Clinical trial results:
SAPROCAN: Saracatinib (AZD0530) and docetaxel in metastatic, castrate-refractory prostate cancer: a phase I/randomised phase II study by the UK NCRI Prostate Clinical Studies Group

Summary

EudraCT number	2010-021447-41
Trial protocol	GB
Global end of trial date	31 December 2017

Results information

Result version number	v1
This version publication date	21 August 2020
First version publication date	21 August 2020

Trial information

Trial identification

Sponsor protocol code	SAPROCAN2011

Additional study identifiers

ISRCTN number	ISRCTN22566729
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow and Clyde
Sponsor organisation address	Ward 11, Dykebar Hospital, Paisley, United Kingdom, PA2 7DE
Public contact	Carol Evans, Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow G12 0YN, 0141 301 7189, carol.evans@glasgow.ac.uk
Scientific contact	Carol Evans, Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow G12 0YN, 0141 301 7189, carol.evans@glasgow.ac.uk
Sponsor organisation name	University of Glasgow
Sponsor organisation address	Room 327 Wolfson Medical School Building, Glasgow, United Kingdom, G12 8QQ
Public contact	Carol Evans, Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow G12 0YN, 0141 301 7189, carol.evans@glasgow.ac.uk
Scientific contact	Carol Evans, Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow G12 0YN, 0141 301 7189, carol.evans@glasgow.ac.uk

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	31 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For the first part of the study (phase I), the primary objective is to find a safe and tolerable dose for saracatinib (AZD0530) given in combination with standard chemotherapy treatment (docetaxel and prednisolone) for patients with metastic castrate-refractory prostate cancer.

For the second part of the study (phase II), the primary objective is to investigate whether we can improve the benefits of chemotherapy cancer treatment for patients with metastic castrate-refractory prostate cancer by adding a new drug, saracatinib (AZD0530).

Protection of trial subjects:

Patients were required to attend for visits and investigations that were considered additional to standard of care. The number and type of visits and assessments were fully explained verbally and in a Patient Information Sheet which patients were given time to read and discuss with family and the research team prior to consent. All staff involved in delivering the study were fully GCP trained. In the dose escalation phase (Phase I), patients were reviewed weekly for Dose Limiting Toxicities, and a Safety Review Committee met at the completion of each dose cohort to review the patient details and confirm the escalation to the next dose level where appropriate. For the Phase II component of the study, patients were made aware that half of the participants would receive study drug and half would receive a placebo, but that the treatment assigned would be unknown to the patient and the study team unless emergency unblinding was required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 152
Worldwide total number of subjects	152
EEA total number of subjects	152

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)	36
From 65 to 84 years	116
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Phase I opened to recruitment in March 2012. 10 patients were recruited into 3 cohorts; 9 were evaluable.
Phase II opened to recruitment in October 2013 and was closed to recruitment in March 2016; 142 patients were randomised.

Pre-assignment

Screening details:

Following consent, all patients underwent screening to determine eligibility, including confirmation of disease progression, physical exam, blood tests (including testosterone), review of prior treatment (prior cytotoxic chemotherapy excluded, washout of >30 days for other IMP required)

Period 1

Period 1 title	Phase I & Phase II
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I Cohort 1

Arm description:

Saracatinib (AZD0530) 50mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days.

Arm type	Experimental
Investigational medicinal product name	Saracatinib
Investigational medicinal product code	AZD0530
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Saracatinib (AZD0530) 50mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression). After cycle 1, dispensed in 21 day cycles.

Arm title	Phase I Cohort 2

Arm description:

Saracatinib (AZD0530) 125mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days

Arm type	Experimental

Investigational medicinal product name	Saracatinib
Investigational medicinal product code	AZD0530
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Saracatinib (AZD0530) 125mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression). After cycle 1, dispensed in 21 day cycles.

Arm title	Phase I Cohort 3

Arm description:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days

Arm type	Experimental
Investigational medicinal product name	Saracatinib
Investigational medicinal product code	AZD0530
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression). After cycle 1, dispensed in 21 day cycles.

Arm title	Phase II Active

Arm description:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression,
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days after 7 day run-in period with Saracatinib.

Arm type	Active comparator
Investigational medicinal product name	Saracatinib
Investigational medicinal product code	AZD0530
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression. Each cycle is 21 days after 7 day run-in period with Saracatinib.

Arm title	Phase II Placebo

Arm description:

Placebo orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression,
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days after 7 day run-in period with placebo.

Arm type	Placebo

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

Dosage and administration details:

Placebo orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression. Each cycle is 21 days after 7 day run-in period with placebo.

Number of subjects in period 1	Phase I Cohort 1	Phase I Cohort 2	Phase I Cohort 3
Started	3	3	4
Completed	3	3	4

Number of subjects in period 1	Phase II Active	Phase II Placebo
Started	71	71
Completed	71	71

Period 2

Period 2 title	Phase I
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I Cohort 1

Arm description:

Saracatinib (AZD0530) 50mg orally once daily continuously, starting on Day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days .

Arm type	Experimental
Investigational medicinal product name	Saracatinib
Investigational medicinal product code	AZD0530
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Saracatinib (AZD0530) 50mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression). After cycle 1, dispensed in 21 day cycles.

Arm title	Phase I Cohort 2

Arm description:

Saracatinib (AZD0530) 125mg orally once daily continuously, starting on Day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days .

Arm type	Experimental
Investigational medicinal product name	Saracatinib
Investigational medicinal product code	AZD0530
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Saracatinib (AZD0530) 125mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression). After cycle 1, dispensed in 21 day cycles.

Arm title	Phase I Cohort 3

Arm description:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting on Day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days .

Arm type	Experimental
Investigational medicinal product name	Saracatinib
Investigational medicinal product code	AZD0530
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression). After cycle 1, dispensed in 21 day cycles.

Arm title	Phase II Patients

Arm description:

Only required to overrule system error that requires the same number or fewer patients in a subsequent period: no summaries or analysis will be provided

Arm type	Required only for issue with system
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Phase I Cohort 1	Phase I Cohort 2	Phase I Cohort 3
Started	3	3	4
Completed	3	3	3
Not completed	0	0	1
Unevaluable (insufficient treatment taken)	-	-	1

Number of subjects in period 2	Phase II Patients
Started	142
Completed	142
Not completed	0
Unevaluable (insufficient treatment taken)	-

Period 3

Period 3 title	Phase II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Blinding implementation details:

Placebo-controlled. Packaging, labelling and preparation of the trial drug and placebo were performed in a way that ensured blinding throughout this part of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase II Active

Arm description:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression,
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days after 7 day run-in period with Saracatinib.

Arm type	Experimental
Investigational medicinal product name	Saracatinib
Investigational medicinal product code	AZD0530
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression. Each cycle is 21 days after 7 day run-in period with Saracatinib.

Arm title	Phase II Placebo

Arm description:

Placebo orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression,
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days after 7 day run-in period with placebo.

Arm type	Placebo

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

Dosage and administration details:

Placebo orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression. Each cycle is 21 days after 7 day run-in period with placebo.

Number of subjects in period 3[1]	Phase II Active	Phase II Placebo
Started	71	71
Completed	70	69
Not completed	1	2
Consent withdrawn by subject	1	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The Phase I and Phase II periods are independent; Phase I was to determine the maximum tolerated dose for Phase II

Baseline characteristics

Reporting groups

Reporting group title	Phase I Cohort 1

Reporting group description:

Saracatinib (AZD0530) 50mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days.

Reporting group title	Phase I Cohort 2

Reporting group description:

Saracatinib (AZD0530) 125mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days

Reporting group title	Phase I Cohort 3

Reporting group description:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days

Reporting group title	Phase II Active

Reporting group description:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression,
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days after 7 day run-in period with Saracatinib.

Reporting group title	Phase II Placebo

Reporting group description:

Placebo orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression,
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days after 7 day run-in period with placebo.

Reporting group values	Phase I Cohort 1	Phase I Cohort 2	Phase I Cohort 3
Number of subjects	3	3	4
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0

Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	1	1
From 65-84 years	3	2	3
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	3	3	4
Phase II stratification factor: Presence of bone metastases			
Only applicable to Phase II patients			
Units: Subjects			
Yes	0	0	0
No	0	0	0
Not applicable	3	3	4
Phase II stratification factor: Presence of visceral (non-lymph node) disease			
Only applicable to Phase II patients			
Units: Subjects			
Yes	0	0	0
No	0	0	0
Not applicable	3	3	4
Baseline PSA Units: ng/mL			
median	53.00	75.00	61.00
inter-quartile range (Q1-Q3)	9.00 to 90.00	15.00 to 179.60	53.00 to 273.70

Reporting group values	Phase II Active	Phase II Placebo	Total
Number of subjects	71	71	152
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	17	36
From 65-84 years	54	54	116
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	71	71	152
Phase II stratification factor: Presence of bone metastases			
Only applicable to Phase II patients			

Units: Subjects			
Yes	64	63	127
No	7	8	15
Not applicable	0	0	10
Phase II stratification factor: Presence of visceral (non-lymph node) disease			
Only applicable to Phase II patients			
Units: Subjects			
Yes	15	16	31
No	56	55	111
Not applicable	0	0	10
Baseline PSA			
Units: ng/mL			
median	68.45	87.80	
inter-quartile range (Q1-Q3)	29.50 to 173.90	20.50 to 287.10	-

Subject analysis sets

Subject analysis set title	Phase I Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Phase I patients with one or more dose of study medication

Subject analysis set title	Phase I Evaluable Study Population
Subject analysis set type	Full analysis

Subject analysis set description:

* Any patient who has experienced a DLT
* Any patient who has received two doses of docetaxel (with no more than 14 days delay in administration of the second dose)
* Any patient who has received at least 80% of scheduled doses of saracatinib within 42 days of first dose of docetaxel

Subject analysis set title	Phase II ITT Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients randomised on to the study

Subject analysis set title	Phase II Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients randomised on to the study with one or more dose of chemotherapy or study medication

Reporting group values	Phase I Safety Population	Phase I Evaluable Study Population	Phase II ITT Population
Number of subjects	10	9	142
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	2	34

From 65-84 years	8	7	108
85 years and over	0	0	0

Gender categorical Units: Subjects			
Female	0	0	0
Male	10	9	142
Phase II stratification factor: Presence of bone metastases			
Only applicable to Phase II patients			
Units: Subjects			
Yes No Not applicable			
Phase II stratification factor: Presence of visceral (non-lymph node) disease			
Only applicable to Phase II patients			
Units: Subjects			
Yes No Not applicable			
Baseline PSA Units: ng/mL median inter-quartile range (Q1-Q3)			

Reporting group values	Phase II Safety Population		
Number of subjects	140		
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)	33		
From 65-84 years	107		
85 years and over	0		
Gender categorical Units: Subjects			
Female	0		
Male	140		
Phase II stratification factor: Presence of bone metastases			
Only applicable to Phase II patients			
Units: Subjects			
Yes No Not applicable			

Phase II stratification factor: Presence of visceral (non-lymph node) disease			
Only applicable to Phase II patients			
Units: Subjects			
Yes No Not applicable			
Baseline PSA Units: ng/mL median inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Phase I Cohort 1

Reporting group description:

Saracatinib (AZD0530) 50mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days.

Reporting group title	Phase I Cohort 2

Reporting group description:

Saracatinib (AZD0530) 125mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days

Reporting group title	Phase I Cohort 3

Reporting group description:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting on day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days

Reporting group title	Phase II Active

Reporting group description:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression,
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days after 7 day run-in period with Saracatinib.

Reporting group title	Phase II Placebo

Reporting group description:

Placebo orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression,
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days after 7 day run-in period with placebo.

Reporting group title	Phase I Cohort 1

Reporting group description:

Saracatinib (AZD0530) 50mg orally once daily continuously, starting on Day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days .

Reporting group title	Phase I Cohort 2

Reporting group description:

Saracatinib (AZD0530) 125mg orally once daily continuously, starting on Day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days .

Reporting group title	Phase I Cohort 3

Reporting group description:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting on Day 11 of 1st cycle of docetaxel (continuing until disease progression),
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days .

Reporting group title	Phase II Patients

Reporting group description:

Only required to overrule system error that requires the same number or fewer patients in a subsequent period: no summaries or analysis will be provided

Reporting group title	Phase II Active

Reporting group description:

Saracatinib (AZD0530) 175mg orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression,
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days after 7 day run-in period with Saracatinib.

Reporting group title	Phase II Placebo

Reporting group description:

Placebo orally once daily continuously, starting 7 days prior to 1st cycle of docetaxel i.e. Day -7 and continuing until disease progression,
Docetaxel 75mg/m2 intravenously on Day 1 every 3 weeks (up to a maximum of 10 cycles),
Prednisolone 5mg orally twice daily continuously starting on Day 1 of 1st cycle of docetaxel (continuing for 21 days after last dose of docetaxel or beyond at Investigator's discretion). Both docetaxel and prednisolone are regarded as nIMPs within the study.
Each cycle is 21 days after 7 day run-in period with placebo.

Subject analysis set title	Phase I Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Phase I patients with one or more dose of study medication

Subject analysis set title	Phase I Evaluable Study Population
Subject analysis set type	Full analysis

Subject analysis set description:

* Any patient who has experienced a DLT
* Any patient who has received two doses of docetaxel (with no more than 14 days delay in administration of the second dose)
* Any patient who has received at least 80% of scheduled doses of saracatinib within 42 days of first dose of docetaxel

Subject analysis set title	Phase II ITT Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients randomised on to the study

Subject analysis set title	Phase II Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients randomised on to the study with one or more dose of chemotherapy or study medication

Primary: Incidence of dose-limiting toxicities

End point title	Incidence of dose-limiting toxicities[1][2]

End point description:

Any of the following events occurring between the first administration of saracatinib and day 42 of first dose of study medication, if, in the opinion of the investigator, the event was due to the combination of saracatinib, docetaxel and prednisolone:

* Greater than 14-day delay in administration of second dose of docetaxel due to drug toxicity
* Grade 4 neutropenia >= 7 days duration
* Grade 3 – 4 neutropenia associated with an oral temperature >=38.5C
* Grade 3 – 4 neutropenia associated with bacteriologically proven sepsis
* Any grade 4 thrombocytopenia
* Grade 3 thrombocytopenia associated with non-traumatic bleeding (except where this can be explained by therapeutic anticoagulation
* Any other clinically significant grade 3 or above toxicity except nausea or vomiting

End point type	Primary

End point timeframe:

Within 42 days of the first administration of saracatinib

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The Phase I part of the trial was to determine the maximum tolerated dose based on descriptive data only and not statistical analysis
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint only applies to Phase I patients

End point values	Phase I Cohort 1	Phase I Cohort 2	Phase I Cohort 3	Phase I Evaluable Study Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	3	9
Units: Patients				
Patients	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Primary analysis: Progression-free survival

End point title	Primary analysis: Progression-free survival

End point description:

End point type	Primary

End point timeframe:

The primary endpoint is PFS, defined as the time from registration onto the study to progression (radiological progression or biochemical progression as defined by the PCWG21 criteria) or death from any cause, whichever occurs first.

End point values	Phase II Active	Phase II Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: Weeks				
median (confidence interval 80%)	19 (18 to 25)	29 (24 to 33)		

Statistical analyses

Statistical analysis title	Cox regression analysis

Statistical analysis description:

A Cox regression model was fitted to the PFS data incorporating terms for study arm and the stratification factors used in the minimisation algorithm (presence of bone metastases, presence of visceral disease and site, which was reparameterised into sites reporting up to and including 10 patients versus those reporting more than 10 patients).

Comparison groups	Phase II Active v Phase II Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.953 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.348
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.072
upper limit	1.695

Notes:

[3] - One-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent until resolution, or for at least 30 days after discontinuation of study medication, whichever comes first or until toxicity has resolved to baseline or < Grade 1, or until the toxicity is considered to be irreversible.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Phase I Cohort 2
Reporting group description: -	
Reporting group title	Phase I Cohort 1
Reporting group description: -	
Reporting group title	Phase II Active
Reporting group description: -	
Reporting group title	Phase II Placebo
Reporting group description: -	
Reporting group title	Phase I Cohort 3
Reporting group description: -	

Serious adverse events	Phase I Cohort 2	Phase I Cohort 1	Phase II Active
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	47 / 69 (68.12%)
number of deaths (all causes)	0	0	6
number of deaths resulting from adverse events	0	0	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY	Additional description: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
HYPERTENSION	Additional description: HYPERTENSION		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 69 (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
HYPOTENSION	Additional description: HYPOTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOEMBOLIC EVENT	Additional description: THROMBOEMBOLIC EVENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 69 (5.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VASCULAR DISORDERS - OTHER, SPECIFY	Additional description: VASCULAR DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
EDEMA LIMBS	Additional description: EDEMA LIMBS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FATIGUE	Additional description: FATIGUE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEVER	Additional description: FEVER		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	7 / 69 (10.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	4 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FLU LIKE SYMPTOMS	Additional description: FLU LIKE SYMPTOMS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY	Additional description: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFUSION SITE EXTRAVASATION	Additional description: INFUSION SITE EXTRAVASATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALAISE	Additional description: MALAISE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-CARDIAC CHEST PAIN	Additional description: NON-CARDIAC CHEST PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
PELVIC PAIN	Additional description: PELVIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
DYSPNEA	Additional description: DYSPNEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPISTAXIS	Additional description: EPISTAXIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
PLEURAL EFFUSION	Additional description: PLEURAL EFFUSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
PLEURITIC PAIN	Additional description: PLEURITIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 69 (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
PNEUMONITIS	Additional description: PNEUMONITIS		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PRODUCTIVE COUGH	Additional description: PRODUCTIVE COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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 - OTHER, SPECIFY	Additional description: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
Psychiatric disorders			
DELIRIUM	Additional description: DELIRIUM		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INSOMNIA	Additional description: INSOMNIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED	Additional description: ALANINE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
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 BILIRUBIN INCREASED	Additional description: BLOOD BILIRUBIN INCREASED		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHOCYTE COUNT DECREASED	Additional description: LYMPHOCYTE COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPHIL COUNT DECREASED	Additional description: NEUTROPHIL COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	16 / 69 (23.19%)
occurrences causally related to treatment / all	1 / 1	1 / 1	17 / 17
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLATELET COUNT DECREASED	Additional description: PLATELET COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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			
HIP FRACTURE	Additional description: HIP FRACTURE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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	Additional description: ATRIAL FIBRILLATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST PAIN - CARDIAC	Additional description: CHEST PAIN - CARDIAC		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEART FAILURE	Additional description: HEART FAILURE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION	Additional description: MYOCARDIAL INFARCTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PALPITATIONS	Additional description: PALPITATIONS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
SINUS TACHYCARDIA	Additional description: SINUS TACHYCARDIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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			
ATAXIA	Additional description: ATAXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
DEPRESSED LEVEL OF CONSCIOUSNESS	Additional description: DEPRESSED LEVEL OF CONSCIOUSNESS		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 69 (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
HEADACHE	Additional description: HEADACHE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LETHARGY	Additional description: LETHARGY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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 - OTHER, SPECIFY	Additional description: NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARESTHESIA	Additional description: PARESTHESIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
PERIPHERAL MOTOR NEUROPATHY	Additional description: PERIPHERAL MOTOR NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
PERIPHERAL SENSORY NEUROPATHY	Additional description: PERIPHERAL SENSORY NEUROPATHY		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
SYNCOPE	Additional description: SYNCOPE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 69 (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			
ANEMIA	Additional description: ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
FEBRILE NEUTROPENIA	Additional description: FEBRILE NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	10 / 69 (14.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	10 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Gastrointestinal disorders			
ABDOMINAL DISTENSION	Additional description: ABDOMINAL DISTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC PERFORATION	Additional description: COLONIC PERFORATION		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
CONSTIPATION	Additional description: CONSTIPATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
DIARRHEA	Additional description: DIARRHEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	10 / 69 (14.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	13 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC ULCER	Additional description: GASTRIC ULCER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEAL OBSTRUCTION	Additional description: ILEAL OBSTRUCTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS	Additional description: PANCREATITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

RECTAL HEMORRHAGE	Additional description: RECTAL HEMORRHAGE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING	Additional description: VOMITING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 69 (5.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
SKIN ULCERATION	Additional description: SKIN ULCERATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY	Additional description: ACUTE KIDNEY INJURY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	6 / 69 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
HEMATURIA	Additional description: HEMATURIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL AND URINARY DISORDERS - OTHER, SPECIFY	Additional description: RENAL AND URINARY DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY INCONTINENCE	Additional description: URINARY INCONTINENCE		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
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			
ARTHRALGIA	Additional description: ARTHRALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AVASCULAR NECROSIS	Additional description: AVASCULAR NECROSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACK PAIN	Additional description: BACK PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST WALL PAIN	Additional description: CHEST WALL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
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 DISORDER - OTHER, SPECIFY	Additional description: MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (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
MYALGIA	Additional description: MYALGIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BRONCHIAL INFECTION	Additional description: BRONCHIAL INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
INFECTIONS AND INFESTATIONS - OTHER, SPECIFY	Additional description: INFECTIONS AND INFESTATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	5 / 69 (7.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT INFECTION	Additional description: JOINT INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 69 (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
LUNG INFECTION	Additional description: LUNG INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	8 / 69 (11.59%)
occurrences causally related to treatment / all	0 / 0	0 / 1	7 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
SEPSIS	Additional description: SEPSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	4 / 69 (5.80%)
occurrences causally related to treatment / all	1 / 1	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
SKIN INFECTION	Additional description: SKIN INFECTION		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY INFECTION	Additional description: UPPER RESPIRATORY INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION	Additional description: URINARY TRACT INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION	Additional description: WOUND INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
ACIDOSIS	Additional description: ACIDOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION	Additional description: DEHYDRATION		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCEMIA	Additional description: HYPERGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
HYPERKALEMIA	Additional description: HYPERKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOGLYCEMIA	Additional description: HYPOGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 69 (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
METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY	Additional description: METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase II Placebo	Phase I Cohort 3	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 71 (53.52%)	2 / 4 (50.00%)	
number of deaths (all causes)	4	0	

number of deaths resulting from adverse events	3	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY	Additional description: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
HYPERTENSION	Additional description: HYPERTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION	Additional description: HYPOTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOEMBOLIC EVENT	Additional description: THROMBOEMBOLIC EVENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	4 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR DISORDERS - OTHER, SPECIFY	Additional description: VASCULAR DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
EDEMA LIMBS	Additional description: EDEMA LIMBS		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE	Additional description: FATIGUE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEVER	Additional description: FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 71 (11.27%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	7 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLU LIKE SYMPTOMS	Additional description: FLU LIKE SYMPTOMS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY	Additional description: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFUSION SITE EXTRAVASATION	Additional description: INFUSION SITE EXTRAVASATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE	Additional description: MALAISE		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-CARDIAC CHEST PAIN	Additional description: NON-CARDIAC CHEST PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
PELVIC PAIN	Additional description: PELVIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
DYSPNEA	Additional description: DYSPNEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS	Additional description: EPISTAXIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION	Additional description: PLEURAL EFFUSION		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURITIC PAIN	Additional description: PLEURITIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS	Additional description: PNEUMONITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRODUCTIVE COUGH	Additional description: PRODUCTIVE COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY	Additional description: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DELIRIUM	Additional description: DELIRIUM		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INSOMNIA	Additional description: INSOMNIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED	Additional description: ALANINE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD BILIRUBIN INCREASED	Additional description: BLOOD BILIRUBIN INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOCYTE COUNT DECREASED	Additional description: LYMPHOCYTE COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED	Additional description: NEUTROPHIL COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 71 (9.86%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	7 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED	Additional description: PLATELET COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
HIP FRACTURE	Additional description: HIP FRACTURE		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION	Additional description: ATRIAL FIBRILLATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN - CARDIAC	Additional description: CHEST PAIN - CARDIAC		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEART FAILURE	Additional description: HEART FAILURE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION	Additional description: MYOCARDIAL INFARCTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PALPITATIONS	Additional description: PALPITATIONS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS TACHYCARDIA	Additional description: SINUS TACHYCARDIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
ATAXIA	Additional description: ATAXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSED LEVEL OF CONSCIOUSNESS	Additional description: DEPRESSED LEVEL OF CONSCIOUSNESS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE	Additional description: HEADACHE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LETHARGY	Additional description: LETHARGY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY	Additional description: NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARESTHESIA	Additional description: PARESTHESIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL MOTOR NEUROPATHY	Additional description: PERIPHERAL MOTOR NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL SENSORY NEUROPATHY	Additional description: PERIPHERAL SENSORY NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE	Additional description: SYNCOPE		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANEMIA	Additional description: ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA	Additional description: FEBRILE NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 71 (9.86%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL DISTENSION	Additional description: ABDOMINAL DISTENSION		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLONIC PERFORATION	Additional description: COLONIC PERFORATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
CONSTIPATION	Additional description: CONSTIPATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHEA	Additional description: DIARRHEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER	Additional description: GASTRIC ULCER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEAL OBSTRUCTION	Additional description: ILEAL OBSTRUCTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS	Additional description: PANCREATITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HEMORRHAGE	Additional description: RECTAL HEMORRHAGE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING	Additional description: VOMITING		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
SKIN ULCERATION	Additional description: SKIN ULCERATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY	Additional description: ACUTE KIDNEY INJURY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMATURIA	Additional description: HEMATURIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL AND URINARY DISORDERS - OTHER, SPECIFY	Additional description: RENAL AND URINARY DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY INCONTINENCE	Additional description: URINARY INCONTINENCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA	Additional description: ARTHRALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
AVASCULAR NECROSIS	Additional description: AVASCULAR NECROSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN	Additional description: BACK PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST WALL PAIN	Additional description: CHEST WALL PAIN		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY	Additional description: MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYALGIA	Additional description: MYALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
BRONCHIAL INFECTION	Additional description: BRONCHIAL INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIONS AND INFESTATIONS - OTHER, SPECIFY	Additional description: INFECTIONS AND INFESTATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT INFECTION	Additional description: JOINT INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION	Additional description: LUNG INFECTION		
alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
SEPSIS	Additional description: SEPSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 71 (7.04%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	2 / 2	0 / 0	
SKIN INFECTION	Additional description: SKIN INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY INFECTION	Additional description: UPPER RESPIRATORY INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION	Additional description: URINARY TRACT INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION	Additional description: WOUND INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
ACIDOSIS	Additional description: ACIDOSIS		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION	Additional description: DEHYDRATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCEMIA	Additional description: HYPERGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALEMIA	Additional description: HYPERKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCEMIA	Additional description: HYPOGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY	Additional description: METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Phase I Cohort 2	Phase I Cohort 1	Phase II Active
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	61 / 69 (88.41%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY	Additional description: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Vascular disorders			
HOT FLASHES	Additional description: HOT FLASHES		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences (all)	0	0	8
HYPERTENSION	Additional description: HYPERTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 69 (5.80%)
occurrences (all)	0	0	10
HYPOTENSION	Additional description: HYPOTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
THROMBOEMBOLIC EVENT	Additional description: THROMBOEMBOLIC EVENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences (all)	0	0	3

LYMPHEDEMA	Additional description: LYMPHEDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
PHLEBITIS	Additional description: PHLEBITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	3	0	0
General disorders and administration site conditions			
CHILLS	Additional description: CHILLS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
EDEMA FACE	Additional description: EDEMA FACE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
EDEMA LIMBS	Additional description: EDEMA LIMBS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	3 / 69 (4.35%)
occurrences (all)	0	2	8
FATIGUE	Additional description: FATIGUE		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	3 / 3 (100.00%)	49 / 69 (71.01%)
occurrences (all)	6	12	238
FEVER	Additional description: FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	6 / 69 (8.70%)
occurrences (all)	0	0	7
FLU LIKE SYMPTOMS	Additional description: FLU LIKE SYMPTOMS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY	Additional description: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY		

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	28 / 69 (40.58%)
occurrences (all)	1	2	77
MALAISE	Additional description: MALAISE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
NON-CARDIAC CHEST PAIN	Additional description: NON-CARDIAC CHEST PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	2
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	5 / 69 (7.25%)
occurrences (all)	0	0	17
Immune system disorders			
ALLERGIC REACTION	Additional description: ALLERGIC REACTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
PELVIC PAIN	Additional description: PELVIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
COUGH	Additional description: COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	10 / 69 (14.49%)
occurrences (all)	0	3	23
DYSPNEA	Additional description: DYSPNEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	11 / 69 (15.94%)
occurrences (all)	0	0	28

EPISTAXIS	Additional description: EPISTAXIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	6 / 69 (8.70%)
occurrences (all)	0	1	14
PNEUMONITIS	Additional description: PNEUMONITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	4
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY	Additional description: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	8 / 69 (11.59%)
occurrences (all)	0	0	24
SINUS DISORDER	Additional description: SINUS DISORDER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
SORE THROAT	Additional description: SORE THROAT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 69 (5.80%)
occurrences (all)	0	0	5
Psychiatric disorders			
ANXIETY	Additional description: ANXIETY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
DEPRESSION	Additional description: DEPRESSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
INSOMNIA	Additional description: INSOMNIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	9 / 69 (13.04%)
occurrences (all)	0	2	25
PERSONALITY CHANGE	Additional description: PERSONALITY CHANGE		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
PSYCHIATRIC DISORDERS - OTHER, SPECIFY	Additional description: PSYCHIATRIC DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED	Additional description: ALANINE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	3
ALKALINE PHOSPHATASE INCREASED	Additional description: ALKALINE PHOSPHATASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
ASPARTATE AMINOTRANSFERASE INCREASED	Additional description: ASPARTATE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	3
NEUTROPHIL COUNT DECREASED	Additional description: NEUTROPHIL COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	6 / 69 (8.70%)
occurrences (all)	0	0	8
WEIGHT GAIN	Additional description: WEIGHT GAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
WEIGHT LOSS	Additional description: WEIGHT LOSS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences (all)	0	0	3
WHITE BLOOD CELL DECREASED	Additional description: WHITE BLOOD CELL DECREASED		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
BRUISING	Additional description: BRUISING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	5 / 69 (7.25%)
occurrences (all)	0	0	22
FALL	Additional description: FALL		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
CARDIAC DISORDERS - OTHER, SPECIFY	Additional description: CARDIAC DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
CHEST PAIN - CARDIAC	Additional description: CHEST PAIN - CARDIAC		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	2
Nervous system disorders			
COGNITIVE DISTURBANCE	Additional description: COGNITIVE DISTURBANCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
CONCENTRATION IMPAIRMENT	Additional description: CONCENTRATION IMPAIRMENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	2
DIZZINESS	Additional description: DIZZINESS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	5 / 69 (7.25%)
occurrences (all)	1	0	11

HEADACHE	Additional description: HEADACHE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	5 / 69 (7.25%)
occurrences (all)	0	0	6
DYSGEUSIA	Additional description: DYSGEUSIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	27 / 69 (39.13%)
occurrences (all)	2	3	94
LETHARGY	Additional description: LETHARGY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 69 (5.80%)
occurrences (all)	0	0	4
MEMORY IMPAIRMENT	Additional description: MEMORY IMPAIRMENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY	Additional description: NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
PARESTHESIA	Additional description: PARESTHESIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	2
PERIPHERAL MOTOR NEUROPATHY	Additional description: PERIPHERAL MOTOR NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	6 / 69 (8.70%)
occurrences (all)	0	1	9
PERIPHERAL SENSORY NEUROPATHY	Additional description: PERIPHERAL SENSORY NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	23 / 69 (33.33%)
occurrences (all)	2	7	80
Blood and lymphatic system disorders			

ANEMIA	Additional description: ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	6 / 69 (8.70%)
occurrences (all)	0	0	14
BLOOD AND LYMPHATIC SYSTEM DISORDERS - OTHER, SPECIFY	Additional description: BLOOD AND LYMPHATIC SYSTEM DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	1	0	2
FEBRILE NEUTROPENIA	Additional description: FEBRILE NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
LEUKOCYTOSIS	Additional description: LEUKOCYTOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
THROMBOTIC THROMBOCYTOPENIC PURPURA	Additional description: THROMBOTIC THROMBOCYTOPENIC PURPURA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
HEARING IMPAIRED	Additional description: HEARING IMPAIRED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
TINNITUS	Additional description: TINNITUS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
VESTIBULAR DISORDER	Additional description: VESTIBULAR DISORDER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

BLURRED VISION	Additional description: BLURRED VISION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	5
CONJUNCTIVITIS	Additional description: CONJUNCTIVITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
DRY EYE	Additional description: DRY EYE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	2
EXTRAOCULAR MUSCLE PARESIS	Additional description: EXTRAOCULAR MUSCLE PARESIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
EYE DISORDERS - OTHER, SPECIFY	Additional description: EYE DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
EYE PAIN	Additional description: EYE PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	5
WATERING EYES	Additional description: WATERING EYES		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	9
Gastrointestinal disorders			
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	3
BLOATING	Additional description: BLOATING		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
CHEILITIS	Additional description: CHEILITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
CONSTIPATION	Additional description: CONSTIPATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	11 / 69 (15.94%)
occurrences (all)	0	0	27
DIARRHEA	Additional description: DIARRHEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	35 / 69 (50.72%)
occurrences (all)	1	1	104
DRY MOUTH	Additional description: DRY MOUTH		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	5 / 69 (7.25%)
occurrences (all)	0	0	21
DYSPEPSIA	Additional description: DYSPEPSIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	6 / 69 (8.70%)
occurrences (all)	2	2	10
FECAL INCONTINENCE	Additional description: FECAL INCONTINENCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
FLATULENCE	Additional description: FLATULENCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	2
GASTRITIS	Additional description: GASTRITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1

GASTROESOPHAGEAL REFLUX DISEASE	Additional description: GASTROESOPHAGEAL REFLUX DISEASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 69 (0.00%)
occurrences (all)	0	2	0
GASTROINTESTINAL DISORDERS - OTHER, SPECIFY	Additional description: GASTROINTESTINAL DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 69 (5.80%)
occurrences (all)	0	0	4
MUCOSITIS ORAL	Additional description: MUCOSITIS ORAL		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	3 / 3 (100.00%)	8 / 69 (11.59%)
occurrences (all)	0	7	22
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	23 / 69 (33.33%)
occurrences (all)	2	0	47
ORAL HEMORRHAGE	Additional description: ORAL HEMORRHAGE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
ORAL PAIN	Additional description: ORAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	3
RECTAL HEMORRHAGE	Additional description: RECTAL HEMORRHAGE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	5 / 69 (7.25%)
occurrences (all)	0	0	8
SALIVARY DUCT INFLAMMATION	Additional description: SALIVARY DUCT INFLAMMATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
STOMACH PAIN	Additional description: STOMACH PAIN		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	2
VOMITING	Additional description: VOMITING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	8 / 69 (11.59%)
occurrences (all)	0	0	15
Hepatobiliary disorders			
HEPATOBILIARY DISORDERS - OTHER, SPECIFY	Additional description: HEPATOBILIARY DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	4
Skin and subcutaneous tissue disorders			
ALOPECIA	Additional description: ALOPECIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	3 / 3 (100.00%)	24 / 69 (34.78%)
occurrences (all)	5	9	118
DRY SKIN	Additional description: DRY SKIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences (all)	0	0	3
ERYTHEMA MULTIFORME	Additional description: ERYTHEMA MULTIFORME		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
NAIL DISCOLORATION	Additional description: NAIL DISCOLORATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	8 / 69 (11.59%)
occurrences (all)	1	0	18
NAIL LOSS	Additional description: NAIL LOSS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
PRURITUS	Additional description: PRURITUS		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	2
NAIL RIDGING	Additional description: NAIL RIDGING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	5
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME	Additional description: PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences (all)	0	0	6
RASH ACNEIFORM	Additional description: RASH ACNEIFORM		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
RASH MACULO-PAPULAR	Additional description: RASH MACULO-PAPULAR		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	6 / 69 (8.70%)
occurrences (all)	0	0	14
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY	Additional description: SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 69 (5.80%)
occurrences (all)	0	0	7
Renal and urinary disorders			
URINARY FREQUENCY	Additional description: URINARY FREQUENCY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
HEMATURIA	Additional description: HEMATURIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
URINE DISCOLORATION	Additional description: URINE DISCOLORATION		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	3
Endocrine disorders			
CUSHINGOID	Additional description: CUSHINGOID		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA	Additional description: ARTHRALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 69 (1.45%)
occurrences (all)	0	2	1
BACK PAIN	Additional description: BACK PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 69 (1.45%)
occurrences (all)	0	2	1
BONE PAIN	Additional description: BONE PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
CHEST WALL PAIN	Additional description: CHEST WALL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	2
GENERALIZED MUSCLE WEAKNESS	Additional description: GENERALIZED MUSCLE WEAKNESS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences (all)	0	0	3
MUSCLE WEAKNESS LOWER LIMB	Additional description: MUSCLE WEAKNESS LOWER LIMB		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	4
MUSCLE WEAKNESS UPPER LIMB	Additional description: MUSCLE WEAKNESS UPPER LIMB		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY	Additional description: MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	2
MYALGIA	Additional description: MYALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	9 / 69 (13.04%)
occurrences (all)	0	0	12
PAIN IN EXTREMITY	Additional description: PAIN IN EXTREMITY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 69 (2.90%)
occurrences (all)	0	3	2
Infections and infestations			
INFECTIONS AND INFESTATIONS - OTHER, SPECIFY	Additional description: INFECTIONS AND INFESTATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	8 / 69 (11.59%)
occurrences (all)	0	2	9
MUCOSAL INFECTION	Additional description: MUCOSAL INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
NAIL INFECTION	Additional description: NAIL INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
PARONYCHIA	Additional description: PARONYCHIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
RHINITIS INFECTIVE	Additional description: RHINITIS INFECTIVE		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
SKIN INFECTION	Additional description: SKIN INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
TOOTH INFECTION	Additional description: TOOTH INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
UPPER RESPIRATORY INFECTION	Additional description: UPPER RESPIRATORY INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
URINARY TRACT INFECTION	Additional description: URINARY TRACT INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	20 / 69 (28.99%)
occurrences (all)	1	3	35
GLUCOSE INTOLERANCE	Additional description: GLUCOSE INTOLERANCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
HYPERCALCEMIA	Additional description: HYPERCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
HYPERGLYCEMIA	Additional description: HYPERGLYCEMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	3
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
HYPOKALEMIA	Additional description: HYPOKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
HYPOPHOSPHATEMIA	Additional description: HYPOPHOSPHATEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 69 (4.35%)
occurrences (all)	0	0	4
METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY	Additional description: METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
LOCALISED OEDEMA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	5

Non-serious adverse events	Phase II Placebo	Phase I Cohort 3	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 71 (95.77%)	4 / 4 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY	Additional description: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
HOT FLASHES	Additional description: HOT FLASHES		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
HYPERTENSION	Additional description: HYPERTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	
occurrences (all)	16	0	
HYPOTENSION	Additional description: HYPOTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
THROMBOEMBOLIC EVENT	Additional description: THROMBOEMBOLIC EVENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
LYMPHEDEMA	Additional description: LYMPHEDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
PHLEBITIS	Additional description: PHLEBITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
CHILLS	Additional description: CHILLS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
EDEMA FACE	Additional description: EDEMA FACE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
EDEMA LIMBS	Additional description: EDEMA LIMBS		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
FATIGUE	Additional description: FATIGUE		
alternative assessment type: Non-systematic			
subjects affected / exposed	54 / 71 (76.06%)	4 / 4 (100.00%)	
occurrences (all)	292	17	
FEVER	Additional description: FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 71 (5.63%)	1 / 4 (25.00%)	
occurrences (all)	4	1	
FLU LIKE SYMPTOMS	Additional description: FLU LIKE SYMPTOMS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY	Additional description: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	26 / 71 (36.62%)	3 / 4 (75.00%)	
occurrences (all)	65	6	
MALAISE	Additional description: MALAISE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
NON-CARDIAC CHEST PAIN	Additional description: NON-CARDIAC CHEST PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 71 (11.27%)	1 / 4 (25.00%)	
occurrences (all)	15	2	
Immune system disorders			
ALLERGIC REACTION	Additional description: ALLERGIC REACTION		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
PELVIC PAIN	Additional description: PELVIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
COUGH	Additional description: COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	
occurrences (all)	12	0	
DYSPNEA	Additional description: DYSPNEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	
occurrences (all)	13	0	
EPISTAXIS	Additional description: EPISTAXIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	
occurrences (all)	9	0	
PNEUMONITIS	Additional description: PNEUMONITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY	Additional description: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 71 (9.86%)	0 / 4 (0.00%)	
occurrences (all)	17	0	
SINUS DISORDER	Additional description: SINUS DISORDER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
SORE THROAT	Additional description: SORE THROAT		

alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
ANXIETY	Additional description: ANXIETY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
DEPRESSION	Additional description: DEPRESSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
INSOMNIA	Additional description: INSOMNIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	
occurrences (all)	16	0	
PERSONALITY CHANGE	Additional description: PERSONALITY CHANGE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
PSYCHIATRIC DISORDERS - OTHER, SPECIFY	Additional description: PSYCHIATRIC DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED	Additional description: ALANINE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
ALKALINE PHOSPHATASE INCREASED	Additional description: ALKALINE PHOSPHATASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
ASPARTATE AMINOTRANSFERASE	Additional description: ASPARTATE AMINOTRANSFERASE INCREASED		

INCREASED			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
NEUTROPHIL COUNT DECREASED	Additional description: NEUTROPHIL COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
WEIGHT GAIN	Additional description: WEIGHT GAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
WEIGHT LOSS	Additional description: WEIGHT LOSS		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
WHITE BLOOD CELL DECREASED	Additional description: WHITE BLOOD CELL DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
BRUISING	Additional description: BRUISING		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	
occurrences (all)	17	0	
FALL	Additional description: FALL		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
CARDIAC DISORDERS - OTHER, SPECIFY	Additional description: CARDIAC DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

CHEST PAIN - CARDIAC	Additional description: CHEST PAIN - CARDIAC		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
COGNITIVE DISTURBANCE	Additional description: COGNITIVE DISTURBANCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
CONCENTRATION IMPAIRMENT	Additional description: CONCENTRATION IMPAIRMENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
DIZZINESS	Additional description: DIZZINESS		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	
occurrences (all)	10	0	
HEADACHE	Additional description: HEADACHE		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
DYSGEUSIA	Additional description: DYSGEUSIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	23 / 71 (32.39%)	1 / 4 (25.00%)	
occurrences (all)	78	1	
LETHARGY	Additional description: LETHARGY		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	2 / 4 (50.00%)	
occurrences (all)	2	2	
MEMORY IMPAIRMENT	Additional description: MEMORY IMPAIRMENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY	Additional description: NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
PARESTHESIA	Additional description: PARESTHESIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
PERIPHERAL MOTOR NEUROPATHY	Additional description: PERIPHERAL MOTOR NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 71 (14.08%)	1 / 4 (25.00%)	
occurrences (all)	13	1	
PERIPHERAL SENSORY NEUROPATHY	Additional description: PERIPHERAL SENSORY NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	29 / 71 (40.85%)	1 / 4 (25.00%)	
occurrences (all)	147	3	
Blood and lymphatic system disorders			
ANEMIA	Additional description: ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	
occurrences (all)	16	0	
BLOOD AND LYMPHATIC SYSTEM DISORDERS - OTHER, SPECIFY	Additional description: BLOOD AND LYMPHATIC SYSTEM DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	
occurrences (all)	12	0	
FEBRILE NEUTROPENIA	Additional description: FEBRILE NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
LEUKOCYTOSIS	Additional description: LEUKOCYTOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
THROMBOTIC THROMBOCYTOPENIC PURPURA	Additional description: THROMBOTIC THROMBOCYTOPENIC PURPURA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
HEARING IMPAIRED	Additional description: HEARING IMPAIRED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
TINNITUS	Additional description: TINNITUS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
VESTIBULAR DISORDER	Additional description: VESTIBULAR DISORDER		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
BLURRED VISION	Additional description: BLURRED VISION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
CONJUNCTIVITIS	Additional description: CONJUNCTIVITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
DRY EYE	Additional description: DRY EYE		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	
occurrences (all)	10	0	
EXTRAOCULAR MUSCLE PARESIS	Additional description: EXTRAOCULAR MUSCLE PARESIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
EYE DISORDERS - OTHER, SPECIFY	Additional description: EYE DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
EYE PAIN	Additional description: EYE PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
WATERING EYES	Additional description: WATERING EYES		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	
occurrences (all)	23	0	
Gastrointestinal disorders			
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
BLOATING	Additional description: BLOATING		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
CHEILITIS	Additional description: CHEILITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
CONSTIPATION	Additional description: CONSTIPATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 71 (7.04%)	2 / 4 (50.00%)	
occurrences (all)	11	2	
DIARRHEA	Additional description: DIARRHEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	36 / 71 (50.70%)	4 / 4 (100.00%)	
occurrences (all)	87	12	
DRY MOUTH	Additional description: DRY MOUTH		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 71 (2.82%)	1 / 4 (25.00%)	
occurrences (all)	9	1	
DYSPEPSIA	Additional description: DYSPEPSIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 71 (15.49%)	0 / 4 (0.00%)	
occurrences (all)	29	0	
FECAL INCONTINENCE	Additional description: FECAL INCONTINENCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
FLATULENCE	Additional description: FLATULENCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
GASTRITIS	Additional description: GASTRITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
GASTROESOPHAGEAL REFLUX DISEASE	Additional description: GASTROESOPHAGEAL REFLUX DISEASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
GASTROINTESTINAL DISORDERS - OTHER, SPECIFY	Additional description: GASTROINTESTINAL DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 71 (5.63%)	1 / 4 (25.00%)	
occurrences (all)	13	1	
MUCOSITIS ORAL	Additional description: MUCOSITIS ORAL		
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 71 (15.49%)	1 / 4 (25.00%)	
occurrences (all)	25	1	
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			

subjects affected / exposed	26 / 71 (36.62%)	2 / 4 (50.00%)	
occurrences (all)	71	7	
ORAL HEMORRHAGE	Additional description: ORAL HEMORRHAGE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
ORAL PAIN	Additional description: ORAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 71 (9.86%)	0 / 4 (0.00%)	
occurrences (all)	21	0	
RECTAL HEMORRHAGE	Additional description: RECTAL HEMORRHAGE		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
SALIVARY DUCT INFLAMMATION	Additional description: SALIVARY DUCT INFLAMMATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
STOMACH PAIN	Additional description: STOMACH PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
VOMITING	Additional description: VOMITING		
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 71 (18.31%)	1 / 4 (25.00%)	
occurrences (all)	16	2	
Hepatobiliary disorders			
HEPATOBILIARY DISORDERS - OTHER, SPECIFY	Additional description: HEPATOBILIARY DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
ALOPECIA	Additional description: ALOPECIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	31 / 71 (43.66%)	3 / 4 (75.00%)	
occurrences (all)	155	15	
DRY SKIN	Additional description: DRY SKIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	2 / 4 (50.00%)	
occurrences (all)	19	3	
ERYTHEMA MULTIFORME	Additional description: ERYTHEMA MULTIFORME		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
NAIL DISCOLORATION	Additional description: NAIL DISCOLORATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	
occurrences (all)	24	0	
NAIL LOSS	Additional description: NAIL LOSS		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
PRURITUS	Additional description: PRURITUS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
NAIL RIDGING	Additional description: NAIL RIDGING		
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 71 (12.68%)	0 / 4 (0.00%)	
occurrences (all)	43	0	
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME	Additional description: PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
RASH ACNEIFORM	Additional description: RASH ACNEIFORM		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	4	0	

RASH MACULO-PAPULAR	Additional description: RASH MACULO-PAPULAR		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 71 (8.45%)	1 / 4 (25.00%)	
occurrences (all)	8	1	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY	Additional description: SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 71 (8.45%)	2 / 4 (50.00%)	
occurrences (all)	7	4	
Renal and urinary disorders			
URINARY FREQUENCY	Additional description: URINARY FREQUENCY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
HEMATURIA	Additional description: HEMATURIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
URINE DISCOLORATION	Additional description: URINE DISCOLORATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
CUSHINGOID	Additional description: CUSHINGOID		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA	Additional description: ARTHRALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
BACK PAIN	Additional description: BACK PAIN		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
BONE PAIN	Additional description: BONE PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
CHEST WALL PAIN	Additional description: CHEST WALL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
GENERALIZED MUSCLE WEAKNESS	Additional description: GENERALIZED MUSCLE WEAKNESS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
MUSCLE WEAKNESS LOWER LIMB	Additional description: MUSCLE WEAKNESS LOWER LIMB		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
MUSCLE WEAKNESS UPPER LIMB	Additional description: MUSCLE WEAKNESS UPPER LIMB		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY	Additional description: MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	
occurrences (all)	12	0	
MYALGIA	Additional description: MYALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 71 (14.08%)	0 / 4 (0.00%)	
occurrences (all)	27	0	
PAIN IN EXTREMITY	Additional description: PAIN IN EXTREMITY		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
INFECTIONS AND INFESTATIONS - OTHER, SPECIFY	Additional description: INFECTIONS AND INFESTATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 71 (11.27%)	2 / 4 (50.00%)	
occurrences (all)	10	3	
MUCOSAL INFECTION	Additional description: MUCOSAL INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
NAIL INFECTION	Additional description: NAIL INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
PARONYCHIA	Additional description: PARONYCHIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
RHINITIS INFECTIVE	Additional description: RHINITIS INFECTIVE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
SKIN INFECTION	Additional description: SKIN INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
TOOTH INFECTION	Additional description: TOOTH INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
UPPER RESPIRATORY INFECTION	Additional description: UPPER RESPIRATORY INFECTION		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
URINARY TRACT INFECTION	Additional description: URINARY TRACT INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 71 (23.94%)	2 / 4 (50.00%)	
occurrences (all)	43	3	
GLUCOSE INTOLERANCE	Additional description: GLUCOSE INTOLERANCE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
HYPERCALCEMIA	Additional description: HYPERCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
HYPERGLYCEMIA	Additional description: HYPERGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
HYPOKALEMIA	Additional description: HYPOKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
HYPOPHOSPHATEMIA	Additional description: HYPOPHOSPHATEMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY	Additional description: METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
LOCALISED OEDEMA			
subjects affected / exposed	8 / 71 (11.27%)	0 / 4 (0.00%)	
occurrences (all)	36	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2014	As per the original study protocol, patients that are un-blinded should discontinue study treatment - this has been clarified in the amended protocol. Update on the information provided for emergency un-blinding of patients to highlight that sites will need log in details for the IVRS system. Information added on wash out periods for Abiraterone and Bicalutamide. Dose Reduction section made clearer at request of sites Updated PV section for clarity and to give further guidance on pregnancy of patients partners.
28 July 2017	Visit schedule during maintenance therapy updated to allow 6-weekly visits. Clarification of AE reporting requirements during follow-up. PV section updated in line with current CRUK CTU Glasgow template. Recruitment period changed to 30 months from 18 months to reflect actual time.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported