Clinical trial results:
A Phase 1b/2 Study of Docetaxel and Prednisone, with or without ISIS 183750 (an eIF4E Inhibitor), in Patients with Castrate-Resistant Prostate Cancer

Summary

EudraCT number	2010-022239-12
Trial protocol	HU
Global end of trial date	15 November 2013

Results information

Result version number	v1 (current)
This version publication date	21 February 2020
First version publication date	21 February 2020

Trial information

Trial identification

Sponsor protocol code	ISIS 183750-CS3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01234025
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Court, Carlsbad, United States, CA 92010
Public contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.com
Scientific contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.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	15 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety and tolerability of EIF4E Rx in combination with docetaxel and prednisone and to estimate progression-free survival in subjects treated with EIF4E Rx in combination with docetaxel and prednisone.

Protection of trial subjects:

Each subject signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 24
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Poland: 24
Worldwide total number of subjects	110
EEA total number of subjects	61

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)	40
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 110 subjects were enrolled in this study at multiple global study centres.

Pre-assignment

Screening details:

A total of 110 subjects were enrolled in this study. 19 subjects were enrolled in Part 1, and 18 received study drug. 93 subjects were randomised in Part 2, and 92 received study drug. The overall study included a 28-day screening period, 10 treatment cycles of 21 days each, and a follow-up period up to approximately 3 years.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Cohort 1

Arm description:

Subjects received ISIS EIF4E Rx 800 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.

Arm type	Experimental
Investigational medicinal product name	ISIS EIF4E Rx
Investigational medicinal product code	
Other name	ISIS 183750
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

ISIS EIF4E Rx 800 mg administered by intravenous infusion at multiple time points in a 21-day cycle.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 5 mg administered orally twice daily at multiple time points in a 21-day cycle.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel 75 mg/m2 administered by intravenous infusion on Day 1 of each cycle.

Arm title	Part 1: Cohort 2

Arm description:

Subjects received ISIS EIF4E Rx 1000 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.

Arm type	Experimental

Investigational medicinal product name	ISIS EIF4E Rx
Investigational medicinal product code	
Other name	ISIS 183750
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

ISIS EIF4E Rx 1000 mg administered by intravenous infusion at multiple time points in a 21-day cycle.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 5 mg administered orally twice daily at multiple time points in a 21-day cycle.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel 75 mg/m2 administered by intravenous infusion on Day 1 of each cycle.

Arm title	Part 2: Arm A

Arm description:

Subjects received prednisone 5 mg administered orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.

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

Dosage and administration details:

Prednisone 5 mg administered orally twice daily at multiple time points in a 21-day cycle.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel 75 mg/m2 administered by intravenous infusion on Day 1 of each cycle.

Arm title	Part 2: Arm B

Arm description:

Subjects received ISIS EIF4E Rx 1000 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.

Arm type	Experimental

Investigational medicinal product name	ISIS EIF4E Rx
Investigational medicinal product code	
Other name	ISIS 183750
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

ISIS EIF4E Rx 1000 mg administered by intravenous infusion at multiple time points in a 21-day cycle.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 5 mg administered orally twice daily at multiple time points in a 21-day cycle.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel 75 mg/m2 administered by intravenous infusion on Day 1 of each cycle.

Number of subjects in period 1	Part 1: Cohort 1	Part 1: Cohort 2	Part 2: Arm A
Started	8	10	49
Completed	3	1	25
Not completed	5	9	24
Significant Protocol Violation	-	-	-
Consent withdrawn by subject	1	-	-
Other	1	2	7
Toxicity which delays treatment for > 3 weeks	1	2	1
Investigator Decision	-	-	1
Disease Progression	1	3	14
Adverse Event or Serious Adverse Event	1	2	1

Number of subjects in period 1	Part 2: Arm B
Started	43
Completed	7
Not completed	36
Significant Protocol Violation	1
Consent withdrawn by subject	3
Other	8
Toxicity which delays treatment for > 3 weeks	3

Investigator Decision	1
Disease Progression	13
Adverse Event or Serious Adverse Event	7

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Cohort 1
Reporting group description:	
Subjects received ISIS EIF4E Rx 800 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.	
Reporting group title	Part 1: Cohort 2
Reporting group description:	
Subjects received ISIS EIF4E Rx 1000 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.	
Reporting group title	Part 2: Arm A
Reporting group description:	
Subjects received prednisone 5 mg administered orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.	
Reporting group title	Part 2: Arm B
Reporting group description:	
Subjects received ISIS EIF4E Rx 1000 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.	

Reporting group values	Part 1: Cohort 1	Part 1: Cohort 2	Part 2: Arm A
Number of subjects	8	10	49
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	71.6	65.3	67.1
standard deviation	± 7.5	± 8.0	± 7.7
Gender categorical Units: Subjects			
Female	0	0	0
Male	8	10	49

Reporting group values	Part 2: Arm B	Total	
Number of subjects	43	110	

Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	66.9		
standard deviation	± 7.2	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	43	110	

End points

End points reporting groups

Reporting group title	Part 1: Cohort 1
Reporting group description:	
Subjects received ISIS EIF4E Rx 800 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.	

Reporting group title	Part 1: Cohort 2
Reporting group description:	
Subjects received ISIS EIF4E Rx 1000 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.	

Reporting group title	Part 2: Arm A
Reporting group description:	
Subjects received prednisone 5 mg administered orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.	

Reporting group title	Part 2: Arm B
Reporting group description:	
Subjects received ISIS EIF4E Rx 1000 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.	

Primary: Progression-free Survival

End point title	Progression-free Survival[1]
End point description:	
Progression-free survival was defined as follows: prostate-specific antigen (PSA) progression according to the Prostate Cancer Clinical Trials Working Group (PCWG2) criteria (including the recommendation that rising PSA alone as the basis for progression should be avoided); tumour progression in lung, liver, lymph nodes and other soft tissue, as per modified RECIST 1.1 criteria; bone progression defined as two or more new lesions on bone scan; worsening symptoms, and/or death. The full analysis set (FAS) included all randomised subjects in Part 2 who received at least one dose of assigned treatment.	
End point type	Primary
End point timeframe:	
Up to approximately 3 years	

Notes:

[1] - 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: Summary analyses were not performed for all arms in this study.

End point values	Part 2: Arm A	Part 2: Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	42		
Units: months				
median (confidence interval 95%)	7.97 (6.80 to 9.90)	7.83 (4.57 to 11.03)		

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Part 2: Arm A v Part 2: Arm B
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 9.5 months.

Adverse event reporting additional description:

The safety population included all subjects who received at least one dose of any study medication, i.e., prednisone, EIF4E Rx, dexamethasone, or docetaxel.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Part 1: Cohort 1

Reporting group description:

Subjects received ISIS EIF4E Rx 800 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.

Reporting group title	Part 1: Cohort 2

Reporting group description:

Subjects received ISIS EIF4E Rx 1000 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.

Reporting group title	Part 2: Arm A

Reporting group description:

Subjects received prednisone 5 mg administered orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.

Reporting group title	Part 2: Arm B

Reporting group description:

Subjects received ISIS EIF4E Rx 1000 mg administered by intravenous injection in combination with prednisone 5 mg orally twice daily at multiple time points in a 21-day cycle. Docetaxel 75 mg/m2 was administered by intravenous injection on Day 1 of each cycle.

Serious adverse events	Part 1: Cohort 1	Part 1: Cohort 2	Part 2: Arm A
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	3 / 10 (30.00%)	9 / 49 (18.37%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (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
Prostate cancer			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (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
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (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			
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (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
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (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
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	2 / 49 (4.08%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
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			
Ischaemic stroke			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (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
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (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			
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (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
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	2 / 49 (4.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (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	Part 2: Arm B		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 43 (32.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Forearm fracture				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachyarrhythmia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 43 (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	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	0 / 43 (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 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fluid retention			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part 1: Cohort 1	Part 1: Cohort 2	Part 2: Arm A
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	10 / 10 (100.00%)	39 / 49 (79.59%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	0 / 49 (0.00%)
occurrences (all)	1	3	0
Deep vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Hypertension			

subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Flushing			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Jugular vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Vena cava thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 8 (62.50%)	2 / 10 (20.00%)	9 / 49 (18.37%)
occurrences (all)	6	5	15
Asthenia			
subjects affected / exposed	2 / 8 (25.00%)	5 / 10 (50.00%)	8 / 49 (16.33%)
occurrences (all)	6	5	13
Oedema peripheral			
subjects affected / exposed	6 / 8 (75.00%)	4 / 10 (40.00%)	2 / 49 (4.08%)
occurrences (all)	9	10	2
Pyrexia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 10 (20.00%)	1 / 49 (2.04%)
occurrences (all)	3	2	1
Chills			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			

subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Device occlusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Generalised oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Scrotal swelling			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Pelvic pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	0 / 49 (0.00%)
occurrences (all)	1	2	0
Cough			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Productive cough			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Pulmonary embolism			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	2	1	0
Hiccups			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	1 / 49 (2.04%)
occurrences (all)	3	2	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	0	2	3
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	1	2	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Blood potassium decreased			

subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences (all)	4	0	2
Neutrophil count decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Blood creatinine increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Blood magnesium decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Body temperature increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	3	0
Platelet count decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Gastroenteritis radiation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Infusion related reaction			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Angina pectoris			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Supraventricular tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Cardiac failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	5 / 8 (62.50%)	1 / 10 (10.00%)	3 / 49 (6.12%)
occurrences (all)	5	1	3
Neuropathy peripheral			
subjects affected / exposed	3 / 8 (37.50%)	1 / 10 (10.00%)	3 / 49 (6.12%)
occurrences (all)	5	1	3
Headache			
subjects affected / exposed	3 / 8 (37.50%)	1 / 10 (10.00%)	2 / 49 (4.08%)
occurrences (all)	3	1	2
Hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Dizziness			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	0	2	1
Peripheral motor neuropathy			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences (all)	6	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	2 / 49 (4.08%)
occurrences (all)	4	1	3
Neuralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Balance disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Dysaesthesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Paraplegia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	6 / 8 (75.00%)	1 / 10 (10.00%)	18 / 49 (36.73%)
occurrences (all)	18	1	36
Anaemia			
subjects affected / exposed	5 / 8 (62.50%)	4 / 10 (40.00%)	10 / 49 (20.41%)
occurrences (all)	12	7	23
Leukopenia			
subjects affected / exposed	3 / 8 (37.50%)	0 / 10 (0.00%)	4 / 49 (8.16%)
occurrences (all)	11	0	10

Thrombocytopenia			
subjects affected / exposed	3 / 8 (37.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	7	2	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	4 / 49 (8.16%)
occurrences (all)	0	0	4
Metamorphopsia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 8 (87.50%)	3 / 10 (30.00%)	6 / 49 (12.24%)
occurrences (all)	10	4	11
Nausea			
subjects affected / exposed	3 / 8 (37.50%)	2 / 10 (20.00%)	9 / 49 (18.37%)
occurrences (all)	4	4	10
Vomiting			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	2	1	1
Constipation			
subjects affected / exposed	3 / 8 (37.50%)	2 / 10 (20.00%)	1 / 49 (2.04%)
occurrences (all)	4	2	1
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Hyperchlorhydria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Abdominal discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			

subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Anal fissure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Cheilitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Faeces discoloured			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 10 (20.00%)	8 / 49 (16.33%)
occurrences (all)	2	5	8
Nail discolouration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	6 / 49 (12.24%)
occurrences (all)	1	0	7
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	1	1	1
Rash			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	1	1	1
Nail disorder			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0

Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Heat rash			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Petechiae			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Skin atrophy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Skin exfoliation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Renal failure acute			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Urinary incontinence			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Anuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	3 / 8 (37.50%)	0 / 10 (0.00%)	7 / 49 (14.29%)
occurrences (all)	3	0	8
Muscular weakness			

subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Back pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	1	1	1
Muscle spasms			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	0 / 49 (0.00%)
occurrences (all)	1	2	0
Flank pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	0 / 49 (0.00%)
occurrences (all)	1	2	0
Fungal skin infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Cellulitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	2 / 8 (25.00%)	3 / 10 (30.00%)	2 / 49 (4.08%)
occurrences (all)	2	8	3
Hypoalbuminaemia			
subjects affected / exposed	4 / 8 (50.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	7	2	0
Hypocalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	2 / 49 (4.08%)
occurrences (all)	1	1	2
Hypokalaemia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 10 (20.00%)	0 / 49 (0.00%)
occurrences (all)	2	2	0
Fluid retention			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	2
Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	1	2	0
Dehydration			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	1	3	0
Diabetes mellitus			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Hyperglycaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Hypomagnesaemia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 49 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Part 2: Arm B		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 43 (95.35%)		

Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Deep vein thrombosis			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Jugular vein thrombosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Thrombosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Vena cava thrombosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 43 (25.58%)		
occurrences (all)	22		
Asthenia			
subjects affected / exposed	9 / 43 (20.93%)		
occurrences (all)	20		
Oedema peripheral			
subjects affected / exposed	12 / 43 (27.91%)		
occurrences (all)	18		
Pyrexia			
subjects affected / exposed	11 / 43 (25.58%)		
occurrences (all)	16		
Chills			

subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Mucosal inflammation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Device occlusion			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Generalised oedema			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Scrotal swelling			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Pelvic pain			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Cough			

subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	3		
Productive cough			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Dyspnoea exertional			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 43 (34.88%)		
occurrences (all)	27		
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 43 (18.60%)		
occurrences (all)	12		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	8		
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	6		
Weight decreased			

subjects affected / exposed	2 / 43 (4.65%)			
occurrences (all)	2			
Blood alkaline phosphatase increased				
subjects affected / exposed	2 / 43 (4.65%)			
occurrences (all)	5			
Blood potassium decreased				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences (all)	1			
Neutrophil count decreased				
subjects affected / exposed	2 / 43 (4.65%)			
occurrences (all)	4			
Blood creatinine increased				
subjects affected / exposed	2 / 43 (4.65%)			
occurrences (all)	4			
White blood cell count decreased				
subjects affected / exposed	3 / 43 (6.98%)			
occurrences (all)	5			
Activated partial thromboplastin time prolonged				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences (all)	0			
Blood magnesium decreased				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences (all)	0			
Body temperature increased				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences (all)	0			
International normalised ratio increased				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences (all)	0			
Platelet count decreased				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences (all)	0			
Prothrombin time prolonged				

subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Gastroenteritis radiation			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Infusion related reaction			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Angina pectoris			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Sinus tachycardia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Supraventricular tachycardia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Cardiac failure			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Neuropathy peripheral			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	7		
Headache			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	2		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Neuralgia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	5		
Paraesthesia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Balance disorder			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Dysaesthesia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Paraplegia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	9 / 43 (20.93%)		
occurrences (all)	16		

Anaemia subjects affected / exposed occurrences (all)	14 / 43 (32.56%) 25		
Leukopenia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 2		
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Metamorphopsia subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	7 / 43 (16.28%) 10		
Nausea subjects affected / exposed occurrences (all)	8 / 43 (18.60%) 10		
Vomiting subjects affected / exposed occurrences (all)	5 / 43 (11.63%) 5		
Constipation subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 3		
Abdominal pain subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Hyperchlorhydria			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Abdominal discomfort			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Anal fissure			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Cheilitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Faeces discoloured			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Rectal haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 43 (23.26%)		
occurrences (all)	11		
Nail discolouration			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	5		

Rash			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Nail disorder			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Heat rash			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Petechiae			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Skin atrophy			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Skin exfoliation			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Renal failure acute			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Urinary incontinence			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Anuria			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	9		
Muscular weakness			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Fungal skin infection			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Cystitis			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	8		
Hypoalbuminaemia			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	10		
Hypocalcaemia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Fluid retention			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Diabetes mellitus			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		

Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2011	Study Design–Part (P)1, for dose selection, P2: added (Ad), "It is possible for another dosing regimen to be selected for P2, or selected regimen to be modified after initiation of P2, as a result of Sponsor's periodic medical review of cumulative clinical safety and tolerability findings during study." Synopsis: Definition of dose-limiting toxicity: exclude Grade (G) 3 fever, transient (≤24h) G3 chills or flu-like symptoms, or G3 fatigue lasting ≤7 days (Ds). Treatment with ISIS EIF4ERx beyond Cycle (C)10, Ad: "During these additional Cs, all applicable procedures listed under Cs1-10 in the Schedule of Procedures will be followed except for docetaxel administration." Tumor assessments at 28-D posttreatment follow (F)-up visit for subjects without prior disease progression, Ad: "If the duration between patient's last treatment cycle-associated tumor assessment and F-up visit is too short to warrant performance of radiological procedures (e.g., ≤27Ds), performance of an unscheduled tumor assessment at 1-3 weeks after visit should be considered rather than waiting until first of every-8-week F-up visits." Ad denosumab to Exclusion Criteria 13. Ad recommended use of Dubois and Dubois formula for body surface area calculation. Permitted omission, reduction, or lengthening of 1h interval between EIF4E Rx and docetaxel infusions on drug administration Ds other than P1, C1, D1. Ad time windows for dexamethasone dosing schedule and allow for changes to schedule on Ds other than P1, C1, D1. Transaminase elevation to >5x upper limit of normal (ULN) and bilirubin >1xULN, dose adjustment changed from "Remove from protocol treatment" to "Hold both docetaxel and ISIS EIF4ERx. Consult with Isis Medical Monitor, or designee, to determine conditions under which treatment may be resumed." Immunogenicity evaluation Ad to P1 and P2, Arm B schedules. Ad coagulation panel to Screen procedures. Reduced circulating tumor cells sampling to C0–D1–predose, C1–D1–predose, C2–D22, and C4–D22.
08 June 2012	Added "(i.e., 1000 mg)" to end of statement "Arm B: docetaxel and prednisone plus ISIS 183750 at dosing regimen identified in Part 1". Revised inclusion criteria #10 subpart "g" to PT <1.3 x ULN (<15 sec) and INR <1.2 x ULN. Added "Serum albumin ≥3.0 g/dL" to inclusion criteria #10 as subpart "I". Clarified: "… delays dosing >7 days …" changed to "… delays in initiating treatment cycle >7 days …" "If treatment cannot be initiated ≤21 days, the patient …." changed to "If a new treatment cycle cannot be initiated ≤21 days from Day 22 of the previous treatment cycle (i.e., the duration between the Days 1 of sequential cycles > 42 days), the patient …." Changed limit for ISIS EIF4E Rx dose reductions to 400 mg and allow for continued treatment with chemotherapeutics in absence of continued ISIS EIF4E Rx dosing. Added reduction of ISIS EIF4E Rx at lower transaminase criteria (i.e., >3.0 to 5.0 x ULN). Added clarification to conditions for resumption of dosing. Section number for section on dose modifications for Grade 3 or 4 or Prolonged Grade 2 Toxicities changed from 7.2.10 to 7.2.11. Introduced new guidance for dose modification in response to albumin reductions.
20 May 2013	Addition of the statement "Once all patients have discontinued from treatment with study drug, the Sponsor may terminate further assessments for disease progression when sufficient events have occurred to support estimation of the effect of study drug on time to disease progression.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported