4
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)	2 / 6 (33.33%)	3 / 23 (13.04%)
occurrences (all)	1	3	5
Headache			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	7 / 23 (30.43%)
occurrences (all)	1	0	9
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 12 (75.00%)	2 / 6 (33.33%)	13 / 23 (56.52%)
occurrences (all)	48	2	45
Thrombocytopenia			
subjects affected / exposed	11 / 12 (91.67%)	0 / 6 (0.00%)	11 / 23 (47.83%)
occurrences (all)	90	0	33
Neutropenia			
subjects affected / exposed	11 / 12 (91.67%)	2 / 6 (33.33%)	5 / 23 (21.74%)
occurrences (all)	51	8	14
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 12 (66.67%)	5 / 6 (83.33%)	17 / 23 (73.91%)
occurrences (all)	11	5	30
Oedema, Peripheral			
subjects affected / exposed	5 / 12 (41.67%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	5	0	0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Abdominal Distension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	3
Abdominal Pain			
subjects affected / exposed	1 / 12 (8.33%)	2 / 6 (33.33%)	8 / 23 (34.78%)
occurrences (all)	4	3	9
Constipation			
subjects affected / exposed	4 / 12 (33.33%)	0 / 6 (0.00%)	5 / 23 (21.74%)
occurrences (all)	4	0	7
Diarrhoea			
subjects affected / exposed	6 / 12 (50.00%)	5 / 6 (83.33%)	16 / 23 (69.57%)
occurrences (all)	11	9	33
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 6 (33.33%)	2 / 23 (8.70%)
occurrences (all)	1	2	2
Stomatitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	2 / 23 (8.70%)
occurrences (all)	2	1	2
Nausea			
subjects affected / exposed	10 / 12 (83.33%)	4 / 6 (66.67%)	19 / 23 (82.61%)
occurrences (all)	12	7	38
Gastrointestinal Reflux Disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	4 / 12 (33.33%)	0 / 6 (0.00%)	13 / 23 (56.52%)
occurrences (all)	9	0	24
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	3 / 23 (13.04%)
occurrences (all)	1	0	3
Dyspnoea			
subjects affected / exposed	4 / 12 (33.33%)	1 / 6 (16.67%)	4 / 23 (17.39%)
occurrences (all)	6	2	4
Epistaxis			

subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	4
Oropharyngeal Pain			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences (all)	2	0	1
Nasal Congestion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	3 / 23 (13.04%)
occurrences (all)	0	1	5
Alopecia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	5
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 12 (25.00%)	0 / 6 (0.00%)	4 / 23 (17.39%)
occurrences (all)	3	0	5
Arthralgia			
subjects affected / exposed	3 / 12 (25.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	3	0	2
Pain in Extremity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Bone Pain			

subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences (all)	2	0	2
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	2 / 23 (8.70%)
occurrences (all)	1	2	3
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	5 / 23 (21.74%)
occurrences (all)	1	0	5
Hypokalaemia			
subjects affected / exposed	3 / 12 (25.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	4	0	8
Hypoalbuminaemia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	3
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	4
Hypophosphataemia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Hyponatraemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Hypomagnesaemia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	6 / 23 (26.09%)
occurrences (all)	3	0	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2014	Amendment 1 changed adavosertib dosing to occur concurrently with chemotherapy and clarified the conduct of the study. Additional guidance and clarification on DLT criteria, TP53 mutation testing, and study windows were provided. Additional dose-limiting criteria were included for Part 1 of the study (Grade 3 thrombocytopenia with bleeding as a haematologic DLT).
18 May 2015	Amendment 2 clarified eligibility criteria in patients with prior adjuvant therapy and reduced the starting dose of gemcitabine from 1000 mg/² to 800 mg/². In addition, the text was updated to better clarify the study conduct.
29 June 2015	Amendment 3 changed the restrictions and the inclusion criteria for the study, including clarifying allowable number of treatment regimens, types of treatment, and stage of disease. This amendment also identified corrections to the edition numbering to bring it back into alignment.
04 December 2015	Amendment 4 updated the study design to an open-label, four-arm lead-in safety and two-arm efficacy study. Enrolment was stopped in Arm A (adavosertib plus gemcitabine) and Arm B (adavosertib plus paclitaxel) beyond the safety cohorts. A treatment arm was added to evaluate safety and efficacy of adavosertib plus PLD (Arm D). In addition, proof of TP53 mutation prior to enrolment was no longer required.
17 August 2016	Amendment 5 aligned the CSP with the most recent adavosertib safety information, and removed the expansion cohort of Arm D (adavosertib plus PLD).
20 January 2017	Amendment 6 expanded Arm B (adavosertib plus paclitaxel) to further assess efficacy, and Arm C (adavosertib plus carboplatin; referred as Arm C2) to optimise the dosing schedule for prolonged adavosertib exposure. Mandatory PK assessments were added for patients in the expansion cohorts and an optional PGx assessment was added for all patients.
19 June 2017	Amendment 7 clarified the inclusion and exclusion criteria relating to allowable prior treatments and patients with a history of Torsades de pointes. The schedule for cfDNA collections was modified for treatment Arm B and Arm C, and text regarding 'Best Regimen' was removed from tumour response assessments.
14 February 2018	Amendment 8 provided new dose modification guidance for the management of haematological events.
05 September 2018	Amendment 9 clarified study procedures and analysis relating to the addition of the FPV for patients who continued to receive adavosertib ± chemotherapy after the time of primary data cut-off.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In some cases the median or confidence interval limits could not be calculated. If the upper limit of the confidence interval could not be calculated 99999.9 was entered.

Notes: