



Clinical trial results:

A phase I/randomised phase II trial of abiraterone acetate or enzalutamide with or without idasanutlin (RO5503781) in patients with metastatic castration resistant prostate cancer who have not previously received docetaxel.

Summary

EudraCT number	2013-002014-13
Trial protocol	GB
Global end of trial date	09 December 2019

Results information

Result version number	v1 (current)
This version publication date	25 December 2020
First version publication date	25 December 2020

Trial information

Trial identification

Sponsor protocol code	MAdCaP2013
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Additional study identifiers

ISRCTN number	ISRCTN38949950
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow & Clyde
Sponsor organisation address	Ward 11, Dykebar Hospital, Paisley, United Kingdom, PA2 7DE
Public contact	Lorna Sweeting, CRUK Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow, G12 0YN, 44 0141 301 7194, lorna.sweeting@glasgow.ac.uk
Scientific contact	Lorna Sweeting, CRUK Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow, G12 0YN, 44 0141 301 7194, lorna.sweeting@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	Lorna Sweeting, CRUK Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow, G12 0YN, 44 0141 301 7194, lorna.sweeting@glasgow.ac.uk
Scientific contact	Lorna Sweeting, CRUK Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow, G12 0YN, 44 0141 301 7194, lorna.sweeting@glasgow.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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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	09 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective (phase I):

To establish a safe and tolerable dose for RO5503781 given in combination with abiraterone or enzalutamide.

Primary objective (phase II):

To establish whether the efficacy of the combination of RO5503781 with abiraterone and prednisolone or enzalutamide merits further study in patients with mCRPC. The primary endpoint will be radiological progression free survival (please note, our commercial partner Roche decided not to provide support for the planned Phase II component of the study and therefore this did not proceed).

Protection of trial subjects:

Patients were required to attend for visits and investigations that were considered to be additional to standard of care. The number and types 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2014
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: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	16
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Phase I: Open to recruitment between 31st March 2014 and 3rd July 2017 with 22 patients recruited over 6 cohorts.

Phase II: Roche, our commercial partner, decided not to provide support for the Phase II component of the study, therefore this did not proceed and no patients were recruited.

Pre-assignment

Screening details:

Following consent, all patients underwent screening to determine eligibility, including confirmation of disease progressions, physical exam, blood tests (including testosterone), review of prior treatment (prior cytotoxic chemotherapy excluded, no other anticancer therapy (apart from LHRH agonist/antagonist) within 4 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort -1

Arm description:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-3 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.

This was repeated every 28 days until progression.

Arm type	Experimental
Investigational medicinal product name	Idasanutlin
Investigational medicinal product code	RO5503781
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-3 of a 28 day cycle

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

Dosage and administration details:

1000mg orally once a day continuously

Arm title	Cohort 1
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Arm description:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.

This was repeated every 28 days until progression.

Arm type	Experimental
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Investigational medicinal product name	Idasanutlin
Investigational medicinal product code	RO5503781
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-5 of a 28 day cycle

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

Dosage and administration details:

1000mg orally once a day continuously

Arm title	Cohort 1*
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Arm description:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.

This was repeated every 28 days until progression.

Arm type	Experimental
Investigational medicinal product name	Idasanutlin
Investigational medicinal product code	RO5503781
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, 200mg orally once daily on days 1-5 of a 28 day cycle

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

Dosage and administration details:

1000mg orally once a day continuously

Arm title	Cohort 2
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Arm description:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, 400mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.

This was repeated every 28 days until progression.

Arm type	Experimental
Investigational medicinal product name	Idasanutlin
Investigational medicinal product code	RO5503781
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, 400mg orally once daily on days 1-5 of a 28 day cycle

Investigational medicinal product name	Abiraterone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1000mg orally once a day continuously	
Arm title	Cohort 3B

Arm description:

RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.

This was repeated every 28 days until progression.

Arm type	Experimental
Investigational medicinal product name	Idasanutlin
Investigational medicinal product code	RO5503781
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle

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

Dosage and administration details:

1000mg orally once a day continuously

Arm title	Cohort 1E
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Arm description:

RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with enzalutamide orally 160mg once daily.

This was repeated every 28 days until progression.

Arm type	Experimental
Investigational medicinal product name	Idasanutlin
Investigational medicinal product code	RO5503781
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle

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

Dosage and administration details:

enzalutamide 160mg once daily continuously

Number of subjects in period 1	Cohort -1	Cohort 1	Cohort 1*
Started	3	3	3
Completed	3	3	3

Number of subjects in period 1	Cohort 2	Cohort 3B	Cohort 1E
Started	3	7	3
Completed	3	7	3

Baseline characteristics

Reporting groups

Reporting group title	Cohort -1
Reporting group description: RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-3 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day. This was repeated every 28 days until progression.	
Reporting group title	Cohort 1
Reporting group description: RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day. This was repeated every 28 days until progression.	
Reporting group title	Cohort 1*
Reporting group description: RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day. This was repeated every 28 days until progression.	
Reporting group title	Cohort 2
Reporting group description: RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, 400mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day. This was repeated every 28 days until progression.	
Reporting group title	Cohort 3B
Reporting group description: RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day. This was repeated every 28 days until progression.	
Reporting group title	Cohort 1E
Reporting group description: RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with enzalutamide orally 160mg once daily. This was repeated every 28 days until progression.	

Reporting group values	Cohort -1	Cohort 1	Cohort 1*
Number of subjects	3	3	3
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)	1	3	2
From 65-84 years	2	0	1
85 years and over	0	0	0

Gender categorical Units: Subjects			
Female	0	0	0
Male	3	3	3

Reporting group values	Cohort 2	Cohort 3B	Cohort 1E
Number of subjects	3	7	3
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)	3	4	3
From 65-84 years	0	3	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	3	7	3

Reporting group values	Total		
Number of subjects	22		
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)	16		
From 65-84 years	6		
85 years and over	0		
Gender categorical Units: Subjects			
Female	0		
Male	22		

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
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Subject analysis set description:

- Any patient who has experienced a DLT
- Any patient who has received 5 consecutive days of treatment with RO5503781 within the first 21 days of combination therapy
- Any patient who has received at least 80% of planned doses of abiraterone or enzalutamide within the first 21 days of combination therapy

Any patient who has dose modifications not permitted by study protocol within the first 21 days will NOT be evaluable unless they experience a DLT

Reporting group values	Phase I Safety Population	Phase I Evaluable Study Population	
Number of subjects	22	21	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	16	15	
From 65-84 years	6	6	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	22	21	

End points

End points reporting groups

Reporting group title	Cohort -1
Reporting group description: RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-3 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day. This was repeated every 28 days until progression.	
Reporting group title	Cohort 1
Reporting group description: RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day. This was repeated every 28 days until progression.	
Reporting group title	Cohort 1*
Reporting group description: RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day. This was repeated every 28 days until progression.	
Reporting group title	Cohort 2
Reporting group description: RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, 400mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day. This was repeated every 28 days until progression.	
Reporting group title	Cohort 3B
Reporting group description: RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day. This was repeated every 28 days until progression.	
Reporting group title	Cohort 1E
Reporting group description: RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with enzalutamide orally 160mg once daily. This was repeated every 28 days until progression.	
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: <ul style="list-style-type: none">Any patient who has experienced a DLTAny patient who has received 5 consecutive days of treatment with RO5503781 within the first 21 days of combination therapyAny patient who has received at least 80% of planned doses of abiraterone or enzalutamide within the first 21 days of combination therapy	
Any patient who has dose modifications not permitted by study protocol within the first 21 days will NOT be evaluable unless they experience a DLT	

Primary: Incidence of dose-limiting toxicities

End point title	Incidence of dose-limiting toxicities ^[1]
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End point description:

Any of the following events beginning between the first administration of RO and 21 days after starting combination therapy if, in the opinion of the investigator, the event is due to the combination of abiraterone/enzalutamide, RO and prednisolone (if applicable) will be considered a dose limiting toxicity (DLT):

- * Grade 4 neutropenia ≥ 7 days duration
- * Grade 3–4 neutropenia associated with an oral temperature $\geq 38.5^{\circ}\text{C}$
- * 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 suboptimally-treated nausea or vomiting

End point type	Primary
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End point timeframe:

Between the first administration of RO and 21 days after starting combination therapy

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

End point values	Cohort -1	Cohort 1	Cohort 1*	Cohort 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: Patients	0	0	0	0

End point values	Cohort 3B	Cohort 1E	Phase I Evaluable Study Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	3	21	
Units: Patients	1	0	1	

Statistical analyses

No statistical analyses for this end point

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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Cohort -1
Reporting group description: -	
Reporting group title	Cohort 1
Reporting group description: -	
Reporting group title	Cohort 1*
Reporting group description: -	
Reporting group title	Cohort 1E
Reporting group description: -	
Reporting group title	Cohort 2
Reporting group description: -	
Reporting group title	Cohort 3B
Reporting group description: -	

Serious adverse events	Cohort -1	Cohort 1	Cohort 1*
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	2 / 3 (66.67%)	2 / 3 (66.67%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MYELODYSPLASTIC SYNDROME	Additional description: MYELODYSPLASTIC SYNDROME		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
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 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
TUMOR PAIN	Additional description: TUMOR PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
THROMBOEMBOLIC EVENT	Additional description: THROMBOEMBOLIC EVENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
SURGICAL AND MEDICAL PROCEDURES - OTHER, SPECIFY	Additional description: SURGICAL AND MEDICAL PROCEDURES - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (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
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%)	0 / 3 (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
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

GENITAL EDEMA alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: GENITAL EDEMA		
	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0 / 1	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders PRODUCTIVE COUGH alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: PRODUCTIVE COUGH		
	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
	0 / 0	0 / 1	0 / 0
	0 / 0	0 / 0	0 / 0
Psychiatric disorders DEPRESSION alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: DEPRESSION		
	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	1 / 1	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
Investigations CREATININE INCREASED alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: CREATININE INCREASED		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0 / 0	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
INVESTIGATIONS - OTHER, SPECIFY alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: INVESTIGATIONS - OTHER, SPECIFY		
	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0 / 1	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
PLATELET COUNT DECREASED alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: PLATELET COUNT DECREASED		
	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
	0 / 0	1 / 1	1 / 1
	0 / 0	0 / 0	0 / 0
Cardiac disorders			

ATRIAL FIBRILLATION alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: ATRIAL FIBRILLATION		
	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	1 / 1	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: MYOCARDIAL INFARCTION		
	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
	0 / 0	1 / 1	0 / 1
	0 / 0	0 / 0	0 / 0
Nervous system disorders TRANSIENT ISCHEMIC ATTACKS alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: TRANSIENT ISCHEMIC ATTACKS		
	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
	0 / 0	0 / 1	0 / 0
	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders ANEMIA alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: ANEMIA		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0 / 0	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders COLITIS alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: COLITIS		
	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
	0 / 0	0 / 0	0 / 1
	0 / 0	0 / 0	0 / 0
COLONIC OBSTRUCTION alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: COLONIC OBSTRUCTION		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0 / 0	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0
DIARRHEA 	Additional description: DIARRHEA		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
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	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
VOMITING	Additional description: VOMITING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
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			
HEMATURIA	Additional description: HEMATURIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY RETENTION	Additional description: URINARY RETENTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (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
Musculoskeletal and connective tissue disorders			
BACK PAIN	Additional description: BACK PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BRONCHIAL INFECTION	Additional description: BRONCHIAL INFECTION		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
LUNG INFECTION	Additional description: LUNG INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	2 / 2
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%)	1 / 3 (33.33%)
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			
HYPERCALCEMIA	Additional description: HYPERCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (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
HYPERGLYCEMIA	Additional description: HYPERGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
HYPOKALEMIA	Additional description: HYPOKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
HYPOPHOSPHATEMIA	Additional description: HYPOPHOSPHATEMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 1E	Cohort 2	Cohort 3B
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	6 / 7 (85.71%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MYELODYSPLASTIC SYNDROME	Additional description: MYELODYSPLASTIC SYNDROME		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
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%)	1 / 3 (33.33%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOR PAIN	Additional description: TUMOR PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
THROMBOEMBOLIC EVENT	Additional description: THROMBOEMBOLIC EVENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
SURGICAL AND MEDICAL PROCEDURES - OTHER, SPECIFY	Additional description: SURGICAL AND MEDICAL PROCEDURES - OTHER, SPECIFY		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
EDEMA LIMBS	Additional description: EDEMA LIMBS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
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			
GENITAL EDEMA	Additional description: GENITAL EDEMA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PRODUCTIVE COUGH	Additional description: PRODUCTIVE COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
DEPRESSION	Additional description: DEPRESSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
CREATININE INCREASED	Additional description: CREATININE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INVESTIGATIONS - OTHER, SPECIFY	Additional description: INVESTIGATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
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%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
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	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION	Additional description: MYOCARDIAL INFARCTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
TRANSIENT ISCHEMIC ATTACKS	Additional description: TRANSIENT ISCHEMIC ATTACKS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
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%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
COLITIS	Additional description: COLITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC OBSTRUCTION	Additional description: COLONIC OBSTRUCTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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%)	0 / 3 (0.00%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
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%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
HEMATURIA	Additional description: HEMATURIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY RETENTION	Additional description: URINARY RETENTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN	Additional description: BACK PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 7 (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
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%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
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 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPERCALCEMIA	Additional description: HYPERCALCEMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCEMIA	Additional description: HYPERGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALEMIA	Additional description: HYPOKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOPHOSPHATEMIA	Additional description: HYPOPHOSPHATEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort -1	Cohort 1	Cohort 1*
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (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 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
FLUSHING	Additional description: FLUSHING		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
HOT FLASHES	Additional description: HOT FLASHES		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	2	15	0
HYPERTENSION	Additional description: HYPERTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
HYPOTENSION	Additional description: HYPOTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
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 / 3 (0.00%)
occurrences (all)	3	0	0
THROMBOEMBOLIC EVENT	Additional description: THROMBOEMBOLIC EVENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
EDEMA FACE	Additional description: EDEMA FACE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
EDEMA LIMBS	Additional description: EDEMA LIMBS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
FATIGUE	Additional description: FATIGUE		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
occurrences (all)	0	7	20
FEVER	Additional description: FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
FLU LIKE SYMPTOMS	Additional description: FLU LIKE SYMPTOMS		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	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	2 / 3 (66.67%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	3	1	1
HYPOTHERMIA	Additional description: HYPOTHERMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
MALAISE	Additional description: MALAISE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	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%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3 (100.00%)	2 / 3 (66.67%)	2 / 3 (66.67%)
occurrences (all)	5	12	2
Immune system disorders			
ALLERGIC REACTION	Additional description: ALLERGIC REACTION		
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Reproductive system and breast disorders			
GYNECOMASTIA	Additional description: GYNECOMASTIA		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
PELVIC PAIN	Additional description: PELVIC PAIN		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, SPECIFY	Additional description: REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
COUGH	Additional description: COUGH		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 2	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
DYSPNEA	Additional description: DYSPNEA		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 3	1 / 3 (33.33%) 1
EPISTAXIS	Additional description: EPISTAXIS		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
LARYNGEAL INFLAMMATION	Additional description: LARYNGEAL INFLAMMATION		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY	Additional description: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY		

<p>SPECIFY</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	1	0	0
	Additional description: SLEEP APNEA		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0	0	0
	Additional description: WHEEZING		
	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	1	0	0
Psychiatric disorders			
ANXIETY	Additional description: ANXIETY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
CONFUSION	Additional description: CONFUSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
DEPRESSION	Additional description: DEPRESSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
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 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED	Additional description: ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

<p>INVESTIGATIONS - OTHER, SPECIFY</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: INVESTIGATIONS - OTHER, SPECIFY		
	0 / 3 (0.00%)	3 / 3 (100.00%)	0 / 3 (0.00%)
	0	4	0
	Additional description: NEUTROPHIL COUNT DECREASED		
	0 / 3 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
<p>NEUTROPHIL COUNT DECREASED</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	0	2	0
	Additional description: PLATELET COUNT DECREASED		
	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
	0	1	0
	Additional description: WEIGHT GAIN		
<p>PLATELET COUNT DECREASED</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0	0	0
	Additional description: WEIGHT LOSS		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0	0	0
<p>WEIGHT GAIN</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: INJURY TO SUPERIOR VENA CAVA		
	Additional description: BRUISING		
	1 / 3 (33.33%)	2 / 3 (66.67%)	0 / 3 (0.00%)
	1	7	0
<p>WEIGHT LOSS</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: FALL		
	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 3 (66.67%)
	1	0	2
	Additional description: FRACTURE		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
<p>INJURY TO SUPERIOR VENA CAVA</p> <p>alternative assessment type: Non-</p>	0	0	0
	Additional description: INJURY TO SUPERIOR VENA CAVA		

systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER, SPECIFY	Additional description: INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
ATRIAL FIBRILLATION	Additional description: ATRIAL FIBRILLATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
CHEST PAIN - CARDIAC	Additional description: CHEST PAIN - CARDIAC		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
DIZZINESS	Additional description: DIZZINESS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
HEADACHE	Additional description: HEADACHE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
LETHARGY	Additional description: LETHARGY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
MEMORY IMPAIRMENT	Additional description: MEMORY IMPAIRMENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
MOVEMENTS INVOLUNTARY	Additional description: MOVEMENTS INVOLUNTARY		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
NEURALGIA	Additional description: NEURALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
OLFACTORY NERVE DISORDER	Additional description: OLFACTORY NERVE DISORDER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	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 / 3 (0.00%)
occurrences (all)	0	0	0
THROMBOTIC THROMBOCYTOPENIC PURPURA	Additional description: THROMBOTIC THROMBOCYTOPENIC PURPURA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
EAR AND LABYRINTH DISORDERS - OTHER, SPECIFY	Additional description: EAR AND LABYRINTH DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
EAR PAIN	Additional description: EAR PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

BLURRED VISION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: BLURRED VISION		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
EYE DISORDERS - OTHER, SPECIFY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: EYE DISORDERS - OTHER, SPECIFY		
	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Gastrointestinal disorders ABDOMINAL PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ABDOMINAL PAIN		
	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
BLOATING alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: BLOATING		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
CONSTIPATION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: CONSTIPATION		
	3 / 3 (100.00%) 5	1 / 3 (33.33%) 3	1 / 3 (33.33%) 1
DIARRHEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: DIARRHEA		
	3 / 3 (100.00%) 8	3 / 3 (100.00%) 6	2 / 3 (66.67%) 20
DYSPEPSIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: DYSPEPSIA		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
GASTROINTESTINAL DISORDERS - OTHER, SPECIFY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: GASTROINTESTINAL DISORDERS - OTHER, SPECIFY		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
GASTROINTESTINAL PAIN alternative assessment type: Non-	Additional description: GASTROINTESTINAL PAIN		

systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
MUCOSITIS ORAL	Additional description: MUCOSITIS ORAL		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	2 / 3 (66.67%)
occurrences (all)	8	7	36
ORAL PAIN	Additional description: ORAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
SALIVARY DUCT INFLAMMATION	Additional description: SALIVARY DUCT INFLAMMATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
STOMACH PAIN	Additional description: STOMACH PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
VOMITING	Additional description: VOMITING		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	2	2	13
Skin and subcutaneous tissue disorders			
DRY SKIN	Additional description: DRY SKIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	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%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
SCALP PAIN	Additional description: SCALP PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	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	2 / 3 (66.67%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	5	2	0
Renal and urinary disorders			
CYSTITIS NONINFECTIVE	Additional description: CYSTITIS NONINFECTIVE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	5
HEMATURIA	Additional description: HEMATURIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	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%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	3	1
URINARY FREQUENCY	Additional description: URINARY FREQUENCY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
URINARY RETENTION	Additional description: URINARY RETENTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

BACK PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: BACK PAIN		
	0 / 3 (0.00%) 0	1 / 3 (33.33%) 2	1 / 3 (33.33%) 1
BONE PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: BONE PAIN		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 3
BUTTOCK PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: BUTTOCK PAIN		
	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
CHEST WALL PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: CHEST WALL PAIN		
	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
FLANK PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: FLANK PAIN		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
MUSCLE WEAKNESS LOWER LIMB alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: MUSCLE WEAKNESS LOWER LIMB		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY		
	1 / 3 (33.33%) 2	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
NECK PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: NECK PAIN		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Infections and infestations			

BLADDER INFECTION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: BLADDER INFECTION		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0	0	0
INFECTIONS AND INFESTATIONS - OTHER, SPECIFY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: INFECTIONS AND INFESTATIONS - OTHER, SPECIFY		
	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 3 (66.67%)
	2	0	2
LARYNGITIS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LARYNGITIS		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0	0	0
LUNG INFECTION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LUNG INFECTION		
	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	1	0	0
PENILE INFECTION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: PENILE INFECTION		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0	0	0
PHARYNGITIS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: PHARYNGITIS		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0	0	0
RHINITIS INFECTIVE alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: RHINITIS INFECTIVE		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0	0	0
SINUSITIS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: SINUSITIS		
	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	0	0	0
SKIN INFECTION alternative assessment type: Non-systematic	Additional description: SKIN INFECTION		

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
SOFT TISSUE INFECTION	Additional description: SOFT TISSUE INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
UPPER RESPIRATORY INFECTION	Additional description: UPPER RESPIRATORY INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
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 / 3 (0.00%)
occurrences (all)	0	0	0
UTERINE INFECTION	Additional description: UTERINE INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	2	0	28
DEHYDRATION	Additional description: DEHYDRATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
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%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
HYPOGLYCEMIA	Additional description: HYPOGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 1E	Cohort 2	Cohort 3B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	7 / 7 (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	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Vascular disorders			
FLUSHING	Additional description: FLUSHING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
HOT FLASHES	Additional description: HOT FLASHES		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
HYPERTENSION	Additional description: HYPERTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
HYPOTENSION	Additional description: HYPOTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
PHLEBITIS	Additional description: PHLEBITIS		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (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%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
EDEMA FACE	Additional description: EDEMA FACE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
EDEMA LIMBS	Additional description: EDEMA LIMBS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
FATIGUE	Additional description: FATIGUE		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3 (100.00%)	1 / 3 (33.33%)	5 / 7 (71.43%)
occurrences (all)	18	1	21
FEVER	Additional description: FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
FLU LIKE SYMPTOMS	Additional description: FLU LIKE SYMPTOMS		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	1 / 7 (14.29%)
occurrences (all)	2	2	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%)	0 / 3 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	4
HYPOTHERMIA	Additional description: HYPOTHERMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
MALAISE	Additional description: MALAISE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 7 (42.86%)
occurrences (all)	9	0	6
NON-CARDIAC CHEST PAIN	Additional description: NON-CARDIAC CHEST PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3 (100.00%)	1 / 3 (33.33%)	4 / 7 (57.14%)
occurrences (all)	6	3	7
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%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
GYNECOMASTIA	Additional description: GYNECOMASTIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
PELVIC PAIN	Additional description: PELVIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, SPECIFY	Additional description: REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			

COUGH alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: COUGH		
	1 / 3 (33.33%) 3	0 / 3 (0.00%) 0	1 / 7 (14.29%) 3
DYSPNEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: DYSPNEA		
	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	4 / 7 (57.14%) 6
EPISTAXIS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: EPISTAXIS		
	0 / 3 (0.00%) 0	1 / 3 (33.33%) 2	1 / 7 (14.29%) 1
LARYNGEAL INFLAMMATION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LARYNGEAL INFLAMMATION		
	1 / 3 (33.33%) 2	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY		
	1 / 3 (33.33%) 2	0 / 3 (0.00%) 0	2 / 7 (28.57%) 2
SLEEP APNEA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: SLEEP APNEA		
	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
WHEEZING alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: WHEEZING		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
Psychiatric disorders ANXIETY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ANXIETY		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
CONFUSION	Additional description: CONFUSION		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 7 (14.29%) 1
DEPRESSION	Additional description: DEPRESSION		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	0 / 7 (0.00%) 0
PSYCHIATRIC DISORDERS - OTHER, SPECIFY	Additional description: PSYCHIATRIC DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	2 / 7 (28.57%) 2
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED	Additional description: ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
INVESTIGATIONS - OTHER, SPECIFY	Additional description: INVESTIGATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
NEUTROPHIL COUNT DECREASED	Additional description: NEUTROPHIL COUNT DECREASED		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 3 (33.33%) 1	4 / 7 (57.14%) 6
PLATELET COUNT DECREASED	Additional description: PLATELET COUNT DECREASED		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 2	4 / 7 (57.14%) 6
WEIGHT GAIN	Additional description: WEIGHT GAIN		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
WEIGHT LOSS	Additional description: WEIGHT LOSS		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	0 / 7 (0.00%) 0
Injury, poisoning and procedural complications			
BRUISING	Additional description: BRUISING		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	2 / 7 (28.57%) 2
FALL	Additional description: FALL		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 7 (14.29%) 1
FRACTURE	Additional description: FRACTURE		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	1 / 7 (14.29%) 1
INJURY TO SUPERIOR VENA CAVA	Additional description: INJURY TO SUPERIOR VENA CAVA		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER, SPECIFY	Additional description: INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 3 (33.33%) 1	2 / 7 (28.57%) 2
Cardiac disorders			
ATRIAL FIBRILLATION	Additional description: ATRIAL FIBRILLATION		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
CHEST PAIN - CARDIAC	Additional description: CHEST PAIN - CARDIAC		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
Nervous system disorders			

DIZZINESS alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: DIZZINESS		
	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	3 / 7 (42.86%) 5
HEADACHE alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: HEADACHE		
	1 / 3 (33.33%) 2	1 / 3 (33.33%) 4	3 / 7 (42.86%) 3
LETHARGY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: LETHARGY		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	3 / 7 (42.86%) 3
MEMORY IMPAIRMENT alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: MEMORY IMPAIRMENT		
	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	1 / 7 (14.29%) 1
MOVEMENTS INVOLUNTARY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: MOVEMENTS INVOLUNTARY		
	1 / 3 (33.33%) 2	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY		
	1 / 3 (33.33%) 2	2 / 3 (66.67%) 2	2 / 7 (28.57%) 4
NEURALGIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: NEURALGIA		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
OLFACTORY NERVE DISORDER alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: OLFACTORY NERVE DISORDER		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 7 (14.29%) 1
Blood and lymphatic system disorders			

ANEMIA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ANEMIA		
	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	3 / 7 (42.86%) 4
THROMBOTIC THROMBOCYTOPENIC PURPURA alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: THROMBOTIC THROMBOCYTOPENIC PURPURA		
	1 / 3 (33.33%) 1	1 / 3 (33.33%) 2	3 / 7 (42.86%) 4
Ear and labyrinth disorders EAR AND LABYRINTH DISORDERS - OTHER, SPECIFY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: EAR AND LABYRINTH DISORDERS - OTHER, SPECIFY		
	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
EAR PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: EAR PAIN		
	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	0 / 7 (0.00%) 0
Eye disorders BLURRED VISION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: BLURRED VISION		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	2 / 7 (28.57%) 2
EYE DISORDERS - OTHER, SPECIFY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: EYE DISORDERS - OTHER, SPECIFY		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
Gastrointestinal disorders ABDOMINAL PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: ABDOMINAL PAIN		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 7 (14.29%) 1
BLOATING alternative assessment type: Non-systematic	Additional description: BLOATING		

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
CONSTIPATION	Additional description: CONSTIPATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 7 (28.57%)
occurrences (all)	1	1	8
DIARRHEA	Additional description: DIARRHEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	2 / 3 (66.67%)	6 / 7 (85.71%)
occurrences (all)	44	6	28
DYSPEPSIA	Additional description: DYSPEPSIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
GASTROINTESTINAL DISORDERS - OTHER, SPECIFY	Additional description: GASTROINTESTINAL DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	1 / 7 (14.29%)
occurrences (all)	0	3	1
GASTROINTESTINAL PAIN	Additional description: GASTROINTESTINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
MUCOSITIS ORAL	Additional description: MUCOSITIS ORAL		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3 (100.00%)	2 / 3 (66.67%)	6 / 7 (85.71%)
occurrences (all)	30	3	32
ORAL PAIN	Additional description: ORAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

SALIVARY DUCT INFLAMMATION alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: SALIVARY DUCT INFLAMMATION		
	1 / 3 (33.33%) 4	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
STOMACH PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: STOMACH PAIN		
	0 / 3 (0.00%) 0	1 / 3 (33.33%) 2	0 / 7 (0.00%) 0
VOMITING alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: VOMITING		
	1 / 3 (33.33%) 1	2 / 3 (66.67%) 2	5 / 7 (71.43%) 8
Skin and subcutaneous tissue disorders DRY SKIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: DRY SKIN		
	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
RASH MACULO-PAPULAR alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: RASH MACULO-PAPULAR		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
SCALP PAIN alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: SCALP PAIN		
	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY		
	0 / 3 (0.00%) 0	1 / 3 (33.33%) 3	1 / 7 (14.29%) 2
Renal and urinary disorders CYSTITIS NONINFECTIVE alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: CYSTITIS NONINFECTIVE		
	1 / 3 (33.33%) 2	0 / 3 (0.00%) 0	1 / 7 (14.29%) 3
HEMATURIA	Additional description: HEMATURIA		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 5	0 / 3 (0.00%) 0	1 / 7 (14.29%) 1
RENAL AND URINARY DISORDERS - OTHER, SPECIFY	Additional description: RENAL AND URINARY DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	2 / 7 (28.57%) 2
URINARY FREQUENCY	Additional description: URINARY FREQUENCY		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	2 / 7 (28.57%) 2
URINARY RETENTION	Additional description: URINARY RETENTION		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	1 / 7 (14.29%) 1
Musculoskeletal and connective tissue disorders			
BACK PAIN	Additional description: BACK PAIN		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 3 (66.67%) 2	3 / 7 (42.86%) 4
BONE PAIN	Additional description: BONE PAIN		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	1 / 7 (14.29%) 1
BUTTOCK PAIN	Additional description: BUTTOCK PAIN		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 7 (0.00%) 0
CHEST WALL PAIN	Additional description: CHEST WALL PAIN		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 2	0 / 7 (0.00%) 0
FLANK PAIN	Additional description: FLANK PAIN		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	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%)	1 / 7 (14.29%)
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	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 7 (28.57%)
occurrences (all)	1	6	3
NECK PAIN	Additional description: NECK PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Infections and infestations			
BLADDER INFECTION	Additional description: BLADDER INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
INFECTIOUS AND INFESTATIONS - OTHER, SPECIFY	Additional description: INFECTIOUS AND INFESTATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	2 / 3 (66.67%)	2 / 7 (28.57%)
occurrences (all)	6	4	2
LARYNGITIS	Additional description: LARYNGITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
LUNG INFECTION	Additional description: LUNG INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
PENILE INFECTION	Additional description: PENILE INFECTION		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
PHARYNGITIS	Additional description: PHARYNGITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
RHINITIS INFECTIVE	Additional description: RHINITIS INFECTIVE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	6	0	0
SINUSITIS	Additional description: SINUSITIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
SKIN INFECTION	Additional description: SKIN INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
SOFT TISSUE INFECTION	Additional description: SOFT TISSUE INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
UPPER RESPIRATORY INFECTION	Additional description: UPPER RESPIRATORY INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
URINARY TRACT INFECTION	Additional description: URINARY TRACT INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	2
UTERINE INFECTION	Additional description: UTERINE INFECTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (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%)	1 / 3 (33.33%)	2 / 7 (28.57%)
occurrences (all)	8	2	7
DEHYDRATION	Additional description: DEHYDRATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
HYPERGLYCEMIA	Additional description: HYPERGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	2
HYPOGLYCEMIA	Additional description: HYPOGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2015	Protocol updated with details of intermediate dose levels to be explored, if required, during the Phase I component of the study. Clarification of the PK requirements for Phase I patients, including timings and the removal of the Day -7 single dose for PK testing from cohort 1* onwards.
04 April 2016	Protocol updated with the addition of enzalutamide as an IMP for the study. As a result of this update, an additional Phase I cohort exploring the combination of idasanutlin (RO5503781) and enzalutamide included in the study protocol.
26 June 2017	Notification that the Phase II component of the study no longer supported by our partner and therefore would not be proceeding. Additionally, clarification provided around the allowed window for study assessments and visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported