Clinical trial results:
A Phase 1/2 Multicenter Study of the Combination of AZD2014 and Palbociclib on a background of Hormonal Therapy in Patients with Locally Advanced/Metastatic Estrogen Receptor Positive Breast Cancer Comprising a Safety, Pharmacokinetic and Preliminary Efficacy Evaluation (PASTOR)

Summary

EudraCT number	2015-003320-30
Trial protocol	GB
Global end of trial date	23 November 2023

Results information

Result version number	v1 (current)
This version publication date	20 June 2024
First version publication date	20 June 2024

Trial information

Trial identification

Sponsor protocol code	D2270C00020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02599714
WHO universal trial number (UTN)	-
Other trial identifiers	Sarah Cannon Development Innovations, LLC: BRE 253

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Melbourn Science Park, Cambridge Road, Melbourn, Royston, Hertfordshire, United Kingdom, SG8 6EE
Public contact	Jan Cosaert, MD, AstraZeneca, +44 7384 807033, jan.cosaert@astrazeneca.com
Scientific contact	Jan Cosaert, MD, AstraZeneca, +44 7384 807033, jan.cosaert@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	23 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2018
Global end of trial reached?	Yes
Global end of trial date	23 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The amended primary objectives for parts A and B were to investigate the safety and tolerability of the combination of AZD2014 and palbociclib on a background of fulvestrant in patients with locally advanced/metastatic ER positive breast cancer and to define the combination dose(s)/schedule(s) for further clinical evaluation.

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:

All patients received Fulvestrant 500 mg by intramuscular injection on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles. Additionally all patients received Palbociclib administered orally with food orally, once daily on days 1-21 of a 28 day cycle (alternative frequencies were instigated in some cohorts - 7 days on, 7 days off on a 28 day cycle).

Evidence for comparator:

Fulvestrant (Faslodex®) has been approved by regulatory agencies in both the US and the UK for treatment of:
• Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.
• HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
• HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib, as initial endocrine based therapy or following disease progression on endocrine therapy.
• HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

Palbociclib (Ibrance®) has been approved by regulatory agencies in both the US and the UK for treatment of adults with HR+, HER2- breast cancer that has spread to other parts of the body (metastatic) in combination with an aromatase inhibitor as the first hormonal based therapy in postmenopausal women or in men, or fulvestrant with disease progression following hormonal therapy.

Actual start date of recruitment	01 December 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: 29
Country: Number of subjects enrolled	United Kingdom: 25
Worldwide total number of subjects	54
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	35
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fifty-four (54) patients were enrolled in the study and received treatment at 7 sites in the US and the UK between 19 January 2016 and 26 September 2017. The last visit of the last patient for data collection occurred on 27 March 2018.

Pre-assignment

Screening details:

Fifty-four (54) patients pased the screening criteria and received treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (Part A)

Arm description:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm type	Experimental
Investigational medicinal product name	Vistusertib
Investigational medicinal product code	AZD2014
Other name	AZD2014
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm title	Cohort 2 (Part A)

Arm description:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm type	Experimental
Investigational medicinal product name	Vistusertib
Investigational medicinal product code	AZD2014
Other name	AZD2014
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm title	Cohort 3 (Part A)

Arm description:

Vistusertib 75 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm type	Experimental

Investigational medicinal product name	Vistusertib
Investigational medicinal product code	AZD2014
Other name	AZD2014
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vistusertib 75 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm title	Cohort 4 (Part A)

Arm description:

Vistusertib 50 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm type	Experimental
Investigational medicinal product name	Vistusertib
Investigational medicinal product code	AZD2014
Other name	AZD2014
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vistusertib 50 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm title	Cohort 5 Low ANC (Part A)

Arm description:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-7, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm type	Experimental
Investigational medicinal product name	Vistusertib
Investigational medicinal product code	AZD2014
Other name	AZD2014
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (7 days on, 7 days off). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm title	Cohort 6 High ANC (Part A)

Arm description:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm type	Experimental
Investigational medicinal product name	Vistusertib
Investigational medicinal product code	AZD2014
Other name	AZD2014
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm title	Cohort 7 (Part B)

Arm description:

Vistusertib 75 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Arm type	Experimental

Investigational medicinal product name	Vistusertib
Investigational medicinal product code	AZD2014
Other name	AZD2014
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vistusertib 75 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Number of subjects in period 1	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)
Started	6	6	6
Completed	6	6	6

Number of subjects in period 1	Cohort 4 (Part A)	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)
Started	6	6	7
Completed	6	6	7

Number of subjects in period 1	Cohort 7 (Part B)
Started	17
Completed	17

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (Part A)
Reporting group description:	
Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 2 (Part A)
Reporting group description:	
Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 3 (Part A)
Reporting group description:	
Vistusertib 75 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 4 (Part A)
Reporting group description:	
Vistusertib 50 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 5 Low ANC (Part A)
Reporting group description:	
Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-7, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 6 High ANC (Part A)
Reporting group description:	
Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 7 (Part B)
Reporting group description:	
Vistusertib 75 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	

Reporting group values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)
Number of subjects	6	6	6
Age categorical Units: Subjects			
Adults (18-64 years)	5	3	4
From 65-84 years	1	3	2
Age Continuous Units: Years			
arithmetic mean	55.0	64.8	58.8
standard deviation	± 5.73	± 7.49	± 7.63
Sex: Female, Male Units: Subjects			
Female	6	6	6
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	5	5	6
Black or African American	1	0	0

Asian	0	1	0
Other	0	0	0
Missing	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	6	6	6
Unknown or Not Reported	0	0	0
ECOG Performance Status at Baseline			
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			
ECOG Score = 0	2	1	4
ECOG Score = 1	4	5	2
Tumour Grade			
G1 = Well Differentiated G2 = Moderately Differentiated G3 = Poorly Differentiated G4 = Undifferentiated GX = Unassessable			
Units: Subjects			
Well Differentiated (G1)	0	1	0
Moderately Differentiated (G2)	4	3	3
Poorly Differentiated (G3)	1	2	3
Undifferentiated (G4)	0	0	0
Unassessable (GX)	1	0	0
Missing	0	0	0
Histology Type Units: Subjects			
Invasive Carcinoma (NOS)	0	1	1
Invasive Ductal	2	3	2
Invasive Ductal -Extensive Intraductal Component	1	0	3
Invasive Lobular	3	1	0
Other	0	1	0
Missing	0	0	0
Overall Disease Classification			
Metastatic or Locally Advanced			
Units: Subjects			
Metastatic	6	6	6
Locally Advanced	0	0	0
Visceral Disease Units: Subjects			
Visceral Disease	3	5	5
No Visceral Disease	3	1	1
Age Continuous | Units: Years			
median	54.0	65.5	57.5
full range (min-max)	50 to 65	53 to 75	48 to 69

Reporting group values	Cohort 4 (Part A)	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)
Number of subjects	6	6	7

Age categorical Units: Subjects			
Adults (18-64 years)	6	5	4
From 65-84 years	0	1	3
Age Continuous Units: Years			
arithmetic mean	47.7	55.5	57.7
standard deviation	± 9.77	± 12.26	± 14.37
Sex: Female, Male Units: Subjects			
Female	6	6	7
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	6	5	6
Black or African American	0	0	0
Asian	0	0	1
Other	0	1	0
Missing	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	6	5	5
Unknown or Not Reported	0	1	2
ECOG Performance Status at Baseline			
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			
ECOG Score = 0	6	4	4
ECOG Score = 1	0	2	3
Tumour Grade			
G1 = Well Differentiated G2 = Moderately Differentiated G3 = Poorly Differentiated G4 = Undifferentiated GX = Unassessable			
Units: Subjects			
Well Differentiated (G1)	1	1	0
Moderately Differentiated (G2)	3	4	1
Poorly Differentiated (G3)	2	0	2
Undifferentiated (G4)	0	1	0
Unassessable (GX)	0	0	2
Missing	0	0	2
Histology Type Units: Subjects			
Invasive Carcinoma (NOS)	2	2	3
Invasive Ductal	4	4	1
Invasive Ductal -Extensive Intraductal Component	0	0	0
Invasive Lobular	0	0	1
Other	0	0	2
Missing	0	0	0

Overall Disease Classification			
Metastatic or Locally Advanced			
Units: Subjects			
Metastatic	6	6	7
Locally Advanced	0	0	0
Visceral Disease Units: Subjects			
Visceral Disease	4	6	3
No Visceral Disease	2	0	4
Age Continuous | Units: Years			
median	46.5	61.0	59.0
full range (min-max)	36 to 60	36 to 68	36 to 75

Reporting group values	Cohort 7 (Part B)	Total	
Number of subjects	17	54	
Age categorical Units: Subjects			
Adults (18-64 years)	8	35	
From 65-84 years	9	19	
Age Continuous Units: Years			
arithmetic mean	62.8		
standard deviation	± 9.49	-	
Sex: Female, Male Units: Subjects			
Female	17	54	
Male	0	0	
Race/Ethnicity, Customized Units: Subjects			
White	12	45	
Black or African American	0	1	
Asian	0	2	
Other	4	5	
Missing	1	1	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	15	49	
Unknown or Not Reported	2	5	
ECOG Performance Status at Baseline			
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			
ECOG Score = 0	12	33	
ECOG Score = 1	5	21	
Tumour Grade			
G1 = Well Differentiated G2 = Moderately Differentiated G3 = Poorly Differentiated G4 = Undifferentiated GX = Unassessable			

Units: Subjects			
Well Differentiated (G1)	2	5	
Moderately Differentiated (G2)	9	27	
Poorly Differentiated (G3)	4	14	
Undifferentiated (G4)	0	1	
Unassessable (GX)	0	3	
Missing	2	4	
Histology Type Units: Subjects			
Invasive Carcinoma (NOS)	2	11	
Invasive Ductal	8	24	
Invasive Ductal -Extensive Intraductal Component	1	5	
Invasive Lobular	5	10	
Other	0	3	
Missing	1	1	
Overall Disease Classification			
Metastatic or Locally Advanced			
Units: Subjects			
Metastatic	17	54	
Locally Advanced	0	0	
Visceral Disease Units: Subjects			
Visceral Disease	10	36	
No Visceral Disease	7	18	
Age Continuous | Units: Years			
median	65.0		
full range (min-max)	47 to 77	-	

Subject analysis sets

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

Subject analysis set description:

The Full Analysis Set includes all patients who received at least 1 dose of study medication.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set includes all patients who received at least 1 dose of AZD2014 or palbociclib.

Subject analysis set title	Pharmacokinetics Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Pharmacokinetics Analysis Set includes all dosed patients with reportable AZD2014 or palbociclib concentrations. However, the number of participants with reportable data varies between PK parameters. Single-dose PK parameters were only determined in Part A, Cohorts 1-4.

Subject analysis set title	Evaluable for Response
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Evaluable for Response analysis set includes all patients who received at least one dose of vistusertib, palbociclib, or fulvestrant with measurable disease at baseline as per RECIST 1.1.

Subject analysis set title	Evaluable for Efficacy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Evaluable for Efficacy Analysis Set includes all patients who received at least 1 dose of study medication and who had efficacy data.

Reporting group values	Full Analysis Set	Safety Analysis Set	Pharmacokinetics Analysis Set
Number of subjects	54	54	53
Age categorical Units: Subjects			
Adults (18-64 years)	35	35	35
From 65-84 years	19	19	18
Age Continuous Units: Years			
arithmetic mean	58.6	58.6	58.4
standard deviation	± 10.68	± 10.68	± 10.71
Sex: Female, Male Units: Subjects			
Female	54	54	53
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	45	45	44
Black or African American	1	1	1
Asian	2	2	2
Other	5	5	5
Missing	1	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	49	49	49
Unknown or Not Reported	5	5	4
ECOG Performance Status at Baseline			
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			
ECOG Score = 0	33	33	33
ECOG Score = 1	21	21	20
Tumour Grade			
G1 = Well Differentiated G2 = Moderately Differentiated G3 = Poorly Differentiated G4 = Undifferentiated GX = Unassessable			
Units: Subjects			
Well Differentiated (G1)	5	5	5
Moderately Differentiated (G2)	27	27	27
Poorly Differentiated (G3)	14	14	14
Undifferentiated (G4)	1	1	1
Unassessable (GX)	3	3	2
Missing	4	4	4
Histology Type Units: Subjects			
Invasive Carcinoma (NOS)	11	11	10

Invasive Ductal	24	24	24
Invasive Ductal -Extensive Intraductal Component	5	5	5
Invasive Lobular	10	10	10
Other	3	3	3
Missing	1	1	1
Overall Disease Classification			
Metastatic or Locally Advanced			
Units: Subjects			
Metastatic	54	54	53
Locally Advanced	0	0	0
Visceral Disease			
Units: Subjects			
Visceral Disease	36	36	53
No Visceral Disease	18	18	0
Age Continuous |			
Units: Years			
median	59.0	59.0	59.0
full range (min-max)	36 to 77	36 to 77	36 to 77

Reporting group values	Evaluable for Response	Evaluable for Efficacy	
Number of subjects	47	54	
Age categorical			
Units: Subjects			
Adults (18-64 years)	33	35	
From 65-84 years	14	19	
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	±	±	
Sex: Female, Male			
Units: Subjects			
Female	47	54	
Male	0	0	
Race/Ethnicity, Customized			
Units: Subjects			
White	38	45	
Black or African American	1	1	
Asian	2	2	
Other	5	5	
Missing	1	1	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	42	49	
Unknown or Not Reported	5	5	
ECOG Performance Status at Baseline			
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			
ECOG Score = 0	28	33	
ECOG Score = 1	19	21	
Tumour Grade			
G1 = Well Differentiated G2 = Moderately Differentiated G3 = Poorly Differentiated G4 = Undifferentiated GX = Unassessable			
Units: Subjects			
Well Differentiated (G1)	4	5	
Moderately Differentiated (G2)	23	27	
Poorly Differentiated (G3)	13	14	
Undifferentiated (G4)	1	1	
Unassessable (GX)	2	2	
Missing	4	4	
Histology Type			
Units: Subjects			
Invasive Carcinoma (NOS)	8	10	
Invasive Ductal	21	24	
Invasive Ductal -Extensive Intraductal Component	4	5	
Invasive Lobular	10	10	
Other	3	3	
Missing	1	1	
Overall Disease Classification			
Metastatic or Locally Advanced			
Units: Subjects			
Metastatic	47	54	
Locally Advanced	0	0	
Visceral Disease			
Units: Subjects			
Visceral Disease	47	36	
No Visceral Disease	0	18	
Age Continuous |			
Units: Years			
median	58.0	59.0	
full range (min-max)	36 to 77	36 to 77	

End points

End points reporting groups

Reporting group title	Cohort 1 (Part A)
Reporting group description:	
Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 2 (Part A)
Reporting group description:	
Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 3 (Part A)
Reporting group description:	
Vistusertib 75 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 4 (Part A)
Reporting group description:	
Vistusertib 50 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 5 Low ANC (Part A)
Reporting group description:	
Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-7, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 6 High ANC (Part A)
Reporting group description:	
Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Reporting group title	Cohort 7 (Part B)
Reporting group description:	
Vistusertib 75 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set includes all patients who received at least 1 dose of study medication.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Analysis Set includes all patients who received at least 1 dose of AZD2014 or palbociclib.	
Subject analysis set title	Pharmacokinetics Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
The Pharmacokinetics Analysis Set includes all dosed patients with reportable AZD2014 or palbociclib concentrations. However, the number of participants with reportable data varies between PK parameters. Single-dose PK parameters were only determined in Part A, Cohorts 1-4.	
Subject analysis set title	Evaluable for Response
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The Evaluable for Response analysis set includes all patients who received at least one dose of vistusertib, palbociclib, or fulvestrant with measurable disease at baseline as per RECIST 1.1.	
Subject analysis set title	Evaluable for Efficacy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Evaluable for Efficacy Analysis Set includes all patients who received at least 1 dose of study medication and who had efficacy data.

Primary: Number of participants who experienced an adverse event.

End point title	Number of participants who experienced an adverse event.[1]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	6	6	6	6

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	6	7	17	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event causally related to vistusertib (regardless of whether also causally related to fulvestrant, but not causally related to palbociclib).

End point title	Number of participants who experienced an adverse event causally related to vistusertib (regardless of whether also causally related to fulvestrant, but not causally related to palbociclib).[2]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[2] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	3	5	3	3

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	3	6	8	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event causally related to palbociclib and vistusertib (irrespective of fulvestrant).

End point title	Number of participants who experienced an adverse event causally related to palbociclib and vistusertib (irrespective of fulvestrant).[3]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[3] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	5	6	5	5

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	

Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	6	7	17	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event causally related to palbociclib (regardless of whether also causally related to fulvestrant, but not causally related to vistusertib).

End point title	Number of participants who experienced an adverse event causally related to palbociclib (regardless of whether also causally related to fulvestrant, but not causally related to vistusertib).[4]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[4] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	5	4	4	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	3	2	4	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced any adverse event of CTCAE grade 3 or higher.

End point title	Number of participants who experienced any adverse event of CTCAE grade 3 or higher.[5]

End point description:

Safety and tolerability were assessed through the incidence of adverse events. Severity grading was defined by the Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03)

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[5] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	6	5	5	4

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	4	6	10	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced any adverse event of CTCAE grade 3 or higher causally related to vistusertib (regardless of whether also causally related to fulvestrant, but not causally related to palbociclib).

End point title	Number of participants who experienced any adverse event of CTCAE grade 3 or higher causally related to vistusertib (regardless of whether also causally related to fulvestrant, but not causally related to palbociclib).[6]

End point description:

Safety and tolerability were assessed through the incidence of adverse events. Severity grading was defined by the Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03)

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[6] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	2	1	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	1	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced any adverse event of CTCAE grade 3 or higher causally related to palbociclib and vistusertib (irrespective of fulvestrant).

End point title	Number of participants who experienced any adverse event of CTCAE grade 3 or higher causally related to palbociclib and vistusertib (irrespective of fulvestrant).[7]

End point description:

Safety and tolerability were assessed through the incidence of adverse events. Severity grading was defined by the Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03)

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[7] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	2	3	2	3

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				

Number of participants	3	5	10	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced any adverse event of CTCAE grade 3 or higher causally related to palbociclib (regardless of whether also causally related to fulvestrant, but not causally related to vistusertib).

End point title	Number of participants who experienced any adverse event of CTCAE grade 3 or higher causally related to palbociclib (regardless of whether also causally related to fulvestrant, but not causally related to vistusertib).[8]

End point description:

Safety and tolerability were assessed through the incidence of adverse events. Severity grading was defined by the Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03)

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[8] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	3	1	2	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	1	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event with outcome of death.

End point title	Number of participants who experienced an adverse event with

	outcome of death.[9]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[9] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	0	0	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced a serious adverse event (SAE).

End point title	Number of participants who experienced a serious adverse event (SAE).[10]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[10] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	3	3	3	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	0	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced a serious adverse event (SAE), causally related to vistusertib (regardless of whether also causally related to fulvestrant, but not casually related to palbociclib).

End point title	Number of participants who experienced a serious adverse event (SAE), causally related to vistusertib (regardless of whether also causally related to fulvestrant, but not casually related to palbociclib).[11]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[11] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	1	0	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				

Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced a serious adverse event (SAE), causally related to palbociclib and vistusertib (irrespective of fulvestrant).

End point title	Number of participants who experienced a serious adverse event (SAE), causally related to palbociclib and vistusertib (irrespective of fulvestrant).[12]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[12] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	1	1	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced a serious adverse event (SAE), causally related to palbociclib (regardless of whether also causally related to fulvestrant, but not casually related to vistusertib).

End point title	Number of participants who experienced a serious adverse event (SAE), causally related to palbociclib (regardless of whether also causally related to fulvestrant, but not casually

	related to vistusertib).[13]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[13] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	0	0	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event leading to discontinuation of vistusertib

End point title	Number of participants who experienced an adverse event leading to discontinuation of vistusertib[14]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[14] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	2	0	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event leading to discontinuation of vistusertib and causally related to vistusertib (regardless of whether also causally related to fulvestrant, but not causally related to palbociclib)

End point title	Number of participants who experienced an adverse event leading to discontinuation of vistusertib and causally related to vistusertib (regardless of whether also causally related to fulvestrant, but not causally related to palbociclib)[15]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[15] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	1	0	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				

Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event leading to discontinuation of vistusertib, causally related to palbociclib and vistusertib (irrespective of fulvestrant)

End point title	Number of participants who experienced an adverse event leading to discontinuation of vistusertib, causally related to palbociclib and vistusertib (irrespective of fulvestrant)[16]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[16] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	1	0	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event leading to discontinuation of vistusertib, causally related to palbociclib (regardless of whether also causally related to fulvestrant, but not causally related to vistusertib).)

End point title	Number of participants who experienced an adverse event leading to discontinuation of vistusertib, causally related to

	palbociclib (regardless of whether also causally related to fulvestrant, but not causally related to vistusertib).)[17]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[17] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	0	0	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event leading to discontinuation of palbociclib

End point title	Number of participants who experienced an adverse event leading to discontinuation of palbociclib[18]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[18] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	2	1	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event leading to discontinuation of palbociclib, causally related to vistusertib (regardless of whether also causally related to fulvestrant, but not causally related to palbociclib)

End point title	Number of participants who experienced an adverse event leading to discontinuation of palbociclib, causally related to vistusertib (regardless of whether also causally related to fulvestrant, but not causally related to palbociclib)[19]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[19] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	0	0	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				

Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event leading to discontinuation of palbociclib, causally related to palbociclib and vistusertib (irrespective of fulvestrant)

End point title	Number of participants who experienced an adverse event leading to discontinuation of palbociclib, causally related to palbociclib and vistusertib (irrespective of fulvestrant)[20]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[20] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	1	0	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who experienced an adverse event leading to discontinuation of palbociclib, causally related to palbociclib (regardless of whether also causally related to fulvestrant, but not causally related to vistusertib)

End point title	Number of participants who experienced an adverse event leading to discontinuation of palbociclib, causally related to

	palbociclib (regardless of whether also causally related to fulvestrant, but not causally related to vistusertib)[21]

End point description:

Safety and tolerability were assessed through the incidence of adverse events.

End point type	Primary

End point timeframe:

Approximately 16 months

Notes:

[21] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Participants				
Number of participants	0	1	1	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Participants				
Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (Part B)

End point title	Progression Free Survival (Part B)[22]

End point description:

Progression (or Progressive Disease) is defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Progressive disease is declared when there is at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Progression Free Survival is the elapsed time from the start of treatment until progression as defined by RECIST v1.1 or death from any cause. This analysis was conducted on the Evaluable for Efficacy Analysis Set.

End point type	Secondary

End point timeframe:

Assessed every 8 weeks for approximately 16 months

Notes:

[22] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 7 (Part B)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Months				
median (confidence interval 80%)	5.7 (3.68 to 8.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (Part B)

End point title	Overall Survival (Part B)[23]

End point description:

Overall Survival is the elapsed time from the start of treatment until death from any cause. The upper limit of the 80% Confidence Interval could not be calculated. This analysis was conducted on the Full Analysis set.

End point type	Secondary

End point timeframe:

Assessed every 8 weeks for approximately 16 months

Notes:

[23] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 7 (Part B)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Months				
median (confidence interval 80%)	11.93 (11.93 to 99999.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Objective Response (Parts A and B)

End point title	Best Objective Response (Parts A and B)

End point description:

The best objective response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. This analysis was conducted on the Evaluable for Response analysis set.

End point type	Secondary

End point timeframe:

Assessed every 8 weeks for approximately 16 months

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	4
Units: Number of Participants				
Complete Response	0	0	0	0
Partial Response	1	1	1	1
Stable Disease ≥ 8 weeks	2	5	5	3
Progression	2	0	0	0
Not Evaluable	0	0	0	0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	16	
Units: Number of Participants				
Complete Response	0	0	0	
Partial Response	1	1	0	
Stable Disease ≥ 8 weeks	3	4	11	
Progression	1	0	4	
Not Evaluable	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (Parts A and B)

End point title	Objective Response Rate (Parts A and B)

End point description:

The objective response rate is calculated as the number of participants who respond to treatment recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). This analysis was conducted on the Evaluable for Response anlaysis set.

End point type	Secondary

End point timeframe:

Assessed every 8 weeks for approximately 16 months

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	4
Units: Percentage				
number (not applicable)				
Lower Bound of 80% C.I.for Objective Response Rate	2.1	1.7	1.7	2.6
Upper Bound of 80% C.I.for Objective Response Rate	58.4	51.0	51.0	68.0

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	16	
Units: Percentage				
number (not applicable)				
Lower Bound of 80% C.I.for Objective Response Rate	2.1	2.1	0	
Upper Bound of 80% C.I.for Objective Response Rate	58.4	58.4	99999.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Experiencing Clinical Benefit at 24 Weeks (Parts A and B)

End point title	Number of Patients Experiencing Clinical Benefit at 24 Weeks (Parts A and B)

End point description:

Patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease to a therapeutic intervention in clinical trials of anticancer treatment are defined to have Clinical Benefit. This analysis was conducted on the Evaluable for Efficacy analysis set.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Percentage				
number (confidence interval 80%)	33.3 (9.3 to 66.7)	66.7 (33.3 to 90.7)	83.3 (49.0 to 98.3)	83.3 (49.0 to 98.3)

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	17	
Units: Percentage				
number (confidence interval 80%)	16.7 (1.7 to 51.0)	57.1 (27.9 to 83.0)	47.1 (29.7 to 65.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Plasma Concentration (Cmax) of Vistusertib After Single Dose (ng/mL) when Administered in Combination with Palbociclib and Fulvestrant (Part A)

End point title	Peak Plasma Concentration (Cmax) of Vistusertib After Single Dose (ng/mL) when Administered in Combination with Palbociclib and Fulvestrant (Part A)[24]

End point description:

Peak Plasma Concentration (also called Cmax) is the maximum concentration of drug in plasma.

End point type	Secondary

End point timeframe:

Up to 12 hours

Notes:

[24] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1395 (± 43.67)	1983 (± 61.08)	1201 (± 30.18)	1016 (± 24.59)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Peak Plasma Concentration (tmax) of Vistusertib After Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)

End point title	Time to Peak Plasma Concentration (tmax) of Vistusertib After Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)[25]

End point description:

The time to peak plasma concentration is the elapsed time from drug administration until the maximum concentration of drug in plasma is reached.

End point type	Secondary

End point timeframe:

Up to 12 hours

Notes:

[25] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: hours				
median (full range (min-max))	2.5 (1 to 6)	1.0 (0.5 to 2.0)	2.0 (0.98 to 3.17)	1.3 (0.5 to 2.98)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-24) (ng·h/mL) of Vistusertib after Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)

End point title	AUC (0-24) (ng·h/mL) of Vistusertib after Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)[26]

End point description:

AUC (0-24) is the area under the plasma concentration - time curve from zero time to 24 hours.

End point type	Secondary

End point timeframe:

Up to 24 hours

Notes:

[26] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	6
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	10830 (± 52.31)	9695 (± 117.4)	8194 (± 31.37)	5712 (± 71.34)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-12) (ng·h/mL) of Vistusertib After Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)

End point title	AUC (0-12) (ng·h/mL) of Vistusertib After Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)[27]

End point description:

AUC (0-12) is the area under the plasma concentration - time curve from zero time to 12 hours.

End point type	Secondary

End point timeframe:

Up to 16 Days

Notes:

[27] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	5
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	9309 (± 49.26)	8417 (± 99.87)	6808 (± 23.01)	4641 (± 55.55)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-t) (ng·h/mL) of Vistusertib after Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)

End point title	AUC (0-t) (ng·h/mL) of Vistusertib after Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)[28]

End point description:

AUC (0-t) is the area under the plasma concentration - time curve from zero time a defined time.

End point type	Secondary

End point timeframe:

Up to 24 hours

Notes:

[28] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	9278 (± 48.97)	8282 (± 100.4)	6483 (± 29.01)	4590 (± 55.64)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-∞) (ng·h/mL) of Vistusertib after Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)

End point title	AUC (0-∞) (ng·h/mL) of Vistusertib after Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)[29]

End point description:

AUC (0-∞) is the area under the plasma concentration - time curve from time zero extrapolated to ∞.

End point type	Secondary

End point timeframe:

Up to 24 hours

Notes:

[29] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	6	6
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	13380 (± 45.97)	10300 (± 129.2)	8617 (± 34.68)	6101 (± 78.42)

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-Life (t½λz) of Vistusertib after Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)

End point title	Elimination Half-Life (t½λz) of Vistusertib after Single Dose when Administered in Combination with Palbociclib and Fulvestrant (Part A)[30]

End point description:

Elimination half-life is the period of time required for the one-half of the amount of drug administered to be eliminated.

End point type	Secondary

End point timeframe:

Up to 24 hours

Notes:

[30] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	6
Units: hours				
arithmetic mean (standard deviation)	5.342 (± 1.448)	4.515 (± 4.010)	4.86 (± 2.021)	5.119 (± 2.465)

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Plasma Concentration (Cmax) of Palbociclib Single Dose (Cmax, ng/mL) when Administered in Combination with Vistusertib and Fulvestrant (Part A)

End point title	Peak Plasma Concentration (Cmax) of Palbociclib Single Dose (Cmax, ng/mL) when Administered in Combination with Vistusertib and Fulvestrant (Part A)[31]

End point description:

Peak Plasma Concentration (also called Cmax) is the maximum concentration of drug in plasma.

End point type	Secondary

End point timeframe:

Up to 12 hours

Notes:

[31] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: ng/mL				
geometric mean (geometric coefficient of variation)	43.06 (± 54.56)	35.73 (± 30.71)	33.07 (± 39.08)	22.56 (± 62.46)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Peak Plasma Concentration (tmax) of Palbociclib Single Dose

when Administered in Combination with Vistusertib and Fulvestrant (Part A)	
End point title	Time to Peak Plasma Concentration (tmax) of Palbociclib Single Dose when Administered in Combination with Vistusertib and Fulvestrant (Part A)[32]

End point description:

The time to peak plasma concentration is the elapsed time from drug administration until the maximum concentration of drug in plasma is reached.

End point type	Secondary

End point timeframe:

Up to 12 hours

Notes:

[32] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: hours				
median (full range (min-max))	5.7 (3.92 to 8.0)	5.0 (2.0 to 8.0)	6.0 (4.0 to 8.0)	7.0 (4.0 to 12.0)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-24) (ng·h/mL) of Palbociclib After Single Dose when Administered in Combination with Vistusertib and Fulvestrant (Part A, Cohorts 1-4)	
End point title	AUC (0-24) (ng·h/mL) of Palbociclib After Single Dose when Administered in Combination with Vistusertib and Fulvestrant (Part A, Cohorts 1-4)[33]

End point description:

AUC (0-24) is the area under the plasma concentration - time curve from zero time to 24 hours.

End point type	Secondary

End point timeframe:

Up to 24 hours

Notes:

[33] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	6	5
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	684.0 (± 64.72)	539.4 (± 35.13)	473.3 (± 26.81)	359.7 (± 74.92)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-∞) (ng·h/mL) of Palbociclib After Single Dose when Administered in Combination with Vistusertib and Fulvestrant (Part A, Cohorts 1-4)

End point title	AUC (0-∞) (ng·h/mL) of Palbociclib After Single Dose when Administered in Combination with Vistusertib and Fulvestrant (Part A, Cohorts 1-4)[34]

End point description:

AUC (0-∞) is the area under the plasma concentration - time curve from time zero extrapolated to ∞.

End point type	Secondary

End point timeframe:

Up to 24 hours

Notes:

[34] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	5	4
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	1161 (± 73.13)	963.6 (± 27.62)	938 (± 32.28)	851.9 (± 82.27)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-t) (ng·h/mL) of Palbociclib After Single Dose when Administered in Combination with Vistusertib and Fulvestrant (Part A, Cohorts 1-4)

End point title	AUC (0-t) (ng·h/mL) of Palbociclib After Single Dose when Administered in Combination with Vistusertib and Fulvestrant (Part A, Cohorts 1-4)[35]

End point description:

AUC (0-t) is the area under the plasma concentration - time curve from zero time a defined time.

End point type	Secondary

End point timeframe:

Up to 24 hours

Notes:

[35] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	684.9 (± 63.83)	548.4 (± 31.21)	484.0 (± 26.36)	378.5 (± 66.48)

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Plasma Concentration (Cmax, ng/mL) of Vistusertib on Cycle 1, Day 16 after Multiple Doses when Administered in Combination with Palbociclib and Fulvestrant (Parts A and B)

End point title	Peak Plasma Concentration (Cmax, ng/mL) of Vistusertib on Cycle 1, Day 16 after Multiple Doses when Administered in Combination with Palbociclib and Fulvestrant (Parts A and B)

End point description:

Peak Plasma Concentration (also called Cmax) is the maximum concentration of drug in plasma as multiple doses accumulate.

End point type	Secondary

End point timeframe:

Up to 16 Days

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	5	5
Units: ng/mL				
geometric mean (geometric coefficient of variation)	2816 (± 43.65)	3153 (± 48.7)	2262 (± 29.89)	1906 (± 44.14)

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	15	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	2278 (± 44.01)	1862 (± 88.39)	1611 (± 49.02)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Peak Plasma Concentration (tmax) of Vistusertib after Multiple Doses when Administered in Combination with Palbociclib and Fulvestrant (Parts A and B)

End point title	Time to Peak Plasma Concentration (tmax) of Vistusertib after Multiple Doses when Administered in Combination with Palbociclib and Fulvestrant (Parts A and B)

End point description:

The time to peak plasma concentration is the elapsed time from drug administration until the maximum concentration of drug in plasma is reached as multiple doses accumulate.

End point type	Secondary

End point timeframe:

Up to 16 Days

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	5	5
Units: hours				
median (full range (min-max))	1.3 (0.5 to 3.0)	1.5 (0.47 to 3.0)	1.5 (1.0 to 2.0)	1.5 (0.5 to 4.02)

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	15	
Units: hours				
median (full range (min-max))	4.0 (1.08 to 8.0)	1.1 (1.0 to 6.0)	2.0 (0.97 to 4.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-12) (ng·h/mL) of Vistusertib on Cycle 1, Day 16 after Multiple Doses when Administered in Combination with Palbociclib and Fulvestrant (Parts A and B)

End point title	AUC (0-12) (ng·h/mL) of Vistusertib on Cycle 1, Day 16 after Multiple Doses when Administered in Combination with Palbociclib and Fulvestrant (Parts A and B)

End point description:

AUC (0-12) is the area under the plasma concentration - time curve from zero time to 12 hours.

End point type	Secondary

End point timeframe:

Up to 16 Days

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	5	5
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	20920 (± 70.42)	20130 (± 111.4)	15000 (± 38.3)	12200 (± 58.5)

End point values	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	15	
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	17900 (± 68.52)	12930 (± 108.6)	10640 (± 65.38)	

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Plasma Concentration (Cmax, ng/mL) of Palbociclib on Cycle 1, Day 16 after Multiple Doses when Administered in Combination with Vistusertib and Fulvestrant (Parts A and B)

End point title	Peak Plasma Concentration (Cmax, ng/mL) of Palbociclib on Cycle 1, Day 16 after Multiple Doses when Administered in Combination with Vistusertib and Fulvestrant (Parts A and B)[36]

End point description:

Peak Plasma Concentration (also called Cmax) is the maximum concentration of drug in plasma as multiple doses accumulate.

End point type	Secondary

End point timeframe:

Up to 16 Days

Notes:

[36] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	4	5
Units: ng/mL				
geometric mean (geometric coefficient of variation)	119.7 (± 43.85)	73.40 (± 17.24)	81.00 (± 14.34)	73.68 (± 28.84)

End point values	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	14		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	80.06 (± 22.86)	66.55 (± 37.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to peak plasma concentration (tmax) of Palbociclib after Multiple Doses when Administered in Combination with Vistusertib and Fulvestrant (Parts A and B)

End point title	Time to peak plasma concentration (tmax) of Palbociclib after Multiple Doses when Administered in Combination with Vistusertib and Fulvestrant (Parts A and B)[37]

End point description:

The time to peak plasma concentration is the elapsed time from drug administration until the maximum concentration of drug in plasma is reached as multiple doses accumulate.

End point type	Secondary

End point timeframe:

Up to 16 Days

Notes:

[37] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	4	5
Units: hours				
median (full range (min-max))	5.2 (4.0 to 6.0)	6.0 (4.0 to 8.0)	4.0 (2.0 to 6.0)	6.0 (4.0 to 12.0)

End point values	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	14		
Units: hours				
median (full range (min-max))	6.0 (4.03 to 6.0)	6.0 (0.0 to 10.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-12) (ng·h/mL) of Palbociclib on Cycle 1, Day 16 after Multiple Doses when Administered in Combination with Vistusertib and Fulvestrant (Parts A and B)

End point title	AUC (0-12) (ng·h/mL) of Palbociclib on Cycle 1, Day 16 after Multiple Doses when Administered in Combination with Vistusertib and Fulvestrant (Parts A and B)[38]

End point description:

AUC (0-12) is the area under the plasma concentration - time curve from zero time to 12 hours.

End point type	Secondary

End point timeframe:

Up to 16 Days

Notes:

[38] - 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: Progression Free Survival was only assessed in Part B.

End point values	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)	Cohort 4 (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	4	5
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	1172 (± 43.19)	714.1 (± 13.47)	819.4 (± 16.73)	724.2 (± 27.79)

End point values	Cohort 6 High ANC (Part A)	Cohort 7 (Part B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	13		
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	756.2 (± 13.69)	639.9 (± 37.03)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events data were collected throughout the life of the trial, until the data cut-off in March 2018.

Adverse event reporting additional description:

All serious adverse events are reported, regardless of causality or frequency. All other AEs (excluding SAEs) that were reported in ≥ 5% of participants in any cohort are reported, regardless of causality or severity. Adverse events are reported for the Safety Analysis Set comprised of all participants who received at least one dose of treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Cohort 1 (Part A)

Reporting group description:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Reporting group title	Cohort 2 (Part A)

Reporting group description:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Reporting group title	Cohort 3 (Part A)

Reporting group description:

Vistusertib 75 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Reporting group title	Cohort 7 (Part B)

Reporting group description:

Vistusertib 75 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Reporting group title	Cohort 5 Low ANC (Part A)

Reporting group description:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-7, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Reporting group title	Cohort 6 High ANC (Part A)

Reporting group description:

Vistusertib 100 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 100 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Reporting group title	Cohort 4 (Part A)

Reporting group description:

Vistusertib 50 mg BD (Days 1 and 2, then off for 5 days each week). Palbociclib 75 mg QD (Days 1-21, then off 7 days). Fulvestrant 500 mg on Cycle 1, Days 1 and 15 and Day 1 only for subsequent cycles.

Serious adverse events	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	3 / 6 (50.00%)
number of deaths (all causes)	4	0	1

number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (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
Cardiac disorders			
Mitral Valve Disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (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
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (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
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest Discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (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
Chest Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	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
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (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

Colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (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
Dysphagia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	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
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	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			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (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

Serious adverse events	Cohort 7 (Part B)	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	4	0	1
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			

Mitral Valve Disease			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
Cerebrovascular Accident			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (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
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
General disorders and administration site conditions			
Chest Discomfort			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Chest Pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
Ascites			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Colitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Dysphagia			

subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
Urinary Tract Infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (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	Cohort 4 (Part A)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Mitral Valve Disease			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cerebrovascular Accident			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest Discomfort			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest Pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1 (Part A)	Cohort 2 (Part A)	Cohort 3 (Part A)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lymphoedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Asthenia			

subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Injection site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Influenza-like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	5 / 6 (83.33%)	5 / 6 (83.33%)	2 / 6 (33.33%)
occurrences (all)	5	6	3
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Catheter site thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Injection site swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nodule			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			

subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	2	4	3
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Localised oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Temperature intolerance			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	4	0	2
Pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Oedema, peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pruritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal dryness			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	3 / 6 (50.00%)
occurrences (all)	2	3	5
Dysphonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	2	2
Dyspnoea, exertional			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Lung consolidation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lung infiltration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	0	1	3
Pneumonitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	2
Rhinitis, allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Sinus congestion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Confusional State			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Depression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Libido Decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Restlessness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Product issues			
Device Occlusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Blood albumin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood urine present			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood insulin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Red cell distribution width increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Protein urine present			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Monocyte count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Urine specific gravity increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Urine leukocyte esterase positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urine bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary sediment present			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Transaminases increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
White blood cells urine positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Foot Fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Humerus fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Road traffic accident			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tooth fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dizziness			

subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Burning Sensation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
Facial Paralysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Memory Impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Neuropathy, peripheral			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Perineurial cyst			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sensory disturbance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sciatica			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Trigeminal neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	4
Anaemia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	3	2	1
Neutropenia			
subjects affected / exposed	4 / 6 (66.67%)	3 / 6 (50.00%)	5 / 6 (83.33%)
occurrences (all)	7	5	21
Thrombocytopenia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	4
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Middle ear effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Dry Eye			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eye movement disorder			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eyelid edema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctival hemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Diplopia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	1	2	3
Photopsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	4
Vitreous floaters			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vitreous haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Abdominal pain, upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal tenderness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	4 / 6 (66.67%)	3 / 6 (50.00%)
occurrences (all)	1	5	7
Dry mouth			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Dyschezia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gingival swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1

Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	4 / 6 (66.67%)	2 / 6 (33.33%)
occurrences (all)	2	5	3
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lip, dry			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia, oral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oesophageal stenosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Reflux gastritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Sensitivity of teeth			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tongue discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	1	1	4
Toothache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Tongue erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis, contact			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Dry Skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 6 (0.00%)	3 / 6 (50.00%)	3 / 6 (50.00%)
occurrences (all)	0	5	7
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	1	4	1
Plantar erythema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Onychomadesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rash erythematous			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash, papular			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Rash, maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	1	2	3
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pollakiura			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Urinary tract pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urine odour abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urine abnormality			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	3
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Masticatory pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ligamentum flavum hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Coccydynia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			

subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Myalgia, intercostal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain in neck			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
Spinal column stenosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Catheter site infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Device related infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Fungal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Helicobacter gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Lower respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Osteolmyelitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Nail infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Purulent discharge			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sialoadenitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Staphylococcal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Urinary Tract Infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	2	4
Sinusitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	1	3

Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoalbunimaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fluid Retention			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypokalemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Decreased Appetite			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	1	3
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	5
Hyperglycemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 7 (Part B)	Cohort 5 Low ANC (Part A)	Cohort 6 High ANC (Part A)

Total subjects affected by non-serious adverse events subjects affected / exposed	17 / 17 (100.00%)	6 / 6 (100.00%)	7 / 7 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lymphoedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	1	1	2
Injection site pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Injection site erythema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Influenza-like illness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	9 / 17 (52.94%)	5 / 6 (83.33%)	6 / 7 (85.71%)
occurrences (all)	10	5	6
Chills			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Chest pain			

subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Catheter site thrombosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Injection site reaction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nodule			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	1 / 17 (5.88%)	2 / 6 (33.33%)	1 / 7 (14.29%)
occurrences (all)	1	3	1
Malaise			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Localised oedema			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Vessel puncture site pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Temperature intolerance			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Swelling			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pyrexia			

subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	4	2
Pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oedema, peripheral			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal pruritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Vulvovaginal dryness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Dysphonia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Dyspnoea, exertional			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Epistaxis			

subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Lung consolidation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Lung infiltration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Pneumonitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Rhinitis, allergic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Sinus congestion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Upper-airway cough syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1

Confusional State			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	1	1	2
Libido Decreased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Restlessness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Product issues			
Device Occlusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Blood albumin decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood urine present			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	2
Blood pressure increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood insulin increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Red cell distribution width increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Protein urine present			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0
Monocyte count decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urine specific gravity increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Weight increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urine leukocyte esterase positive			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Urine bilirubin increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Urinary sediment present			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
White blood cells urine positive			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Foot Fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Humerus fracture			

subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Road traffic accident			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tooth fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysarthria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	2 / 17 (11.76%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Burning Sensation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 6 (33.33%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Facial Paralysis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	2 / 17 (11.76%)	1 / 6 (16.67%)	3 / 7 (42.86%)
occurrences (all)	2	1	3
Memory Impairment			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	4	1	0

Neuropathy, peripheral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Perineurial cyst			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	3
Sensory disturbance			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Trigeminal neuralgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Anaemia			
subjects affected / exposed	3 / 17 (17.65%)	4 / 6 (66.67%)	1 / 7 (14.29%)
occurrences (all)	5	7	3
Neutropenia			
subjects affected / exposed	10 / 17 (58.82%)	5 / 6 (83.33%)	5 / 7 (71.43%)
occurrences (all)	27	11	9
Thrombocytopenia			

subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	2	4	2
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Middle ear effusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Dry Eye			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Eye movement disorder			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Eyelid edema			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Conjunctival hemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Visual impairment			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Photopsia			

subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vitreous haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Abdominal pain, upper			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Abdominal tenderness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	3 / 7 (42.86%)
occurrences (all)	1	1	3
Diarrhoea			
subjects affected / exposed	8 / 17 (47.06%)	3 / 6 (50.00%)	3 / 7 (42.86%)
occurrences (all)	9	3	4
Dry mouth			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Dyschezia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Glossodynia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gingival swelling			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 17 (5.88%)	2 / 6 (33.33%)	2 / 7 (28.57%)
occurrences (all)	1	2	2
Gastritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Haemorrhoids			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Odynophagia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	5 / 17 (29.41%)	4 / 6 (66.67%)	5 / 7 (71.43%)
occurrences (all)	6	5	6
Mouth ulceration			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Lip, dry			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia, oral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Oesophageal stenosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Reflux gastritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sensitivity of teeth			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tongue discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	3 / 17 (17.65%)	1 / 6 (16.67%)	4 / 7 (57.14%)
occurrences (all)	3	2	5
Toothache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tongue erythema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis, contact			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dermatitis			

subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Alopecia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dry Skin			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	3 / 17 (17.65%)	2 / 6 (33.33%)	2 / 7 (28.57%)
occurrences (all)	5	3	2
Pruritus			
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Plantar erythema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Onychomadesis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nail disorder			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Skin irritation			
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0

Rash, papular			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash, maculo-papular			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pollakiura			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Urinary incontinence			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urinary tract pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Urine odour abnormal			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Urine abnormality			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 17 (29.41%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	6	1	1
Arthralgia			

subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	3	0	1
Muscle spasms			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	2
Masticatory pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ligamentum flavum hypertrophy			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Coccydynia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Bone pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	3 / 17 (17.65%)	2 / 6 (33.33%)	0 / 7 (0.00%)
occurrences (all)	3	3	0
Myalgia, intercostal			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pain in neck			
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			

subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Spinal column stenosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Spinal osteoarthritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Bacterial infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Catheter site infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Helicobacter gastritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Herpes virus infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Localised infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Osteolmyelitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nail infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Purulent discharge			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Sialoadenitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Staphylococcal infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Tooth infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 17 (23.53%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	4	1	0
Skin Infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Conjunctivitis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 6 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Urinary Tract Infection			
subjects affected / exposed	2 / 17 (11.76%)	2 / 6 (33.33%)	3 / 7 (42.86%)
occurrences (all)	4	2	4
Sinusitis			
subjects affected / exposed	2 / 17 (11.76%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Sepsis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 17 (17.65%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Metabolism and nutrition disorders			
Hypoalbunimaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fluid Retention			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypokalemia			

subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Hyponatraemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Decreased Appetite			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Dehydration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hyperglycemia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Hyperuricaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4 (Part A)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Lymphoedema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Asthenia			

subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Injection site pain				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Injection site erythema				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Influenza-like illness				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Fatigue				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Chills				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Chest pain				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Catheter site thrombosis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Injection site reaction				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Injection site swelling				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Nodule				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Mucosal inflammation				

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Localised oedema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vessel puncture site pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Temperature intolerance			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Swelling			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Oedema, peripheral			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vulvovaginal pruritis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vulvovaginal dryness			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dyspnoea, exertional			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Lung consolidation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Lung infiltration			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pneumonitis			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rhinitis, allergic			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Sinus congestion			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Upper-airway cough syndrome			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Confusional State			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Libido Decreased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Restlessness			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Product issues			
Device Occlusion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Blood albumin decreased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	3		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Blood pressure increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood insulin increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Red cell distribution width increased			

subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Protein urine present				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Neutrophil count decreased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	2			
Monocyte count decreased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Glycosylated haemoglobin increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Urine specific gravity increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Weight increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Weight decreased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Urine leukocyte esterase positive				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Urine bilirubin increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Urinary sediment present				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			

Transaminases increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
White blood cells urine positive			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Foot Fracture			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Humerus fracture			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Muscle strain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Road traffic accident			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Tooth fracture			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dizziness			

subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Burning Sensation				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Dysgeusia				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Facial Paralysis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Headache				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Memory Impairment				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Migraine				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Neuropathy, peripheral				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Perineurial cyst				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Presyncope				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Syncope				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Sensory disturbance				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Sciatica				

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Trigeminal neuralgia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Anaemia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	7		
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Middle ear effusion			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry Eye			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Eye movement disorder			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Eyelid edema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Conjunctival hemorrhage			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Diplopia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Visual impairment			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Photopsia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ocular hyperaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vitreous floaters			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vitreous haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Abdominal pain, upper				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Abdominal tenderness				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Colitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Constipation				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	2			
Dry mouth				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Dyschezia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Glossodynia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gingival swelling				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gastritis				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			

Haemorrhoids				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Odynophagia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	3 / 6 (50.00%)			
occurrences (all)	3			
Mouth ulceration				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Lip, dry				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Hypoaesthesia, oral				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Oesophageal stenosis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Reflux gastritis				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Rectal haemorrhage				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Oral pain				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Sensitivity of teeth				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Tongue discomfort				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			

Stomatitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Vomiting				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Toothache				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Tongue erythema				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Skin and subcutaneous tissue disorders				
Dermatitis, contact				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Dermatitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Alopecia				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Dry Skin				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Rash				
subjects affected / exposed	3 / 6 (50.00%)			
occurrences (all)	6			
Pruritus				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Plantar erythema				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Palmar-plantar erythrodysaesthesia syndrome				

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Onychomadesis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nail disorder			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rash erythematous			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Skin irritation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rash, papular			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rash, maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Micturition urgency			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pollakiura			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Urinary incontinence			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Urinary tract pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Urine odour abnormal			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Urine abnormality			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Masticatory pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ligamentum flavum hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Coccydynia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Myalgia, intercostal			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pain in neck			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Spinal column stenosis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Spinal osteoarthritis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Catheter site infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Device related infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Ear infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Fungal skin infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Helicobacter gastritis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Herpes virus infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Localised infection				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Laryngitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Osteolmyelitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Oral candidiasis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			

Nail infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Otitis media				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Purulent discharge				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Rash pustular				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Sialoadenitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Staphylococcal infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Tooth infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Upper Respiratory Tract Infection				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Skin Infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Conjunctivitis				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Urinary Tract Infection				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Sinusitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			

Sepsis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypoalbunimaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Fluid Retention			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypokalemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Decreased Appetite			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	5		
Hyperglycemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2015	Protocol Amendment 1: 1) The protocol was amended to include ophthalmological assessments and more intensive blood glucose monitoring in order to address the potential for overlapping toxicities associated with combination therapy with palbociclib and vistusertib and the potential for sustained hyperglycemia with accompanying visual toxicity. 2) The protocol was amended to add information regarding patients receiving a sensitive CYP3A substrate with a narrow therapeutic index may need to be have the dose of the agent reduced as palbociclib may increase their exposure to it. 3) The protocol was amended to specify that any case of elevated AST or ALT (≥3x ULN) and total bilirubin (≥2x ULN) (Hy's Law) is defined to be a DLT since there was a liver safety concern. 4) To protect against the possibility of a study-wide type I error the protocol was amended to specify that if p-values were calculated at the time of the administrative interim analysis in Part C, the Haybittle-Peto boundary (p-value significance threshold of 0.001) to the endpoint of the planned Part C analysis was to be used.
03 December 2015	Protocol Amendment 2: 1) The protocol was amended to include fulvestrant as an Investigational Medicinal Product. Further, the duration of safety follow-up was increased to to 5 times the half-life of fulvestrant (250 days following last dose). 2) The protocol was amended to specify that patients under 50 years of age were required to have medically-confirmed irreversible premature ovarian failure, bilateral oophorectomy, bilateral salpingectomy, or complete or partial hysterectomy. 3) Virology for Hepatitis B, Hepatitis C and Human Immunodeficiency Virus (HIV) assessments were added to the screening tests and patients with these infections were excluded from the study. 4) The following criteria were added as a required parameter before retreatment after interruption for toxicity or at the start of each treatment cycle: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.0 times the upper limit of normal (ULN) (CTCAE Grade 1) or back to baseline values and total bilirubin <1.5 x ULN (CTCAE Grade 1) or back to baseline values.

16 December 2015	Amendment 3: Improve the feasibility of the study by permitting patients to be enrolled in Part A who have received prior fulvestrant, everolimus or agents with a MOA through inhibition of the PI3K-mTOR pathway. Further changes or clarifications include: 1) Amended Exclusion Criterion # 6 to make it specific to protocol Parts B and C. This now permits inclusion into Part A for patients who have received priortreatment with fulvestrant, or with everolimus, or any agent whose mechanism of action is to inhibit the PI3K-mTOR pathway. 2) Clarification that patients from Part A who will be included in the Part B1 assessment of recommended phase 2 dose must meet the specific eligibility for Part B1, in addition to having measurable disease evaluable for response. 3) Amended Overall Benefit/Risk and Ethical Assessment Conclusion: Clarification that the starting dose for palbociclib is one dose level below the standard dose for palbociclib. 4) Modified Exclusion Criterion # 2 to permit patients to enter the study who have been exposed to potent or moderate inhibitors or inducers of CYP2C8 taken within the wash-out period before the first dose. 5) Updated protocol to remove restrictions around CYP2C8 inhibitors and inducers. 6) Amended protocol to remove 1 day window for visits with palbociclib or AZD2014 PK assessments during Part B2 and Part C. 7) The Schedule of assessments was updated to require ECG, Biochemistry and Haematology, Coagulation, Lipid Panel, Glucose and Insulin C-Peptide to be done at Cycle 0 Day 1 in Part B3. 8) Amended Table 34 to state that all dosed patients with reportable AZD2014, palbociclib or fulvestrant plasma concentrations will be included in the PK analysis set, regardless of whether they have available PK parameters. 9) Clarification that the rules are the same for handling PK parameters and plasma concentrations at a given timepoint, which for example, have non-quantifiable values.
16 December 2016	Note - There was no amendment 4 due to a change in the protocol template whereby updated protocols were referred to a "versions" rather than amendments. Version 5: 1) The protocol was amended to remove Parts B2 and B3. This was no longer considered required. 2) The protocol was amended to remove fulvestrant PK sampling. 3) The protocol was modified to allow flexibility to test alternative dosing schedules of AZD2014 and palbociclib in Part A, and to apply those schedules to Parts B and C. 4) The protocol was modified to remove the AZD2014 monotherapy period (Cycle 0) for the assessment of single dose PK from Part B (formerly Part B1) as this was no longer considered required because the data was already available for the program through PK/PD modelling and to avoid collection of unnecessary samples from patients. 5) The protocol was amended to prohibit PPI use in the drug interaction (DDI) and dose limiting toxicity (DLT) evaluation period since PPIs may reduce palbociclib Cmax and AUC by 41% and 13%, respectively and could affect the DDI evaluation and MTD determination of the combination. 6) The protocol was updated to conform to current guidance for investigators, as a clinically relevant PK drug interaction with sensitive substrates of P450 enzymes and transporters is unlikely. 7) The sample size of Part B was increased from 9-15 to 27 patients in order to allow internal decision making at the end of Part B based on Clinical Benefit Rate (CBR). 8) The protocol was amended to allow enrollment of a different patient population for Part B to understand tolerability in a population that is more in line with the proposed Part C population. 9) The protocol was amended to allow flexibility in Part A to enroll additional cohorts for patients with specific ranges of neutrophil (ANC). The rationale for this was the hypothesis that baseline ANC value may be a risk factor for a DLT.

14 June 2017	Protocol Version 6: 1) Consent to tumor biopsy was made a mandatory part of the study. The study design, exploratory objectives and end points, inclusion criteria, study plan, description of biopsy collection, and description of the analysis sets were updated. 2) The guidelines for dose modifications and interruptions, Appendix N, were revised so that dose modifications could be made in consultation with the AZ Medical Director as well as the Sarah Cannon Development Innovations medical monitor and that dose interruption decisions can be made by the Investigator on a case by case basis. In addition the recommendation for dose interruption in the case of uncomplicated Grade 3 neutropenia was removed and there was clarification that dose interruption in the case of QTc prolongation and hematological events should be assessed based on severity. 3) The safety portion of the protocol was updated to clarify the overdose reporting process by directing that overdoses should be reported on the Overdose Reporting Form. 4) The protocol was amended to allow patients to have extended vital signs monitoring done during long PK days or only up to the point that they leave the clinic. 5) Amended to allow patients to have last fasting glucose at the time of leaving the clinic if they are not staying overnight for assessment.'
12 December 2017	Protocol Version 7: 1) The protocol was amended to end enrollment in Part B after 17 patients and not to perform the Futility Interim analysis. This decision was made based on the result of a strategic portfolio review by the sponsor. Further, Part C of the protocol was removed. No patients were enrolled into Part C. 2) The protocol was amended to establish the primary data cut-off after the Cycle 7 Day 1 visit for the last patient enrolled in the study. Following the data cut-off patients continued to receive study treatment and attended for dispensing and SAE reporting. Assessments were no longer performed for the purposes of the study after the data cut-off, instead assessments were only as per standard of care in accordance with the palbociclib label or as clinically indicated. This decision was made based on the result of a strategic portfolio review.

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 cases where the upper limit of a Confidence Interval could not be calculated the value 99999.9 was entered because the software does not permit no numeric entries such as NC (not calculated) or NA (not available)

Notes: